ORIGINAL ARTICLE

Comparative clinical outcomes of insulin degludec and insulin glargine 300 U/mL after switching from other basal insulins in real-world patients with type 1 and type 2 diabetes

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ABSTRACT

Aims/Introduction: To evaluate and compare the efficacy of insulin degludec (IDeg) and insulin glargine 300 U/mL (Gla300) 6 months after switching from other basal insulins by assessing the changes in glycated hemoglobin (HbA1c), body mass index (BMI), and insulin doses in patients with type 1 and type 2 diabetes in a real-world clinical setting.

Materials and Methods: A total of 307 patients with type 1 diabetes and 294 patients with type 2 diabetes with HbA1c >7.0% were studied. Adjusted mean changes in HbA1c, BMI, and insulin doses were compared between IDeg (IDeg group) and Gla300 (Gla300 group) switchers. Multivariable logistic regression analyses were carried out to examine whether the IDeg or Gla300 group was associated with HbA1c or insulin dose reduction and BMI gain.

Results: HbA1c was significantly decreased in both the IDeg and Gla300 groups. Adjusted mean changes in HbA1c (approximately −0.3% and −0.5% in type 1 diabetes and type 2 diabetes patients, respectively) and BMI were similar between both groups. The mean change in insulin dose was slightly larger for dose reduction in the IDeg group than in the Gla300 group. Multivariable logistic regression models showed that the IDeg group was significantly associated with insulin dose reduction after adjusting for basal insulin type, insulin dose, and number of basal insulin injections at baseline and other confounding factors.

Conclusions: The current study suggested that IDeg and Gla300 have similar effects in reducing HbA1c and gaining BMI after switching from other basal insulins in Japanese patients with type 1 diabetes and type 2 diabetes. IDeg selection was associated with insulin dose reduction.

INTRODUCTION

First-generation long-acting basal insulin analogs, such as insulin glargine 100 U/mL (Gla100) and insulin detemir (IDet), have been widely used over the past decade due to their longer and more stable action than neutral protamine Hagedorn (NPH) insulin[1–3]. However, pharmacokinetic studies have shown that the duration of action of Gla100 and IDet was <24 h in some people[3], which might require twice-daily injections to improve glycemic control, leading to increased insulin doses[4] or decreased treatment satisfaction[5].

Insulin degludec (IDeg) and insulin glargine 300 U/mL (Gla300) are ultra-long-acting, second-generation basal insulin analogs with a more constant and prolonged pharmacokinetic and pharmacodynamic profile than Gla100 and IDet[6,7]. Both insulin preparations have been shown to yield similar glycemic control with fewer episodes of hypoglycemia than Gla100[8,9]. Furthermore, switching from first-generation insulins to these second-generation insulin analogs would represent an effective option in patients with poorly controlled diabetes[10,11]. There

have been several head-to-head studies comparing the action and efficacy of IDeg and Gla300[12]. However, there has been limited information on the differences in the efficacy between these insulins when switched from other basal insulins[11,13]. Thus, the purpose of the present study was to compare the efficacy of IDeg and Gla300 after switching from other basal insulins in patients with type 1 and type 2 diabetes in a real-world clinical setting.

MATERIALS AND METHODS

Patient selection

We carried out a single-center, retrospective, observational study using the electronic medical records of the hospital. Patients with type 1 diabetes and type 2 diabetes were first extracted if their glycated hemoglobin (HbA1c) exceeded 7.0% for at least 6 months by basal–bolus insulin regimen or basal insulin with or without non-insulin glucose-lowering agents. Among these patients, selected were patients in whom basal insulin had been switched from NPH, IDet or Gla100 to IDeg (IDeg group) or to Gla300 (Gla300 group) between September 2015 and February 2019. Excluded were patients with missing data on bodyweight, undergoing hemodialysis, renal transplantation, any surgery or steroid therapy, with pancreatic diseases or carcinomas, admitted into the hospital, transferred to another hospital and discontinuation of IDeg

or Gla300 within several months. Figure 1 shows the study flowchart.

Collection of clinical and laboratory data

Data on age, sex, type of diabetes, anthropometric measurements, HbA1c levels, duration of diabetes and use of glucose-lowering agents were obtained from the medical records. Body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). HbA1c values were measured using the high-performance liquid chromatography method (Adams A1c HA-8160; Arkray, Kyoto, Japan) and were reported as percentage assigned by the National Glycohemoglobin Standardization Program[14]. Data of fasting blood glucose levels were collected from patients whose self-monitoring of blood glucose (SMBG) records were available for at least 15 days of the 1 month before and after switching.

