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Treatment intensification following glucagon-like peptide-1 receptor agonists in type 2 diabetes: Comparative effectiveness analyses between different basal insulins. RESTORE-G real-world study

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Abstract

Aim: To compare the effectiveness of different basal insulins (BI) prescribed as an add-on to or switch from glucagon-like peptide-1 receptor agonist (GLP-1 RA) therapy.

Materials and Methods: Retrospective, real-world data from electronic medical records of 32 Italian diabetes clinics were used, after propensity score adjustment, to compare effectiveness after 6 months of treatment with second- versus first-generation BI (2BI vs. 1BI) or glargine 300 U/ml versus degludec 100 U/ml (Gla-300 vs. Deg-100), when added to (ADD-ON) or in substitution of (SWITCH) GLP-1 RA. Only comparisons, including a minimum of 100 patients per group, were performed to ensure adequate robustness of the analyses.

Results: In the ADD-ON cohort (N = 700), greater benefits of 2BI versus 1BI were found in glycated haemoglobin {HbA1c; estimated mean difference: −0.32% [95% confidence interval (CI) −0.62; −0.02]; $p = .04$} and fasting blood glucose [FBG; −20.73 mg/dl (95% CI −35.62; −5.84); $p = .007$]. In the SWITCH cohort (N = 2097), greater benefits of 2BI versus 1BI were found in HbA1c [−0.22% (95% CI −0.42; −0.02); $p = .03$], FBG [−10.15 mg/dl (95% CI −19.04; −1.26); $p = .03$], and body weight [−0.67 kg (95% CI −1.30; −0.04); $p = .04$]. In the SWITCH cohort starting 2BI (N = 688), marked differences in favour of Gla-300 versus Deg-100 were

documented in HbA1c [−0.89% (95% CI −1.26; −0.52); $p < .001$] and FBG [−17.89 mg/dl (95% CI −32.45; −3.33); $p = .02$]. Using propensity score matching as a sensitivity analysis, the benefit on HbA1c was confirmed [−0.55% (95% CI −1.02; −0.08); $p = .02$]. BI titration was suboptimal in all examined cohorts.

Conclusions: 2BI are a valuable option to intensify GLP-1 RA therapy. Switching to Gla-300 versus Deg-100 was associated with greater HbA1c improvement.

KEYWORDS

basal insulin, degludec 100 U/ml, effectiveness, fixed-ratio combination, glargine 300 U/ml, glucagon-like peptide-1 receptor agonists, insulin naïve, safety, type 2 diabetes

1 | INTRODUCTION

The beneficial effects of therapy based on glucagon-like peptide-1 receptor agonists (GLP-1 RA) extend beyond glycaemic control and include cardiovascular protection and better body weight control.[1,2] Consistently, most recent guidelines recommend GLP-1 RA as first-line treatment in patients with type 2 diabetes mellitus (T2D) and established atherosclerotic cardiovascular disease without chronic heart failure or as second-line therapy in patients without atherosclerotic cardiovascular disease.[3,4] However, when GLP-1 RA therapy fails to provide adequate gluco-metabolic control, basal insulin (BI) might be either added to the ongoing GLP-1 RA treatment or used as an alternative to the GLP-1 RA therapy, with or without the concomitant use of oral antihyperglycaemic drugs (OHA).[3,4] By carefully titrating the administered dose, BI treatment can be personalized to the individual needs of the patient's target fasting blood glucose (FBG) levels and integrate GLP-1 RA action on postprandial plasma glucose and FBG, obtained through the stimulation of glucose-dependent insulin secretion, inhibition of glucagon secretion, slowing of gastric emptying, increased satiety, and body weight loss.[5] Furthermore, barriers to the initiation of BI, such as fear of hypoglycaemia and body weight gain,[6] can be minimized with the concomitant use of GLP-1 RA and second-generation BI (2BI).[7] Therefore, the combined use of 2BI and GLP-1 RA deserves accurate consideration.

In most recent years, in addition to first-generation BIs (1BI), i.e. insulin detemir and glargine 100 U/ml (Gla-100), 2BI [degludec 100 U/ml (Deg-100) and glargine 300 U/ml (Gla-300)] reached the market. The clinical research programmes leading to the drug approval, BEGIN for Deg-100 and EDITION for Gla-300, proved that 2BI provide similar or improved efficacy with a better safety profile compared with Gla-100.[8] So far, the BRIGHT study[9] represents the only available head-to-head randomized clinical trial comparing Gla-300 and Deg-100 in insulin-naïve patients with T2D. The two 2BI provided similar improvements in glycaemic control, with relatively low hypoglycaemia risk. A lower rate of hypoglycaemia with Gla-300 during the dose titration period was also documented.[9]

Recently, real-world research programmes have been implemented as a complement to randomized clinical trials. In the United States, by using electronic health care records, the DELIVER programme[10] assessed prescribing patterns and clinical outcomes in real-life clinical practice among people with T2D who initiated insulin treatment with Gla-300 or switched to Gla-300 from other BI, compared with 1BI (Gla-100 or insulin detemir) or Deg-100. Overall, Gla-300 provided similar glucose control associated with a lower risk of hypoglycaemia versus 1BI in people switching BI. In insulin-naïve patients, initiation with Gla-300 was associated with improved effectiveness and a similar or lower risk of hypoglycaemia versus Gla-100. In both insulin-naïve patients and those switching from 1BI to 2BI, antihyperglycaemic effectiveness and risk of hyperglycaemia were shown to be similar with Gla-300 and Deg-100.[10]

The RESTORE-G was a descriptive, real-world study designed to specifically assess intensification approaches after GLP-1 RA treatment and the role of BIs, in particular 2BI.[11] The aim of the current pre-defined subgroup analysis was to compare the effectiveness on metabolic control and body weight of the different BIs used as add-on to GLP-1 RA therapy or as a switch from GLP-1 RA therapy. The titration of BIs was also considered, being a recognized major component of clinical inertia.[12]

As GLP-1 RA treatment is suggested to be the first injectable drug to be used in patients with T2D and the addition of BI is the most appropriate approach to initiating insulin in patients failing to reach the target glucose control with GLP-1 RA, the current study aims to clarify and dissect the approaches used in clinical practice when GLP-1 RA therapy is considered ineffective and needs intensification with BI.

