ORIGINAL RESEARCH

Initiation of the Fixed Combination IDegLira in Patients with Type 2 Diabetes on Prior Injectable Therapy: Insights from the EASY French Real-World Study

Blandine Tramunt · Emmanuel Disse · Nicolas Chevalier ·

Lyse Bordier · Laurent Cazals · Olivier Dupuy · Michel Marre ·

Odette Matar · Laurent Meyer · Chloé Noilhan · Caroline Sanz ·

Paul Valensi · Fritz-Line Velayoudom · Jean-François Gautier ·

Pierre Gourdy 🔟

ABSTRACT

Introduction: Combining basal insulin (BI) with glucagon-like peptide-1 receptor agonist (GLP-1RA) is recognized as a relevant option to optimize glucose control in type 2 diabetes (T2D). The EASY real-world study aimed to evaluate the modalities of initiation and the effectiveness of the insulin Degludec plus Liraglutide (IDegLira) fixed-ratio combination in the French health care system.
Methods: A retrospective analysis included all patients with T2D and prior injectable therapy (GLP1-RA and/or insulin) who started treatment with IDegLira from September 2016 to December 2017 in 11 French diabetes centers. Baseline characteristics, reasons for IDegLira initiation,

B. Tramunt · L. Cazals · C. Noilhan · P. Gourdy (✉)
Service de Diabétologie, Maladies Métaboliques et Nutrition, CHU et Université de Toulouse, TSA 50032, 31059 Toulouse Cedex 9, France
e-mail: gourdy.p@chu-toulouse.fr

B. Tramunt · P. Gourdy
Institut des Maladies Métaboliques et Cardiovasculaires, UMR1297 INSERM/UT3, Toulouse, France

E. Disse
Service d'Endocrinologie, Diabète et Nutrition, Centre Hospitalier Lyon Sud, Hospices Civils de Lyon, Lyon, France

N. Chevalier
Université Côte d'Azur, Centre Hospitalier Universitaire, INSERM U1065, C3M, Nice, France

L. Bordier
Service d'Endocrinologie, Hôpital d'instruction des Armées Begin, Saint-Mandé, France

O. Dupuy
Service de Diabétologie et Endocrinologie, Groupe Hospitalier Saint-Joseph, Paris, France

M. Marre
Clinique Ambroise Paré, Neuilly-sur-Seine, France

O. Matar
Service d'Endocrinologie, Diabétologie et Nutrition, Hôpital Bichat, Paris, France

L. Meyer
Service d'Endocrinologie, Diabète et Maladies Métaboliques, CHU de Strasbourg, Strasbourg, France

C. Sanz
Cabinet d'Endocrinologie, de Diabétologie et de Nutrition, Clinique Pasteur, Toulouse, France

P. Valensi
Unit of Endocrinology, Diabetology and Nutrition, Jean Verdier Hospital, Paris Nord University, Bondy, France

and modes of implementation were collected from the medical records. Changes in HbA_{1c} and body weight were determined in patients with available follow-up data (nearest 6-month visit).

Results: IDegLira was initiated in 629 patients previously treated with GLP-1RA alone (11.6%), insulin alone (31.5% including 16.5% with BI and 14.9% with multiple daily injections [MDI]) or a free combination of GLP-1RA and insulin (56.9% including 44.8% with BI and 12.1% with MDI), associated or not with oral agents. IDegLira starting dose (mean of 29 ± 11 dose steps) most often exceeded the recommended dose, and was significantly correlated with prior BI but not GLP-1RA dosage. At initiation, mean age, body mass index (BMI) and HbA_{1c} were 60.1 ± 10.2 years, 33.4 ± 6.2 kg/m^2 and $8.8 \pm 1.7\%$, respectively. In 461 patients with available follow-up (median 178 days), HbA_{1c} decreased in all subgroups submitted to treatment intensification ($-1.7 \pm 1.8\%$ [$p < 0.0001$], $-1.2 \pm 1.8\%$ [$p < 0.001$] and $-0.8 \pm 1.8\%$ [$p = 0.0026$] in patients with prior GLP-1RA, BI or MDI therapy, respectively) but also in those switching from BI and GLP-1RA free combination ($-0.2 \pm 0.9\%$, $p = 0.0419$). Significant body weight gain occurred in patients previously treated with GLP-1RA alone ($+1.5 \pm 5.8$ kg, $p = 0.0572$) or combined to BI ($+1.0 \pm 3.1$ kg, $p < 0.0001$) while those on BI (-1.4 ± 4.6 kg, $p = 0.0139$) or MDI (-1.4 ± 5.0 kg, $p = 0.0484$) experienced weight loss.

Conclusions: While providing new information on the use of IDegLira in the French healthcare system, these data confirm the effectiveness of this fixed-ratio combination in the management of T2D.

Keywords: Type 2 diabetes; Insulin; GLP-1RA; Fixed-ratio combination; Real-world study

Key Summary Points

Why carry out this study?

The combination of basal insulin and glucagon-like peptide-1 receptor agonist (GLP-1RA) is a relevant option to optimize glucose control in type 2 diabetes (T2D).

The modalities of initiation and the effectiveness of the fixed-ratio combination of insulin degludec and liraglutide (IDegLira) have not been investigated so far in the French health care system.

What was learned?

This real-world observational multicenter study provides new information about the use of IDegLira in France where more than half of initiations aimed to simplify the therapeutic scheme by switching from a free combination of GLP-1RA and insulin.

Follow-up data demonstrate the effectiveness of IDegLira to maintain or improve glucose control in patients with T2D requiring either therapeutic intensification or simplification, thus reinforcing the conclusions of previous real-world studies.

However, the proportion of patients reaching the recommended HbA_{1c} targets remained low, highlighting the critical need to develop strategies aimed at optimizing IDegLira dose titration.

F.-L. Velayoudom
Service d'Endocrinologie-Diabétologie, CHU de Guadeloupe, Pointe-À-Pitre, France

J.-F. Gautier
Service de Diabétologie et d'Endocrinologie, Hôpital Lariboisière, AP-HP, Paris Cité, INSERM 1151, Paris, France

J.-F. Gautier
Université Paris Cité, INSERM UMR-S1151, CNRS UMR-S8253, Institut Necker Enfants Malades, 75015 Paris, France

INTRODUCTION

Combined administration of glucagon-like peptide-1 receptor agonist (GLP-1RA) and basal insulin (BI) is recognized as a highly effective glucose-lowering strategy in people with type 2 diabetes (T2D) requiring intensification of their injectable therapy [1–3]. As compared with intensified insulin regimens which require prandial insulin administration, such combinations were indeed demonstrated to provide similar improvement in HbA_{1c} with clear benefits in terms of weight change and risk of hypoglycemia in patients with T2D receiving either BI or GLP-1RA as background therapy [4, 5].