Outcome measurements

The primary outcomes were changes in HbA1c levels, BMI, and basal and total insulin doses 6 month after the switch from other basal insulins to IDeg or Gla300. The secondary outcomes were HbA1c reduction (<0.0%), BMI gain (>0.0 kg/m^2), and reduction of basal and total insulin doses (>0 units/kg) 6 months after the switch to IDeg or Gla300. These outcomes were analyzed in patients with type 1 diabetes and type 2
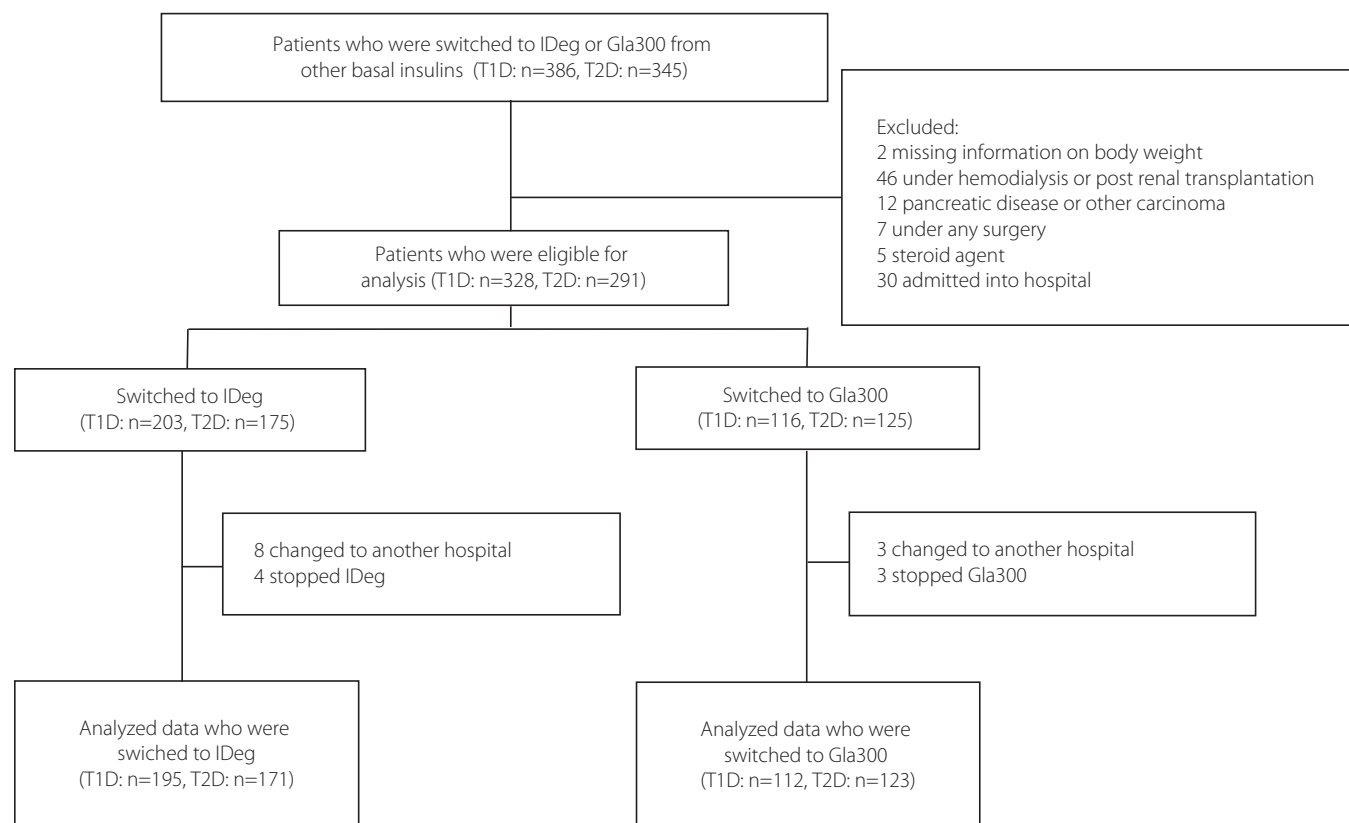
Figure 1 | Study flowchart. Gla300, glargine 300 U/mL; IDeg, degludec; T1D, type 1 diabetes; T2D, type 2 diabetes.

diabetes, separately. In addition, the frequency of hypoglycemic episodes (<70 mg/dL) during the 1 month before and after switching to IDeg or Gla300 was investigated.

Statistical analysis

Continuous variables are presented as medians and interquartile ranges, and are compared using the Mann–Whitney U-test. Categorical data are expressed as proportions, and are compared using the χ^2-test.

