Nutrition, Metabolism & Cardiovascular Diseases (2024) **34**, 1846–1853

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

RESEARCH PAPER

Treatment intensification following glucagon-like peptide-1 receptor agonist in type 2 diabetes: Comparative effectiveness analyses between free vs. fixed combination of GLP-1 RA and basal insulin. RESTORE-G real-world study

Riccardo Candido [a], Antonio Nicolucci [b,*], Monica Larosa [c], Maria Chiara Rossi [b], Raffaele Napoli [d,e] on behalf of the RESTORE-G (Retrospective analysis on the therapeutic approaches after GLP-1 RA treatment in type 2 diabetes patients) Study Group[1]

[a] *Diabetes Centre District 3, Azienda Sanitaria Universitaria Integrata, Trieste, Italy*
[b] *CORESEARCH, Center for Outcomes Research and Clinical Epidemiology, Pescara, Italy*
[c] *Medical Affairs, Sanofi S.r.l., Milan, Italy*
[d] *Department of Translational Medical Sciences, Unit of Internal Medicine and Diabetes, Federico II University School of Medicine and Institute of Experimental Endocrinology and Oncology, National Research Council, Napoli, Italy*
[e] *AOU Federico II, Napoli, Italy*

Received 20 December 2023; received in revised form 19 March 2024; accepted 20 March 2024
Handling Editor: S. Piro
Available online 23 March 2024

KEYWORDS
Type 2 diabetes;
GLP-1 receptor agonists;
Basal insulin;
Naïve;
Glargine 300;
Degludec 100;
iDegLira;
iGlarLixi;
Fixed-ratio combination;
Effectiveness;
Safety

Abstract *Background and aims:* Add-on of basal insulin (BI) to intensify the ongoing therapy with glucagon-like peptide 1 receptor agonist (GLP-1 RA) is recommended, but it is unclear if free or fixed combination of BI and GLP-1 RA produce similar outcomes. A retrospective comparative effectiveness analysis of the add-on of glargine 300 U/mL (Gla-300) to ongoing GLP-1 RA vs. switch to fixed ratio combination of degludec and liraglutide (iDegLira) was performed.
Methods and results: Real-world data collected in electronic medical records by 32 Italian diabetes clinics. Propensity score (PS) adjustment was applied to assess changes in glycated hemoglobin (HbA1c), fasting blood glucose (FBG), body weight, and BI dose after 6 months from Gla-300 or iDegLira initiation.

Compared to iDegLira group (N = 260), Gla-300+GLP-1 RA group (N = 255) had older age and higher levels of HbA1c (9.1 vs. 8.9%). After 6 months, statistically significant greater FBG improvement [estimated mean difference and 95% confidence intervals: −24.05 mg/dl (−37.04; −11.06; p = 0.0003) and BI dose increase [+0.03 U/kg (95%CI 0.00; 0.06); p = 0.009] were found in the free vs. fixed combination group, although low doses of BI (0.2 U/kg) were reached in both groups. Trends of larger HbA1c and body weight reductions with the free combination were also found, without reaching the statistical significance.
Conclusion: Although inertia in insulin initiation and titration was documented in both groups, higher benefit on FBG control was obtained with free vs. fixed combination, likely due to a better titration of BI and GLP-1 RA.

* Corresponding author. CORESEARCH, Center for Outcome Research and Clinical Epidemiology, Corso Umberto I, 103, 65122 Pescara, Italy.
E-mail address: nicolucci@coresearch.it (A. Nicolucci).
[1] The full list of collaborator list RESTORE-G Study Group are listed in Appendix B.

https://doi.org/10.1016/j.numecd.2024.03.023

1. Introduction

Many changes occurred in the treatment of type 2 diabetes (T2D) in the last years. Several clinical practice guidelines, including the ADA/EASD and Italian AMD/SID, recommend glucagon-like peptide-1 receptor agonist (GLP-1 RA) as the first injectable agent ahead of basal insulin (BI) for most patients with T2D [1,2]. When the ongoing GLP-1 RA treatment needs intensification, many options are available and BI is a common choice, preferably as an add-on to GLP-1 RA rather than as a switch therapy [3]. In fact, the combined use of GLP-1 RA and BI has the advantages of a lower hypoglycemic risk and better body weight control with non-inferior potency of glycemic control compared to the basal-bolus insulin regimen [3–5].

In the choice of BI, it should be considered that, compared to the first generation (1BI), second-generation basal insulins (2BI) show improved and more stable pharmacokinetic/pharmacodynamic profiles and clinical benefits [6,7].

When adding BI to the ongoing GLP-1 RA, a fixed-ratio combination (FRC) of BI and GLP-1 RA may represent a potential option. iGlarLixi, a once-daily titratable FRC of insulin glargine 100 units/mL and lixisenatide, and iDegLira, an association of insulin degludec 100 units/mL with liraglutide, are the currently available FRCs. Efficacy and safety of these agents have been established through the LixiLan (iGlarLixi) and DUAL (iDegLira) programs [8–13].