Aimed first at simplifying treatment administration, two distinct fixed-ratio formulations combining a BI analog and a GLP-1RA have been developed and made available in recent years: insulin degludec plus liraglutide (IDegLira) and insulin glargine plus lixisenatide (IGlarLixi) [6]. In adults with inadequately controlled T2D, efficacy and safety have been demonstrated for both IDegLira and IGlarLixi, used as first- or second-line injectable therapy in the DUAL and LIxiLan phase 3 clinical trial programs, respectively [6]. Noteworthy, in addition to the expected benefits in terms of quality of life and medication adherence, simultaneous adjustment of insulin and GLP-1RA doses is likely to promote therapeutic efficacy along with optimal tolerance [7, 8]. In fact, the progressive dose titration makes it possible to limit the adverse gastro-intestinal side effects frequently observed during the initiation of GLP-1RA therapy [9]. Current guidelines thus indicate that prescribing one of these fixed-ratio combinations might be considered when association of both injectable therapies is indicated, noting that BI titration cannot be carried out beyond the dose associated with the maximal GLP-1RA dosage [3].

In the last years, several observational studies reported the efficacy and cost-effectiveness of IDegLira and IGlarLixi in real-world settings, especially in European countries [10–14], Israel [15], or the United States [16]. However, none of them included data from people treated for T2D in France where IDegLira was marketed in September 2016 and still remains the only fixed-ratio combination available. Therefore, we conducted a multicenter study with the purpose to describe the modalities of IDegLira initiation in patients with T2D within the framework of the French healthcare system, then to evaluate the efficacy of this fixed-ratio combination during the first months of administration.

METHODS

Study Design

The EASY French study is a multicenter retrospective non-interventional chart review study which involved investigators from 11 French diabetes centers: Bichat Hospital (APHP, Paris), Lariboisière Hospital (APHP, Paris), Saint-Joseph Hospital (Paris), Begin Hospital (Saint-Mandé), Jean-Verdier Hospital (APHP, Bondy), Lyon-Sud Hospital (HCL, Lyon), Nice University Hospital (Nice), Strasbourg University Hospital (Strasbourg), Guadeloupe University Hospital (Pointe-à-Pitre), Pasteur private clinic (Toulouse) and Toulouse University Hospital (Toulouse). Promoted by Toulouse University Hospital, the study was designed in accordance with the Declaration of Helsinki and conducted in compliance with the French legislation applicable to non-interventional retrospective chart review studies assessing health assessments of public interest (MR004, RC19-0268). According to the French ethic and regulatory law, studies based on the exploitation of usual care data did not have to be submitted to a specific ethic committee but had to be declared or covered by reference methodology of the French National Commission for Informatics and Liberties (CNIL). Toulouse University Hospital signed a commitment of compliance to the reference methodology MR-004 of the CNIL (CNIL number: 2206723 v 0). The study was thus approved by Toulouse University Hospital after evaluation by the data protection officer and according to the General Data Protection Regulation.

Participating centers were asked to identify all patients with T2D who initiated IDegLira

between September 9, 2016 (date of IDegLira availability in France) and December 31, 2017, through specific queries in the local electronic medical files. Eligible participants for the present analysis were adults with T2D, previous injectable glucose-lowering therapy, and available medical report at the time of IDegLira initiation without restriction regarding a set of minimum available data or other exclusion criteria.

Study Objectives

The primary objective was to describe the characteristics of patients with T2D initiating IDegLira in the real-life French clinical care settings, with a specific focus on reasons (therapeutic intensification or simplification) and modalities of IDegLira prescription.

The secondary objective was to evaluate the effectiveness of IDegLira, assessed by changes in HbA_{1c} level and body weight during the first months of use, along with the adaptation of both IDegLira doses and associated glucose-lowering medications.

Baseline and Follow-up Data Collection

Data collection was retrospectively performed in each center by clinical research associates and/or physicians in charge of the patients, using a standardized case report form provided by the promoter. They systematically reviewed the medical files of all selected patients and collected patient characteristics as well as the modalities of IDegLira initiation. These baseline collected data included demographic (birth date, gender) and clinical (diabetes duration, height/weight or body mass index [BMI], history of cardiovascular risk factors and of micro/macrovascular complications, HbA_{1c} level) characteristics as well as precise information about glucose-lowering therapy: prior regimen (including therapeutic classes for oral agents, molecules and dosages for insulins and GLP-1RAs) and therapeutic changes at IDegLira initiation, reason for initiating IDegLira (intensification or simplification of therapeutic

scheme), IDegLira initiation dose and support for titration.

They were then asked to identify those participants for whom one or more follow-up visits had been carried out in a time window of 3–18 months after IDegLira initiation and collected data for the visit closest to 6-month follow-up time point after initiation. This time point was chosen since it corresponds to the recommended period for evaluating the effectiveness of a newly introduced glucose-lowering therapy [2, 3]. The 3-to-18-month time window was proposed to respect the minimum time required to assess the effectiveness (3 months) and to gather follow-up data of patients visiting the diabetes center only once a year (followed up in the meantime by their general practitioner). Accordingly, participants for whom a single follow-up visit was recorded less than 3 months after IDegLira initiation were considered out of range for longitudinal evaluation and those with a single visit recorded more than 18 months after initiation or without follow-up visit were considered as lost of follow-up. At follow-up visit, continuation or discontinuation of IDegLira was recorded as well as, in case of discontinuation, the date and reason for stopping the treatment. In patients still treated with IDegLira, the following data were systematically collected: HbA_{1c}, weight or BMI, changes in associated glucose-lowering drugs, dose of IDegLira and prandial insulin if appropriate, any titration difficulties or adverse effects mentioned in the medical report.

At both time points, GLP1-RA doses have been expressed in defined daily dose (DDD) to allow comparisons between the different molecules, according to the World Health Organization Index, as previously described [10]. All data were indirectly anonymized in each center to allow optimal verification of their quality and the formulation of specific queries during the database freeze procedures conducted by the promoter.

Statistical Analyses

Baseline characteristics and modalities of IDegLira initiation were assessed on the full

analysis set (FAS), which included all patients with T2D who started IDegLira treatment between September 9, 2016 and December 31, 2017. Follow-up data were assessed on the effectiveness analysis set (EAS), which included patients of the FAS who maintained IDegLira treatment and for whom at least one follow-up visit has been recorded during the 3-to-18-month period following initiation. Quantitative data were expressed as mean ± standard deviation (SD) and categorical variables were given as number (%) of patients. The differences between groups were analyzed using unpaired t test or ANOVA, as appropriate, whereas chi-squared test was used to compare the distribution of qualitative variables.