The Wilcoxon signed-rank test was used to compare HbA1c, BMI, and basal or total insulin doses before and 6 months after switching from other basal insulins. Analysis of covariance (ANCOVA) was used to calculate least square mean changes in HbA1c, BMI, and basal or total insulin doses between IDeg and Gla300 groups, after adjustment for the following covariates: age, sex, HbA1c, BMI, index date, type of basal insulin at baseline, number of basal insulin injections at baseline and basal or total insulin doses at baseline, and the use of antidiabetic medications other than insulin for patients with type 2 diabetes. Index date was dichotomized at the median date. Multivariable logistic regression analyses were carried out to calculate odds ratios (ORs) and their 95% confidence intervals (95% CIs) for the effect on the secondary end-points. The aforementioned covariates were also included in the logistic regression model.

Fasting blood glucose data from SMBG records were analyzed to evaluate changes in the rate of hypoglycemic episodes between before and after switching by paired t-test.

All statistical analyses were carried out using R (version 3.6.2; R Foundation for Statistical Computing, Vienna, Austria). The P-values were based on two-sided tests, and the cut-off point for statistical significance was set at 0.05.

Sensitivity analysis

Although Gla300 has been commercially available since September 2015 in Japan, there might be a limit to the number of insulin prescriptions in the first year. Hence, physicians might have been more likely to prescribe IDeg during that period. We, therefore, carried out sensitivity analyses restricting to 196 patients with type 1 diabetes and 193 patients with type 2 diabetes who changed basal insulins between September 2016 and February 2019.

Ethical considerations

The study was approved by the Ethics Review Committee of Tokyo Women's Medical University (Approval no. 5496-R, date: 25 February 2020). All clinical investigations were carried out in accordance with the tenets of the Declaration of Helsinki.

RESULTS

Baseline characteristics of study patients

A total of 307 patients with type 1 diabetes and 294 patients with type 2 diabetes met the aforementioned eligibility criteria for the present study. In patients with type 1 diabetes, the Gla300 group had a later index date, higher proportion of Gla100, lower proportion of IDet and lower proportion of twice daily injection of basal insulin than those of IDeg group (Table 1). In patients with type 2 diabetes, the Gla300 group had a later index date, shorter duration of diabetes, higher proportion of Gla100, lower proportion of IDet, and higher proportion of glucagon-like peptide-1 receptor agonists and sodium–glucose cotransporter 2 inhibitors use than the IDeg group (Table 1). Eight patients with type 1 diabetes had taken metformin, despite it not being approved under Japanese health insurance; however, we confirmed the cases as type 1 diabetes with positive islet-related autoantibodies results. The mean starting dose of the IDeg group was reduced by 10.5%, and that of the Gla300 group was reduced by 5.5% when compared with the previous basal insulin dose in patients with type 1 diabetes ($P = 0.018$). The mean starting dose of IDeg and Gla300 was reduced by 2–3% for patients with type 2 diabetes with basal–bolus insulin regimen when compared with those under the previous basal insulin dose. Conversely, the mean starting dose of the IDeg group was increased by 5.8% and that of the Gla300 group was increased by 2.8% in patients with type 2 diabetes with basal insulin with or without non-insulin glucose lowering agents when compared with those under the previous insulin dose.

Changes in outcomes at 6 months after switching from other basal insulins

For patients with type 1 diabetes, changes to IDeg were associated with significantly decreased HbA1c levels, increased BMI, and decreased basal and total insulin doses. For patients with type 2 diabetes, changes to IDeg were also associated with significantly decreased HbA1c and increased BMI, but basal and total insulin doses remained unchanged (Table 2). In both type 1 diabetes and type 2 diabetes patients after switching to Gla300, significantly decreased HbA1c levels were observed and BMI remained unchanged. In patients with type 2 diabetes, switching to Gla300 was associated with significantly increased basal and total insulin doses (Table 2). Table 2 also shows the adjusted mean changes of HbA1c and BMI were similar between the IDeg and Gla300 group among both type 1 diabetes and type 2 diabetes patients. The mean reductions of HbA1c were 0.28% and 0.55% in patients with type 1 diabetes and type 2 diabetes, respectively. In type 2 diabetes patients, the mean BMI increase was significantly larger in the IDeg group than the Gla300 group. In type 1 diabetes patients, the mean basal or total insulin dose reduction was significantly larger in the IDeg group than the Gla300 group after adjusting for age, sex, HbA1c at baseline, BMI at baseline, index date, type of basal insulin at baseline, number of basal insulin injections at baseline and basal or total insulin dose at baseline. Similar findings were shown in type 2 diabetes patients after additional adjustment for the use of non-insulin glucose-lowering agents at baseline. Detailed analyses for six patterns of