Recently, the evidence relative to the addition of BI to ongoing GLP-1 RA, or the switch to FRC when GLP-1 RA treatment fails, has been systematically reviewed to evaluate efficacy and safety of the free-up titration of BI and FRC in T2D patients inadequately controlled with GLP-1 RA [14]. Four eligible RCTs were included in the meta-analysis: De Vries et al. [15] and BEGIN ADD TO GLP-1 Study [16] evaluated the effect of the addition and free up-titration of BI, while the DUAL III [17] and the LixiLan-G [10] showed the outcome of switching to FRC; all these strategies were compared to the ongoing GLP-1 RA treatment without insulin. No significant differences were found between free and fixed combinations regarding the decrease in HbA1c, fasting plasma glucose (FPG), and hypoglycemic risk. In these RCTs, titration algorithms, based upon values of self-measured fasting blood glucose of the last three preceding days, were used for dose adjustment of BI or FRC. However, target ranges for self-measured blood glucose were dissimilar (from 72-80 to 90–108 mg/dl). Insulin doses were up-titrated to a mean of 0.4–0.5 U/Kg in all the trials [10,14–17].

In Italy, the RESTORE-G program is a descriptive, real-world study designed to specifically assess the treatment intensification approaches at GLP-1 RA treatment failure and the role of BIs, and in particular of 2BIs [3,18]. This study provided a comprehensive overview of the intensification strategies adopted in the real world following GLP-1 RA treatment, showing that less than 40% of the patients treated with a GLP-1 RA intensified their therapy with BI or FRC; the most common approach was the discontinuation of GLP-1 RA and the switch to insulin treatment. However, no direct comparative analysis between different therapeutical approaches was performed in this study.

The aim of this RESTORE-G sub-study was to compare the effectiveness on metabolic control and body weight of Gla-300 in free combination with GLP-1 RA and Deg-100 in FRC with the GLP-1 RA liraglutide (iDegLira), representing the most utilized free an FRC combinations in the RESTORE-G study. A focus on titration of BI and FRC was also considered, being a recognized major component of clinical inertia [19].

2. Methods

RESTORE-G was a real world, pre-post, retrospective cohort study, based on anonymous patient-level data extracted from electronic medical records (EMRs, i.e. SmartDigitalClinic, METEDA, San Benedetto del Tronto, Italy) [3,18].

Inclusion criteria were: insulin naïve adult patients with diagnosis of T2D treated with GLP-RA ± oral hypoglycemic agents (OHA) and changing their therapy; initiation of BI in free or fixed-ratio combination (FRC), in addition to, or in substitution of GLP-1 RA, with index date (i.e. date of the first prescription of BI/FRC) from January 2011 to 2021; prescription of GLP-1 RA (weekly or daily) ± OHA before initiating BI/FRC or switching to BI/FRC.

Exclusion criteria were: diagnosis of type 1 diabetes; prescription of any insulin within 12 months before GLP-1 RA therapy; more than one type of BI/FRC prescribed at index date or prescription of other BI/FRC within 3 months after initiating BI; switch back to GLP-1 RA after initiation of BI/FRC within 3 months after index date.

Centers recorded data on EMRs according to their clinical practice. Patients with T2D were generally seen by the diabetes center on a 3–6 month basis, according to Italian guidelines [2].

Baseline (T0) variables included: age, gender, HbA1c, fasting blood glucose (FBG), body weight, body mass index (BMI), diabetes duration, diabetes treatment (classified according ATC codes), comorbidities (classified according to ICD-9-CM system), estimated glomerular filtration rate (eGFR), albuminuria, lipid profile, and arterial pressure.

Follow-up information at 6 months (T6) included: HbA1c, FBG, body weight, BMI, and BI dose.

Treatment approaches investigated included the add-on of BI to ongoing therapy with GLP-1 RA (ADD-ON cohort), and the switch from GLP-1 RA therapy to either BI (SWITCH-

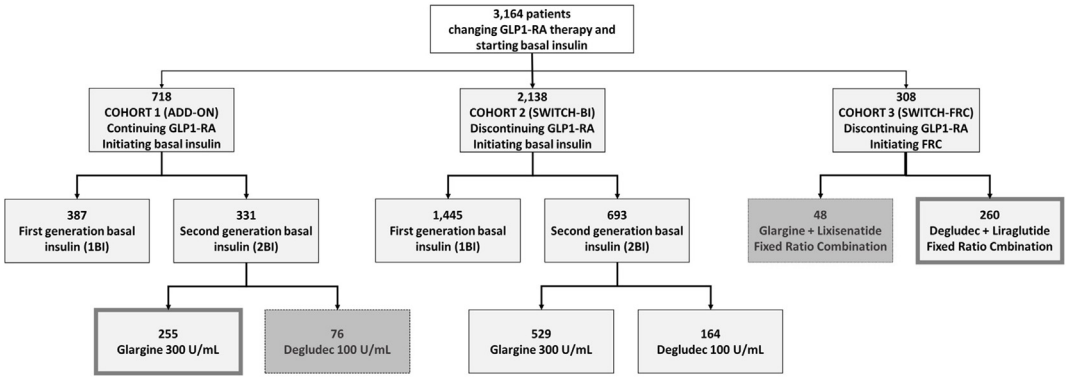


Figure 1 RESTORE-G study flow-chart: identification of cohorts eligible for comparative effectiveness analysis. Subgroups selected for the comparative effectiveness analysis are in grey box. In dark grey are presented the subgroups not included in the analyses due to small samples.

