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ORIGINAL RESEARCH

Safety and Clinical Outcomes of Insulin Degludec in Korean Patients with Diabetes in Real-World Practices: A Prospective, Observational Study

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ABSTRACT

Introduction: To investigate the safety and effectiveness of insulin degludec (IDeg) in a real-world population of Korean patients with diabetes requiring insulin therapy.
Methods: This was a multicenter, prospective, single-arm, open-label, non-interventional study. Patients aged ≥ 12 months and treated with previous glucose-lowering medications were eligible to switch to IDeg. The primary endpoint was the incidence of adverse events (AEs), and the secondary endpoints were changes in glycated hemoglobin (HbA1c), fasting plasma glucose (FPG), postprandial glucose (PPG), and target HbA1c < 7.0%.
Results: In total, 3225 and 2450 patients were included in the safety analysis set (SAS) and effectiveness analysis set (EAS), respectively. The mean baseline HbA1c and duration of diabetes were 9.4% and 13.0 years, respectively. Adverse events were reported in 740 patients (22.9%); the majority were mild and resolved. Significant improvements were observed in HbA1c, FPG, and PPG at week 26 (all

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$p < 0.0001$). The target of HbA1c < 7% was achieved in 22.2% of patients at week 26.
Conclusion: In real-world clinical practice, 26 weeks of IDeg treatment resulted in significant reductions in glycemic parameters with a low incidence of AEs in Korean patients with diabetes. No new safety signals were observed.
Clinical Trials Registry and Registration Number: This trial is registered under ClinicalTrials.gov (NCT02779413) and the universal trial number is [U1111-1176-2287].

Keywords: Basal insulin; Diabetes; Glycemic control; Insulin treatment; Real-world practice

Key Summary Points

Why carry out the study?

The prevalence of diabetes is increasing in Korea, but there are limited data on the effectiveness and safety of insulin degludec in real-world practice.

This multicenter, prospective, open-label, non-interventional study investigated the safety and effectiveness of IDeg in patients with diabetes requiring insulin therapy in the Asian population.

What was learned from the study?

The study results confirmed the randomized clinical study in the real world with a low incidence of AEs and significant reductions in glycemic parameters of FPG, PPG, and HbA1c at week 26.

In real-world clinical practice, treatment with IDeg improved glycemic control with a low rate of hypoglycemia, supporting the use of IDeg for diabetic patients requiring insulin therapy.

INTRODUCTION

Type 2 diabetes (T2D) is a progressive disease, and many people with T2D will eventually require insulin therapy to maintain adequate glycemic control [1]. As well-controlled blood glucose prevents micro-macrovascular complications, restores quality of life, and reduces comorbidities, [2, 3], the comprehensive approach is central to the optimal management of T2D to control blood glucose levels as well as hypertension and dyslipidemia [4]. It is well known that insulin is the most effective therapy to lower hyperglycemia [5], and the safety profiles of basal, bolus, and premixed insulin are also well investigated [6–9]. However, there is clinical inertia regarding initiating and intensifying insulin therapy because of a fear of injections, complexities of regimens, and other personal factors [10, 11]. This delayed insulin initiation can increase the glycemic burden and risk of long-term complications [12].

Insulin degludec (IDeg) (Tresiba®FlexTouch®, Novo Nordisk A/S) is ultra-long-acting basal insulin indicated for the treatment of type 1 diabetes (T1D) and T2D. IDeg has a well-established efficacy and safety profile. Several randomized controlled trials (RCTs) and meta-analyses have demonstrated the clinical benefits of IDeg in reducing glycated hemoglobin (HbA1c), fasting plasma glucose (FPG), and postprandial glucose (PPG) with a favorable safety profile including lower hypoglycemia [13–18]. Randomized controlled trials are the gold standard to evaluate the efficacy and safety of drugs for a specific patient population [19]. However, there is a growing need for real-world data to provide the necessary evidence for a broad range of patients in routine clinical practice. The real-world data of IDeg from the larger patient population, specifically for Asian patients, are limited [20].

The present study aimed to evaluate the safety and effectiveness of IDeg in real-world clinical practice in Korea. This study also provided clinical factors associated with better responses to IDeg treatment in patients with diabetes who were previously treated with various glucose-lowering medications.