Table 1 | Baseline characteristics

	Type 1 diabetes			Type 2 diabetes		
	Degludec	Glargine 300 U/mL	*P*-value	Degludec	Glargine 300 U/mL	*P*-value
n	195	112		171	123	
Index date, year/month (IQR)	2016/10 (2016/1–2018/1)	2017/10 (2016/12–2018/10)	<0.001	2016/10 (2016/1–2017/6)	2017/6 (2016/10–2018/10)	<0.001
Age, years (IQR)	47 (39–59)	47 (38–60)	0.818	65 (56–72)	64 (55–72)	0.863
Sex, men (%)	30.8	32.1	0.903	58.5	56.1	0.773
Bodyweight, kg (IQR)	60.0 (53.7–68.0)	63.4 (56.0–70.2)	0.107	66.6 (57.1–76.9)	68.8 (60.8–80.0)	0.175
BMI, kg/m^2 (IQR)	23.4 (21.2–26.4)	23.5 (21.7–27.0)	0.362	25.4 (22.2–29.2)	26.1 (23.7–28.6)	0.114
Duration of diabetes, years (IQR)	20.5 (13.3–28.6)	21.9 (12.4–29.7)	0.928	22.4 (14.8–29.5)	17.2 (12.1–26.0)	0.014
HbA1c, % (IQR)	8.2 (7.7–9.0)	8.2 (7.8–8.9)	0.818	8.6 (7.9–9.6)	8.4 (7.7–9.2)	0.114
Previous basal insulin, *n* (%)						
NPH	14 (7.2)	6 (5.4)	0.041	11 (6.4)	4 (3.3)	0.037
Gla100	133 (68.2)	84 (75.0)		113 (66.1)	92 (74.8)	
IDet	48 (24.6)	22 (19.6)		47 (27.5)	27 (21.9)	
Previous prandial insulin, *n* (%)						
None	0 (0.0)	0 (0.0)	0.547	43 (25.1)	40 (32.5)	0.078
Regular	30 (15.4)	19 (17.0)		22 (12.9)	7 (6.7)	
Rapid-acting analogs	165 (84.6)	93 (83.0)		106 (62.0)	76 (61.8)	
Twice daily injection of basal insulin, *n* (%)	62 (31.8)	20 (17.5)	0.012	16 (9.3)	7 (5.7)	0.350
Basal insulin doses				0.22 (0.16–0.29)	0.23 (0.17–0.34)	0.144
Basal ± non-insulin glucose lowering agents, *n* (%)	0	0		43 (25.1)	40 (32.5)	
Previous dose, units/kg (IQR)	–	–		0.20 (0.14–0.26)	0.19 (0.15–0.27)	0.895
Starting dose, units/kg (IQR)	–	–		0.20 (0.15–0.26)	0.20 (0.16–0.27)	0.974
Basal–bolas, *n* (%)	195 (100)	112 (100)		128 (74.9)	83 (67.5)	
Previous dose, units/kg (IQR)	0.24 (0.18–0.34)	0.25 (0.19–0.34)	0.493	0.22 (0.17–0.30)	0.25 (0.17–0.36)	0.144
Starting dose, units/kg (IQR)	0.22 (0.16–0.29)	0.23 (0.18–0.32)	0.018	0.21 (0.16–0.28)	0.25 (0.17–0.32)	0.005
Total insulin doses, units/kg (IQR)	0.70 (0.58–0.86)	0.73 (0.54–0.95)	0.617	0.53 (0.31–0.71)	0.51 (0.29–0.74)	0.679
Non-insulin glucose lowering agents, *n* (%)						
Metformin	2 (0.1)	6 (0.5)	0.055	51 (29.8)	48 (39.0)	0.128
Sulfonylurea	0 (0.0)	0 (0.0)		37 (21.6)	22 (17.9)	0.519
DPP-4 inhibitors	0 (0.0)	0 (0.0)		70 (40.9)	49 (39.8)	0.945
Thiazolidinediones	0 (0.0)	0 (0.0)		11 (6.4)	15 (12.2)	0.132
GLP-1 RAs	0 (0.0)	0 (0.0)		7 (4.1)	15 (12.2)	0.017
α-Gls	3 (0.2)	8 (0.7)	0.062	17 (9.9)	18 (14.7)	0.285
Glinides	0 (0.0)	0 (0.0)		2 (1.1)	6 (4.8)	0.118
SGLT-2 inhibitors	0 (0.0)	1 (0.1)	0.779	3 (1.8)	20 (16.2)	<0.001
Retinopathy, *n* (%)						
None	129 (66.2)	65 (58.0)	0.223	70 (40.9)	56 (45.5)	0.798
Simple	49 (25.1)	29 (25.9)		63 (36.9)	45 (36.6)	
Proliferative	17 (8.7)	18 (16.1)		38 (22.2)	22 (17.9)	
Nephropathy, *n* (%)						
None	174 (89.2)	96 (85.7)	0.786	113 (66.1)	90 (73.2)	0.463
Microalbuminuria	18 (9.2)	14 (12.5)		37 (21.6)	24 (19.5)	
Macroalbuminuria	3 (1.6)	2 (1.8)		21 (12.3)	9 (7.3)	
Mean FBG according to SMBG data						
Basal ± non-insulin glucose lowering agents, *n* (%)	0 (0.0)	0 (0.0)		24 (55.8)	26 (65.0)	
Mean FBG (mg/dL)	–	–		170 (136–202)	152 (120–195)	0.515
Basal-bolas, *n* (%)	118 (60.5)	110 (64.3)		76 (59.3)	47 (56.6)	
Mean FBG (mg/dL)	144 (128–170)	151 (125–191)	0.205	156 (124–186)	145 (125–173)	0.449

