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Efficacy and Safety of IDegAsp in a Real-World Korean Population with Type 2 Diabetes Mellitus

Shinae Kang, Yu-Bae Ahn, Tae Keun Oh, Won-Young Lee, Sung Wan Chun, Boram Bae, Amine Dahaoui, Jin Sook Jeong, Sungeun Jung, Hak Chul Jang

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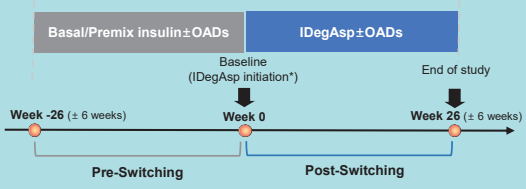
Efficacy and Safety of IDegAsp in a Real-World Korean Population With Type 2 Diabetes

Subjects

T2D, n=196
- IDegAsp initiation from basal or premix insulin

- Multicenter
- Medical chart review

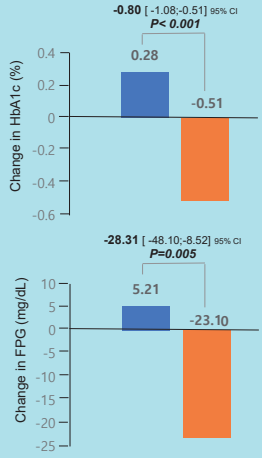
Study Design

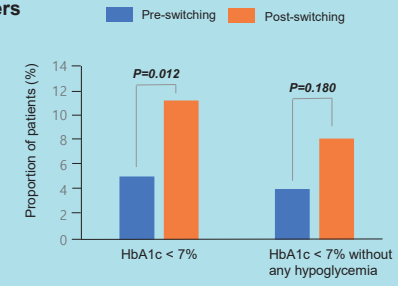


*Switched to IDegAsp from Mar 2018 to Sep 2020

Result

Changes in glycemic parameters





Incidence of hypoglycemia

- The rates of overall and nocturnal hypoglycemia were similar in the two periods.
- No severe hypoglycemic events occurred in any subjects.

Conclusion

In real-world clinical practice in Korea, switching patients with uncontrolled T2D from basal or premix insulin to IDegAsp was associated with an improvement in glycemic control without increase of hypoglycemia.

Highlights

- **Switching uncontrolled T2D patients from basal or premix insulin to IDegAsp was studied in Korea.**
- **Differences in HbA1c and FPG were significant between Pre-Switching and Post-Switching periods.**
- **A greater proportion of patients achieved HbA1c<7.0% during the Post-Switching period.**
- **No significant differences were observed in body weight change, and total daily insulin dose.**
- **The rates of overall and severe hypoglycemia were similar in the two periods.**

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Efficacy and Safety of IDegAsp in a Real-World Korean Population with Type 2 Diabetes Mellitus

Shinae Kang[1], Yu-Bae Ahn[2], Tae Keun Oh[3], Won-Young Lee[4], Sung Wan Chun[5], Boram Bae[6], Amine Dahaoui[7], Jin Sook Jeong[6], Sungeun Jung[7], Hak Chul Jang[8]

[1]Division of Endocrinology, Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul,
[2]Division of Endocrinology and Metabolism, Department of Internal Medicine, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, Seoul,
[3]Department of Internal Medicine, Chungbuk National University Hospital, Chungbuk National University College of Medicine, Cheongju,
[4]Division of Endocrinology and Metabolism, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul,
[5]Division of Endocrinology and Metabolism, Department of Internal Medicine, Soonchunhyang University Cheonan Hospital, Soonchunhyang University College of Medicine, Cheonan,
[6]Novo Nordisk Pharma Korea Limited, Seoul, Korea,
[7]Novo Nordisk Region Asia Pacific, Dubai, United Arab Emirates,
[8]Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Korea