METHODS

Study Design

This was a multicenter, prospective, single-arm, open-label, non-interventional study conducted between March 2014 and March 2020 across 58 sites in Korea. The actual treatment with IDeg (index date) occurred between June 2016 and March 2020. This study was conducted according to the Declaration of Helsinki [21] and the Guidelines for Good Pharmacoepidemiology Practices (2016) [22]. The protocol, any amendments, patient information/informed consent form, and any other written information provided to the patients were reviewed and approved by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) of each site. Before participation in this study, all patients provided written informed consent. Data were collected at 0 weeks (baseline), 13 weeks, and 26 weeks after IDeg initiation. Since the baseline visit, a time window of 2 weeks was given for data collection in each visit, and the data collection reflected routine clinical practices.

Study Population

Patients who were first injected with IDeg and who met the eligibility criteria were enrolled. Patients were eligible for inclusion in this study if they were aged $\geq$ 12 months and had a clinical diagnosis of T1D or T2D. The decision to switch the regimen to IDeg was at the discretion of the treating physician and independent from the study. Likewise, other glucose-lowering medications could be adjusted by physicians under routine clinical practice. Patients were excluded from the study if they had previously been treated with IDeg. Those who were pregnant, breastfeeding, or of child-bearing potential and not using adequate contraceptive methods were also excluded. Inclusion/exclusion criteria were aligned with the Korean Prescribing Information under routine clinical practice.

Study Endpoints

The primary endpoint in this study was safety, which was measured by the incidence rate (IR) of all adverse events (AEs) at weeks 13 and 26. The secondary safety endpoints such as serious AE (SAE), hypoglycemic episode (severe [an episode requiring another person's assistance] or blood glucose confirmed [< 56 mg/dl]), weight gain, and insulin dose were also measured at weeks 13 and 26. The other secondary effectiveness endpoints which were measured at weeks 13 and 26 included the change from baseline in HbA1c, FPG, and PPG and the percentage of patients achieving the target of HbA1c < 7.0% or < 7.5%. The laboratory tests for FPG and PPG were conducted at hospital visits under routine clinical practice. The time interval of PPG after a meal was assessed according to the laboratory protocol of each hospital. A subgroup analysis was performed on various clinical factors associated with HbA1c < 7.0%, and incidence of AEs. In the safety analysis, factors such as age (< 65 years vs. $\geq$ 65 years), duration of diabetes (< 5 years, 5 to < 10 years, 10 to < 20 years, and $\geq$ 20 years), a daily dose of IDeg (< 10 units, 10 to < 20 units, 20 to < 30 units, and $\geq$ 30 units), and previous insulin experiences (insulin naive vs. insulin experienced) were assessed to evaluate the effects on the incidence of adverse events. Previous insulin treatment was defined as any insulin regimen within 4 weeks before the treatment of IDeg (first visit). In the effectiveness analysis, factors such as age (< 65 years vs. $\geq$ 65 years), sex (male vs. female), duration of diabetes (< 5 years vs. 5 to < 10 years vs. $\geq$ 10 years), macro-/microvascular complications (yes or no), previous insulin experiences (insulin naive vs. insulin experienced), and a daily dose of study medication (< 20 units vs. $\geq$ 20 units) were assessed for the target achievement at week 26. Diabetes complications were assessed by the information from patients' medical history in electronic medical records and consultations with patients in routine clinical practice. The glycemic targets were to be individualized based on patient and disease features. Furthermore, in this study, the achievement of the HbA1c target of 7.0% was

assessed to observe the glycemic control of IDeg according to the American Diabetes Association guidelines [23].

Statistical Analysis

Both patients with T1D and T2D were included in the safety analysis set (SAS) and the effectiveness analysis set (EAS). All patients that were treated with IDeg at least once and completed safety follow-ups were included in the SAS analysis. Among them, patients whose glucose controls were assessable on the second visit (treated with IDeg for at least 11 weeks) were included in the EAS analysis. Continuous variables were summarized with descriptive statistics (mean, SD, min, max, Q1, median, and Q3). For categorical variables, the number and percentage were calculated. A chi-square test or Fisher's exact test was performed. Paired *t*-test was performed for testing changes in continuous variables and mean change. Univariate and multivariate analyses were performed using logistic regression with all the covariates one at a time. All statistical tests were performed as two-sided and at a 5% significance level and a 95% confidence interval (CI) of AE, incidence rate was calculated by the exact method. Bonferroni adjustment of *p* values was done for multiple testing of incidence of adverse events by a daily dose of IDeg and duration of diabetes. All AEs were categorized by the preferred term (PT) using MedDRA version 22.1. All patients prescribed IDeg under routine clinical practice according to the approved label were termed SAS. Among these, patients who had at least one post-baseline measurement concerning HbA1c, FPG, and PPG values were included in EAS. The statistical assessment was performed by using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Baseline and Demographic Characteristics