Data are presented as the median (interquartile range [IQR]). Mean fasting blood glucose (FBG) according to self-monitoring of blood glucose (SMBG) data show the mean of FBG during the previous 1 month from SMBG data. α-Gls, α-glucosidase inhibitors; BMI, body mass index; DPP-4, dipeptidyl peptidase 4; Gla100, glargine 100 U/mL; GLP-1 RAs, glucagon-like peptide 1 receptor agonists; IDet, Insulin detemir; NPH, neutral protamine Hagedorn; SGLT2, sodium–glucose cotransporter 2.

Table 2 | Comparison of outcomes before and after switching to insulin degludec and insulin glargine 300 U/mL and adjusted mean changes in outcomes at 6 months

	Degludec		Glargine 300 U/mL		Degludec vs glargine 300 U/mL
	Before	After	Before	After	Adjusted mean changes
Type 1 diabetes[§]					
HbA1c (%)	8.4 ± 1.0	8.2 ± 1.1[†]	8.4 ± 1.0	8.2 ± 0.9[†]	−0.28 (0.11) vs −0.29 (0.08)
BMI (kg/m^2)	23.8 ± 3.7	24.0 ± 3.7[††]	24.5 ± 4.5	24.6 ± 4.5	0.11 (0.08) vs 0.11 (0.11)
Basal insulin doses (units/kg)	0.27 ± 0.13	0.24 ± 0.11[††]	0.27 ± 0.11	0.27 ± 0.11	−0.04 (0.01)[‡‡] vs −0.02 (0.01)
Total insulin doses (units/kg)	0.74 ± 0.24	0.71 ± 0.23[††]	0.77 ± 0.32	0.78 ± 0.31	−0.05 (0.01)[‡‡] vs −0.02 (0.02)
Type 2 diabetes[¶]					
HbA1c (%)	8.8 ± 1.3	8.6 ± 1.4[††]	8.7 ± 1.2	8.4 ± 1.3[†]	−0.62 (0.17) vs −0.50 (0.17)
BMI (kg/m^2)	26.0 ± 4.7	26.1 ± 4.6[††]	26.7 ± 4.2	26.5 ± 4.3	0.15 (0.15)[‡‡] vs −0.09 (0.15)
Basal insulin doses (units/kg)	0.24 ± 0.11	0.23 ± 0.10	0.25 ± 0.12	0.26 ± 0.12[††]	−0.01 (0.01)[‡] vs 0.00 (0.01)
Total insulin doses (units/kg)	0.54 ± 0.30	0.53 ± 0.30	0.54 ± 0.33	0.56 ± 0.34[††]	−0.02 (0.02)[‡] vs 0.00 (0.02)

Data of outcomes are presented as the mean ± standard deviation. Data of adjusted mean changes in outcomes are presented as the adjusted mean change (standard error). [††]$P < 0.001$, [†]$P < 0.05$: outcomes of after switching versus those of before switching. [‡‡]$P < 0.01$, [‡]$P < 0.05$: adjusted mean changes in outcomes in the degludec group versus glargine 300 U/mL group. [§]Adjusted for age, sex, glycated hemoglobin (HbA1c) at baseline, body mass index (BMI) at baseline, index date, type of basal insulin at baseline, number of basal insulin injection at baseline, basal insulin dose at baseline and total insulin dose at baseline in type 1 diabetes patients. [¶]Adjusted for age, sex, HbA1c at baseline, BMI at baseline, index date, type of basal insulin at baseline, number of basal insulin injection at baseline, basal insulin dose at baseline, total insulin dose at baseline and use of metformin, sulfonylurea, dipeptidyl peptidase-4, thiazolidinediones, glucagon-like peptide-1 receptor agonists, α-glucosidase inhibitors, glinides and sodium–glucose cotransporter 2 inhibitors in type 2 diabetes patients.

switching (from NPH, Gla100, or IDet to IDeg or Gla300) are shown in Table S1. The adjusted mean changes of HbA1c were similar between patterns of switching in patients with type 1 diabetes and type 2 diabetes, except in the switching NPH to Gla300 group, which showed a larger reduction than in the switching Gla100 to IDeg group, in patients with type 1 diabetes. The adjusted mean BMI changes showed larger BMI gain in the switching IDet to IDeg or Gla300 group than in the switching Gla100 to Gla300 group, in patients with type 2 diabetes. In analyses of the adjusted mean changes of basal and total insulin doses, the switching IDet to IDeg group showed larger reductions in basal and total insulin doses than the switching Gla100 to Gla300 group in patients with type 1 diabetes and type 2 diabetes.