2 | MATERIALS AND 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).[11–15] Data collected referred to the period between 2011 and 2021 from 32 diabetes outpatient clinics.

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

The 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; or switch back to GLP-1 RA after initiation of BI/FRC within 3 months after index date.

The centres recorded data on EMRs according to their clinical practice. Patients with T2D were generally examined by the diabetes centre on a 3-6-month basis, according to the Italian guidelines.[4]

Baseline variables included: age, sex, HbA1c, FBG, body weight, body mass index (BMI), diabetes duration, diabetes treatment (classified according to ATC codes), comorbidities (classified according to the ICD-9-CM system), estimated glomerular filtration rate (eGFR), albuminuria, lipid profile and arterial blood pressure. Follow-up information at 6 months (T6) included: HbA1c, FBG, body weight, BMI, BI dose and diabetes treatment.

The investigated treatment approaches 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-BI cohort) or FRC (SWITCH-FRC cohort). Further details on study methods are reported elsewhere.[11]

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

2.1 | Statistical methods

As a predefined subgroup analysis, each study cohort was stratified by the type of BI/FRC prescribed at T0. Types of BI included 1BI or 2BI. Among 2BI, cohorts were further stratified by Gla-300 versus Deg-100.

Propensity score (PS) adjustment[13] was applied only for comparisons, including a minimum of 100 patients per group, to ensure adequate robustness of the analyses.

The PS for each cohort was estimated taking into consideration age, sex, diabetes duration, baseline HbA1c, BMI, FBG, BI dose, eGFR <60 ml/min/1.73 m^2, history of diabetes complications, and concomitant glucose-lowering treatments [metformin, secretagogues, DPP4 inhibitors, glitazones, acarbose, sodium-glucose cotransporter protein-2 inhibitors (SGLT2is), short-acting insulin].

Subjects with missing PS values were excluded from the cohorts.

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. A non-significant interaction test documents a good balance.

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

The changes in HbA1c, FBG, body weight and BI dose were assessed using mixed models for repeated measurements. Results are expressed as the estimated mean or estimated mean difference from T0 with their 95% confidence interval (95% CI). The paired and unpaired t-tests derived from linear mixed models for repeated measurements were applied for the within- and between-group comparisons. Values for $p < .05$ were considered statistically significant and reported in bold text.

2.2 | Sensitivity analysis

PS matching[13] was applied as a sensitivity analysis for a more stringent head-to-head comparison between Gla-300 versus Deg-100. A PS-matching algorithm on a 1-to-1 basis was used. A logistic regression model was used to predict the probability of receiving Gla-300 versus Deg-100. The variables considered in the logistic model were the same as those used for the PS adjustments. A 5-to-1 greedy matching algorithm was used to identify a unique matched control for each Gla-300 patient according to the PS. The adequacy of balance for the covariates in the matched sample was assessed via the standardized mean difference between the two groups, considering differences of <0.10 (absolute value) as good balance. Longitudinal models were adjusted for unbalanced variables after PS matching.

3 | RESULTS

In the time window 2011-2021, 3164 patients treated with GLP-1 RA changed their therapy by adding BI or switching to BI after a median GLP-1 RA therapy duration of 27.4 months (interquartile range 11.8-53.5). The stratification of study cohorts by type of intensification with BI is shown in Figure 1. As PS adjustment was applied only for comparisons including a minimum of 100 patients per group, the comparative effectiveness analysis between Gla-300 and Deg-100 in the ADD-ON cohort and between the two available FRCs in the SWITCH-FRC cohort was not performed (Figure 1). In the analysed groups, the interaction test was never significant for any covariate, indicating a good balance between the groups.

3.1 | Add-on cohort: second-generation basal insulin versus first-generation basal insulin

Baseline patients' characteristics (patients with non-missing PS) are reported in Table 1. In the ADD-ON cohort, 382 patients added 1BI (Gla-100 or detemir) and 318 added 2BI to the ongoing GLP-1 RA therapy. Compared with patients adding 1BI, patients adding 2BI were significantly older and more frequently men. No statistically significant differences emerged in the other clinical characteristics.

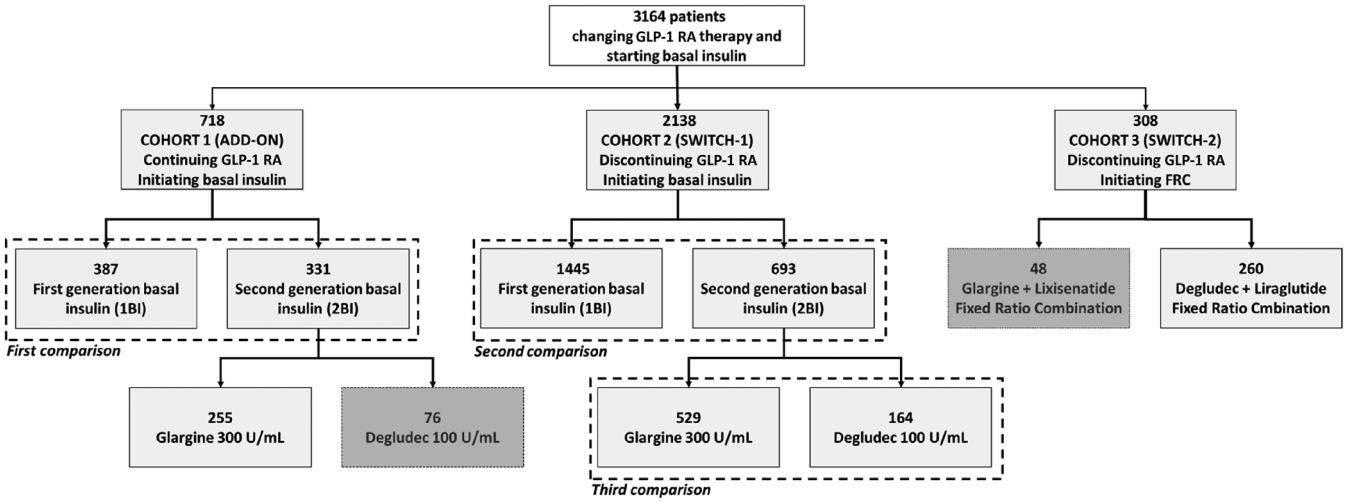

FIGURE 1 RESTORE-G study. Flow-chart of the post-hoc analyses. Identification of cohorts eligible for comparative effectiveness analyses. Only groups including at least 100 subjects were considered eligible for the comparative effectiveness analyses. Non-eligible groups are in the grey box. FRC, fixed-ratio combination; GLP-1 RA, glucagon-like peptide-1 receptor agonist.