Out of 3303 patients enrolled, 3225 (T1D, $n = 211$, T2D, $n = 3014$) and 2450 (T1D, $n = 164$, T2D, $n = 2286$) patients were included in the SAS and EAS, respectively (Fig. S1). Table 1 shows the baseline characteristics in both sets. On average, patients were 58.5 years old, with a duration of diabetes > 13 years, with suboptimal glycemic control (mean HbA1c, 9.4%, and 9.3% in SAS and EAS, respectively), and mean BMI of 24.7 kg/m^2. About half of the patients were treated only with oral antidiabetic drugs (OADs). The proportion of pediatric patients < 19 years was only 1.2% ($n = 37$), so these did not make meaningful impacts on the study.

Adverse Events of IDeg

Of all the patients for SAS ($n = 3225$), 740 patients (22.9%) experienced AEs; of 1139 AEs reported, 225 cases were serious. For mild, moderate, and severe AEs, there were 909, 194, and 36 events, respectively (Table S1). The most frequently experienced AEs ($n = 183$; 5.7%) and serious adverse events (SAEs) ($n = 31$; 1.0%) were hypoglycemia (Table 2). No dose changes were carried out in IDeg for 946 AEs (83.1%) (Table S2). About 89% of AEs were reported as recovered or recovering during the study period (Table S3). Three cases were fatal (sepsis, toxic shock syndrome, and liver cirrhosis), of which the causal relationships were reported as unlikely with IDeg by the investigators.

Based on the analysis of the incidence of AEs by age, the incidence rate of AEs was 25.2% (302 patients) in the elderly and 21.6% (438 patients) in the remaining patients (< 65 years). This difference in AEs incidence was found to be statistically significant ($p = 0.0198$). The incidence of AEs was 25.7% (315 patients) in those who were pre-treated with insulin treatment and 21.3% (425 patients) in those who were not ($p = 0.0037$). Based on the prespecified analysis, in patients having the duration of disease < 5 years, 5 to < 10 years, 10 to < 20 years, and ≥ 20 years, the incidence of AEs was 16.2% (112 patients), 20.7% (107 patients), 24.2% (260 patients), and 28.9% (214 patients), respectively. The difference in the incidence of AEs regarding the duration of diabetes was found to be statistically significant ($p < 0.0001$). Based on the analysis of the incidence of AEs by the daily

Table 1 Baseline and demographic characteristics

Characteristic	Safety analysis set						Effectiveness analysis set					
	T1D (*n* = 211)		T2D (*n* = 3014)		Total (*n* = 3225)		T1D (*n* = 164)		T2D (*n* = 2286)		Total (*n* = 2450)	
	n		*n*		*n*		*n*		*n*		*n*	
Male, %	105	49.8	1658	55.0	1763	54.7	81	49.4	1267	55.4	1348	55.0
Age (years)	211	36.7 (17.3)	3014	60.0 (13.2)	3225	58.5 (14.7)	164	37.0 (17.3)	2286	60.2 (12.9)	2450	58.7 (14.5)
Age (years)—range, %												
< 20 years	33	15.6	10	0.3	43	1.3	25	15.2	10	0.4	35	1.4
≥ 20 to < 40 years	96	45.5	208	6.9	304	9.4	73	44.5	135	5.9	208	8.5
≥ 40 to < 65 years	66	31.3	1613	53.5	1679	52.1	53	32.3	1250	54.7	1303	53.2
≥ 65 years	16	7.6	1183	39.3	1199	37.2	13	7.9	891	39.0	904	36.9
BMI (kg/m^2)	161	22.3 (3.7)	1758	24.9 (4.0)	1919	24.7 (4.1)	126	22.4 (3.8)	1364	24.9 (4.0)	1490	24.7 (4.1)
SBP (mmHg)	164	120.1 (15.7)	2406	127.0 (15.6)	2570	126.6 (15.7)	130	121.1 (16.0)	1860	127.0 (15.3)	1990	126.6 (15.4)
DBP (mmHg)	164	72.0 (10.9)	2406	74.8 (11.1)	2570	74.6 (11.1)	130	72.5 (10.9)	1860	74.6 (11.0)	1990	74.5 (11.0)
Duration of diabetes (years)	200	9.9 (8.1)	2822	13.3 (9.3)	3022	13.0 (9.3)	157	10.4 (7.9)	2145	13.8 (9.2)	2302	13.6 (9.2)
Diabetic macrovascular complications[a], *n*, %	18	8.5	725	24.1	743	23.0	16	9.8	602	26.3	618	25.2
Diabetic microvascular complications[b], *n*, %	74	35.1	1406	46.7	1480	45.9	57	34.8	1120	49.0	1177	48.0
HbA1c (%)	174	9.1 (2.4)	2221	9.5 (2.0)	2395	9.4 (2.1)	150	8.9 (2.2)	1870	9.3 (2.0)	2020	9.3 (2.0)
FPG (mg/dl)	126	194.6 (95.7)	1952	196.5 (89.1)	2078	196.4 (89.5)	108	185.4 (86.0)	1658	193.0 (86.7)	1766	192.5 (86.7)
PPG (mg/dl)	89	246.4 (115.2)	1264	290.3 (119.1)	1353	287.4 (119.3)	72	241.6 (122.2)	988	283.0 (115.5)	1060	280.2 (116.3)
Previous glucose-lowering medication[c], %	189	89.6	2650	87.9	2839	88.0	146	89.0	2053	89.8	2199	89.8
OAD only[d], %	16	7.6	1547	51.3	1563	48.5	11	6.7	1182	51.7	1193	48.7