The significance of changes observed between baseline and the follow-up visit was examined using paired t test. McNemar test was used to compare the distributions of matched qualitative variables. Finally, the correlation between IDegLira starting dose and either previous BI or GLP-1RA dosage was examined using a multiple regression analysis model. STATA 16.0 statistical software (StataCorp 4905 Lakewave Drive College Station, TX, USA) was used to perform all data analyses and $p < 0.05$ was considered significant.

RESULTS

Characteristics of Patient Initiating IDegLira

A total of 629 individuals with T2D who initiated IDegLira treatment while previously receiving injectable therapy were included in the FAS population. Their baseline characteristics are shown in Table 1. Combined or not with oral anti-hyperglycemic agents, prior injectable regimen included a GLP-1RA alone in 11.6% of patients, insulin alone in 31.5% (16.5% with BI alone and 14.9% with multiple daily injections [MDI]) and a free combination of GLP-1RA and insulin in 56.9% of them (44.8% with BI alone and 12.1% with MDI).

A mean age of 60.1 ± 10.2 years, a slight male predominance, and a mean diabetes duration of 15.7 ± 8.7 years were observed in the whole population. Mean BMI was 33.4 ± 6.2 kg/m^2 with the highest value found in patients receiving a free combination of GLP-1RA and MDI (Table 1). Mean HbA$_{1c}$ was $8.8 \pm 1.7\%$ but initial glucose control was less impaired in the subgroups previously treated with a free combination of GLP-1RA and insulin, whereas the highest HbA$_{1c}$ value found in patients receiving GLP-1RA alone (distribution of HbA$_{1c}$ values is shown in Supplementary Fig. 1). Macrovascular and microvascular complications were respectively reported in 24.3% and 66.3% of individuals in the whole population, with a higher prevalence observed in patients on MDI, irrespective of combined GLP-1RA treatment (Table 1).

Prior injectable therapy was combined with oral anti-hyperglycemic agents in most cases (88.4%), although less frequently in patients on MDI. Metformin and sulfonylurea/glinides were the most used molecules (Table 1 and Supplementary Table 1). Liraglutide (68.5–81.9% in subgroups of GLP-1RA-treated patients) and dulaglutide (14.2–21.1%) were the most prescribed GLP-1RAs before IDegLira initiation. To take into account the specificities of the different molecules used, GLP-1RA DDD was estimated, ranging from 1.2 ± 0.3 to 1.3 ± 0.3 in the different subgroups (Table 1 and Supplementary Table 1). The mean daily dose of BI was around 35 UI and 40 UI in individuals with basal alone and those on MDI regimen, respectively. Glargine 100 UI/ml was the most used BI, ahead of detemir insulin (Supplementary Table 1). In patients with MDI scheme, the mean dose of prandial insulin was slightly higher in case of free combination with GLP-1RA (Table 1).

Modes of IDegLira Initiation

As expected, the main objective sought by the prescribers in initiating IDegLira was intensification of the therapeutic strategy in patients previously treated with GLP-1RA or insulin alone, and simplification of administration constraints in those on free combination of both injectable therapies (Table 2). IDegLira initiation was carried out in outpatient settings

Table 1 Demographic and clinical characteristics of patients with T2D at initiation of IDegLira

	Available Data (n)	Whole FAS population	GLP-1RA ± OAD	Insulin ± OAD		Insulin + GLP-1RA ± OAD	
				Basal	**MDI**	**Basal**	**MDI**
FAS, n (%)		629 (100.0)	73 (11.6)	104 (16.5)	94 (14.9)	282 (44.8)	76 (12.1)
Age, years	626	60.1 ± 10.2	58.6 ± 10.4	60.6 ± 9.8	59.1 ± 12.3	60.6 ± 9.8	60.5 ± 11.3
Female sex, n (%)	627	306 (48.8)	34 (46.6)	47 (45.2)	44 (46.8)	145 (51.6)	36 (48.0)
Diabetes duration, years	607	15.7 ± 8.7	13.2 ± 7.7	14.1 ± 8.2	16.2 ± 8.3	15.9 ± 8.2	19.3 ± 11.3
Body weight, kg	627	92.8 ± 18.4	94.3 ± 18.2	89.6 ± 19.1	92.0 ± 18.2	92.7 ± 17.8	97.4 ± 19.0
Body mass index, kg/m^2	602	33.4 ± 6.2	33.6 ± 6.6	32.3 ± 6.0	33.6 ± 6.1	33.3 ± 5.8	34.8 ± 6.6
HbA$_{1c}$, %	623	8.8 ± 1.7	9.9 ± 1.7	9.2 ± 1.7	9.5 ± 1.8	8.4 ± 1.4	8.1 ± 1.5
HbA$_{1c}$ ≤ 7%, n (%)	623	65 (10.4)	2 (2.7)	3 (2.9)	6 (6.5)	36 (12.9)	18 (24.0)
HbA$_{1c}$ ≤ 8%, n (%)	623	217 (34.8)	5 (6.9)	24 (23.1)	21 (22.8)	125 (44.8)	42 (56.0)
Hypertension, n (%)	612	490 (77.9)	52 (71.2)	82 (78.9)	74 (78.7)	218 (77.3)	64 (84.2)
Dyslipidemia, n (%)	610	447 (71.1)	45 (61.6)	67 (64.4)	69 (73.4)	211 (74.8)	55 (72.3)
Macrovascular complications, n (%)	629	153 (24.3)	14 (19.2)	22 (21.1)	31 (33.0)	65 (23.1)	21 (27.6)
Microvascular complications, n (%)	629	417 (66.3)	49 (67.1)	64 (61.5)	68 (72.3)	182 (64.5)	54 (71.1)
Prior medications other than insulin,	629						
OAD users, n (%)		556 (88.4)	69 (94.5)	98 (94.2)	64 (68.1)	271 (96.1)	54 (71.1)
GLP-1RA, DDD		–	1.2 ± 0.3	–	–	1.3 ± 0.3	1.2 ± 0.3
Prior insulin therapy,	629						
Total daily dose, U		–	–	34.5 ± 18.7	72.5 ± 35.8	35.3 ± 15.3	81.5 ± 45.6
Basal daily dose, U		–	–	34.5 ± 18.7	37.9 ± 20.3	35.3 ± 15.3	41.7 ± 20.1
Prandial daily dose, U		–	–	–	36.2 ± 22.6	–	43.8 ± 31.7

Hypertension corresponds to patients receiving at least one anti-hypertensive treatment. Dyslipidemia corresponds to patients receiving at least one lipid-lowering treatment. Macrovascular complications include history of ischemic heart disease, stroke, and/or peripheral artery diseases. Microvascular complications include retinopathy, chronic kidney disease and/or neuropathy. *DDD* defined daily dose. Results are expressed as number of patients (%) or as mean ± SD

