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Title: Clinical Research out of Insulin Glargine U300 basal bolus therapy and Insulin Degludec/Aspart Co-Formulation in Type 2 Diabetes Mellitus: A Real World Experience

Short Title: IGlarU300 And IDegAsp in Type 2 DM

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Abstract

Aims/Introduction: Insulin Degludec/Aspart (IDegAsp) and Insulin Glargine U300 (IGlarU300) have recently emerged as popular new-generation insulin analogs. The aim of this real-life study was to investigate the patient profiles in which IGlarU300 and IDegAsp were preferred and the insulin combinations after which each of them were mostly used, and also to analyze the effect of these two insulin analogs on blood glucose regulation and hypoglycemia.

Materials and Methods: The retrospective study included 174 patients that were switched from basal insulin, basal+bolus insulin, or premixed insulin to IGlarU300 or IDegAsp due to uncontrolled blood glucose levels or history of hypoglycemia. Hypoglycemia, body weight, body mass index (BMI), fasting blood glucose (FBG), and HbA1c levels over three-month periods were evaluated for each patient.

Results: There were 84 and 90 patients in the IGlarU300 and IDegAsp groups, respectively. Body weight was similar in both groups. Baseline FBG and HbA1c levels in the IGlarU300 and IDegAsp groups were 9.0%, 175.5 mg/dl and 9.4%, 193.5 mg/dl, respectively. A significant decrease was found in FBG and HbA1c levels in both groups (138.5, 7.8 *vs.* 141.5, 8.2; $p<0.001$ for all). Moreover, a significant weight gain was observed in both groups ($p<0.05$ for both). The prevalence of hypoglycemia in both groups decreased significantly and consistently between month 1 and 9 ($p<0.001$). At month 12, although this decrease continued in the IGlarU300 group ($p=0.013$), no significant decrease was observed in the IDegAsp group($p=0.057$).

Conclusion: Both twice-daily IDegAsp±bolus insulin and IGlarU300+bolus insulin therapies are effective and safe treatment modalities.

Keywords: Hypoglycemia, insulin Glargin U300 Basal–bolus therapy, insulin DegludegAspart twice-daily injection therapy

What's New : The effect of Twice daily degludec/Aspart and IGlarU300 + bolus therapy on blood glucose regulation and hypoglycemia was analyzed.

This is the first real-life study, that was to investigate the patient profiles in which IGlarU300 and IDegAsp were preferred and the insulin combinations after which each of them were mostly used.

This study will give physicians information about which insulin regimen to choose for which patient profile in real life.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a progressive disease developing on the basis of insulin resistance, characterized by increased blood sugar due to decreased insulin activity [1]. Insulin therapy remains the most effective treatment for T2DM while it may lead to disadvantages such as weight gain and hypoglycemia. The quest for insulin molecules that do not cause weight gain and hypoglycemia have led to the development of new-generation insulin analogs such as insulin degludec (IDeg) and insulin glargine U300 (IglarU300). These two analogs have been shown to be ultra-long-acting basal insulins causing less hypoglycemia compared to insulin glargine U100 (IglarU100) [2–6]. It has also been reported that in patients whose blood glucose could not be controlled with basal insulin, IDegAsp causes more hypoglycemia despite showing similar efficacy to IGlarU100 in reaching blood glucose target [7,8].

The present study was designed to investigate the effect of two different insulin analogs, IGlarU300 and IDegAsp, on real-life parameters (fasting blood glucose [FBG], HbA1c, body weight, and hypoglycemia). The second aim of the study was to examine the patient profiles in which IGlarU300 and IDegAsp were preferred and the insulin

combinations after which each of them were mostly used, and to analyze the effect of these two insulin analogs on blood glucose regulation and hypoglycemia.

MATERIALS AND METHODS

The retrospective study included patients that were diagnosed with T2DM at **** between May 2017 and May 2019. The study protocol was approved by *** Ethics Committee (Approval Date: January 28, 2020; No: 24237859-206) and the study was conducted in accordance with the principles laid out by the 18th World Medical Assembly (Helsinki, 1964) and all its subsequent amendments (up to 2013) and with the International Society for Pharmacoepidemiology guidelines for Good Pharmacoepidemiology Practice and local regulations, including local data protection regulations.

Inclusion criteria were as follows:

1) Aged over 18 years,

2) Documented T2DM,

3) An ongoing insulin therapy with a basal insulin, basal-bolus insulin, or a premixed insulin regimen,

4) Experiencing one or both of the following conditions in association with the diabetes therapy:

a) Daytime or nighttime hypoglycemia,

b) Uncontrolled blood glucose levels.