BI cohort) or fixed-ratio combination (FRC) (SWITCH-FRC cohort).

As predefined, each study cohort was stratified by type of BI/FRC prescribed at T0. Types of BI included 1BIs or 2BIs. Among 2BIs, cohorts were further stratified by Gla-300 vs. Deg-100. Among FRC, cohorts were further stratified by iDegLira and iGlarLixi. Stratification of study cohorts by type of BI or FRC is shown in Fig. 1.

This sub-study was focused on the comparison between add-on of 2BI in free combination with the pre-existing GLP-1 RA from the ADD-ON cohort and the switch from GLP-1 RA to the fixed ratio combination from the SWITCH-FRC cohort. Given that the number of patients treated with GLP-1 RA and Degludec in free combination or switching to iGlarLixi precluded the possibility of performing a robust comparison (sample size of 76 and 46, respectively), the current analysis focused on the comparison between Gla-300 in free combination with the pre-existing GLP-1 RA therapy and the switch from GLP-1 RA to FRC iDegLira.

Further details on main study methods are reported in the previous publications relative to the RESTORE-G study [3].

2.1. Statistical methods

Descriptive data were summarized as mean and standard deviation or proportion. Baseline patient characteristics according to the treatment intensification approach were compared using the Mann–Whitney U test in case of continuous variables and the chi-square test for categorical variables.

Propensity score (PS) adjustment was applied to compare effectiveness of add-on of Gla-300 to ongoing GLP-1 RA vs. switch to iDegLira. PS for each evaluable cohort was estimated taking into consideration age, gender, diabetes duration, baseline HbA1c, BMI, FBG, BI dose, eGFR$<$60 ml/min*1.73 m^2, history of diabetes complications (i.e. presence of at least 1 complication among coronary reperfusion/revascularization, coronary heart disease, heart failure, myocardial infarction, lower limb complications, stroke), concomitant glucose-lowering treatments (i.e. metformin, secretagogues, DPPIV inhibitors, glitazones, acarbose, SGLT2 inhibitors).

For each covariate, individuals with the same PS should have, on average, the same distribution of that covariate irrespective of treatment decision (covariate balance). This can be checked using interaction tests between each covariate and PS. Not statistically significant interaction test indicates a good balance.

Changes in HbA1c, FBG, body weight, and BI dose were assessed using mixed models for repeated measurements. Results are expressed as estimated mean or estimated mean difference from T0 with their 95% confidence interval (95% CI). Paired and unpaired t-test derived from linear mixed models for repeated measurements were applied for within- and between-group group comparisons. P-values <0.05 were considered as statistically significant.

3. Results

Overall, 255 patients were included in the free combination Gla-300 + GLP-1 RA cohort and 260 patients were included in the fixed ratio combination of iDegLira cohort (Fig. 1).

Baseline patients' characteristics are reported in Table 1. Patients intensifying GLP-1 RA therapy by adding-on Gla-300 were significantly older (61.3 vs. 58.5 years) than those switching to iDegLira; they also had significantly higher levels of FBG (211 vs. 194 mg/dl) and a more prevalent use of antihypertensive drugs. Starting doses of basal insulin were significantly different in the two groups (12.3 U vs. 16.9 U) in spite of similar BMI levels.

As for use of the different GLP-1 RA, patients in the Gla-300 + GLP-1 RA group were more frequently treated with dulaglutide (53.5%), whereas those in the iDegLira group were previously treated with liraglutide in half of the cases (51.1%). Metformin (71.2% and 78.2% in Gla-300 and iDegLira group, respectively) and secretagogues (37.6% and 45.9% in Gla-300 and iDegLira group, respectively) were the most frequently oral antihyperglycemic drugs associated to both groups (Table 1). About one in ten patients in both groups were also treated with SGLT2i (7.4% and 12.2% in Gla-300 and iDegLira group, respectively).

In the cohorts analyzed, the interaction test between each covariate and PS never reached statistical significance, indicating a good balance between groups.

Table 1 Baseline patients' characteristics of the populations selected for the comparative effectiveness analysis.