PS adjusted changes from T0 to T6 in the continuous endpoints (HbA1c, FBG, body weight and BI dose) in the two treatment groups, along with within- and between-group comparisons, are reported in Figure 2 and Table S1. In the ADD-ON cohort, statistically significant greater benefits of 2BI versus 1BI were found at T6 both in terms of HbA1c [estimated mean difference of −0.32% (95% CI −0.62; −0.02); $p = .04$] and FBG [estimated mean difference of −20.73 mg/dl (95% CI −35.62; −5.84); $p = .007$]. No statistically significant between-group differences were documented in weight change (Figure 2 and Table S1). The BI dose increased from 0.13 U/kg at T0 to 0.20 U/kg in both groups (between-group p-value = .79) (Table S1).

3.2 | Switch cohort: second-generation basal insulin versus first-generation basal insulin

Baseline patients' characteristics (patients with non-missing PS) are reported in Table 1. In the SWITCH cohort, 1406 patients discontinued GLP-1 RA and switched to 1BI, whereas 691 discontinued GLP-1 RA and switched to 2BI. Compared with patients switching to 1BI, patients switching to 2BI had significantly lower BMI, total cholesterol, LDL-cholesterol, blood pressure levels; they were also less frequently treated with secretagogues, antihypertensive and lipid-lowering drugs. All groups had baseline HbA1c levels ≥9.0%. The proportion of patients also initiating short-acting insulin in combination with BI was lower in the group switching to 2BI versus the group switching to 1BI (16.9% vs. 24.5%; $p < .0001$).

PS adjusted changes from T0 to T6 in the continuous endpoints (HbA1c, FBG and body weight) in the different treatment groups, along with within- and between-group comparisons, are reported in Figure 2 and Table S2. In the SWITCH cohort, statistically significant greater benefits of 2BI versus 1BI were found at T6 in terms of HbA1c [estimated mean difference of −0.22% (95% CI −0.42; −0.02); $p = .03$], FBG [estimated mean difference of −10.15 mg/dl (95% CI −19.04; −1.26); $p = .03$], and body weight [estimated mean difference of −0.67 kg (95% CI −0.04; −1.30); $p = .04$] (Figure 2 and Table S2). BI dose increased from 0.14 U/kg at T0 to 0.19 U/kg in the 1BI group and from 0.14 U/kg at T0 to 0.20 U/kg in the 2BI group (between-group $p = .13$) (Table S2). In both groups, there was an increase in short-acting and total insulin doses, without differences between groups.

3.3 | Switch cohort: glargine 300 U/ml versus degludec 100 U/ml

In the SWITCH cohort initiating 2BI, 525 patients were prescribed Gla-300 and 163 with Deg-100. Compared with patients treated with Deg-100, those treated with Gla-300 had a lower BMI, a lower prevalence of diabetes complications, a lower BI dose at T0 and a more frequent use of SGLT2is (Table 2).

Longitudinal analyses showed marked statistically significant between-group differences in favour of Gla-300 versus Deg-100 at T6 in terms of HbA1c [estimated mean difference of −0.89% (95% CI −1.26; −0.52); $p < .001$] and FBG [estimated mean difference of −17.89 mg/dl (95% CI −32.45; −3.33); $p = .02$]. No statistically significant between-group differences were documented in weight (Figure 3 and Table S3). BI dose increased from 0.14 U/kg at T0 to 0.20 U/kg in the Gla-300 group and from 0.14 U/kg at T0 to 0.19 U/kg in the Deg-100 group (between-group p-value = .37) (Table S3).

As a slight, although not significant ($p = .21$, Table 2 and Figure 3), different estimated mean HbA1c levels were found in the two groups at T0 (9.49% in Gla-300 vs. 9.12% in Deg-100), PS matching was applied as a sensitivity analysis. The same set of covariates included in the PS adjustment was considered, and cohorts were balanced for most of the covariates, as documented by standardized differences below the absolute value of 10 (Table S4). Covariates

TABLE 1 Baseline patients' characteristics of the populations selected for the comparative effectiveness analyses of 2BI vs. 1BI.