Table 1 continued

Characteristic	Safety analysis set						Effectiveness analysis set					
	T1D (n = 211)		T2D (n = 3014)		Total (n = 3225)		T1D (n = 164)		T2D (n = 2286)		Total (n = 2450)	
	n		*n*		*n*		*n*		*n*		*n*	
≥ 1 OAD + insulin[e]	28	13.3	848	28.1	876	27.2	20	12.2	685	30.0	705	28.8
≥ 1 OAD + GLP-1RA	0	0	63	2.1	63	2.0	0	0	53	2.3	53	2.2
Insulin[e] only	145	68.7	207	6.9	352	10.9	115	70.1	148	6.5	263	10.7
GLP-1RA only	0	0	3	0.1	3	0.1	0	0	3	0.1	3	0.1
Insulin[e] + GLP-1RA	0	0	18	0.6	18	0.6	0	0	18	0.8	18	0.7

Data are presented as mean (standard deviation) unless otherwise indicated

BMI body mass index, *DBP* diastolic blood pressure, *FPG* fasting plasma glucose, *GLP-1RA* glucagon-like peptide-1 receptor agonists, *HbA1c* glycated hemoglobin, n, number of patients, *OAD* oral antidiabetic drug, *PPG* postprandial glucose, *SBP* systolic blood pressure, *T1D* type 1 diabetes, *T2D* type 2 diabetes

[a]Diabetic macrovascular complications include peripheral vascular disease, coronary heart disease, and stroke

[b]Diabetic microvascular complications include diabetic retinopathy, diabetic nephropathy, and diabetic neuropathy

[c]The data on previous glucose-lowering medication within 4 weeks of the treatment of IDeg were collected and evaluated

[d]The group of "OAD only" was defined as a patient who has never administered an injectable therapy before and has only administered OADs

[e]Human, basal, bolus, or pre-mixed insulins were administered

Table 2 Incidence of adverse events (≥ 0.5%) and serious adverse events

Adverse events (AEs)	Safety analysis set (*n* = 3225)	Number of events
All adverse events	**740 (23.0)**	**1139**
Hypoglycemia	183 (5.7)	208
Patients with T1D	27 (12.8)	30
Patients with T2D	156 (5.2)	178
Diabetes mellitus inadequate control[a]	47 (1.5)	48
Dizziness	28 (0.9)	28
Nasopharyngitis	28 (0.9)	29
Edema peripheral	25 (0.8)	28
Hypoesthesia	18 (0.6)	18
Asthenia	18 (0.6)	18
Diarrhea	16 (0.5)	16
All serious adverse events (SAEs)	**186 (5.8)**	**225**
Hypoglycemia	31 (1.0)	33
Diabetes mellitus inadequate control	28 (0.9)	29
Cataract	7 (0.2)	8
Asthenia	7 (0.2)	7
Diabetic foot	7 (0.2)	7
Pneumonia	4 (0.1)	4
Cerebral infarction	4 (0.1)	5