VARIABLE	CATEGORY	Gla300 + GLP-1 RA	iDegLira	p-value[a]
N. Group	.	255	260	
Age (years)		61.3 ± 10.2	58.5 ± 9.8	**0.002**
Gender (%)	Women	34.9	36.2	0.77
	Men	65.1	63.9	
Diabetes duration (years)		11.3 ± 8.2	10.4 ± 6.9	0.50
Diabetes duration in classes (%)	≤5 years	23.9	22.3	0.23
	6–10 years	25.9	27.3	
	11–20 years	31.8	38.5	
	>20 years	13.7	8.5	
	NA	4.7	3.5	
BMI (Kg/m^2)		33.6 ± 5.9	32.8 ± 5.6	0.37
HbA1c (%)		9.1 ± 1.2	8.9 ± 1.5	0.29
Fasting blood glucose (mg/dl)		211.3 ± 41.6	194.0 ± 45.0	**<0.0001**
Systolic blood pressure (mmHg)		137.7 ± 17.5	138.7 ± 18.8	0.46
Diastolic blood pressure (mmHg)		79.3 ± 10.5	79.4 ± 9.2	0.66
Total cholesterol (mg/dl)		165.2 ± 37.1	168.4 ± 40.3	0.63
LDL-cholesterol (mg/dl)		86.6 ± 31.3	87.8 ± 30.4	0.78
HDL-cholesterol (mg/dl)		44.3 ± 12.2	43.6 ± 11.4	0.88
Triglycerides (mg/dl)		191.3 ± 119.4	190.7 ± 132.7	0.40
eGFR <60 ml/min*1.73m^2		25.6	22.5	0.62
Micro/macroalbuminuria (%)		38.2	35.8	0.75
Antihypertensive drugs (%)		73.3	58.5	**0.0004**
Lipid-lowering drugs (%)		59.2	55.8	0.43
Diabetes complications (%)		4.7	13.9	**0.0004**
Basal insulin dose (U)		12.3 ± 5.2	16.9 ± 6.0	**<0.0001**
Metformin (%)		71.2	78.2	0.09
Secretagogues (%)		37.6	45.9	0.07
DPPIV inhibitors (%)		7.9	11.8	0.16
Glitazones (%)		7.0	7.4	0.86
Acarbose (%)		2.6	3.1	0.78
SGLT2 inhibitors (%)		7.4	12.2	0.08
Short-acting insulin (%)		0.8	0.4	0.55
Last GLP-1 RA prescribed before T0 (%):				
Daily:				
Exenatide		8.4	11.4	**<0.0001**
Liraglutide		26.7	51.1	
Lixisenatide		3.0	0.5	
Weekly:				
Dulaglutide		53.5	34.2	
Semaglutide		8.4	2.8	

Data are means and standard deviations or proportions.
Statistically significant p-values ($p < 0.05$) are in bold.
[a] Mann-Whitney U test in case of continuous variables and the chi-square test for categorical variables.

PS adjusted changes in HbA1c, FBG, and body weight after 6 months are shown in Fig. 2 and supplementary table 1.

Treatment with Gla-300 + GLP-1 RA induced a greater improvement in FBG compared to iDegLira at T6 [estimated mean difference of −24.05 mg/dl (95%CI -37.04; −11.06; p = 0.0003].

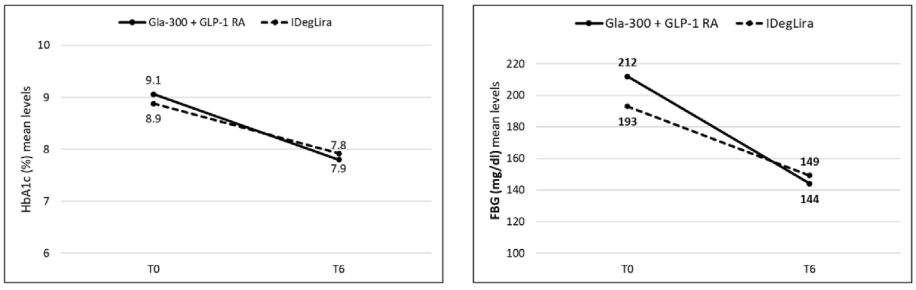
No statistically significant between-group differences were documented in HbA1c (Gla-300 + GLP-1 RA group vs. iDegLira group estimated mean difference −0.30%; 95% CI -0.70; 0.10; p = 0.15) and body weight (estimated mean difference −0.68 Kg; 95%CI -2.04; 0.68; p = 0.33).

PS adjusted changes in basal insulin dose are shown in Fig. 3 and supplementary table 1. A statistically significant larger increase in the dose in the Gla-300 + GLP-1 RA group than in iDegLira group was documented (Gla-300 + GLP-1 RA group vs. iDegLira group estimated mean difference 0.03 U/kg; 95%CI -0.00; 0.06; p = 0.009), although doses of about 0.2 U/Kg were reached at T6 in both groups.

4. Discussion

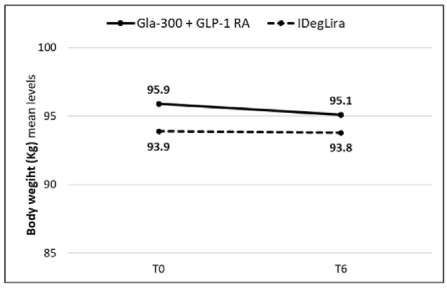
This analysis compared two innovative approaches to intensify GLP-1 RA therapy in T2D Italian patients. In fact, GLP-1 RA and BI may act through a synergistic action on fasting and post-prandial glycemia.

In our analysis, compared to the fixed combination of iDegLira, the free combination of Gla-300 and GLP-1 RA appears to provide a greater benefit on FBG. Results also suggest that the free combination of Gla-300 and GLP-1-RA could be associated with moderate improvements in HbA1c and body weight as compared to FRC; however, the between-group differences were not statistically significant.