		ADD-ON of 2BI vs. 1BI to ongoing GLP-1 RA therapy			SWITCH from GLP-1 RA therapy to 2BI vs. 1BI		
Variable	**Category**	**1BI**	**2BI**	***p*-Value**	**1BI**	**2BI**	***p*-Value**
N. Group*		382	318		1.406	691	
Age, years		57.4 ± 9.6	60.1 ± 9.6	**.0004**	58.9 ± 9.9	59.8 ± 11.1	.01
Sex, %	Female	45.5	37.7	**.04**	669 (47.58)	307 (44.43)	.17
	Male	54.5	62.3		52.4	55.6	
Diabetes duration, years		10.4 ± 7.3	10.7 ± 7.5	.75	10.4 ± 8.4	10.4 ± 9.1	.43
Diabetes duration in classes, %	≤5 years	23.3	23.3	.98	23.7	26.6	.26
	6-10 years	29.3	28.9		31.1	30.0	
	11-20 years	34.3	33.3		33.7	30.1	
	>20 years	8.6	10.1		9.1	10.3	
	NA	4.4	4.4		2.3	3.0	
BMI, kg/m^2		33.4 ± 5.7	33.3 ± 5.9	.78	33.4 ± 6.07	32.1 ± 6.6	**.0005**
HbA1c, %		9.1 ± 1.2	9.0 ± 1.3	.35	9.4 ± 1.5	9.4 ± 1.6	.25
Fasting blood glucose, mg/dl		202.9 ± 60.2	210.7 ± 61.7	.24	211.7 ± 66.6	216.5 ± 67.0	.41
Systolic blood pressure, mmHg		136.0 ± 16.7	136.8 ± 17.4	.82	137.6 ± 19.5	133.4 ± 16.4	**.005**
Diastolic blood pressure, mmHg		79.5 ± 9.3	79.5 ± 10.4	.40	80.2 ± 9.6	78.4 ± 10.0	**.01**
Total cholesterol, mg/dl		173.4 ± 39.0	167.1 ± 39.1	.09	178.0 ± 42.7	172.2 ± 45.0	**.01**
LDL-cholesterol, mg/dl		93.5 ± 35.4	87.7 ± 31.8	.14	96.1 ± 35.1	88.2 ± 34.7	**.002**
HDL-cholesterol, mg/dl		43.5 ± 11.1	45.7 ± 13.5	.37	44.5 ± 12.4	44.4 ± 11.7	.95
Triglycerides, mg/dl		185.3 ± 81.0	186.8 ± 116.7	.40	205.7 ± 201.3	211.0 ± 157.6	.20
eGFR <60 ml/min/1.73 m^2		23.6	27.9	.52	24.7	29.8	.14
Micro/macroalbuminuria, %		29.1	37.9	.17	31.0	37.8	.09
Antihypertensive drugs, %		70.2	73.9	.27	58.5	46.6	**<.0001**
Lipid-lowering drugs, %		56.3	61.6	.15	48.7	41.2	**.001**
Diabetes complications, %		8.9	7.5	.52	9.3	10.0	.62
Basal insulin dose, U		11.9 ± 6.2	12.46 ± 5.46	.06	12.5 ± 5.4	12.1 ± 5.2	.16
Metformin, %		79.6	73.0	.05	77.2	73.4	.07
Secretagogues, %		47.8	41.4	.10	54.5	47.4	**.003**
DPP-4 inhibitors, %		6.2	7.4	.55	17.1	18.6	.41
Glitazones, %		7.5	8.1	.80	9.7	7.8	.16
Acarbose, %		3.5	1.7	.18	4.40	3.5	.35
SGLT2 inhibitors, %		3.5	7.4	**.03**	9.1	20.5	.35
Short-acting insulin, %		2.1	1.3	.40	24.5	16.9	**<.0001**

Note: Patients with not evaluable propensity score were excluded. Data are means and standard deviations or proportions. Statistically significant *p*-values ($p < .05$) are in bold.

Abbreviations: 1BI, first-generation basal insulin; 2BI, second-generation basal insulin; BMI, body mass index; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SGLT2, sodium-glucose cotransporter 2.

associated with a SD ≥|10| or a $p < .05$ in the post-PS matching cohort were used as adjustment variables in the longitudinal models (Table S4).

After the application of PS matching, longitudinal models confirmed statistically significant between-group differences in favour of Gla-300 versus Deg-100 at T6 in terms of HbA1c [estimated mean difference of −0.55% (95% CI −1.02; −0.08); $p = .02$]. No statistically significant between-group differences were documented in FBG, weight and BI dose changes (Figure 3 and Table S5). Dose changes at 6 months were superimposable to those of the PS adjustment cohort (Table S5).

4 | DISCUSSION

Using a pre-defined subgroup analysis comparing effectiveness endpoints between the PS-adjusted RESTORE-G study cohorts from Italian clinical practices, we show that, in patients continuing or