Background: This study investigated the real-world efficacy and safety of insulin degludec/insulin aspart (IDegAsp) in Korean adults with type 2 diabetes mellitus (T2DM), whose insulin treatment was switched to IDegAsp.
Methods: This was a multicenter, retrospective, observational study comprising two 26-week treatment periods, before and after switching to IDegAsp, respectively. Korean adults with uncontrolled T2DM treated with basal or premix insulin (±oral antidiabetic drugs) were enrolled. The primary objective was to compare the degree of glycosylated hemoglobin (HbA1c) change in each 26-week observation period. The analyses included changes in HbA1c, fasting plasma glucose (FPG), body weight, proportion of participants achieving HbA1c <7.0%, hypoglycemic events, and total daily insulin dose (ClinicalTrials.gov, number NCT04656106).
Results: In total, 196 adults (mean age, 65.95 years; mean T2DM duration, 18.99 years) were analyzed. The change in both HbA1c and FPG were significantly different between the pre-switching and the post-switching period (0.28% vs. −0.51%, $P<0.001$; 5.21 mg/dL vs. −23.10 mg/dL, $P=0.005$), respectively. After switching, the rate of achieving HbA1c <7.0% was significantly improved (5.10% at baseline vs. 11.22% with IDegAsp, $P=0.012$). No significant differences (before vs. after switching) were observed in body weight change, and total daily insulin dose. The rates of overall and severe hypoglycemia were similar in the two periods.
Conclusion: In real-world clinical practice in Korea, the change of insulin regimen to IDegAsp was associated with an improvement in glycemic control without increase of hypoglycemia, supporting the use of IDegAsp for patients with T2DM uncontrolled with basal or premix insulin.

Keywords: Databases, factual; Diabetes mellitus, type 2; Glycemic control; Hypoglycemia; Insulin degludec, insulin aspart drug combination

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a progressive disease characterized by impaired glucose tolerance and deterioration of β-cell function [1]. With increase of the ageing population and changes in lifestyle, the estimated prevalence of diabetes in Korea was 16.7% in 2020 [2], and the mortality associated with T2DM was relatively higher than other countries from the Or-

Corresponding author: Hak Chul Jang https://orcid.org/0000-0002-4188-6536
Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, 82 Gumi-ro 173beon-gil, Bundang-gu, Seongnam 13620, Korea
E-mail: janghak@snu.ac.kr

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ganisation for Economic Co-operation and Development (OECD) [3]. Given the increased morbidity, mortality, and health care expenditures associated with T2DM, the Clinical Practice Guidelines of the Korean Diabetes Association have emphasized the importance of individualised care and early initiation of oral antidiabetic drugs (OADs) followed by glucagon-like peptide-1 receptor agonists or insulins in parallel [4].

In general, basal insulin is administered as the first form of the insulin therapy for T2DM. The second-generation basal insulin analogues such as insulin degludec (IDeg), provides effective glycemic control with lower rates of hypoglycemia owing to their longer duration of action and flat pharmacodynamic profile [5-7]. When uncontrolled with basal insulin, the addition of prandial insulin or switching to premix insulin can be a feasible option of insulin intensification in routine clinical practices [4,5].

Insulin degludec/insulin aspart (IDegAsp) is a fixed ratio co-formulation of IDeg (70%) and insulin aspart (IAsp, 30%). It can be administered simply while each of insulin analogue's components preserve their pharmacodynamic nature [8]. Given the shorter duration of action of basal insulin formulated in other premix insulins, IDegAsp can provide both better coverage of whole-day insulin needs with a lower day-to-day glucose variability (with an ultra-long duration of action with IDeg) and rapid mealtime onset (with relatively short duration of action with IAsp) for optimal glucose control with fewer injections [9]. These clinical benefits of the fixed ratio co-formulation of IDeg and IAsp were proven in several randomized controlled studies [10-14]. Although these randomized controlled studies found that IDegAsp was efficacious and safe, however, the generalizability of these findings into a real-world setting remains unclear. To date, several observational studies have been conducted but it remains uncertain whether IDegAsp results in better clinical outcomes in routine clinical settings due to heterogeneous baseline clinical and socioeconomic factors, previous treatments, and differences in study design. Recent real-world data from East Asia showed that even with the same ethnicity, glycemic control can be different across countries given different strategies of insulin intensification, practices of education and monitoring, and titration [15]. Furthermore, there is very limited data in patients uncontrolled with other premix insulins whereas 2021 Clinical Practice Guidelines in Korea positioned both basal insulin and premix insulin in parallel [4].

Therefore, this study aimed to investigate the efficacy and related clinical outcomes of switching uncontrolled patients with T2DM with basal or premix insulin to IDegAsp in routine clinical practice in Korea.

METHODS

This study was a multicenter, retrospective study based on a medical chart review that consisted of two consecutive 26-week treatment periods. The medical records of participants who were switched to IDegAsp from March 6, 2018 to September 2, 2020, were reviewed and collected.