Data are presented as numbers (percentage) unless otherwise indicated. MedDRA version 23.1, *n*: number of patients experiencing at least one event. *%*: percentage of patients experiencing at least one event. *events*: number of events. *SAEs*: an adverse event is a serious adverse event if the event results in death, a life-threatening experience, inpatient hospitalization, or prolongation of hospitalization, persistent or significant disability, and a congenital anomaly or birth defects. The table is sorted in descending order by the total percentage of patients experiencing at least one event. Adverse events with preferred terms were reported for at least 0.5% of patients who took treatment

T1D type 1 diabetes, *T2D* type 2 diabetes

[a]This term includes both the Preferred Terms of 'diabetes mellitus inadequate control' and 'hyperglycemia.' The result includes and is mostly driven by 'hyperglycemia' data

dose of IDeg, the differences in daily insulin dose could not be associated with the incidence of AEs. Age and duration of diabetes were significantly associated with the increase in the incidence of AEs contrary to previous insulin experiences which were associated with decreased incidence of AEs (Table S4).

Among a total of 1139 AEs assessed for causality to study drug in SAS, 778 cases were unlikely related to IDeg, and 361 cases were related to IDeg judged by the physicians (data not shown). Data on diabetes types are also shown in Table S5 and Table S6.

Hypoglycemic Events

Hypoglycemic events were reported by 5.7% of patients (183 patients) with 2.7% of patients (86 patients) experienced hypoglycemic episodes defined as being severe or blood glucose-confirmed hypoglycemia (Table S7).

Change in Body Weight

The mean (SD) body weight at baseline was 65.9 (13.4) kg, and the change was + 1.2 (3.4) kg in 963 patients evaluated at week 26 ($p < 0.0001$) (Table S8).

Glycemic Control of IDeg

Mean HbA1c reduced significantly by − 1.0% [95% CI − 1.1; − 0.9] at week 13, and this was maintained at week 26 (− 1.0% [95% CI − 1.1; − 0.9]) ($p < 0.0001$ for both). Mean FPG decreased significantly by − 51.7 mg/dl [95% CI − 56.5; − 47.0] at week 13 and − 47.1 mg/dl [95% CI − 52.1; − 42.1] at week 26 (all $p < 0.0001$). Mean PPG decreased significantly by − 52.6 mg/dl [95% CI − 61.9; − 43.4] at week 13 and − 50.9 mg/dl [95% CI − 61.2; − 40.6] at week 26 compared with baseline (all $p < 0.0001$) (Fig. S2, Table S9). The glycemic controls in patients with T2D are shown in Fig. 1. By status of insulin therapy as previous medications (Table 3), both insulin-naïve and -experienced patients showed significant improvement in glycemic control at week 26 compared with baseline. In insulin-naïve patients, the mean HbA1c, FPG, and PPG were decreased by − 1.4% [95% CI − 1.6; − 1.3], − 60.7 mg/dl [95% CI − 67.4; − 54.0], and − 60.6 mg/dl [95% CI − 73.9; − 47.2] at the week 26, respectively (all $p < 0.0001$). In insulin-experienced patients, the mean HbA1c, FPG, and PPG were decreased by − 0.5% [95% CI − 0.6; − 0.4], − 26.9 mg/dl [95% CI − 34.1; − 19.7], and − 35.2 mg/dl [95% CI − 51.2; − 19.1] at the week 26, respectively (all $p < 0.0001$).

The mean (SD) daily dose of IDeg was 21.3 (11.4) units at baseline. At week 26, the dose increased by 1.1 (5.9) units ($p < 0.0001$). The effectiveness of HbA1c, FPG, and PPG control as the concomitant glucose-lowering medication is shown in Tables S10, S11, and S12, respectively. The mean PPG decreased significantly by − 68.5 mg/dl [95% CI − 91.0; − 46.1; $p < 0.0001$] with IDeg monotherapy. In the analysis by the combined medications with OAD, the mean PPG decrease was only shown in IDeg and DPP-4 inhibitor (− 50.9 mg/dl [95% CI − 67.2; − 34.7], $p < 0.0001$) and IDeg and bolus or premixed insulin therapy (− 49.3 mg/dl [95% CI − 77.6; − 21.0], $p = 0.0008$) at the week 26 (Table S12).