T2D type 2 diabetes, *IDegLira* insulin degludec plus liraglutide, *FAS* full analysis set, *GLP-1RA* glucagon-like peptide-1 receptor agonist, *OAD* oral anti-hyperglycemic drug, *MDI* multiple daily injections, *DDD* defined daily dose

Table 2 Modes of IDegLira initiation according to prior injectable therapy

	Available Data (n)	Whole FAS population	GLP-1RA ± OAD	Insulin ± OAD		Insulin + GLP-1RA ± OAD	
				Basal	MDI	Basal	MDI
FAS, n (%)		629 (100.0)	73 (11.6)	104 (16.5)	94 (14.9)	282 (44.8)	76 (12.1)
Reason for IDegLira initiation, n (%)	629						
Treatment intensification		292 (46.4)	70 (95.9)	93 (89.4)	72 (76.6)	44 (15.6)	13 (17.1)
Treatment simplification		312 (49.6)	2 (2.7)	7 (6.7)	15 (16.0)	226 (80.1)	62 (81.6)
Other reason		25 (4.0)	1 (1.4)	4 (3.9)	7 (7.5)	12 (4.2)	1 (1.3)
Patient condition, n (%)	627						
Outpatient		396 (63.2)	36 (49.3)	53 (51.0)	36 (38.3)	215 (76.5)	56 (74.7)
Hospitalization		231 (36.8)	37 (50.7)	51 (49.0)	58 (61.7)	66 (23.5)	19 (25.3)
IDegLira starting dose,	625						
Mean dose, DS		29.0 ± 11.2	21.0 ± 7.9	24.1 ± 9.0	29.0 ± 10.8	31.2 ± 10.4	35.6 ± 13.2
Dose > 16 DS, n (%)		519 (82.5)	44 (60.3)	73 (70.2)	78 (83.0)	259 (91.8)	65 (85.5)
Provision of a titration support, n (%)	629	331 (52.6)	44 (60.3)	51 (49.0)	49 (52.1)	155 (55.0)	32 (42.1)
Dose change compared to previous treatment,	625						
GLP-1RA, DDD		–	– 0.6 ± 0.4	–	–	– 0.3 ± 0.4	– 0.1 ± 0.4
Basal insulin, U/day		–	–	– 10.6 ± 16.5	– 8.7 ± 18.5	– 4.1 ± 11.7	– 6.0 ± 14.1
Use of medications other than insulin,	629						
Metformin, n (%)		521 (82.8)	62 (84.9)	85 (81.7)	72 (76.6)	251 (89.0)	51 (67.1)
Sulfonylurea/glinides, n (%)		334 (53.1)	53 (72.6)	62 (59.6)	19 (20.2)	190 (67.3)	10 (13.2)
DPP4 inhibitor, n (%)		0	0	0	0	0	0
Prandial insulin, n (%)		127 (20.2)	0	2 (1.9)	50 (53.2)	14 (5.0)	61 (80.3)

Results are expressed as number of patients (%) or as mean ± SD

IDegLira insulin degludec plus liraglutide, *FAS* full analysis set, *GLP-1RA* glucagon-like peptide-1 receptor agonist, *OAD* oral anti-hyperglycemic drug, *MDI* multiple daily injections, *DS* dose step, *DDD* defined daily dose, *DPP4* dipeptidyl peptidase 4 inhibitors

in approximatively 75% of individuals with prior free combination versus 50% of those on GLP-1RA or BI alone and only 38.3% in case of previous MDI scheme (Table 2).

IDegLira starting dose most often exceeded the recommended 16 dose steps (DS) with a mean value of 29 ± 11 DS in the whole population, and only 52.6% of patients were provided with a support for adequate titration (Table 2 and Supplementary Table 2). In patients previously treated with GLP-1RA, the DDD was initially reduced by 0.6 in those receiving GLP-1RA alone, and by 0.3 or 0.1 in case of free combination with BI or MDI, respectively (Table 2). Initial reduction in BI dose was also observed, ranging from -4.1 to -10.6 UI/day according to prior therapeutic regimen. However, in patients with prior insulin therapy, IDegLira starting dose was significantly correlated with current BI dose, especially in case of free combination with GLP-1RA (Supplementary Fig. 2). No correlation was found with prior GLP-1RA DDD (data not shown).

At the time of IDegLira initiation in patients on MDI, prandial insulin administration was stopped in 19.7 and 46.8% of those with or without prior association with GLP-1RA, respectively. Introduction of prandial insulin was infrequent in the other subgroups (Table 2).

Efficacy of IDegLira at Follow-up Visit

From the whole FAS population, 66 patients were lost of follow-up (10.5%). Among individuals with available data, 48 (8.5%) discontinued IDegLira before the follow-up visit, 30 (5.3%) visited the initiating diabetes center out of the defined period, and 24 (4.3%) had no available HbA_{1c} value at baseline or at follow-up. Thus, 461 patients were finally included in the EAS population (73.3% of the FAS), with a mean follow-up duration of 193 ± 81 days (median follow-up = 178 days) (see flow chart, Supplementary Fig. 3). Their main demographic and clinical characteristics were very close to those of the FAS population with a similar distribution in the different subgroups according

to prior treatment regimen (Supplementary Table 3).

Mean change in HbA_{1c} from IDegLira initiation to follow-up visit showed significant decrease in the whole EAS population ($-0.6 \pm 1.6\%$, $p < 0.0001$) and in all subgroups submitted to treatment intensification, namely patients with prior GLP-1RA (-1.7 ± 1.8, $p < 0.0001$), BI ($-1.2 \pm 1.8\%$, $p < 0.001$) or MDI therapy ($-0.8 \pm 1.8\%$, $p = 0.0026$) (Fig. 1). A weak improvement in mean HbA_{1c} level was also observed in patients with prior free combination of GLP-1RA with either BI ($-0.2 \pm 1.2\%$, $p = 0.0419$) or MDI ($-0.2 \pm 0.9\%$, $p = 0.0794$). The proportion of patients achieving the different HbA_{1c} targets significantly increase in subgroups with either GLP-1RA or insulin as prior therapy. IDegLira use was also associated with a significant increase in HbA_{1c} values $< 8\%$ in patients with previous free combination of BI and GLP-1RA (Table 3).

Concomitant body weight gain was observed in case of prior treatment with GLP-1RA used alone ($+1.5 \pm 5.8$ kg, $p = 0.0572$) or in combination with BI ($+1.0 \pm 3.1$ kg, $p < 0.0001$), contrasting with a significant weight loss in patients with either basal (-1.4 ± 4.6 kg, $p = 0.0139$) or MDI (-1.4 ± 5.0 kg, $p = 0.0484$) insulin scheme.