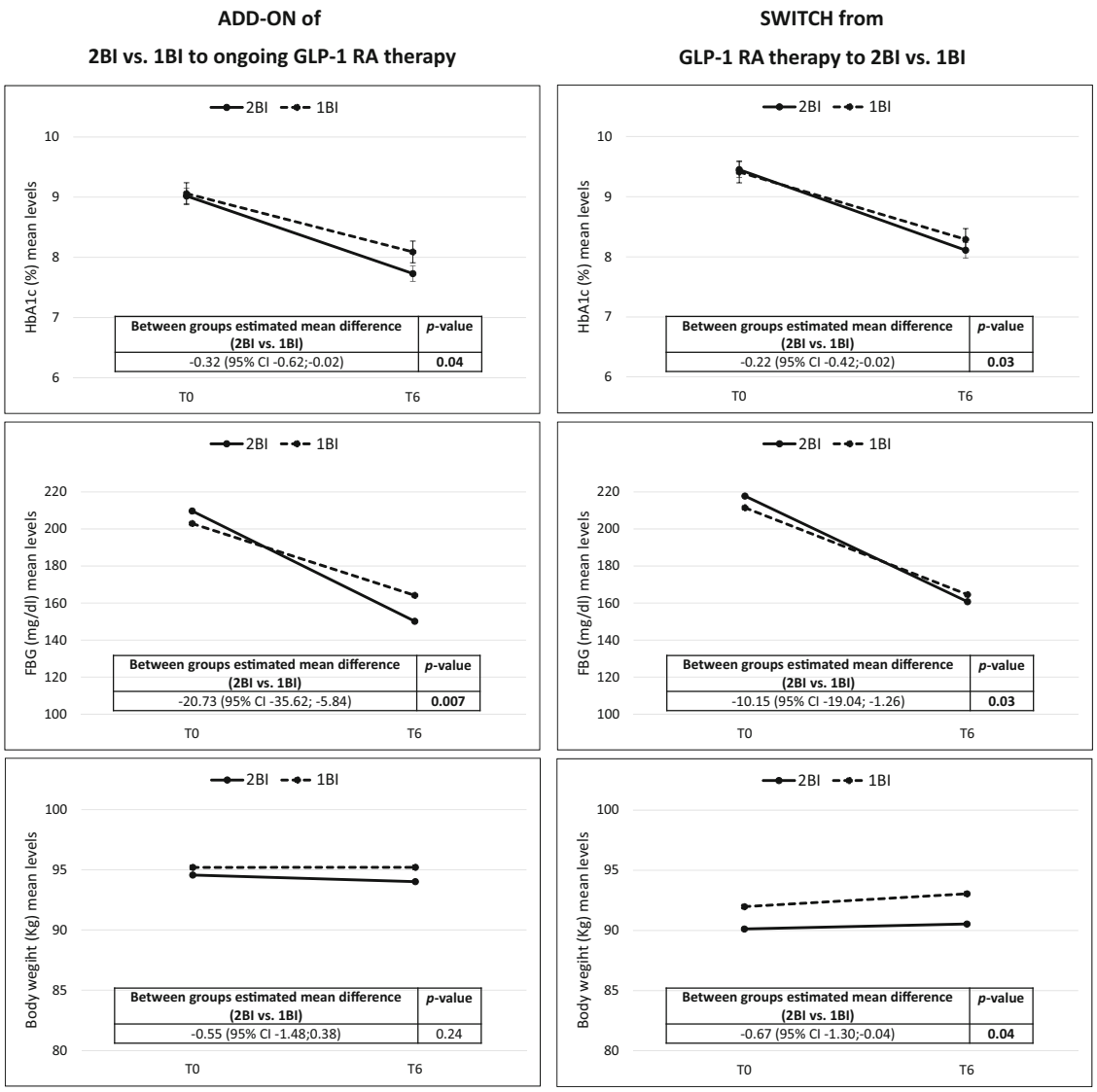

FIGURE 2 Comparative effectiveness analyses of 2BI vs 1BI in the ADD-ON and SWITCH-BI cohorts. Propensity score adjusted changes in estimated mean levels of continuous endpoints (HbA1c, FBG and body weight) from T0 to T6 by cohort and treatment. Statistically significant *p*-values ($p < .05$) are in bold. Details on estimated mean levels at T0 and T6 and data availability for each outcome at T0 and T6 are presented in Tables S1 and S2. 1BI, first-generation basal insulin; 2BI, second-generation basal insulin; BI, basal insulin; CI, confidence interval; FBG, fasting blood glucose; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; T0, date of the first prescription of 1BI or 2BI; T6, follow-up at 6 months.

interrupting the therapy with GLP-1 RA, greater benefits in HbA1c and FBG levels were obtained using 2BI (Gla-300 or Deg-100) rather than 1BI.

In the ADD-ON cohort, the improvement in either HbA1c or FBG was significantly more relevant with 2BI than with 1BI after 6 months (the difference between the two approaches was 0.32% for HbA1c levels and 20 mg/dl for FBG levels).

Similarly, in the SWITCH cohort, after 6 months, HbA1c and FBG levels were 0.22% and 10 mg/dl lower with 2BI versus 1BI, respectively, without any change in body weight. Weight gain was significantly greater with 1BI versus 2BI (0.67 kg).

Such a difference between the two generations of insulin occurred in spite of similar doses of BI and might be because of, at least in part, the less frequent simultaneous initiation of short-acting insulin in association with 2BI. In addition, better adherence, thanks to the better safety profile,[7] can presumably contribute to these findings.

In addition, in patients with T2D switching from GLP-1 RA therapy to insulin treatment, a greater improvement in HbA1c and FBG could be shown when using Gla-300 rather than Deg-100. In the comparison between the two 2BI, the improvement in HbA1c after 6 months was greater (between-group difference of 0.89%) with Gla-300 than Deg-100. Furthermore, FBG levels at T6 were lower in the Gla-300 group than the Deg-100 group, and no difference was documented in weight. After application of PS matching as a sensitivity analysis, a statistically significant, clinically relevant between-group

TABLE 2 Baseline patients' characteristics of the populations selected for the comparative effectiveness analyses of Gla-300 vs. Deg-100 in the SWITCH cohort.

Variables	Category	Gla-300	Deg-100	*p*-Value
N		525	163	
Age, years		59.9 ± 11.3	59.1 ± 10.5	.18
Sex, %	Female	44.8	44.2	.89
	Male	55.2	55.8	
Diabetes duration, years		10.6 ± 9.7	9.8 ± 7.1	.61
BMI, kg/m^2		31.6 ± 6.5	33.4 ± 6.5	**.01**
HbA1c, %		9.5 ± 1.6	9.2 ± 1.6	.21
Fasting blood glucose, mg/dl		218.8 ± 67.1	209.8 ± 65.8	.15
Systolic blood pressure, mmHg		133.4 ± 15.9	133.4 ± 17.5	.89
Diastolic blood pressure, mmHg		78.1 ± 9.2	78.8 ± 11.2	.73
Total cholesterol, mg/dl		172.3 ± 45.7	172.2 ± 42.3	.94
LDL-cholesterol, mg/dl		88.1 ± 34.2	88.4 ± 36.3	.93
HDL-cholesterol, mg/dl		44.7 ± 11.9	43.7 ± 11.1	.78
Triglycerides, mg/dl		207.4 ± 159.0	223.5 ± 155.3	.67
eGFR <60 ml/min/1.73 m^2		31.5	22.4	.15
Micro/macroalbuminuria, %		36.9	39.6	.72
Antihypertensive drugs, %		44.2	55.2	**.01**
Lipid-lowering drugs, %		39.8	46.6	.12
Diabetes complications, %		8.6	14.1	**.04**
Basal insulin dose, U		11.9 ± 5.1	13.0 ± 5.7	**.01**
Metformin, %		72.2	76.9	.27
Secretagogues, %		45.5	53.7	.08
DPP-4 inhibitors, %		19.0	17.0	.59
Glitazones, %		7.5	8.8	.60
Acarbose, %		3.8	2.7	.55
SGLT2 inhibitors, %		23.2	11.6	**.002**
Short-acting insulin, %		16.8	18.4	.63

Note: Four patients in the Gla-300 group and one patient in the Deg-100 group with not evaluable propensity score were excluded. Data are means and standard deviations or proportions. Statistically significant *p*-values ($p < .05$) are in bold.
Abbreviations: BMI, body mass index; Deg-100, degludec 100 U/ml; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; Gla-300, glargine 300 U/ml; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SGLT2, sodium-glucose cotransporter 2.

difference in HbA1c levels in favour of Gla-300 versus Deg-100 (−0.55%) was confirmed. No statistically significant between-group differences were documented in FBG and weight.