Patients with T2DM were enrolled if aged ≥19 years at the time of IDegAsp initiation; treated with basal or premix insulin±OADs for at least 26 weeks followed by changing the regimen to IDegAsp for at least 26 weeks. Patients treated by continuous subcutaneous insulin infusion prior to receiving IDegAsp were excluded from the study. The decision to change the regimen depended on each investigator's clinical judgment in routine clinical practice in accordance with Korea Prescribing Information. IDegAsp was administered once or twice daily at each investigator's discretion. Data were collected 26 weeks before (defined as the "pre-switching" period) and 26 weeks after switching to IDegAsp (defined as the "post-switching" period), allowing a time window of ±6 weeks for each period. The week 0 timepoint was defined as the timepoint where IDegAsp was initiated (also defined as the baseline) (Supplementary Fig. 1).

The primary endpoint was to compare the degree of glycosylated hemoglobin (HbA1c) change between the pre-switching and the post-switching period. The secondary endpoints were to compare the changes in fasting plasma glucose (FPG), body weight, daily total insulin doses, and the incidence of overall and severe hypoglycemia during each 26-week period. The proportions of patients achieving HbA1c <7%, and <7% without any hypoglycemia were also assessed. The severity of hypoglycemia was categorized as per the Korean Clinical Practice Guidelines, defined as either overall hypoglycemia (levels 1, 2, and 3) and severe hypoglycemia (level 3) [4]. Subgroup analysis was conducted according to the previous insulin regimen before switching to IDegAsp.

The data analysis was performed using IBM SPSS Statistics for Windows, version 21 (IBM Corp., Armonk, NY, USA). Categorical variables were reported as numbers (*n*) and percentages (%); continuous variables were presented as mean and standard deviation or confidence interval (CI). A Paired *t*-

test was performed to assess changes in HbA1c, FPG, body weight, and daily total insulin dose between pre-switching and post-switching periods, and to determine the significance of the mean difference between these two periods. McNemar's test was used to assess the proportion of patients achieving HbA1c <7%, and <7% without any hypoglycemia, and the incidence of overall and nocturnal hypoglycemia. In addition, subgroups of previous insulin regimens were compared using analysis of one-way variance (ANOVA) followed by Bonferroni's *post hoc* analysis for pairwise differences. Multiple regression analysis was used to describe the relationship between HbA1c from week 0 to week 26 and the independent predictors. Missing data were not imputed, and a two-sided $P<0.05$ was considered significant. The *P* value was not adjusted for multiple testing.

The study was conducted in accordance with the Declaration of Helsinki [16]. The study protocol was reviewed and approved by the Institutional Review Boards (IRBs) in all institutions (IRB no. CBNUH 2021-02-001-001, no. SCHCA 2021-02-001, no. KBSMC 2021-02-001, no. VC21RSDI0016, no. 3-2020-0531, no. B-2102/669-102). The study is registered with ClinicalTrials.gov, number NCT04656106.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

RESULTS

Baseline characteristics of the study population

A total of 200 patients treated with either basal or premix insulin, with or without OADs were enrolled (Table 1). All patients successfully completed the study; however, four patients were excluded from the full analysis set due to deviation from the protocol. At baseline (week 0), the mean age of the participants was 65.95 years with 60.20% being male. The mean duration of T2DM was 18.99 years, with body weight 69.21 kg. The baseline HbA1c was 8.78%, and FPG 163.03 mg/dL. Among the 196 participants, 159 (81.12%) were diagnosed with hyperlipidemia, 140 (71.42%) with hypertension, 18 (9.18%) had experienced a stroke, and 60 (30.61%) had coronary artery disease. Prior to switching to IDegAsp, patients were being treated with either only basal insulin (53.57%), basal-prandial insulin (10.20%), or only premix insulin (36.22%) (Table 1, Supplementary Table 1).

Table 1. Baseline characteristics of the study population

Characteristic	Full analysis set (*n*=196)
Age, yr	65.95±11.23
Age group, yr	
19–64	85 (43.36)
≥65	111 (56.63)
Sex	
Male	118 (60.20)
Female	78 (39.80)
Duration of T2DM, yr	18.99±9.15
Duration of insulin treatment, yr	6.13±5.36
BMI, kg/m^2	25.94±4.32
Body weight, kg	69.21±14.33
HbA1c, %	8.78±1.25
FPG, mg/dL	163.03±65.63
Blood pressure, mm Hg	
Systolic blood pressure	130.46±17.01
Diastolic blood pressure	74.24±11.35
Lipid profile, mg/dL	
Total cholesterol	149.78±35.91
LDL-C	84.19±27.37
HDL-C	46.98±11.49
Triglyceride	146.86±94.23
Comorbidities	
Hyperlipidemia	159 (81.12)
Hypertension	140 (71.42)
Stroke	18 (9.18)
Coronary artery disease	60 (30.61)
Insulin treatment 26 week before IDegAsp initiation	
Basal insulin	105 (53.57)
Basal insulin with prandial insulin	20 (10.20)
Premix insulin	71 (36.22)