Titration of IDegLira and Changes in Associated Glucose-Lowering Medications During Follow-up

The daily dose of IDegLira was increased by 6.9 DS in patients with prior GLP-1RA treatment alone, reaching 28 DS at the follow-up visit. Titration of IDegLira dose was lower in patients previously on insulin therapy, irrespective of associated GLP-1RA administration, with a mean dose increase ranging from 1.5 to 4.0 DS (Fig. 2).

As compared to treatment prior to IDegLira initiation, mean GLP-1RA dose was decreased by 0.3 DDD at follow-up visit in patients previously on GLP-1RA alone or associated to BI, and by 0.1 DDD in those with the free
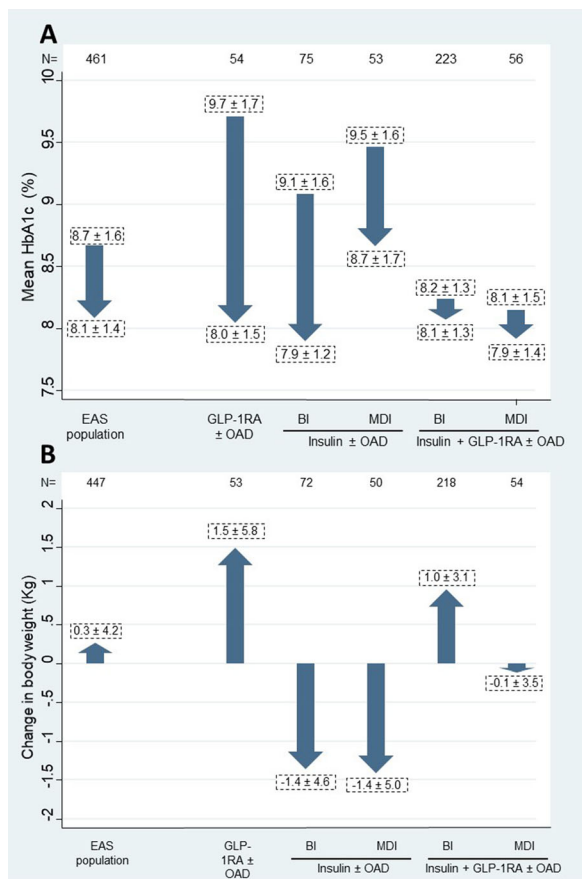
Fig. 1 Changes in HbA$_{1c}$ (**A**) and body weight (**B**) from IDegLira initiation to follow-up visit

combination of GLP-1RA and MDI (Table 4 and Supplementary Table 4). Mean BI daily dose remained stable in individuals with previous free combination of BI and GLP-1RA but was reduced in other groups, from 4.4 to 8.0 units. Of note, 41.5% of patients with previous MDI insulin scheme without associated GLP-1RA have stopped the administration of prandial insulin at follow-up visit but this percentage fell to 17.9% in case of prior free combination of both therapies (Supplementary Table 4). The use of metformin was maintained in the majority of patients while the administration of sulfonylureas was more frequently interrupted or initiated (Supplementary Table 4).

DISCUSSION

The present study is the first to evaluate the use of IDegLira within the framework of the French healthcare system. Besides details on the real-life modalities of IDegLira initiation in this specific context, the data confirm the effectiveness of this fixed-ratio combination in patients with T2D requiring either intensification or simplification of their prior injectable therapy, in full agreement with the conclusions of previous randomized controlled trials and real-world studies.

More than half of IDegLira treatment initiations (56.9%) consisted of switching from a free combination of GLP-1RA and insulin with the objective to simplify prior therapeutic regimens in most cases. The proportion of patients who benefited from this simplification approach is greater than in most other real-world studies such as the European Xultophy Treatment Retrospective Audit (EXTRA) where only 29.4% of individuals with T2D receiving injectable therapy prior to IDegLira initiation were concerned by such a switch procedure [10]. The discrepancy probably stems from the fact that financial coverage by the French national health insurance was initially restricted to patients with T2D previously treated with a free combination of BI and liraglutide, in association with metformin. In line with this initial scope of reimbursement, liraglutide was the most used GLP-1RA before IDegLira initiation in our population, especially in the subgroup with free combination of GLP-1RA and insulin. Note, however, that dulaglutide had just been marketed for a few months and that semaglutide was not yet available in France when the study was carried out. The French authorities only extended the reimbursement to clinical situations requiring therapeutic intensification from December 2017. However, according to indications adopted by the European Medical Agency, therapeutic intensification was already sought in our population in patients receiving either insulin (31.5%) or GLP-1RA (11.6%) therapy combined or not with oral anti-hyperglycemic molecules.

Table 3 Patients achieving HbA$_{1c}$ targets at baseline and at follow-up visit

	Available Data (n)	Whole EAS population	GLP-1RA ± OAD	Insulin ± OAD		Insulin + GLP-1RA ± OAD	
				Basal	MDI	Basal	MDI
EAS, n		461	54	75	53	223	56
HbA$_{1c}$ < 7.0%							
Baseline, n (%)	461	51 (11.1)	2 (3.7)	3 (4.0)	2 (3.8)	31 (13.9)	13 (23.2)
Follow-up, n (%)	461	99 (21.5)	14 (25.9)	22 (29.3)	7 (13.9)	43 (19.3)	13 (23.2)
p		< 0.0001	0.0013	< 0.0001	0.0250	0.0510	1.0000
HbA$_{1c}$ < 7.5%, n (%)							
Baseline, n (%)	461	108 (23.4)	3 (5.6)	8 (10.7)	6 (11.3)	70 (31.4)	21 (37.5)
Follow-up, n (%)	461	184 (39.9)	28 (51.8)	33 (44.0)	13 (24.5)	82 (36.7)	28 (50.0)
P		< 0.0001	< 0.0001	< 0.0001	0.0190	0.0960	0.1080
HbA$_{1c}$ < 8.0%, n (%)							
Baseline, n (%)	461	176 (38.2)	5 (9.3)	18 (24.0)	10 (18.9)	111 (49.8)	32 (57.1)
Follow-up, n (%)	461	263 (57.1)	32 (59.3)	43 (57.3)	23 (43.4)	127 (57.0)	38 (67.9)
p		< 0.0001	< 0.0001	< 0.0001	0.0016	0.0422	0.1088

Results are expressed as number of patients (%)

EAS efficacy analysis set, *GLP-1RA* glucagon-like peptide-1 receptor agonist, *OAD* oral anti-hyperglycemic drug, *MDI* multiple daily injections