Exclusion criteria were as follows:

1- Patients with acute coronary syndrome, cerebrovascular event, pregnancy, heart failure, chronic liver disease, renal function test abnormality, and cancer,

2- Use of drugs such as steroids that could elevate blood glucose levels,

3- History of alcohol or drug abuse,

4- A previous diagnosis of T1DM or latent autoimmune diabetes in adults (LADA),

5- Patients that showed poor compliance with the treatment or did not take insulin injections regularly.

Treatment planning

Each patient was given a diabetic diet appropriate for their body mass index (BMI) by the dieticians in our hospital. The insulin regimens and doses administered throughout the treatment were recorded for each patient.

Target FBG level was defined as 80-130 mg/dl and the target postprandial glucose (PPG) level was defined as <180 mg/dl.

Dose adjustment was performed using the routine dose adjustment protocols defined in the current guidelines of our clinic.

When switching from a previous insulin regimen to IGlarU300;

a) *In patients that were switched to IGlarU300 due to the presence of hypoglycemia,* insulin was administered at the same dose or a dose reduced by

20%, and 50% of the total insulin dose was distributed to IGlarU300 and the remaining 50% was appropriately distributed to three main meals based on the nutritional status and previous blood glucose measurements of the patients,

b) *In patients that were switched to IGlarU300 due to uncontrolled blood glucose levels*, insulin was administered at the same dose or a dose increased by 20%, and 50% of the total insulin dose was distributed to IGlarU300 and the remaining 50% was appropriately distributed to three main meals based on the nutritional status and previous blood glucose measurements of the patients.

When switching from a previous insulin regimen to IDegAsp;

a) *In patients that were switched to IDegAsp due to the presence of hypoglycemia;* insulin was administered at the same dose or a dose reduced by 20%, with the total insulin dose equally divided into two doses and administered before the morning and evening meals. As needed, the insulin was titrated by adding 4-6 units of aspart at the third main meal.

b) *In patients that were switched to IDegAsp due to uncontrolled blood glucose levels*; insulin was administered at the same dose or a dose increased by 20%, with the total insulin dose equally divided into two doses and administered before the morning and evening meals. As needed, the insulin was titrated by adding 4-6 units of aspart at the third main meal.

The morning dose of IGlarU300 was increased by 2-4 units upon the detection of FBG >130 mg/dl and was increased by 4-8 units upon the detection of FBG was >180 mg/dl.

Moreover, it was reduced by 2-4 units if the FBG was <70 mg/dl and was reduced by 4-8 units if the FBG was <56 mg/dl.

The morning dose of IDegAsp was increased by 2-4 units if the FBG was >130 mg/dl, based on the meal with non-target PPG (>180 mg/dl).

Moreover, the IDegAsp dose was reduced by 2-4 units if the FBG was <70 mg/dl and was reduced by 4-8 units if the FBG was <56 mg/dl. If there was no target PPG for both meals, the IDegAsp dose was increased by 2-4 units prior to each meal. The total IDegAsp dose was reduced by 2-4 units upon the detection of FBG <70 mg/dl and was reduced by 4-8 units upon the detection of FBG <56 mg/dl.

Upon the detection of PPG <70 mg/dl, the meal after which hypoglycemia occurred was determined and then the insulin dose before that meal was decreased by 2-4 units after investigating patient's diet compliance.

Each patient was advised to perform seven-point self-monitoring of blood glucose (SMBG) and to visit the outpatient clinic for a period of 5-7 days until reaching target glucose levels.

When switching to new-generation insulin regimens, the secretagogue treatment was discontinued in each patient due to the risk of hypoglycemia. Oral antidiabetic agents (OAD) were added or changed in patients whose blood glucose did not reach the target despite intensive insulin therapy.

Data collection and recording

Clinical data of the patients were retrieved from electronic records. For each patient, data on body weight, BMI, FBG, and HbA1c levels were evaluated over three-month periods. For patients with more than one record of FBG level over a three-month period, the average level was taken for the analysis. Basal and bolus insulin doses were evaluated for each patient. Hypoglycemia was defined as blood glucose level <70 mg/dl, either symptomatic or asymptomatic, or measured in hospital or at home.

Biochemical analysis

Blood samples of all patients were taken from the antecubital vein after an overnight fasting period of at least eight hours. Biochemical parameters were studied from plasma samples. Plasma glucose levels were measured using enzymatic reference method with hexokinase (Beckman Coulter AU5800), and plasma HbA1c levels were measured by high-performance liquid chromatography (HPLC) and mass spectroscopy method (Premier HB9210). Low-density lipoprotein (LDL) was measured using enzymatic colorimetric assay (Beckman Coulter AU5800) and plasma creatinine was assessed using the kinetic Jaffé method (Beckman Coulter AU5800). Urine protein level was measured by the protein error of indicator method (IQ 200/iChem velocity).