BI titration was similar and suboptimal in all examined cohorts (from about 0.1 U/kg at baseline to 0.2 U/kg after 6 months) with an average FBG >150 mg/dl.

Our study previously showed that about 40% of the patients intensified their GLP-1 RA therapy with BI in a free or fixed combination after a median GLP-1 RA therapy duration of 27 months.[11] In addition, we documented very high HbA1c levels at the time of intensification, a suboptimal BI dose titration, and a large proportion of patients with HbA1c >8% 1 year after intensification.[11]

This is the first real-world study documenting greater benefits for HbA1c with 2BI versus 1BI. In fact, in previous studies comparing 2BI versus 1BI in patients with T2DM (insulin-naïve or switchers) pre-treated or not with GLP-1 RA, no difference in HbA1c was found.[8,15]

As for real-world evidence on 2BI, in the DELIVER D+ study,[14] where 17% of patients were treated with GLP-1 RA, switching from 1BI to 2BI (Gla-300 or Deg-100) was associated with similar improvements in glycaemic control (−0.63% vs. −0.58%, $p = .49$) and hypoglycaemia rates. Even the LIGHTNING study,[15] where GLP-1 RA were used in 25-35% of patients initiating 2BI, revealed comparable reductions in HbA1c with Gla-300 versus 1BI and Deg-100. Lower rates of severe hypoglycaemia with Gla-300 versus 1BI and similar rates versus Deg-100 both in insulin-naive and switch cohorts were also documented.

Regarding real-world evidence on Gla-300, the DELIVER-G study documented that in US clinical practice, the addition of Gla-300 to daily or weekly GLP-1 RA therapy significantly improved glycaemic control (HbA1c reduction of −0.97% after 6 months), without significantly increasing hypoglycaemia.[16] In the ADD-ON cohort of our study, we showed that adding either Gla-300 or Deg-100 was capable