Between groups estimated mean difference (Gla-300+GLP1RA vs. IDegLira)	p-value
-0.30 (95% CI -0.62;-0.02)	0.15

Between groups estimated mean difference (Gla-300+GLP1RA vs. IDegLira)	p-value
-24.05 (95% CI -37.04;-11.06)	**0.0003**



Between groups estimated mean difference (Gla-300+GLP1RA vs. IDegLira)	p-value
-0.68 (95% CI -2.04;0.68)	0.33

Figure 2 Comparative effectiveness analyses of add-on of free and fixed combination of basal insulin to GLP-1 RA therapy (Gla-300 + GLP-1 RA vs iDegLira). PS adjusted changes in estimated mean levels of HbA1c, FBG and body weight from T0 to T6 by cohort and treatment. T0 = date of the first prescription of Gla-300 or iDegLira, T6 = follow-up at 6 months. Results are expressed as estimated mean difference from T0 and 95% confidence interval (95% CI). Unpaired t-test derived from linear mixed models for repeated measures were applied for between-group comparisons. p-values <0.05 were statistically significant and reported in bold text.

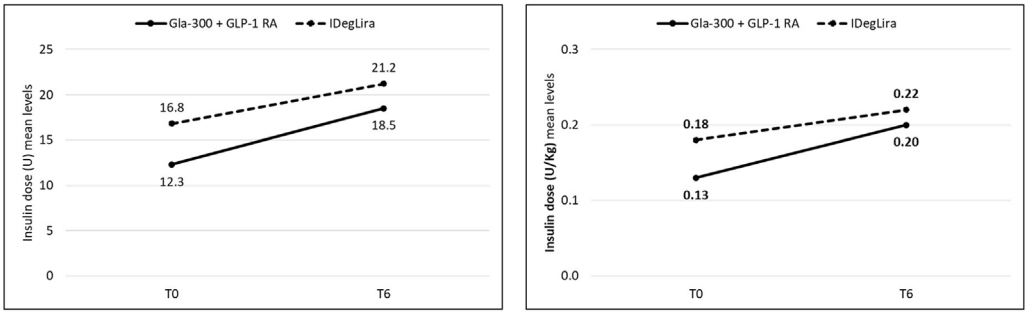
Insulin titration deserves considerations. At T0, doses/Kg were lower in Gla-300 vs. iDegLira (0.13 vs. 0.18 U/Kg). PS-adjusted longitudinal models showed a statistically significant larger dose increase in Gla-300 + GLP-1 RA group than in iDegLira group. This aspect is of particular relevance since an easier titration with the free combination could be a key to overcome therapeutic inertia. However, it should be noted that doses of about 0.2 U/Kg were reached at T6 in both groups, documenting the need for optimization of titration.

Furthermore, RESTORE-G study [3] documented that intensification of GLP-1 RA therapy required a median time of 27 months (interquartile range 11.8–53.5 months) and that the switch to BI is still the prevalent approach to GLP-1 RA therapy intensification. However, the add-on of BI to GLP-1 RA should be preferred since it is recommended by current guidelines. In fact, their combination is supported by: complementary targets of glycemic control for BI and GLP-1 RA, the potential of GLP-1 RA to overcome fear of hypoglycemia and weight gain, the benefits on extra-glycemic targets, and the simplification of insulin therapy with GLP-1 RA delaying the adoption of short-acting insulin [1,2]. A large real-world data analysis involving over 66,000 patients treated with GLP-1 RA [20] documented a significant delay in intensification with insulin in patients with T2D inadequately controlled with GLP-1 RA. In this study, earlier addition of insulin was associated with better glycemic control, while switching to insulin was not clinically beneficial during 2 years of treatment. More recently, the effectiveness of adding basal insulin to GLP-1 RA was confirmed by the DELIVER G study, showing that adding Gla-300 to GLP-1 RA significantly improved glycemic control without significantly increasing hypoglycemia in T2D [21].

RESTORE-G study [18] also documented that 2BI vs. 1BI were associated with significantly greater improvements in HbA1c and FBG both in add-on and switch approaches; in addition, in the switch approach, 2BI produced lower weight gain versus 1BI. Furthermore, Gla-300 vs. Deg-100 was associated with larger HbA1c decrease in the switch approach, while in the add-on approach analysis was not performed due to the low subgroup size [18].

What this RESTORE-G sub-study further adds is the evidence of larger benefits of free vs. fixed combination in people uncontrolled on GLP-1 RA, likely due to a better titration of the individual components in these patients. Free combination also allows to maintain the maximum dosage of GLP-1 RA in patients who require small amounts of BI, thus reducing the risk of over-basalization and this could be particularly relevant for elderly people. These findings deserve consideration and a prospective study designed and powered to further elucidate these key aspects of the GLP-1 RA therapy intensification with BI is needed.

Moreover, a meta-analysis by Jung et al. [14] suggested that in patients who failed to reach target HbA1c levels despite the GLP-1 RA treatment, both strategies of adding basal insulin, i.e. free up-titration and FRC, are comparable options; however, results were based on indirect comparisons and based on experimental conditions (RCTs).