Statistical analysis

Data were analyzed using SPSS 23.0 for Windows (Armonk, NY: IBM Corp.). Descriptives were expressed as frequencies (n) and percentages (%) for categorical variables and as mean, median, standard deviation (SD), minimum, and maximum for continuous variables. Normal distribution of data was assessed using One-Sample Kolmogorov Smirnov test. Independent continuous variables were compared using Mann-Whitney U test as they did not show a normal distribution. For dependent

continuous variables, two variables were compared using Wilcoxon signed-rank test and three or more variables were compared using Friedman test as they did not show a normal distribution. Dependent categorical variables were compared using McNemar's test. A *p* value of <0.05 was considered significant.

RESULTS

A total of 174 patients were included in the study, comprising 84 and 90 patients in the IGlarU300 and IDegAsp groups, respectively. Body weights of the patients were similar in both groups. Baseline FBG and HbA1c levels in the IGlarU300 and IDegAsp groups were 175.5 mg/dl, 9.0% and 193.5 mg/dl, 9.4 % respectively. In the IGlarU300 group, younger female patients with higher BMI values were more common when compared to the IDegAsp group ($p<0.05$ for all) (Table 1). The groups were similar with regard to duration of diabetes and presence of hypertension, FBG, HbA1c, macrovascular complications, and microvascular complications except for retinopathy. In the IGlarU300 group, there were significantly more patients with retinopathy when compared to the IDegAsp group ($p=0.010$). Previous bolus insulin and basal insulin doses were also significantly higher in the IGlarU300 group compared to the IDegAsp group ($p=0.001$ and $p=0.016$, respectively). Previous hypoglycemic events were more commonly reported by the patients in the IGlarU300 group compared to the IDegAsp group (48% *vs.* 32%) ($p=0.004$).

Baseline anti-hyperglycemic drugs are detailed in Table 2. Previous treatment regimens including OAD and insulin were similar in both groups. In the IGlarU300 and IDegAsp groups, 60 (71.4%) and 66 (73.3%) patients used metformin for hyperglycemic control.

Overall, IGlarU100 was used for almost half of the patients (50.6%) that required basal insulin.

Baseline characteristics of the groups in relation to previous treatment regimens are summarized in Table 3. IGlarU100 was the most common basal insulin used prior to the study. Of the 26 patients that were using a premixed regimen, 24 (92%) of them were switched to IDegAsp.

The median number of outpatient visits was significantly higher in the IGlarU300 group compared to the IDegAsp group (7 *vs.* 6; p=0.039). However, the duration and the ratio of the duration of follow-up to the total number of outpatient visits were similar in both groups (p>0.05).

Metformin was the most common OAD in both groups. There was a significant difference between the two groups with regard to baseline SGLT requirement (p=0.015). However, after the administration of the new insulin, 1 and 3 patients in the IGlarU300 and IDegAsp groups were initiated on SGLT inhibitors, respectively. No significant difference was found between the two groups with regard to the requirement of other OAD (Table 4).

The daily insulin requirement profiles of the patients are summarized in Table 5. At the end of the trial, significant differences were found between the groups with regard to daily total dose of injected insulin, injection number, and the ratio of total dose of injected insulin to body weight (p<0.001 for all). In the IDegAsp group, the median values of total daily dose of injected insulin, injection number, and ratio of total dose of injected insulin to body weight were significantly lower than those in the IGlar U300 group. Although no significant changes were observed in the median dose of injected

insulin, and the ratio of total dose of injected insulin to body weight in the IGlar U300 group, there were significant increases in the IDegAsp group in both parameters ($p \leq 0.001$ and $p=0.001$). There was significant decreases observed in the total bolus insulin dose, in the IDegAsp group(p=0,05).

Both groups had similar durations of follow-up and similar ratios of total duration of follow-up to total number of outpatient visits ($p=0.804$).

The serum alanine aminotransferase (ALT), low-density lipoprotein (LDL), and creatinine values decreased significantly in the IDegAsp group after the treatment ($p<0.05$ for all). However, no significant change was detected in the IGlar U300 group with regard to these three parameters.

Table 6 presents the prevalence of hypoglycemic events in both groups. Prior to the study, the IGlarU300 group had a higher prevalence compared to the IDegAsp group (57.1% *vs.* 35.6%; $p=0.004$). In the following months, a significant decrease was observed in the IGlarU300 group ($p<0.05$) and a significant decrease was observed in the IGlarU300 group except for month 12 ($p<0.05$) compared to the baseline values.

The effect of treatment on body weight, FBG, and HbA1c levels of all patients and patients that were followed up until month 12 are given in Table 7 and 9, respectively. In both groups, the FBG and HbA1c levels decreased significantly when compared to baseline values ($p<0.05$ for both). In contrast, body weight increased in both groups at the end of the treatment ($p<0.05$).