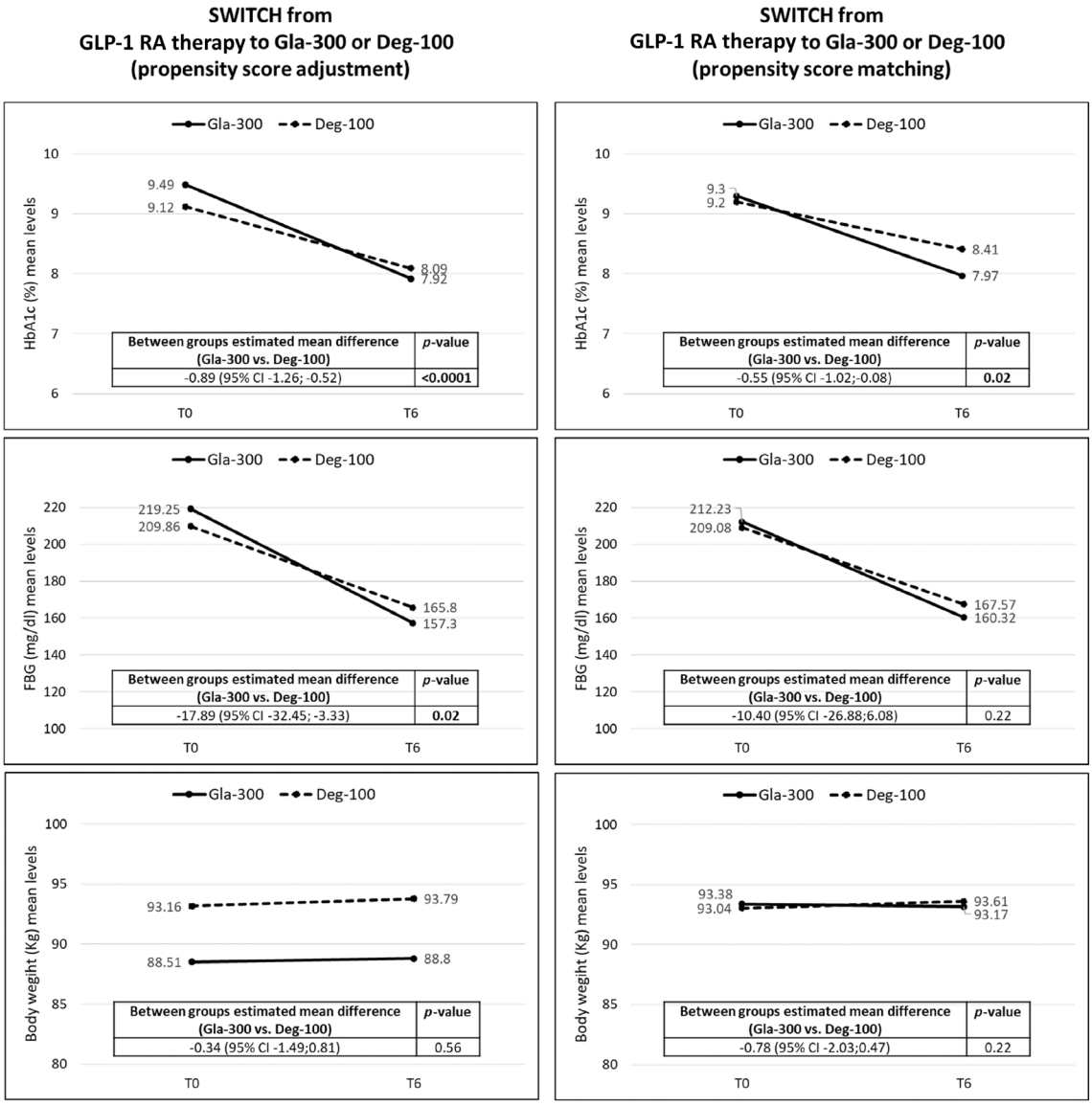

FIGURE 3 Comparative effectiveness analyses Gla-300 vs. Deg-100 in the SWITCH cohort. Propensity score adjusted changes in estimated mean levels of continuous endpoints (HbA1c, FBG and body weight) from T0 to T6 by cohort and treatment; between-group comparisons. Statistically significant *p*-values ($p < .05$) are in bold (unpaired t-test derived from linear mixed models for repeated measurements). Details on estimated mean levels at T0 and T6 and data availability for each outcome at T0 and T6 are presented in Tables S3 and S4. CI, confidence interval; Deg-100, degludec 100 U/ml; FBG, fasting blood glucose; Gla-300, glargine 300 U/ml; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; T0, date of the first prescription of Gla-300 or Deg-100; T6, follow-up at 6 months.

of improving HbA1c by 1.3% without affecting body weight. Therefore, in our study, the effect of 2BI on HbA1c appears to be greater than in the DELIVER-G study. Consistently with our data, in the DELIVER-G, the addition of Gla-300 to the GLP-1 RA treatment occurred at an HbA1c value over 9%, pointing to clinical inertia towards insulin initiation.

Other comparative effectiveness analyses were performed in BI-naïve or switcher cohorts treated with different background antihyperglycaemic agents, including GLP-1 RA, in variable proportions of patients. In the PS-matched cohort of the DELIVER D Naïve Study,[17] where subjects treated with GLP-1 RA represented about 20% of the whole cohort, initiation of Gla-300 or Deg-100 resulted in sustained and comparable improvements in HbA1c levels (−1.67% and −1.58%; $p = .51$) and similar rates of hypoglycaemia. This study confirmed the findings from the BRIGHT main study[9] on the primary endpoint (HbA1c at 24 weeks: −1.64% and −1.59% for Gla-300 and Deg-100, respectively; $p_{\text{non-inferiority}} < .0001$). On the other hand, in the BRIGHT renal sub-analysis,[18] in insulin-naïve people with T2D and impaired renal function, use of Gla-300 versus Deg-100 resulted in greater HbA1c reduction over the full study period, without differences in hypoglycaemia incidence. In our study, the HbA1c improvement obtained with Gla-300 after 6 months (−1.57%) in the

SWITCH cohort was in line with previous data from the literature.[9,17] However, HbA1c improvement with Gla-300 was significantly greater than with Deg-100, both in the main analysis and in the sensitivity analysis.

No effectiveness data on FBG, weight gain and BI titration were attainable from the database used in US studies. In the Italian RESTORE-2 study,[19,20] where about 23% of BI naïve patients and about 10% of switchers from 1BI to 2BI were treated with GLP-1 RA, initiation of Gla-300 or Deg-100 was associated with similar improvements in glycaemic control, without weight gain and with low hypoglycaemia rates, and no severe episodes during 6 months of treatment; late BI initiation and slow titration were clearly identified even in this study.

Differently from the BRIGHT trial renal sub-analysis,[18] real-world studies did not show differences between 2BI on glycaemic outcomes; however, they were not specifically conducted on GLP-RA pre-treated populations. This RESTORE-G sub-group analysis is the first real-world comparative study showing differences in HbA1c reduction between Gla-300 and Deg-100 in a population with T2D treated with GLP-1 RA for >2 years.

The RESTORE-G study[11] documented that the switch approach is still the prevalent one for GLP-1 RA therapy intensification. However, the combined use of BI and GLP-1 RA is supported by a strong rationale, such as complementary targets of glycaemic control, the potential of GLP-1 RA to overcome barriers such as fear of hypoglycaemia and weight gain, and the simplification of insulin therapy when GLP-1 RA delays the intensification with short-acting insulin.[6] The use of 2BI is supported by the most recent guidelines because of its safer profile.[3,4] Real-world data on the effectiveness and safety of the ADD-ON approach can reassure physicians and promote this model of intensification after GLP-1 RA treatment for most of the patients.[3,4] On the other hand, FRC may represent a strategy to simplify and de-intensify basal bolus regimens in some patients.[21]

To our knowledge, this is the second study where a greater reduction of HbA1c with Gla-300 versus Deg-100 was found. The difference in glycaemic control between Gla-300 and Deg-100 observed in the BRIGHT renal and elderly sub-analysis has been attributed to BI characteristics, such as pharmacokinetics/pharmacodynamics or mechanism of action, possible differences in renal handling of insulin catabolism at lower eGFR levels, or concomitant treatments.[22,23] These findings arising from specific populations (i.e. patients with T2D pre-treated with GLP-1 RA or with renal disfunction) are relevant and require further ad hoc investigation.

This is one of the few comparative real-world studies available on GLP-1 RA intensification approaches and their outcomes. In addition, the generalizability of the results (a large sample of patients with T2D routinely cared for by centres located in different areas of Italy) and the efficient use of EMR data for research purposes represent a strength of the study. Furthermore, the double approach of PS adjustment and matching using a wide set of covariates provided a robust estimate of effectiveness. Finally, additional endpoints (FBG, body weight, insulin doses) were available compared with other real-world studies.

The limitations of the study were the small sample size of the Deg-100 group in the ADD-ON cohort, which prevented the comparative analyses between 2BI in this cohort. In addition, in the SWITCH cohort, the sample size of insulin-treated subjects was not large. The lack of robust safety data for subgroup analyses represents an additional limitation. Furthermore, the number of SGLT2i users was significantly different among comparison cohorts, suggesting differences in sociodemographic or other characteristics not considered in the study.

In conclusion, this pre-defined subgroup analysis of the RESTORE-G confirms that the addition of 2BI to intensify GLP-1 RA therapy can be considered a valuable therapeutic option to improve metabolic control and prevent weight gain. Furthermore, the study suggests that switching from GLP-1 RA to Gla-300 versus Deg-100 seems to be associated with a greater HbA1c improvement after 6 months. The current analysis, in line with our previous work, confirms the urgent need to reduce clinical inertia, as witnessed by the very high HbA1c levels at the time of intensification, and the suboptimal BI titration even of the newest insulin analogues.