Clinical Factors Which Affect the Target Achievement

The patients who achieved HbA1c < 7.0% were 22.2% (363/1635 patients) and < 7.5% were 34.6% (566/1635 patients) at week 26 (Table S13). In insulin-naïve patients, 23.2% and 34.6% of patients achieved the goal of HbA1c < 7.0% (208/895 patients) and < 7.5% (310/895 patients) at week 26, respectively. In insulin-experienced patients, 21.0% and 34.6% of patients attained HbA1c < 7.0% (155/740 patients) and HbA1c < 7.5% (256/740 patients) at week 26. The proportions of target achievements in T1D and T2D are given in Table S14. Among patients who achieved HbA1c < 7.0%, individuals with a duration of diabetes < 5 years (OR 2.6 [95% CI 1.7; 3.9], $p < 0.0001$) and a low daily dose of IDeg (OR 1.5 [95% CI 1.2; 1.9], $p = 0.0018$) showed statistical significance in glycemic target achievement in multivariate analysis (Fig. 2, Table S15). Data on diabetes types are also shown in Tables S16 and S17.

DISCUSSION

The present study confirmed the safety and effectiveness of IDeg under conditions of routine clinical practices in patients with diabetes in Korea. This large-scale observational study showed that initiating or switching to IDeg in real-world practice was associated with significant reductions in glycemic parameters with a low incidence of adverse events in patients treated with other glucose-lowering treatments.

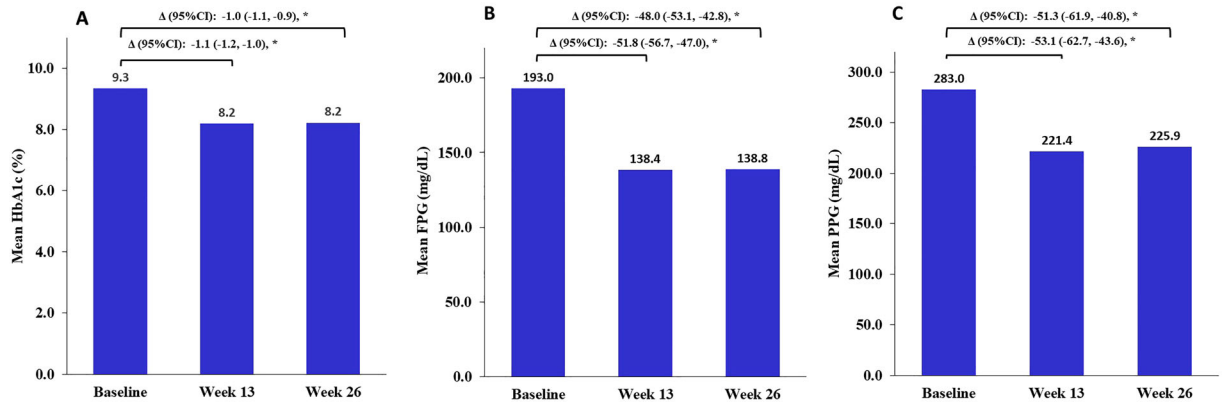

Fig. 1 Change in HbA1c, FPG, and PPG at week 13 and week 26 from baseline in patients with T2D. **A** Change in mean HbA1c (%). **B** Change in mean FPG (mg/dl). **C** Change in mean PPG (mg/dl). *CI* confidence interval, *FPG* fasting plasma glucose, *HbA1c* glycated hemoglobin, *PPG* postprandial glucose, *T2D* type 2 diabetes. Δ: Mean difference; *$p < 0.000$

Table 3 Summary of glycemic control endpoint by prior treatment type

	Total	Prior insulin treatment	
		Insulin-naïve	Insulin-experienced
HbA1c (%)			
Baseline	9.3 (2.0)	9.7 (2.0)	8.8 (1.9)
Week 26	8.2 (1.6)	8.2 (1.6)	8.2 (1.6)
Mean change from baseline to week 26 (95% CI)	− 1.0 (− 1.1; − 0.9)*	− 1.4 (− 1.6; − 1.3)*	− 0.5 (− 0.6; − 0.4)*
FPG (mg/dl)			
Baseline	192.5 (86.7)	203.5 (89.0)	174.4 (79.7)
Week 26	139.4 (58.4)	137.4 (56.3)	142.2 (61.2)
Mean change from baseline to week 26 (95% CI)	− 47.1 (− 52.1; − 42.1)*	− 60.7 (− 67.4; − 54.0)*	− 26.9 (− 34.1; − 19.7)*
PPG (mg/dl)			
Baseline	280.2 (116.3)	298.6 (114.0)	248.1 (113.5)
Week 26	223.4 (92.3)	230.5 (86.7)	211.5 (100.0)
Mean change from baseline to week 26 (95% CI)	− 50.9 (− 61.2; − 40.6)*	− 60.6 (− 73.9; − 47.2)*	− 35.2 (− 51.2; − 19.1)*