Between groups estimated mean difference (Gla-300+GLP1RA vs. IDegLira)	p-value
1.74 (95% CI -0.28; 3.76)	0.09

Between groups estimated mean difference (Gla-300+GLP1RA vs. IDegLira)	p-value
0.03 (95% CI 0.00; 0.06)	**0.009**

Figure 3 Comparative effectiveness analyses of add-on of free and fixed combination of basal insulin to GLP-1 RA therapy (Gla-300 + GLP-1 RA vs iDegLira). PS adjusted changes in estimated mean levels of basal insulin dose from T0 to T6 by cohort and treatment. T0 = date of the first prescription of Gla-300 or iDegLira, T6 = follow-up at 6 months. Results are expressed as estimated mean difference from T0 and 95% confidence interval (95% CI). Unpaired t-test derived from linear mixed models for repeated measures were applied for between-group comparisons. p-values <0.05 were statistically significant and reported in bold text.

Furthermore, in the included trials titration protocols were implemented, and doses of BI and FRC were two times higher compared to our real-life study. It is important to underline that in our study Gla-300 dose increase was significantly higher than that of iDegLira, suggesting an easier titration for clinicians and patients of free vs. fixed ratio combinations, although additional training to both patients and physicians regarding the importance of the dose appropriateness is needed for both approaches. Each of the two approaches has theoretical advantages. While the free combination allows an easier titration of both BI and GLP-1 RA, FRC can simplify treatment, thus increasing patient adherence and acceptance of therapy [5,22]. However, existing data do not conclusively support the evidence in favor of one approach over the other. Additional head-to-head trials and real-world studies are warranted to further elucidate this issue.

The results of main and post-hoc analyses of the RESTORE-G study suggest the need to promote the add-on rather than the switch approach from GLP-1 RA to BI, as also recommended by current guidelines. In fact, the switch from GLP-1 RA to BI is still common, and often associated with the use of short-acting insulin, although more recent data suggest an increase in the add-on approach [3].

All RESTORE-G analyses [3,18] highlighted the effectiveness and safety of adding-on BI or switching to BI/FRC, but also the urgent need to reduce clinical inertia, witnessed by not only the suboptimal titration, but also the very high HbA1c levels at the time of intensification, and the large proportion of patients with HbA1c >8% during the follow-up. The role of the BI/FRC doses and their titration are strictly linked to effectiveness. Therefore, attitudes of clinicians in the BI/FRC dosing need to be accurately investigated to promote the reduction of the documented clinical inertia.

The study has strengths and limitations. Among the strengths, this is one of the first comparative real-world studies available on GLP-1 RA treatment intensification approaches and its outcomes. Another strength regards the generalizability of the results of the main study (large sample of patients with T2D routinely cared for by centers located in different areas of Italy) and the efficient use of EMR data for research purposes. Additional endpoints (FBG and body weight) were available compared to other real-world studies. The main limitation was the small sample size of the two selected subgroups which prevented a robust estimate of safety. However, results of the main study documented that the rate of hypoglycemia (BG < 54 mg/dl) was low with all intensification strategies, and no severe hypoglycemia episode was registered [3].

In conclusion, larger benefits on FBG control in free (Gla-300+GLP-1 RA) vs. fixed (iDegLira) combination have been found in people uncontrolled on GLP-1 RA, likely due to a better titration of the components in these patients. However, inertia in insulin initiation was documented in both groups. A study designed and powered to further elucidate these key aspects of the GLP-1 RA therapy intensification with BI is needed.

Funding

The study was funded by Sanofi S.r.l., Milan, Italy.

Statement of human and animal rights

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. The study protocol was approved by all local ethics committees of the participating centers. Informed consent was obtained from all patients for being included in the study.

Author contributors

RC, AN, ML, MCR, and RN made substantial contributions to the conception and design of the work. RC and RN

contributed to the data collection. MCR and AN conducted the statistical analyses and drafted the article. All authors revised the article critically for important intellectual content. All authors approved the final version to be published. All authors agreed all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request. Qualified researchers may request access to patient-level data and related documents [including, e.g., the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications]. Patient-level data will be anonymized, and study documents will be redacted to protect the privacy of trial participants.

Declaration of competing interest

Riccardo Candido has received consultancy fees from Boehringer Ingelheim, Eli-Lilly, Novo Nordisk, AstraZeneca, Sanofi-Aventis, Roche Diabetes Care; speaking fees from Astra Zeneca, Boehringer Ingelheim, Eli-Lilly, Novo Nordisk, Sanofi-Aventis, Mundipharma Pharmaceutical, Abbott, MSD, Neopharmed Gentili, Menarini, Essex Italia, Ascensia Diabetes.

Antonio Nicolucci and Maria Chiara Rossi have received funding for research from Sanofi, NovoNordisk, Alfasigma, Artsana, AstraZeneca, Johnson&Johnson, Medtronic, Shionogi, SOBI, Meteda and Theras.

Monica Larosa is an employee of Sanofi and may hold shares and/or stock options in the company.

Raffaele Napoli has served on advisory board panels, received consultancy and speaker's fees or financial support for research from AstraZeneca, Boerhinger Ingelheim, Eli Lilly, Novo Nordisk, MSD, Sanofi.

Acknowledgments

The authors thank the participating centers and all the collaborators from SANOFI, CORESEARCH and OPIS involved in the study. *Additional Assistance:* CORESEARCH (Pescara, Italy) was the Clinical Research Organization involved in the data management (Giuseppe Prosperini, Michele Sacco), statistical analysis (Giuseppe Lucisano, Antonio Nicolucci), and medical writing (Maria Chiara Rossi, Antonio Nicolucci) of the study. Medical writing assistance was funded by Sanofi. Meteda (San Benedetto, Italy) developed the software for the data extraction. OPIS (Milano, Italy) was the Clinical Research Organization involved in regulatory activities of the study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2024.03.023.