AUTHOR CONTRIBUTIONS

RN, AN, ML, MCR and RC 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.

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CONFLICT OF INTEREST STATEMENT

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Shionogi, SOBI, Meteda and Theras. ML is an employee of Sanofi and may hold shares and/or stock options in the company. RC has received consultancy fees from Boehringer Ingelheim, Eli-Lilly, Novo Nordisk, Astra-Zeneca, 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 and Ascensia Diabetes.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

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.

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REFERENCES

1. Ferrari F, Scheffel RS, Martins VM, Santos RD, Stein R. Glucagon-like Peptide-1 receptor agonists in type 2 diabetes mellitus and cardiovascular disease: the past, present, and future. *Am J Cardiovasc Drugs*. 2022;22:363-383.
2. Palmer SC, Tendal B, Mustafa RA, et al. Sodium-glucose cotransporter protein-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists for type 2 diabetes: systematic review and network meta-analysis of randomised controlled trials. *BMJ*. 2021;13(372):m4573. doi:10.1136/bmj.m4573
3. Buse JB, Wexler DJ, Tsapas A, et al. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of diabetes (EASD). *Diabetologia*. 2018;2020(63):221-228.
4. SID-AMD Standard italiani per la cura del diabete mellito 2018. https://aemmedi.it/wp-content/uploads/2009/06/AMD-Standard-unico1.pdf Last access: May 2020.
5. Anderson SL, Trujillo JM. Basal insulin use with GLP-1 receptor agonists. *Diabetes Spectr*. 2016;29:152-160.
6. Peyrot M, Rubin RR, Lauritzen T, et al. Resistance to insulin therapy among patients and providers: results of the cross-national diabetes attitudes, wishes, and needs (DAWN) study. *Diabetes Care*. 2005;28:2673-2679.
7. Owens DR, 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;45:330-340.
8. 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;44:402-409.
9. Rosenstock J, Cheng A, Ritzel R, et al. More similarities than differences testing insulin glargine 300 units/ml versus insulin Degludec 100 units/ml in insulin-naive type 2 diabetes: the randomized head-to-head BRIGHT trial. *Diabetes Care*. 2018;41:2147-2154.
10. Blonde L, Bailey T, Sullivan SD, Freemantle N. Insulin glargine 300 units/ml for the treatment of individuals with type 2 diabetes in the real world: a review of the DELIVER programme. *Diabetes Obes Metab*. 2021;23:1713-1721.
11. 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 Metab Cardiovasc Dis*. 2023;33:2294-2305.
12. Khunti K, Giorgino F, Berard L, Mauricio D, Harris SB. The importance of the initial period of basal insulin titration in people with diabetes. *Diabetes Obes Metab*. 2020;22:722-733.
13. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med*. 2009;10:3083-3107.
14. Sullivan SD, Bailey TS, Roussel R, et al. Clinical outcomes in real-world patients with type 2 diabetes switching from first- to second-generation basal insulin analogues: comparative effectiveness of insulin glargine 300 units/ml and insulin degludec in the DELIVER D+ cohort study. *Diabetes Obes Metab*. 2018;20:2148-2158.
15. Pettus J, Roussel R, Liz Zhou F, et al. Rates of hypoglycemia predicted in patients with type 2 diabetes on insulin glargine 300 U/ml versus first- and second-generation basal insulin analogs: the real-world LIGHTNING study. *Diabetes Ther*. 2019;10:617-633.
16. 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 Metab*. 2022;24:1617-1622.
17. Sullivan SD, Nicholls CJ, Gupta RA, et al. Comparable glycaemic control and hypoglycaemia in adults with type 2 diabetes after initiating insulin glargine 300 units/ml or insulin degludec: the DELIVER naive D real-world study. *Diabetes Obes Metab*. 2019;21:2123-2132.
18. Haluzík M, Cheng A, Müller-Wieland D, et al. Differential glycaemic control with basal insulin glargine 300 U/ml versus degludec 100 U/ml according to kidney function in type 2 diabetes: a subanalysis from the BRIGHT trial. *Diabetes Obes Metab*. 2020;22:1369-1377.
19. Fadini GP, Buzzetti R, Nicolucci A, et al. Comparative effectiveness and safety of glargine 300 U/ml versus degludec 100 U/ml in insulin-naïve patients with type 2 diabetes. A multicenter retrospective real-world study (RESTORE-2 NAIVE STUDY). *Acta Diabetol*. 2022;59:1317-1330.
20. Buzzetti R, Fadini GP, Nicolucci A, Larosa M, Rossi MC, Cucinotta D; RESTORE-2 Study Group. Comparative effectiveness of glargine 300 U/ml vs. Degludec 100 U/ml in patients with type 2 diabetes switching from 1° generation basal insulins. *Nutr Metab Cardiovasc Dis*. 2022;32:2255-2263.
21. Bonora BM, Rigato M, Frison V, et al. Deintensification of basal-bolus insulin after initiation of GLP-1 RA in patients with type 2 diabetes under routine care. *Diabetes Res Clin Pract*. 2021;173:108686.
22. Kawaguchi Y, Sawa J, Hamai C, Kumeda Y. Differential effect of hypoalbuminemia on hypoglycemia on type 2 diabetes patients treated with insulin glargine 300 U/ml and insulin degludec. *Diabetes Ther*. 2019;10:1535-1541.
23. Pieber TR, Bardtrum L, Isendahl J, Wagner L, Nishimura R, Nishimura R. Commentary to "Differential Effect of Hypoalbuminemia on Hypoglycemia on Type 2 Diabetes Patients Treated with Insulin Glargine 300 U/ml and Insulin Degludec" by Kawaguchi et al. Diabetes therapy 201900. *Diabetes Ther*. 2020;11:561-567.

SUPPORTING INFORMATION

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

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APPENDIX A

RESTORE-G Study Group

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