Values are presented as mean±standard deviation or number (%).
T2DM, type 2 diabetes mellitus; BMI, body mass index; HbA1c, glycosylated hemoglobin; FPG, fasting plasma glucose; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; IDegAsp, insulin degludec/insulin aspart.

Glycemic control after switching to IDegAsp

The HbA1c and FPG increased during the pre-switching period and decreased during the post-switching period (Table 2). Post-switching to IDegAsp, significant improvements in the HbA1c and FPG levels were observed (0.28% vs. –0.51%, *P*<

Table 2. Changes in clinical parameters

Variable	Pre-switching			Post-switching			*P* value[a,b] (pre- vs. post-switching)
	Week –26	Week 0	*P* value[a]	Week 0	Week 26	*P* value[b]	
HbA1c, %	8.50±1.31	8.78±1.25	0.002	8.78±1.25	8.27±1.17	<0.001	-
Change in the 26-week period	0.28±1.27		-	–0.51±1.12		-	<0.001
FPG, mg/dL	158.03±63.98	163.24±65.64	0.369	163.24±65.64	140.15±55.37	<0.001	-
Change in the 26-week period	5.21±80.41		-	–23.10±78.65		-	0.005
Proportion of achieving HbA1c <7%	18 (9.18)	10 (5.10)	0.057	10 (5.10)	22 (11.22)	0.012	-
Proportion of achieving HbA1c <7% without any hypoglycemia	6 (4.08)		-	12 (8.16)		-	0.180
Body weight, kg	69.11±13.54	69.74±13.97	0.010	69.74±13.97	69.75±13.74	0.980	-
Change in the 26-week period	0.63±2.84		-	0.01±2.36		-	0.113
Daily total insulin dose, U	37.42±21.80	39.15±20.92	0.079	39.15±20.92	41.14±22.91	0.001	-
Change in the 26-week period	1.72±13.69		-	1.98±8.54		-	0.828
Daily total insulin dose, U/kg	0.53±0.27	0.56±0.28	0.075	0.56±0.28	0.58±0.29	0.024	-
Change in the 26-week period	0.03±0.18		-	0.02±0.11		-	0.765

Values are presented as mean±standard deviation or number (%).
HbA1c, glycosylated hemoglobin; FPG, fasting plasma glucose; U, units.
[a]Paired *t*-test, [b]McNemar's exact test.