The association of selection of Gla300 and IDeg for HbA1c reduction, BMI gain and insulin dose reduction

Multivariable logistic regression models showed that the selection of either IDeg or Gla300 was not associated with HbA1c reduction or BMI gain among the patients with type 1 diabetes and type 2 diabetes (Table 3). However, the selection of IDeg was significantly associated with the greater reduction of basal insulin doses, with an adjusted OR of 2.31 (95% CI 1.21–4.41) and 2.44 (95% CI 1.29–4.62) in patients with type 1 diabetes and type 2 diabetes, respectively. Similarly, the selection of IDeg, not Gla300, was significantly associated with the reduction of total insulin doses, with an adjusted OR of 2.65 (95% CI 1.64–4.28) and 3.44 (95% CI 1.80–6.58) in patients with type 1 diabetes and type 2 diabetes, respectively. Furthermore,

not once daily, but twice daily insulin injections at baseline showed a significant association with the total insulin dose reduction in type 2 diabetes patients, with an adjusted OR of 2.98 (95% CI 1.06–8.39).

Hypoglycemia

Patients were asked the frequency of symptomatic hypoglycemic episodes at every visit before and after switching. Eight (4.1%) and four (3.6%) patients with type 1 diabetes, and one (0.6%) and two (1.6%) patients with type 2 diabetes in the IDeg and Gla300 groups, respectively, confirmed more frequent symptomatic hypoglycemic episodes after than before switching. There were no significant differences in change of frequency of symptomatic hypoglycemia pre- and post- switching between the IDeg and Gla300 groups. Among the patients with fasting blood glucose data available from SMBG records, the rates of frequency of hypoglycemic episodes (<70 mg/dL) are shown in Table 4. In patients in both groups with type 1 diabetes and type 2 diabetes, the rates of hypoglycemic episodes were significantly reduced after switching.

Sensitivity analysis

Sensitivity analysis was carried out on 99 new users of IDeg and 97 new users of Gla300 for type 1 diabetes, and 92 IDeg new users and 101 Gla300 new users for type 2 diabetes. The adjusted mean reduction in HbA1c between IDeg and Gla300 users was similar to the main results (−0.36 vs −0.39%, $P = 0.28$ in type 1 diabetes patients, −0.55 vs −0.41%, $P = 0.35$ in type 2 diabetes patients, respectively). The adjusted mean

Table 3 | Association between choice of not insulin glargine 300 U/mL, but insulin degludec, and glycated hemoglobin reduction, body mass index gain, and basal and total insulin dose reduction

	Type 1 diabetes Multivariable ORs (95% CI)[†]	Type 2 diabetes Multivariable ORs (95% CI)[‡]
HbA1c reduction		
Type of new basal insulin (IDeg vs Gla300)	0.89 (0.56–1.42)	1.61 (0.86–3.02)
No. basal insulin injections at baseline (twice vs once)	0.84 (0.47–1.50)	2.71 (0.97–7.58)
BMI gain		
Type of insulin (IDeg vs Gla300)	1.44 (0.79–2.63)	1.32 (0.71–2.45)
No. basal insulin injections at baseline (twice vs once)	1.27 (0.72–2.22)	0.70 (0.27–1.80)
Basal insulin dose reduction		
Type of insulin (IDeg vs Gla300)	2.31 (1.21–4.41)	2.44 (1.29–4.62)
No. basal insulin injections at baseline (twice vs once)	1.59 (0.82–3.08)	1.28 (0.48–3.42)
Total insulin dose reduction		
Type of insulin (IDeg vs Gla300)	2.65 (1.64–4.28)	3.44 (1.80–6.58)
No. basal insulin injections at baseline (twice vs once)	1.73 (0.94–3.17)	2.98 (1.06–8.39)

BMI, body mass index; CI, confidence interval; Gla300, glargine 300 U/mL; IDeg, insulin degludec; OR, odds ratio. [†]Adjusted for age, sex, glycated hemoglobin (HbA1c) at baseline, body mass index (BMI) at baseline, index date, type of basal insulin at baseline, number of basal insulin injection at baseline, basal insulin dose at baseline and total insulin dose at baseline in type 1 diabetes patients. [‡]Adjusted for age, sex, HbA1c at baseline, BMI at baseline, index date, type of basal insulin at baseline, number of basal insulin injection at baseline, basal insulin dose at baseline, total insulin dose at baseline and use of metformin, sulfonylurea, dipeptidyl peptidase-4, thiazolidinediones, glucagon-like peptide-1 receptor agonists, α-glucosidase inhibitors, glinides and sodium–glucose cotransporter 2 inhibitors in type 2 diabetes.