Baseline clinical and biological characteristics of patients included in the present study are close to those observed in the European EXTRA study, although longer duration of diabetes, higher level of HbA$_{1c}$, and lower BMI were reported here in those with either insulin or GLP-1RA prior therapy [10]. Illustrating the need for intensification of glucose-lowering therapy in these subgroups, especially in case of prior treatment with GLP-1RA, less than 10% and 25% of patients initially met HbA$_{1c}$ targets ≤ 7% and ≤ 8%, respectively. However, although therapeutic simplification was the main clinical reason given for initiating IDegLira in patients previously treated with free combination of insulin and GLP-1RA, most of them did not achieve the HbA$_{1c}$ targets and were therefore also eligible for intensification of glucose control. As expected, metformin was the oral medication most often combined with prior injectable therapy and glargine U100 the most used BI, noting that sodium-glucose co-
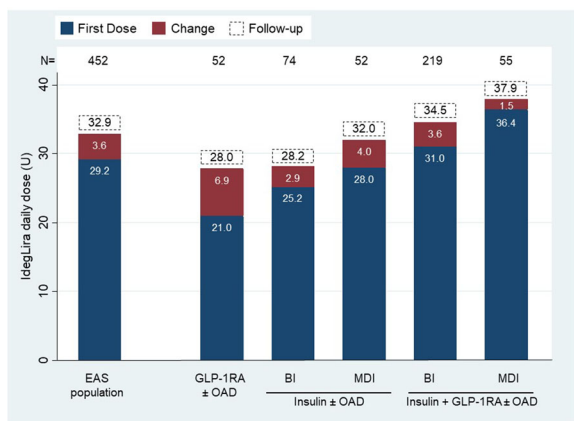
Fig. 2 Titration of IDegLira dose from initiation to follow-up visit

transporter-2 (SGLT2) inhibitors as well as insulin degludec were not yet available in France over the study period.

An important objective of our study was to describe the real-life practices of IDegLira initiation including adaptations of prior treatments. The starting dose of IDegLira was frequently higher than that recommended, especially in patients previously on either intensified insulin therapy (MDI) or free combination of insulin and GLP-1RA. Thus, the initial dose of IDegLira was greater than 20 DS in 65.5% of patients in the present study compared to 37.0% in the EXTRA study [10], which is probably explained, at least in part, by the greater proportion of patients previously on free combination. In this particular situation, prescribers essentially relied on the last dose of BI to propose the initial dose of IDegLira, which minimize the initial reduction in both BI dose and GLP-1RA DDD. As previously reported [10], a greater decrease in BI dose or GLP-1RA DDD occurred in patients on previous injectable treatment with either insulin or GLP-1. Furthermore, our results also reveal that while the vast majority of patients

Table 4 Changes in basal insulin and GLP-1RA daily doses from IDegLira initiation to follow-up visit in the EAS population

	Whole EAS population	GLP-1RA ± OAD	Insulin ± OAD		Insulin + GLP-1RA ± OAD	
			Basal	**MDI**	**Basal**	**MDI**
EAS, n (%)	461 (100.0)	54 (11.7)	75 (16.3)	53 (11.5)	223 (48.3)	56 (12.2)
Available data (% of EAS population)	452 (98.0)	52 (96.3)	71 (94.7)	52 (98.1)	208 (93.3)	49 (87.5)
Basal insulin						
Prior dose (U/day)	–	–	36.2 ± 25.1	38.3 ± 23.2	34.8 ± 14.9	42.1 ± 18.3
IDegLira initiation (U/day)	29.2 ± 10.9	21.3 ± 7.5	25.1 ± 8.3	28.0 ± 10.0	31.0 ± 10.3	36.6 ± 12.7
Follow-up visit (U/day)	32.9 ± 11.7	28.1 ± 12.4	28.2 ± 10.3	32.0 ± 12.4	34.5 ± 11.0	37.7 ± 11.9
GLP-1RA						
Prior dose (DDD)	-	1.2 ± 0.3	-	-	1.3 ± 0.3	1.2 ± 0.3
IDegLira initiation (DDD)	0.9 ± 0.3	0.6 ± 0.2	0.8 ± 0.3	0.8 ± 0.3	0.9 ± 0.3	1.1 ± 0.4
Follow-up visit (DDD)	1.0 ± 0.4	0.8 ± 0.4	0.8 ± 0.3	0.9 ± 0.4	1.0 ± 0.3	1.1 ± 0.4

GLP-1RA glucagon-like peptide-1 receptor agonist, *IDegLira* insulin degludec plus liraglutide, *EAS* efficacy analysis set, *OAD* oral anti-hyperglycemic drug, *MDI* multiple daily injections, *DDD* defined daily dose. Results are expressed as number of patients (%) or as mean ± SD

do not achieve glycemic control goals at initiation, only 50% received support dedicated to guide them in IDegLira dose titration.

Few changes were made at IDegLira initiation to associated oral anti-hyperglycemic medications apart from the systematic discontinuation of dipeptidyl peptidase-4 (DPP-4) inhibitors, in accordance with current recommendations. Noteworthy, in patients with prior MDI treatment, discontinuation of prandial insulin injections has been proposed at IDegLira initiation in nearly 50% of patients without and 20% of patients with prior GLP-1RA free combination.

The DUAL program definitely established the efficacy of IDegLira in improving glucose control in patients with T2D receiving either BI [17–19] or GLP-1RA [20] as previous therapy. These benefits have also been confirmed by several real-life studies in the last years [10, 13, 15, 16]. Accordingly, our follow-up data demonstrate a significant decrease in HbA_{1c} level in individuals initiating IDegLira from a BI (-1.2%) or a GLP-1RA (-1.7%) therapy background. The improvement in HbA_{1c} level in both subgroups was, however, greater than that reported in previous observational studies conducted in Europe [10] and the United States [16]. This discrepancy must be interpreted taking into account the higher baseline HbA_{1c} level in our study, probably due to the recruitment of patients with more severe clinical profiles by the specialists working in French diabetes centers. As expected, initiation of IDegLira resulted in significant weight loss in patients with previous BI therapy but weight gain in those with prior GLP-1RA treatment.

Noteworthy, in patients with uncontrolled T2D despite prior therapy including BI (glargine U100) and metformin, the DUAL-VII study demonstrated the non-inferiority of IDegLira versus basal-bolus in terms of HbA_{1c} reduction, as well as significant benefits regarding hypoglycemia rates and changes in body weight [19]. The fixed combination can therefore be considered as an effective and safe alternative to basal-bolus when intensification of patients receiving BI therapy is required, but it could also be an attractive option for selected patients already on a complex insulin regimen [21].