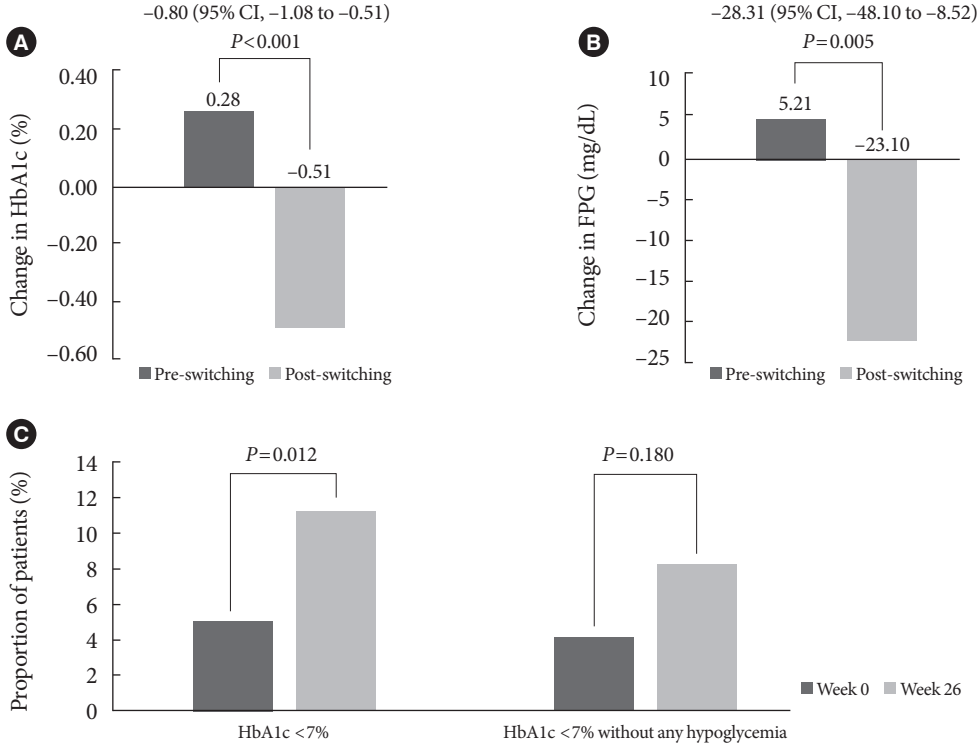

Fig. 1. Changes in glycemic parameters between pre-switching and post-switching of insulin degludec/insulin aspart. Mean changes in glycosylated hemoglobin (HbA1c) (A), and fasting plasma glucose (B) in pre-switching and post-switching period, and proportions of patients who achieved HbA1c less than 7% and proportions of participants who achieved HbA1c less than 7% without any hypoglycemia (C) in week 0 and week 26. Full analysis set. FPG, fasting plasma glucose; CI, confidence interval.

0.001; 5.21 mg/dL vs. –23.10 mg/dL, *P*=0.005) (Table 2, Fig. 1A and B). A greater proportion of patients achieved HbA1c <7% (5.10% for week 0 vs. 11.22% for week 26, *P*=0.012), and HbA1c <7% without any hypoglycemia (4.08% for week 0 vs. 8.16% for week 26, *P*=0.180) (Table 2, Fig. 1C) in the post-switching period.

In a subgroup analysis according to the type of insulin regimen in the pre-switching period, significant differences in HbA1c levels were observed between the two periods for the group of patients previously treated with basal insulin (–1.02%; 95% CI, –1.43 to –0.62) and with premix insulin (–0.58%; 95% CI, –1.01 to –0.14) whereas no significant differences were seen in the subgroup with basal-prandial insulin therapy (–0.37%; 95% CI, –1.30 to 0.56). The FPG changes were significant only in the subgroup using premix insulin (Supplementary Table 2).

Table 3. Incidence of hypoglycemia

Variable	Pre-switching	Post-switching	*P* value[a]
Overall hypoglycemic events	34 (23.13)	32 (21.77)	0.860
Severe hypoglycemic events	0	0	NA
Nocturnal hypoglycemic events	6 (4.76)	6 (4.76)	1.000

Values are presented as number (%) (with ≥1 hypoglycemic events). Nocturnal hypoglycemia was an event for which the words 'nocturnal' or 'night' or their equivalent were recorded and/or the time of the event was recorded as being between midnight and 6:00 AM.
NA, not applicable.
[a]McNemar's exact test.

Changes in body weight and total daily insulin dose post-switching to IDegAsp

The change in body weight was 0.63 kg, and 0.01 kg in the pre-switching and the post-switching periods, which was not significantly different (*P*=0.113) (Table 2). The total daily insulin dose did not change significantly in the pre-switching period, whereas a small but significant increment up to 2 U was seen in the post-switching period (Table 2). The change in insulin dose was significant between the two observation periods only in the subgroup treated with basal-prandial insulin therapy (15.65 U; 95% CI, 2.84 to 28.46) (Supplementary Table 2).

Incidence of hypoglycemia

There were no significant differences in the rate of overall and nocturnal hypoglycemia between the pre-switching and post-switching periods (Table 3). In particular, there were no severe hypoglycemic events in any subjects. The incidence of nocturnal hypoglycemia was low in both periods (6% in each).

Clinical predictors of HbA1c improvement during the post-switching period

To identify predictors associated with improved glycemic control after switching to IDegAsp, a multiple regression analysis was performed with the degree of HbA1c change from baseline (week 0) to week 26 as a dependent variable (Table 4). Older age and higher HbA1c levels at baseline were significantly associated with HbA1c improvement on IDegAsp treatment in the post-switching period.