Table 4 | Change of frequency of hypoglycemic episodes

	Type 1 diabetes		Type 2 diabetes	
	Degludec	Glargine 300 U/mL	Degludec	Glargine 300 U/mL
n	118	110	100	73
Baseline (−1 to 0 month)				
Episodes	267	179	42	35
Rate	2.63	1.77	0.43	0.57
After 6 months (6–7 months)				
Episodes	151	91	21	5
Rate	1.42*	1.07*	0.22*	0.08*

Rate, the rate of hypoglycemic episodes per patient-month of exposure. $*P < 0.05$ vs baseline.

changes in BMI of IDeg and Gla300 users were similar in both type 1 diabetes and type 2 diabetes patients. The adjusted mean changes in basal or total insulin doses of IDeg and Gla300 users were −0.04 versus −0.02 units/kg ($P < 0.001$) and −0.05 versus −0.02 units/kg ($P = 0.04$) in type 1 diabetes patients, and −0.02 versus 0.00 units/kg ($P = 0.03$) and −0.05 versus −0.01 units/kg ($P = 0.03$) in type 2 diabetes patients, respectively. Multivariable logistic regression models showed that the selection of either IDeg or Gla300 was not associated with HbA1c reduction or BMI gain among the patients with type 1 diabetes and type 2 diabetes. The selection of IDeg was significantly associated with the greater reduction of basal insulin doses, with an adjusted OR of 2.48 (95% CI 1.30–4.76) and 2.43 (95% CI 1.00–5.88) in patients with type 1 diabetes and type 2 diabetes, respectively. The selection of IDeg, not Gla300, was significantly associated with the reduction of total insulin doses,

with an adjusted OR of 3.34 (95% CI 1.74–6.43) and 2.77 (95% CI 1.39–5.52) in patients with type 1 diabetes and type 2 diabetes, respectively. These findings were consistent with the main results.

DISCUSSION
The present study showed that in both type 1 diabetes and type 2 diabetes patients, 6-month change in HbA1c and BMI values were similar between the IDeg group whose basal insulins were switched to IDeg and the Gla300 group whose basal insulins were switched to Gla300. Both these second ultra-long-acting insulins of IDeg and Gla300 significantly reduced the HbA1c, with BMI almost unchanged after switching. Switching to IDeg was significantly associated with a reduction of basal and total insulin doses in patients with type 1 diabetes and type 2 diabetes. To our knowledge, this is the first study to

compare the efficacy of IDeg and Gla300 after switching from other basal insulin in Japanese patients with type 1 diabetes.

A previous study showed the comparison of the efficacy between IDeg and Gla300 switching from Gla100 or IDet in real-world settings among patients with type 2 diabetes[11]. Switching from Gla100 or IDet to IDeg or Gla300 was associated with a reduction of HbA1c to the same extent, which was consistent with the present findings.

Another study with type 2 diabetes insulin-naïve adults[15] reported that the initiation of IDeg or Gla300 resulted in comparable improvements in glycemic control. The BRIGHT trial[12], the first head-to-head randomized controlled trial to investigate the efficacy of IDeg and Gla300 in insulin-naïve patients with type 2 diabetes also showed similar improvement in glycemic control. These studies did not include Japanese patients. In a small, randomized, cross-over study of Japanese patients with type 2 diabetes using continuous glucose monitoring profiles, there was no difference in the mean percentage of time within the target glucose range of 70–180 mg/dL between the IDeg and Gla300 groups. However, IDeg treatment has shown higher 24-h coefficients of variation of glucose and means of daily difference of glucose than Gla300 treatment[16]. These findings might suggest that the efficacy of glycemic control of IDeg and Gla300 are similar.

In the current study, the mean reductions of HbA1c in Japanese patients with type 1 diabetes and type 2 diabetes were approximately 0.3% and 0.5–0.6%, respectively. Our results were consistent with the findings of several previous, retrospective, observational studies that investigated the effects of IDeg or Gla300 switching from other basal insulins. In the EUropean TREsiba AudiT (EU-TREAT) study[10], a real-world study that evaluated the clinical effectiveness of switching from other basal insulins (Gla100, IDet and NPH) to IDeg reported a reduction of 0.2% and 0.5% in HbA1c at 6 months from baseline in patients with type 1 diabetes and type 2 diabetes, respectively. Additionally, the Differentiate Gla-300 clinical and Economic in real-world Via EMR (DELIVER) D+ cohort study[11] reported HbA1c reduction of 0.58% and 0.63% at 6 months after switching to IDeg or Gla300 from IDet or Gla100, respectively, in patients with type 2 diabetes. The mean HbA1c at baseline of these studies and the present study were similar (8.5–9.0% and 8.7–8.8%, respectively), and it might lead to similar results.