Data are shown as mean (standard deviation) unless otherwise specified
CI confidence interval, *FPG* fasting plasma glucose, *HbA1c* glycated hemoglobin, *PPG* postprandial glucose
*$p < 0.0001$

Regarding the effectiveness and safety according to the study background and design, real-world data reported that switching to IDeg from basal insulins and other glucose-lowering medications showed 0.5% and 0.8% HbA1c reduction from the EUropean TREsiba AudiT (EU-TREAT) study (n = 2550) [24] and Thai population (n = 55) [20], respectively. Both studies also showed the reduced risks of patient-reported hypoglycemia. Another real-world study by Ponzani et al. [25] (n = 247) reported − 1.68 and − 0.57% improvements in HbA1c in basal insulin-naïve and experienced patients, respectively. Hypoglycemia is a very common (> 10%) adverse event with insulin treatment [26]. The meta-analyses of 15 RCTs assessing the efficacy and safety of IDeg revealed that the incidence of overall hypoglycemia was lower [17]. The risks for all and nocturnal confirmed hypoglycemia were significantly lower in the IDeg compared to insulin glargine [27]. This study for the Korean population demonstrated the consistent safety profile and effectiveness of IDeg by significantly decreasing the HbA1c, FPG, and PPG with no new safety concerns as shown in the previous clinical trials and meta-analyses [13–17, 25, 27, 28].

Notably, this study is the first to our knowledge to evaluate the PPG control of basal insulin and concomitant glucose-lowering medications. We found that the mean PPG decreased significantly in the group of patients treated with IDeg as monotherapy and combined with the DPP-4 inhibitor, or bolus/premixed insulin at week 26. Based on these findings, we postulate that an improved β-cell function and insulin sensitivity by reducing glucose toxicity [29] and a stable and flat glucose-lowering effect