Table 4. Factors associated with improved HbA1c in the post-switching period of IDegAsp

Variable	Unstandardized coefficients		Standardized coefficient	*t*	*P* value
	B	SE	β		
Age	–0.018	0.009	–0.178	–2.037	0.044
Female sex	0.118	0.173	0.050	0.683	0.496
BMI	0.021	0.021	0.079	0.993	0.323
HbA1c (week 0)	–0.458	0.069	–0.496	–6.681	<0.001
Duration of T2DM, yr	0.011	0.011	0.088	1.001	0.319
Duration of insulin treatment, yr	0.010	0.016	0.045	0.592	0.555
Insulin doses (week 0)	0.001	0.004	0.017	0.209	0.835

Values are presented as unstandardized coefficients (B) and standardized coefficient (β) using multiple regression analysis (Enter method of independent variables). Dependent variable was baseline value in HbA1c at week 0; *R* square (adjusted *R* square): 0.315 (0.279); F=8.74. This analysis was performed using multiple regression (Enter method of independent variables).
HbA1c, glycosylated hemoglobin; IDegAsp, insulin degludec/insulin aspart; BMI, body mass index; T2DM, type 2 diabetes mellitus.

DISCUSSION

The present study is a multicenter, retrospective observational study investigating the efficacy and safety of switching to IDegAsp from either basal or premix insulin in patients with T2DM. The findings from this study demonstrated that the switch to IDegAsp led to an improvement in glycemic control without an increase in body weight or hypoglycemia in real-world clinical practice. A 26-week treatment with basal or premix insulin therapy (pre-switching period) was associated with an increase in HbA1c with no significant change in FPG levels, and significantly small increase in body weight (0.63 kg). In contrast, switching to IDegAsp resulted in significant reductions in HbA1c and FPG, and greater proportions of patients achieved a target of HbA1c <7% with no increase of body weight. Importantly, no differences were reported in the incidence of overall, severe, and nocturnal hypoglycemia.

The high baseline HbA1c (8.78%) and FPG (163.03 mg/dL) in this study highlights inadequate glycemic control under real-world conditions in patients receiving insulin regimen. This coupled with other characteristics like long standing T2DM, insulin treatment >6 years, implies a strong unmet need for newer insulin analogues in this patient population.

Previous real-world studies demonstrated the effectiveness and safety of IDegAsp for the treatment of T2DM [15,17-19]. In two studies, compared to basal insulin, IDegAsp showed a significant reduction in HbA1c with no difference in FPG levels [17,18]. However, the changes in total daily insulin doses were inconsistent across studies, which may be attributed to different treatment approaches across countries under real-world clinical practice [15,17-19]. In the a ryzodeg initiation and switch effectiveness (ARISE) study for East Asian population, not only HbA1c but also FPG reduction was demonstrated after switching to IDegAsp. However, in contrast to the present study, the ARISE study included all patients with any antidiabetic medications, except IDegAsp before the switch, and the participants had higher HbA1c levels at baseline compared to the present study [15].

The current study confirms the previous effect of IDegAsp for improving the glycemic parameters in patients with uncontrolled T2DM previously treated with basal or premix insulin (±OADs). Furthermore, our findings examined clinical factors associated with improved HbA1c which were not investigated in real-world data to date. Older age and higher baseline HbA1c levels were the predictors for greater HbA1c reduction at week 26 after switching to IDegAsp. Sex, body mass index, duration of T2DM, duration of insulin therapy, or baseline insulin doses were not associated with HbA1c reduction of IDegAsp.

In the subgroup analysis by insulin regimen in the pre-switching period, significant HbA1c reduction changes between the two periods were shown in patients treated with 'basal insulin' or 'premix insulin' whereas these changes were not significant in the group previously treated with 'basal-prandial insulin' which has limited number of study population (n=20). To the best of our knowledge, there is only one observational study that evaluated the benefits of switching to IDegAsp from basal-prandial insulin therapy, which makes it difficult to compare the results with our study. Different levels of HbA1c at baseline (9.8% for the ARISE study [15] vs. 8.78% for the current study), and differences in titrations and monitoring practices might have contributed to varying results. However, considering the treatment complexity and number of injections, IDegAsp might also provide benefits to those using basal-prandial insulin therapy.

There are several unique points in our study. The study was designed to compare the clinical outcomes 6 months before and after the treatment with IDegAsp, which enabled the investigators to assess the robust benefits of IDegAsp for a given treatment period of intensification under real-world clinical practice. Also, the predictors associated with HbA1c improvement will be able to provide further insights into clinical decisions. The subgroup analysis by previous insulin regimen before switching to IDegAsp may warrant larger, longer-term observational studies to further dissect our findings.