Another retrospective study[17], similar to the present study, investigated the effects of IDeg and Gla300 after switching from NPH, IDet and Gla100 in patients with type 1 diabetes, and showed a smaller reduction of HbA1c (−0.14% and −0.20%, respectively) than that of our study. This discrepancy might be due to the lower mean HbA1c (7.9%) and larger percentage of Gla100 (95%) at baseline in the study than those of the present study. A review of Japanese real-world clinical effectiveness of switching from their current insulin regimen to IDeg showed a smaller reduction of mean change in HbA1c (−0.3%) than that of the present study, which could be due to including unspecific types of diabetes[18].

In the current study, although there was no association between BMI gain and selection of second-generation insulin analogs, BMI slightly increased in the IDeg group among both type 1 diabetes and type 2 diabetes patients. A prospective, observational study in Japan showed that BMI in type 1 diabetes patients increased after switching to IDeg from Gla100 or IDet, whereas BMI in type 2 diabetes patients did not change[19]. Another study[20] reported that the bodyweight of the IDeg group with type 2 diabetes did not change after switching from other insulin therapy. The changes in post-switch BMI in the current study were <1% in both type 1 diabetes and type 2 diabetes patients, indicating the absence of adverse clinical effects.

The basal or total insulin dose decreased in the IDeg group with type 1 diabetes, and increased in the Gla300 group with type 2 diabetes. Furthermore, basal or total insulin dose reduction was positively associated with IDeg selection. Previous studies that investigated the clinical effect of switching to IDeg from other basal insulin have yielded controversial results. Several studies[10,21] reported a 12–13% mean reduction of basal or total insulin dose in type 1 diabetes patients, and 3% mean reduction in type 2 diabetes patients after switching compared with baseline, whereas another study[19] reported 2 U of basal insulin dose gain after switching, although the study included patients without basal insulin before starting IDeg.

The present results showed that the mean change of basal or total insulin before and after switching to IDeg was −14.8% and −6.8% in type 1 diabetes patients, and −4.2% and −3.7% in type 2 diabetes patients, respectively. A report from Japan[19] showed smaller changes in insulin dose than the present study, which might be due to the smaller dose usage in that study than in the present study. A report[21], which studied the clinical outcomes of switching to Gla300 from Gla100 in type 1 diabetes patients, showed that the dose of basal insulin post-switch tended to increase, although the change was insignificant. The EDITION phase 3 trial[22] reported that Gla300 required a higher dose of basal insulin than Gla100 in type 1 diabetes patients. The present results showed that the mean change of basal or total insulin before and after switching to Gla300 were −7.4% and −2.6% in type 1 diabetes, 1.6% and 0.7% in type 2 diabetes, respectively. Although switching to IDeg might be more effective for insulin reduction than that of switching to Gla300, the mean change differences of basal or total insulin dose after switching to Gla300 compared with IDeg were approximately 1–2 U, and the clinical significance seemed to be weak.

Several limitations should be noted. First, our study design was retrospective and observational, limiting the ability to determine causality. Second, there might be a bias in the selection of IDeg or Gla300. When diabetologists and patients changed the basal insulin, they might have had the intention of choosing the same setting; that is, patients using IDet were switched to IDeg and patients using Gla100 were switched to Gla300, which allowed the use of the same type of insulin device from the same pharmaceutical company. Third, differences in index

date because of commercial time lag might have caused the difference in glucagon-like peptide-1 receptor agonists and sodium–glucose cotransporter 2 inhibitors use between IDeg and Gla300 among patients with type 2 diabetes. Fourth, the observational period of the study might not be long enough. Fifth, we were unable to collect sufficient and precise data on the frequency of hypoglycemia in all patients, although IDeg and Gla300 have the beneficial effect to reduce hypoglycemia[6,8–11,15–19,21,23]. However, few patients reported having more symptomatic hypoglycemic episodes than before at every visit. Additionally, although only among a limited number of patients, fasting blood glucose data from SMBG data showed fewer hypoglycemic episodes after switching than before switching, which might indicate that the reduction of HbA1c in the present study was caused by the favorable effects of IDeg and Gla300, and not frequent hypoglycemia. Despite these limitations, this was the first study to clarify the efficacy of IDeg and Gla300 after switching from other basal insulins among more than 100 Japanese patients with type 1 diabetes and type 2 diabetes at a real clinical setting.

In conclusion, the present retrospective, observational study showed that IDeg and Gla300 have a similar effect on HbA1c and BMI after switching from other basal insulins in Japanese patients with type 1 diabetes and type 2 diabetes. The selection of IDeg was associated with insulin dose reduction.

DISCLOSURE
The authors declare no conflict of interest.

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SUPPORTING INFORMATION

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

Table S1 | Comparison of adjusted mean changes in each outcome at 6 months between before and after switching to insulin degludec and insulin glargine 300 U/mL from other basal insulins.