Although the DUAL program did not evaluate the use of IDegLira in this latter indication, recent real-life observational studies reported significant decrease in HbA_{1c} (ranging from 0.3 to 1.0% up to 6-month follow-up) and body weight in patients who switched from MDI regimen to IDegLira along with substantial decrease in insulin requirement generally associated with body weight loss [10–14]. Furthermore, data reported from US real-world practice showed that patients on more than one insulin injection daily were able to switch to IDegLira without compromising on glycemic control (HbA_{1c} change of -0.16%) [16]. Accordingly, the randomized pragmatic BEYOND trial recently demonstrated that switching from MDI (basal-bolus) regimen to either a once-daily fixed-ratio BI plus GLP-1RA combination or once-daily gliflozin plus BI scheme is safe and non-inferior to basal-bolus titration in terms of HbA_{1c} reduction, at least during the first 6 months of follow-up [22]. Demonstrating improved HbA_{1c} level (-0.8%) and decrease in body weight (-1.4 kg) in the MDI subgroup, the present study also provides data supporting the relevance of such a therapeutic strategy. However, depending on the initial decision of the prescribing physician, then on the evolution of the glycemic balance during the first months of treatment, only 41.5% of patients were no longer administering prandial insulin injections at follow-up visit. Altogether, these observations indicate that switching from MDI regimen to IDegLira should be offered to selected patients and, since only limited series of patients have been published so far, highlights the need to better characterize the clinical profiles likely to benefit from this therapeutic change.

As already mentioned, the majority of patients included in our study shifted from a free combination of insulin (either basal alone or MDI) to IDegLira, although this strategy first aimed at simplifying the administration scheme has not been evaluated by any randomized controlled trial. However, some real-life data suggested that the switch approach could lead to a significant improvement in HbA_{1c} level without associated weight gain. That was the case in the EXTRA study with a

0.6% decrease in HbA$_{1c}$ in individuals with prior insulin plus GLP-1RA free combination (mean value of 8.3% at baseline), despite limited titration of IDegLira (+ 6 DS) at 6 months resulting in a slight but significant decrease in GLP-1RA dose (1.1 DDD versus 1.3 DDD at baseline) [10]. A retrospective study conducted in Israel led to similar conclusions with a significant improvement in HbA$_{1c}$ level (− 0.42% from a baseline value of 8.43%) [15]. Only a slight decrease in HbA$_{1c}$ (− 0.2%) was found here in patients with prior free combination of GLP-1RA with either BI or MDI. This must be interpreted taking into account the very limited titration of IDegLira performed during the follow-up of both subgroups (+ 3.6 and + 1.5 DS, respectively). The lack of optimal titration, already underlined by most real-life studies devoted to insulin therapy, is all the more regrettable since only a small number of patients (19.3 and 23.2%, respectively) achieved the objective of HbA$_{1c}$ < 7% at the follow-up visit. Beside the titration issue, we can also speculate that reduction in the injection burden might have resulted in improved adherence to the treatment, thus contributing to improved glucose control. Switch to fixed-ratio combination was neutral on body weight in case of prior MDI scheme, as previously reported [10, 15], but individuals in the BI subgroup experienced modest but significant body weight gain, probably related to the reduction in GLP-1RA dose as compared to baseline (− 0.3 DDD).

Some limitations must be acknowledged for proper interpretation of this real-world study. First, the recruitment was exclusively carried out in expert centers and, as already mentioned, across the initial phase of availability during which IDegLira was reimbursed only for switching from free association of insulin and GLP-1RA. This may have influenced patient clinical profiles as well as practitioner's choices when initiating IDegLira. In addition, the data collection did not make it possible to determine whether the cardiovascular benefit demonstrated with liraglutide in the LEADER trial could have been a motivation for initiating IDegLira, especially in those with macrovascular complications (more than 20% of patients without prior GLP-1RA treatment) [23]. Second,

the retrospective design of the study did not make it possible to collect follow-up data for the entire population having initiated the treatment, nor to precisely control the date of the follow-up visits. To cope with this last point, we chose a follow-up window between 3 and 18 months, knowing that the vast majority of the follow-up timings used were close to 6 months. Third, as illustrated by the study flow chart, we were not able to specify the status (IDegLira maintenance, changes in HbA$_{1c}$ and body weight) of the 66 patients who did not benefit from follow-up visits. Fourth, among the 563 patients who had at least one follow-up visit, it was finally not possible to precisely define the reasons (lack of efficacy, safety issues, etc.) for stopping IDegLira treatment in 48 of them (8.5%). However, the rate of early discontinuation of treatment is relatively low, in agreement with studies claiming good persistence with IDegLira in clinical practice [12]. Then, the retrospective data collection from electronic medical records, in which the description of possible side effects was neither systematic nor standardized, made it not possible to reliably assess the incidence and the intensity of adverse events occurring during the follow-up period. This included the incidence of hypoglycemia which is more specifically expected to be lowered by switching from MDI to IDegLira. The ongoing prospective real-life studies, such as the Italian multicenter REX study [24], will probably provide more relevant observations on this important issue. Finally, the growing use of weekly GLP-1RAs, due to reduced frequency of administration and to increased potency in terms of glycemic and weight control, could call into question the relevance of our data for current clinical practice. However, pending the future marketing of weekly fixed-ratio combinations including one of these molecules, prescribing IDegLira or IGlarLixi in patients requiring concomitant use of GLP-1RA and BI remains an attractive alternative for clinicians given their ease of use and excellent tolerance profile during dose titration periods.

The strengths of this first study dedicated to fixed-ratio combination of BI and GLP-1RA in France should also be highlighted, starting with

its national multicenter design. In addition, the systematic identification of patients who initiated treatment from electronic records certainly led to limiting selection bias. We also structured data collection in order to obtain a precise and standardized recording of phenotypic characteristics and therapeutic schemes at baseline and follow-up visits, as well as changes in HbA_{1c} and body weight, leading to a limited number of missing data. Finally, due to the initial conditions of reimbursement in France, we constituted a large subgroup of patients switching from a free combination of BI and GLP-1RA, which provides additional information on the modalities of IDegLira initiation in this clinical situation insufficiently studied until now.

CONCLUSIONS

This real-world observational multicenter study provides the first view on IDegLira use in France where switching from a free combination of GLP-1RA and insulin accounted for more than half of treatment introduction during the first months of availability. In clinical practice, the choice of the starting dose by the practitioners is mainly driven by the prior dose of BI, leading in parallel to a slight reduction in GLP-1RA administered dose. This simplified therapeutic option decreases administration constraints and seems relevant from the point of view of prescribers. In the near future, new advances are expected with the current development of a weekly fixed-ratio combination of BI and GLP-1RA, which could further improve acceptability and persistence of treatment [25].

Reinforcing the conclusions of previous real-world studies, follow-up data demonstrate the effectiveness of IDegLira to preserve or improve glucose control in patients with T2D requiring either intensification or simplification of their therapeutic regimen. However, the proportion of patients reaching the recommended HbA_{1c} targets still remains clearly insufficient, and our data highlight the critical need to develop strategies aimed at optimizing IDegLira dose titration following initiation.