This study also has potential limitations. First, due to the nature of retrospective design, First, due to the nature of retrospective design, there is the possibility that overall and nocturnal hypoglycemia may not have been adequately reported, with a recall bias. Also, the reasons of clinical decision for switching to IDegAsp were not assessed in the present study. It is pertinent to note that they may align with reasons elucidated in previous studies [15,17,19], including the needs for further glycemic control, reduction of hypoglycemia, and improvement of compliance. Second, factors such as insulin adherence, dietary habits, and physical activity levels, that could impact overall glycemic control, were not documented. Finally, subgroup analysis by previous insulin regimen was based on low sample size which may limit our findings in these subgroups. Nonetheless, given that limited data are available on clinical

outcomes of IDegAsp in Korean adults with T2DM, our study provides important real-world insights on the use of IDegAsp in insulin intensification. Future investigations with larger sample size and various clinical parameters such as insulin secretion capacity are needed to further elucidate the effectiveness and safety of IDegAsp in the Korean population.

To summarize, the current study demonstrated that when T2DM subjects are uncontrolled with conventional basal insulin therapy or premix insulin therapy, switching to IDegAsp can provide additional clinical benefits including improved glycemic control, with no difference in weight gain or incidence of hypoglycemia.

SUPPLEMENTARY MATERIALS

Supplementary materials related to this article can be found online at https://doi.org/10.4093/dmj.2023.0297.

CONFLICTS OF INTEREST

Hak Chul Jang has been international editorial board of the *Diabetes & Metabolism Journal* since 2023.

Boram Bae, Amine Dahaoui, Jin Sook Jeong, and Sungeun Jung are employees of Novo Nordisk. The other authors declare no conflict of interest with respect to the study.

AUTHOR CONTRIBUTIONS

Conception or design: S.K.
Acquisition, analysis, or interpretation of data: all authors.
Drafting the work or revising: all authors.
Final approval of the manuscript: all authors.

ORCID

Shinae Kang *https://orcid.org/0000-0002-9719-4774*
Hak Chul Jang *https://orcid.org/0000-0002-4188-6536*

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Supplementary Table 1. Antidiabetic treatment at each time point

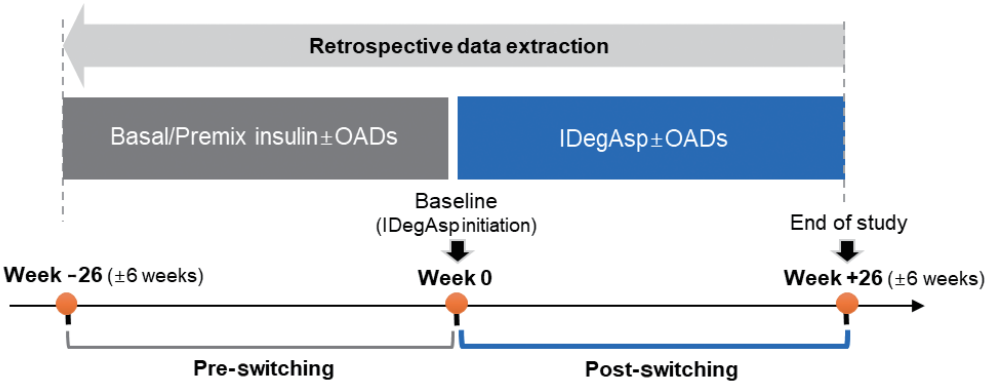
Treatment patterns	No. (%)	Daily total insulin dose, U
Week –26 (pre-switching)		
OADs	177 (90.30)	-
Insulin regimens	196 (100.00)	37.43±21.80
Basal insulin	105 (53.57)	28.59±16.51
Basal-prandial insulin	20 (10.20)	54.75±29.00
Premix insulin	71 (36.22)	45.62±20.50
GLP-1 RA	7 (3.57)	-
Week 0 (baseline)		
OADs	176 (89.80)	-
Insulin regimens	196 (100.00)	39.15± 20.90
IDegAsp	183 (93.37)	39.30±21.15
IDegAsp plus prandial insulin	13 (6.63)	37.08±17.85
GLP-1 RA	1 (0.51)	
Week 26 (post-switching)		
OADs	176 (89.80)	-
Insulin regimens	196 (100.00)	41.14±22.91
IDegAsp	180 (91.84)	40.91±23.25
IDegAsp plus prandial insulin	16 (8.16)	43.69±19.11
GLP-1 RA	1 (0.51)	-

Values are presented as number (%) or mean±standard deviation.
OAD, oral antidiabetic drug; GLP-1 RA, glucagon-like peptide-1 receptor agonist; IDegAsp, insulin degludec/insulin aspart.