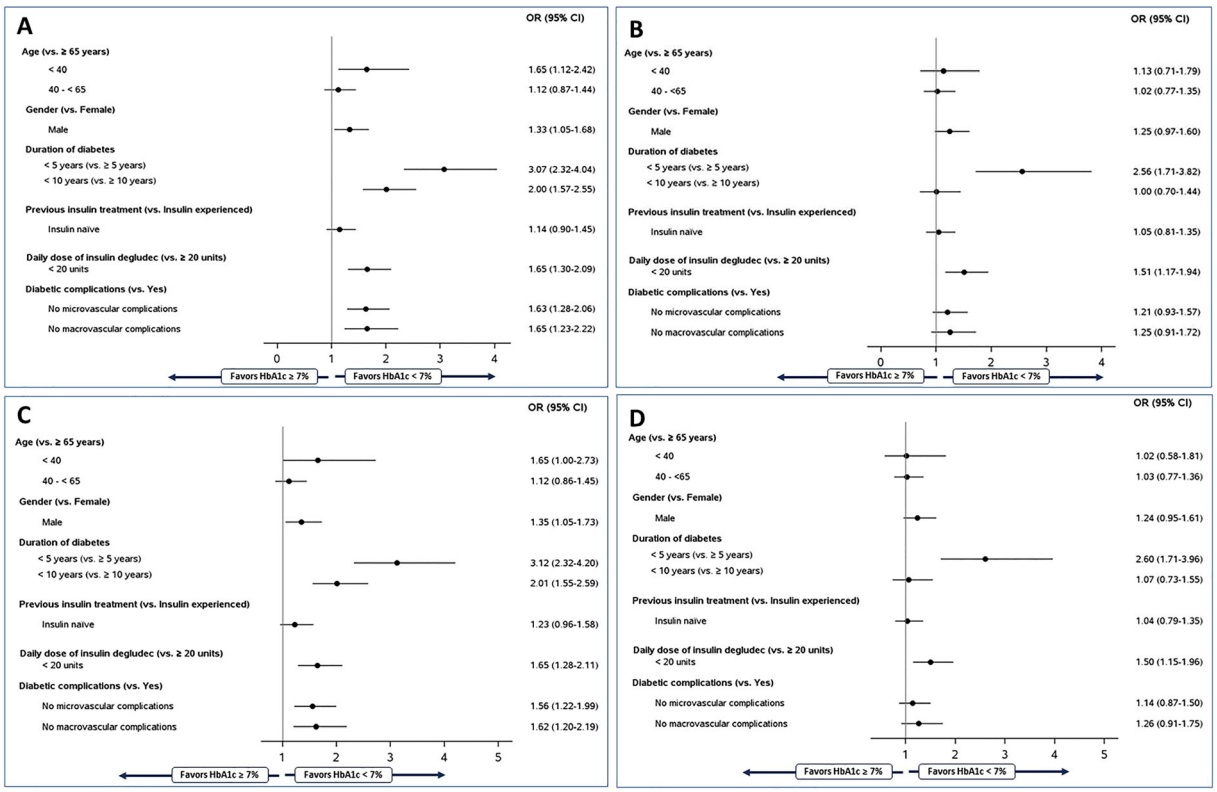

Fig. 2 Forest plot of clinical factors associated with target achievements in 26 weeks. **A** Univariate logistic regression of total EAS. **B** Multivariate logistic regression of total EAS. **C** Univariate logistic regression of T2D. **D** Multivariate logistic regression of T2D. Multivariate analysis was done using all variables of baseline characteristics. *CI* confidence interval, *EAS* effectiveness analysis set, *HbA1c* glycated hemoglobin, *OR* odds ratio, *T2D* type 2 diabetes

with less 24-h variability of IDeg might provide the PPG effects [28]. Further studies are still needed to support these findings.

Regarding the practical relevance on clinical factors affecting safety and glycemic target achievements under routine clinical practices, the relatively higher rate of AEs was observed in patients with a longer diabetes duration and with experienced insulin patients. The mean doses of IDeg were 18.9 units and 23.9 units in insulin-naïve and experienced patients, respectively (data not shown). Our study revealed that insulin-naïve patients and patients having a duration of diabetes < 5 years had a low incidence of AEs. Regarding clinical factors affecting glycemic target achievements (HbA1c < 7%) at week 26, univariate analysis revealed that clinical factors such as male sex, diabetes duration < 5 years and < 10 years, daily dose of IDeg < 20 units, and patients without micro- or macrovascular complications significantly favored achieving HbA1c < 7%. Similarly, multivariate analysis revealed that the clinical factors duration of disease < 5 years and a daily dose of IDeg < 20 units were more significant in achieving glycemic control (HbA1c < 7%) at week 26. As beta-cell function obviously deteriorates around 5 years of diagnosis of T2D [29], our study assessed the effects of the duration of the disease with a 5-year interval. It demonstrated that the target achievement rate (HbA1c < 7%) has been linked with a shorter duration of diabetes (< 5 years). Thus, combining the practical relevance of safeness and effectiveness, we postulate that the need for early initiation of insulin therapy might contribute to glycemic benefits with less hypoglycemia.

There are some limitations of this study. First, due to the inherent nature of an open-label, observational study with a lack of a comparator arm, there could be a potential observer and selection bias. The interpretation could not also extend to a comparison with other second-generation insulin such as insulin glargine. Second, because of the post-marketing surveillance study focusing on the safety assessment, there are uncollected data in the effectiveness parameters. Third, all confounding factors that occurred in actual clinical practices could not be adjusted in this design of the observational study; also, most of this study population was adults > 19 years age and diagnosed with T2D. These are the common limitations of the observational study. A statistical method was applied to overcome them using multivariate logistic regression analysis in our study.

The strengths of this study were the large sample numbers and real-world practice setting in patients with Asian ethnic backgrounds. To our best knowledge, this is the largest study under routine clinical practice in Asia and the first study to investigate the effect on PPG control of basal insulin by comedications that patients receive under routine clinical practices. In addition, this study also revealed clinically meaningful findings in defining the optimal patient characteristics to treat with IDeg with subgroup analysis.

CONCLUSION

In real-world practice, 26 weeks of treatment with IDeg showed significant improvement in glycemic parameters with a low incidence of adverse events in Korean patients with diabetes. No new safety signal was observed. The exploratory analysis of the effectiveness of IDeg across several clinical factors revealed that the target achievement (HbA1c < 7%) rate has been linked with a low daily dose (< 20 units) and shorter duration of diabetes (< 5 years); thus, addressing the early initiation can contribute to better glycemic control. As the majority were adult T2D patients, further studies are needed to confirm our findings in various diabetic populations.

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Compliance with Ethics Guidelines. This study was conducted according to the Declaration of Helsinki and the guidelines for good pharmacoepidemiology practices (2016). The protocol was approved by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) of each site and regulatory authority in Korea (Table S18). Written informed consent was obtained from all participants. The study was registered at ClinicalTrials.gov (NCT02779413) on May 20, 2016, and the universal trial number is [U1111-1176-2287].

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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