REFERENCES

1. Holst JJ, Vilsbøll T. Combining GLP-1 receptor agonists with insulin: therapeutic rationales and clinical findings. Diabetes Obes Metab. 2013;15: 3–14.

2. American Diabetes Association Professional Practice Committee, Draznin B, Aroda VR, Bakris G, Benson G, Brown FM, et al. 9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes-2022. Diabetes Care. 2022;45:S125–43.

3. Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, et al. Management of hyperglycemia in type 2 diabetes, 2022. A American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2022. https://doi.org/10.2337/dci22-0034.

4. Eng C, Kramer CK, Zinman B, Retnakaran R. Glucagon-like peptide-1 receptor agonist and basal insulin combination treatment for the management of type 2 diabetes: a systematic review and meta-analysis. Lancet. 2014;384:2228–34.

5. Maiorino MI, Chiodini P, Bellastella G, Capuano A, Esposito K, Giugliano D. Insulin and glucagon-like peptide 1 receptor agonist combination therapy in type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. Diabetes Care. 2017;40:614–24.

6. Valentine V, Goldman J, Shubrook JH. Rationale for, initiation and titration of the basal insulin/GLP-1RA fixed-ratio combination products, IDegLira and IGlarLixi, for the management of type 2 diabetes. Diabetes Ther. 2017;8:739–52.

7. Perreault L, Rodbard H, Valentine V, Johnson E. Optimizing fixed-ratio combination therapy in type 2 diabetes. Adv Ther. 2019;36:265–77.

8. Harris S, Abrahamson MJ, Ceriello A, Charpentier G, Evans M, Lehmann R, et al. Clinical considerations when initiating and titrating insulin degludec/liraglutide (IDegLira) in people with type 2 diabetes. Drugs. 2020;80:147–65.

9. Rayner CK, Wu T, Aroda VR, Whittington C, Kanters S, Guyot P, et al. Gastrointestinal adverse events with insulin glargine/lixisenatide fixed-ratio combination versus glucagon-like peptide-1 receptor agonist s in people with type 2 diabetes mellitus: a network meta-analysis. Diabetes Obes Metab. 2021;23:136–46.

10. Price H, Blüher M, Prager R, Phan T-M, Thorsted BL, Schultes B, et al. Use and effectiveness of a fixed-ratio combination of insulin degludec/liraglutide (IDegLira) in a real-world population with type 2 diabetes: Results from a European, multicentre, retrospective chart review study. Diabetes Obes Metab. 2018;20:954–62.

11. Taybani Z, Bótyik B, Katkó M, Gyimesi A, Várkonyi T. Simplifying complex insulin regimens while preserving good glycemic control in type 2 diabetes. Diabetes Ther. 2019;10:1869–78.

12. Eliasson B, Ekelund J, Miftaraj M, Ranthe MF, Mårdby A-C, Da Rocha Fernandes JD, et al. Persistence with IDegLira in patients in clinical practice: a nationwide observational study in Sweden. Diabetes Ther. 2020;11:1807–20.

13. Zenari L, Da Porto A, De Moliner L, Lugli F, Guazzoni V, Groppelli G, et al. Real-world evaluation of glycemic outcomes and extra-glycemic parameters in diabetic patients treated with the combined formulation degludec-liraglutide (IDegLira). Diabetes Ther. 2021;12:197–209.

14. Persano M, Nollino L, Sambataro M, Rigato M, Negro I, Marchetto S, et al. Real-world study on the effectiveness and safety of basal insulin IDegLira in type 2 diabetic patients previously treated with multi-injective insulin therapy. Eur Rev Med Pharmacol Sci. 2021;25:923–31.

15. Melzer-Cohen C, Chodick G, Naftelberg S, Shehadeh N, Karasik A. Metabolic control and adherence to therapy in type 2 diabetes mellitus patients using IDegLira in a real-world setting. Diabetes Ther. 2020;11:185–96.

16. Egede LE, Bogdanov A, Fischer L, Da Rocha Fernandes JD, Kallenbach L. Glycemic control among patients newly prescribed IDegLira across prior therapy group in US real-world practice. Diabetes Ther. 2020;11:1579–89.

17. Buse JB, Vilsbøll T, Thurman J, Blevins TC, Langbakke IH, Bøttcher SG, et al. Contribution of liraglutide in the fixed-ratio combination of insulin degludec and liraglutide (IDegLira). Diabetes Care. 2014;37:2926–33.

18. Lingvay I, Pérez Manghi F, García-Hernández P, Norwood P, Lehmann L, Tarp-Johansen MJ, et al. Effect of insulin glargine up-titration vs insulin degludec/liraglutide on glycated hemoglobin levels in patients with uncontrolled type 2 diabetes: the DUAL V randomized clinical trial. JAMA. 2016;315: 898–907.

19. Billings LK, Doshi A, Gouet D, Oviedo A, Rodbard HW, Tentolouris N, et al. Efficacy and safety of IDegLira versus basal-bolus insulin therapy in patients with type 2 diabetes uncontrolled on metformin and basal insulin: the DUAL VII

randomized clinical trial. Diabetes Care. 2018;41: 1009–16.

20. Linjawi S, Bode BW, Chaykin LB, Courrèges J-P, Handelsman Y, Lehmann LM, et al. The efficacy of IDegLira (insulin degludec/liraglutide combination) in adults with type 2 diabetes inadequately controlled with a GLP-1 receptor agonist and oral therapy: dual III randomized clinical trial. Diabetes Ther. 2017;8:101–14.

21. Giugliano D, Scappaticcio L, Longo M, Caruso P, Maiorino MI, Bellastella G, et al. Simplification of complex insulin therapy: a story of dogma and therapeutic resignation. Diabetes Res Clin Pract. 2021;178: 108958.

22. Giugliano D, Longo M, Caruso P, Di Fraia R, Scappaticcio L, Gicchino M, et al. Feasibility of simplification from a basal-bolus insulin regimen to a fixed-ratio formulation of basal insulin plus a GLP-1RA or to basal insulin plus an SGLT2 inhibitor: BEYOND, a randomized. Pragmat Trial Diabetes Care. 2021;44:1353–60.

23. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JFE, Nauck MA, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2016;375:311–22.

24. Fadini GP, Buzzetti R, Fittipaldi MR, D'Incau F, Da Porto A, Girelli A, et al. IDegLira for the real-world treatment of type 2 diabetes in Italy: protocol and interim results from the REX observational study. Diabetes Ther. 2022;13:1483–97.

25. Kalra S, Bhattacharya S, Kapoor N. Contemporary classification of glucagon-like peptide 1 receptor agonists (GLP1RAs). Diabetes Ther. 2021;12: 2133–47.