Supplementary Table 2. Difference of the changes in clinical factors according to the regimen of insulin use at week –26

Variable	Basal insulin (n=105)		Basal-prandial insulin (n=20)		Premix insulin (n=71)		P value[b]
	Mean (95% CI)	P value[a]	Mean (95% CI)	P value[a]	Mean (95% CI)	P value[a]	
HbA1c, %							
Δ Pre-switching	0.43 (0.16 to 0.70)	0.002	0.15 (–0.36 to 0.65)	0.552	0.11 (–0.15 to 0.37)	0.397	0.235
Δ Post-switching	–0.60 (–0.81 to –0.38)	<0.001	–0.23 (–0.83 to 0.38)	0.445	–0.47 (–0.72 to –0.21)	<0.001	0.360
Change value[f]	–1.02 (–1.43 to –0.62)	<0.001	–0.37 (–1.30 to 0.56)	0.413	–0.58 (–1.01 to –0.14)	0.010	0.211
FPG, mg/dL							
Δ Pre-switching	5.56 (–10.99 to 22.12)	0.507	–1.53 (–29.45 to 26.39)	0.910	6.51 (–12.43 to 25.44)	0.495	0.927
Δ Post-switching	–12.98 (–26.49 to 0.53)	0.060	–16.68 (–52.01 to 18.64)	0.334	–39.49 (–60.91 to –18.08)	<0.001	0.085
Change value[f]	–18.54 (–44.54 to 7.45)	0.160	–15.16 (–62.29 to 31.98)	0.508	–46.00 (–83.09 to –8.91)	0.016	0.405
Body weight, kg							
Δ Pre-switching	0.03 (–0.57 to 0.64)	0.911	2.13 (–1.07 to 5.32)	0.171	1.11 (0.45 to 1.77)	0.001	0.018[c<d]
Δ Post-switching	0.45 (–0.04 to 0.93)	0.070	–0.53 (–2.35 to 1.30)	0.539	–0.47 (–1.19 to 0.24)	0.190	0.073
Change value[f]	0.41 (–0.55 to 1.37)	0.395	–2.65 (–7.38 to 2.08)	0.243	–1.58 (–2.74 to –0.42)	0.008	0.015[c>e]
Insulin dose, U							
Δ Pre-switching	4.72 (2.85 to 6.60)	<0.001	–11.50 (–22.83 to –0.17)	0.047	1.01 (–1.98 to 4.01)	0.502	<0.001[c,e>d]
Δ Post-switching	2.65 (1.11 to 4.19)	0.001	4.15 (–0.99 to 9.29)	0.108	0.39 (–1.61 to 2.40)	0.696	0.112
Change value[f]	–2.08 (–4.70 to 0.55)	0.120	15.65 (2.84 to 28.46)	0.019	–0.62 (–4.22 to 2.98)	0.732	<0.001[c,e<d]
Insulin dose, U/kg							
Δ Pre-switching	0.07 (0.03 to 0.10)	0.001	–0.12 (–0.29 to 0.04)	0.129	0.01 (–0.04 to 0.06)	0.650	0.002[c>d]
Δ Post-switching	0.03 (0.01 to 0.16)	0.006	0.04 (–0.04 to 0.11)	0.331	0.00 (–0.03 to 0.04)	0.865	0.295
Change value[f]	–0.03 (–0.08 to 0.02)	0.184	0.16 (–0.01 to 0.33)	0.067	–0.01 (–0.07 to 0.06)	0.799	0.024[c<d]

CI, confidence interval; HbA1c, glycosylated hemoglobin; FPG, fasting plasma glucose; U, units.
[a]Paired *t*-test between pre-switching (week –26 to week 0) and post-switching (week 0 to week 26) period repeatedly in the order from top to bottom, [b]One-way analysis of variance (ANOVA) among ([c]) basal insulin, ([d]) basal-prandial insulin, and ([e]) premix insulin group at week –26. The Bonferroni *post hoc* test was used for pairwise comparisons when the ANOVA test was significant, [f]The difference between the change at pre- and post-switching (post-switching–pre-switching) period.



Supplementary Fig. 1. Study flow diagram. OAD, oral antidiabetic drug; IDegAsp, insulin degludec/insulin aspart.