Appendix B

RESTORE-G Study Group: Participating centers (by town alphabetical order): Enrico Gabellieri, Azienda Ospedaliera di Alessandria, Alessandria; Elena Tortato, Presidio Ospedaliero di Ricerca INRCA Ancona, Ancona; Rosa Anna Rabini, Ospedale Mazzoni, Ascoli Piceno; Dalia Crazzolara, Ospedale di Bolzano, Bolzano; Luigi Lucibelli, Distretto 56 ASL NA 3 Sud, Bosco Reale; Concetta Aragiusto, Distretto 43 ASL NA2 Nord, Casoria; Gianluigi Panzolato, Ospedale S. Pellegrino di Castiglione delle Stiviere, Castiglione delle Stiviere; Maurizio Di Mauro, Policlinico Vittorio Emanuele, Catania; Andrea Del Buono, ASL Caserta Distretto 14, Cellole; Giuseppe Placentino, Azienda Sanitaria Locale del Verbano Cusio Ossola, Domodossola; Graziano Di Cianni, ASL 6 Livorno, Livorno; Gabriele Brandoni, ASUR Marche Ospedale Generale Provinciale, Macerata; Stefano Fazion, Ospedale Carlo Poma Mantova, Mantova; Giovanna Gregori, Centro Polispecialistico Monterosso, Massa Carrara; Antonino Di Benedetto, AOU Policlinico G Martino, Messina; Carlo De Riva, Ospedale Dell'Angelo, Mestre; Annamaria Terracciano, ASL Caserta Distretto 23, Mondragone; Raffaele Napoli, AOU Federico II, Napoli; Luciano Zenari, Ospedale Sacro Cuore, Negrar; Giuseppe Placentino, Azienda Sanitaria Locale del Verbano Cusio Ossola, Omegna; Franco Cavalot, AOU San Luigi Gonzaga di Orbassano, Orbassano; Francesca Porcellati, Ospedale S. Maria della Misericordia, Perugia; Roberto Anichini, Ospedale San Jacopo, Pistoia; Giuseppe Citro, ASP Potenza, Potenza; Paola D'Angelo, Ospedale S. Pertini Roma, Roma; Marcello Arca, Policlinico Umberto I, Roma; Lelio Morviducci, ASL Roma 1, Roma; Rosa Anna Rabini, Ospedale Madonna del Soccorso, San Benedetto; Valeria Montani, Ospedale San Liberatore, Teramo; Luigi Lucibelli, Distretto 56 ASL NA 3 Sud, Torre Annunziata; Giuseppe Placentino, Azienda Sanitaria Locale del Verbano Cusio Ossola, Verbania; Paolo Fiorentini, ASL di Viterbo, Viterbo.

References

[1] Buse JB, Wexler DJ, Tsapas A, Rossing P, Mingrone G, Mathieu C, et al. 2019 update to: management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2020;63:221–8. https://doi.org/10.1007/s00125-019-05039-w.

[2] SID-AMD Standard italiani per la cura del diabete mellito. 2021. https://www.siditalia.it/pdf/LG_379_diabete_2_sid_amd.pdf. [Accessed 31 October 2023].

[3] Candido R, Nicolucci A, Larosa M, Rossi MC, Napoli R. Treatment intensification following glucagon-like Peptide-1 receptor agonist treatment in type 2 diabetes: The RESTORE-G real-world study, Nutr Metabol Cardiovasc Dis, https://doi.org/10.1016/j.numecd.2023.07.025.

[4] Diamant M, Nauck MA, Shaginian R, Malone JK, Cleall S, Reaney M, et al. Glucagon-like peptide 1 receptor agonist or bolus insulin with optimized basal insulin in type 2 diabetes. Diabetes Care 2014;37(10):2763–73. https://doi.org/10.2337/dc14-0876.

[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(4):614–24. https://doi.org/10.2337/dc16-1957.
[6] Owens DR, S Bailey T, Fanelli CG, Yale JF, Bolli GB. Clinical relevance of pharmacokinetic and pharmacodynamic profiles of insulin degludec (100, 200 U/mL) and insulin glargine (100, 300 U/mL) - a review of evidence and clinical interpretation. Diabetes Metab 2019;45:330–40. https://doi.org/10.1016/j.diabet.2018.11.004.
[7] Roussel R, Ritzel R, Boëlle-Le Corfec E, Balkau B, Rosenstock J. Clinical perspectives from the BEGIN and EDITION programmes: trial-level meta-analyses outcomes with either degludec or glargine 300U/mL vs glargine 100U/mL in T2D. Diabetes Metab 2018; 44:402–9. https://doi.org/10.1016/j.diabet.2018.02.002.
[8] Aroda VR, Rosenstock J, Wysham C, Unger J, Bellido D, González-Gálvez G, et al. Efficacy and safety ofLixiLan, a Titratable fixed-ratio combination of insulin Glargine plusLixisenatide in type 2 diabetes inadequately controlled on basal insulin and metformin: the LixiLan-L randomized trial. Diabetes Care 2016;39(11): 1972–1980.11. https://doi.org/10.2337/dc16-1495.
[9] Rosenstock J, Aronson R, Grunberger G, Hanefeld M, Piatti P, Serusclat P, et al. Benefits of LixiLan, aTitratable fixed-ratio combination of insulin Glargine plusLixisenatide, versus insulin Glargine and Lixisenatide Monocomponents in type 2 diabetes inadequately controlled on Oralagents: the LixiLan-O randomized trial. Diabetes Care 2016;39(11):2026–2035.12. https://doi.org/10.2337/dc16-0917.
[10] Blonde L, Rosenstock J, Del Prato S, Henry R, Shehadeh N, Frias J, et al. Switching to iGlarLixi versus continuing daily or weekly GLP-1 RA in type 2 diabetes inadequately controlled by GLP-1 RA and Oral Antihyperglycemic therapy:the LixiLan-G randomized clinical trial. Diabetes Care 2019;42(11):2108–2116.13. https://doi.org/10.2337/dc19-1357.
[11] Gough SC, Bode B, Woo V, Rodbard HW, Linjawi S, Poulsen P, et al. Efficacy and safety of a fixed-ratiocombination of insulin degludec and liraglutide (iDegLira) comparedwith its components given alone: results of a phase 3, open-label,randomised, 26-week, treat-to-target trial in insulin-naive patientswith type 2 diabetes. Lancet Diabetes Endocrinol 2014;2(11):885–93. https://doi.org/10.1016/S2213-8587(14)70174-3.
[12] 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(11):2926–33. https://doi.org/10.2337/dc14-0785. 15.
[13] Linjawi S, Bode B, Chaykin LB, Courrèges JP, Handelsman Y, Lehmann LM, et al. The efficacy of iDegLira (insulinDegludec/Liraglutide combination) in adults with type 2 diabetesinadequately controlled with a GLP-1 receptor agonist and Oral therapy: DUAL III randomized clinical trial. Diabetes Ther 2017;8:101–14. https://doi.org/10.1007/s13300-016-0218-3.
[14] Jung HN, Cho YK, Min SH, Kim HS, Kim YJ, Park JY, et al. Free versus fixed-ratio combination of basal insulin and GLP-1 receptor agonists in type 2 diabetes uncontrolled with GLP-1 receptor agonists: a systematic review and indirect treatment comparison. Front Endocrinol 2022 May 20;13:870722. https://doi.org/10.3389/fendo.2022.870722.
[15] DeVries JH, Bain SC, Rodbard HW, Seufert J, D'Alessio D, Thomsen AB, et al. Sequential intensification of metformin treatment in type 2 diabetes with liraglutide followed by randomized addition of basal insulin Prompted by A1c targets. Diabetes Care 2012;35(7):1446–54. https://doi.org/10.2337/dc11-1928.
[16] Aroda VR, Bailey TS, Cariou B, Kumar S, Leiter LA, Raskin P, et al. Effect of adding insulin degludec to treatment in patients with type 2 diabetes inadequately controlled with metformin and liraglutide: a Double-blind randomized controlled trial (begin: add to glp-1 study). Diabetes Obes Metabol 2016;18(7):663–70. https://doi.org/10.1111/dom.12661.
[17] Linjawi S, Bode BW, Chaykin LB, Courrèges JP, 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(1):101–14. https://doi.org/10.1007/s13300-016-0218-3.
[18] Napoli R, Larosa M, Nicolucci A, Rossi MC, Candido R, Restore-G Study Group; 779-P. Intensification of glucagon-like peptide-1 receptor agonists therapy with first and second generation basal insulins—the RESTORE-G real-world study. Diabetes 20 June 2023; 72(Supplement_1):779–P. https://doi.org/10.2337/db23-779-P.
[19] Khunti K, Nikolajsen A, Thorsted BL, Andersen M, Davies MJ, Paul SK. Clinical inertia with regard to intensifying therapy in people with type 2 diabetes treated with basal insulin. Diabetes Obes Metabol 2016;18:401–9. https://doi.org/10.1111/dom.12626.
[20] Montvida O, Klein K, Kumar S, Khunti K, Paul SK. Addition of or switch to insulin therapy in people treated with glucagon-like peptide-1 receptor agonists: a real-world study in 66 583 patients. Diabetes Obes Metabol 2017 Jan;19(1):108–17. https://doi.org/10.1111/dom.12790.
[21] Bailey TS, Gill J, Jones SM, Shenoy L, Nicholls C, Westerbacka J. Real-world outcomes of addition of insulin glargine 300 U/mL (Gla-300) to glucagon-like peptide-1 receptor agonist (GLP-1 RA) therapy in people with type 2 diabetes: the DELIVER-G study. Diabetes Obes Metabol 2022;24:1617–22. https://doi.org/10.1111/dom.14739.
[22] Skolnik N, Hinnen D, Kiriakov Y, Magwire ML, White Jr JR. Initiating titratable fixed-ratio combinations of basal insulin analogs and glucagon-like peptide-1 receptor agonists: what you need to know. Clin Diabetes 2018 Apr;36(2):174–82. https://doi.org/10.2337/cd17-0048.