At month 12, body weight increased significantly while FBG and HbA1c level decreased significantly in both groups. Moreover, Both IDegAsp and IGlarU300 was

found to have a significant effect on FBG and HbA1c level (p<0.001, p<0.001 and p=0.012, p=0.002, respectively) (Figure 3).

DISCUSSION

The results indicated that both IGlarU300 and IDegAsp led to a significant improvement in glycemic control and a significant decrease in the prevalence of hypoglycemic events.

The insulin regimes of the patients included in the present study were not homogeneous due to the real-life nature of the study. Premixed insulins are commonly preferred in daily practice since they are highly practical and increase patient compliance, although they can frequently cause hypoglycemia due to the molecular properties of Neutral Protamine Hagedorn (NPH) inherent in their structure. Moreover, IDegAsp has been shown to be superior to premixed insulin in reducing the risk of hypoglycemia and providing better glycemic control [9,10]. In our study, IDegAsp was the most common insulin analog preferred in patients using premixed insulin due to its practicality (86%) (Figure 1). Moreover, it was also preferred in the majority (70%) of patients using basal insulin ± OAD. Meaningfully, IDegAsp is the insulin of choice in old-age patients and in those using less complex insulin regimens mainly due to its practicality. By contrast, IGlarU300 was mostly preferred in patients using multiple injections such as basal + bolus and in patients using more complex insulin regimens (70%) (Figure 2).

An analysis of OAD requirement in our patients indicated that patients that were not using metformin prior to the study were detected with diseases that could lead to lactic acidosis, including chronic kidney failure, heart failure, lung failure, and cirrhosis. On the other hand, after switching to new-generation insulin regimens, the secretagogue

therapy was discontinued due to the risk of hypoglycemia in all 10 patients that were receiving that therapy. SGLT2 was initiated in two patients due to the requirement of >200 insulin units, in two patients for reducing proteinuria, and in one patient after the discontinuation of GLP-1 agonist therapy. In one of these patients, SGLT2 was discontinued after the detection of its side effects. The GLP-1 treatment after intensive insulin therapy was discontinued in four patients due to its high costs. The DPP-4 treatment was initiated in 10 and was discontinued in one patient. All the 10 patients that were initiated on DPP-4 treatment could not receive metformin therapy due to the risk of lactic acidosis and also were not suitable for SGLT2 therapy.

The analyses indicated that the prevalence of hypoglycemic events in both groups decreased significantly and consistently between month 1 and 9 (p<0.001). At month 12, although this decrease continued in the IGlarU300 group (p=0.013), no significant decrease was observed in the IDegAsp group (p=0.057). Both IDeg and IGlarU300 have been shown to reduce the frequency of hypoglycemia when compared to IGlarU100 [2–6]. Moreover, a previous randomized head-to-head trial compared IGlarU300 and IDeg and found similar hypoglycemia incidence rates for both insulins [11]. In line with the literature, we also found that IGlarU300 decreased the frequency of hypoglycemia. However, no comparison could be performed with the literature since IDeg is not available as a basal insulin in Turkey. Previous phase III trials indicated that IDegAsp provided similar outcomes to those of IGlarU100 in terms of glycemic control, although it led to an increased frequency of hypoglycemia [7,8]. On the other hand, studies comparing IDegAsp once- to twice-daily injection and basal + bolus therapy have provided contradictory results. Among these, some studies found similar hypoglycemia incidence rates [9,12], while some others reported that these two insulin regimens had

lower hypoglycemia incidence rates compared to IGlarU300 + Insulin Glulisine and IDegAsp [13]. In our study, unlike in other studies, the insulin treatment of the patients using a premixed regimen with many different combinations was changed to IDegAsp twice-daily injection. Moreover, IDegAsp was found to have favorable effects on hypoglycemia. Of note, in the IDegAsp group, no hypoglycemia was seen within the first three months of treatment in 9 (82%) out of 11, in 7 (70%) out of 10, and in 6 (38%) out of 16 patients that were previously using basal insulin ± OAD, premixed insulin ± OAD, and basal + bolus insulin ± OAD, respectively. Moreover, the increase in the frequency of hypoglycemia was greater in patients using basal insulin ± OAD and premixed insulin ± OAD than in patients using basal + bolus insulin ± OAD. These findings could be attributed to the fact that the management of patients using basal + bolus insulin ± OAD can be relatively more difficult and these patients may have reduced beta-cell reserves.

Previous randomized open-label studies reported that transition to IGlarU300 led to a significant reduction in hypoglycemia although it did not achieve better control over blood sugar [2–4]. In contrast, the DELIVER study, indicated that IGlarU300 led to a significant reduction in HbA1C levels at the end of the 6-month follow-up period compared to IGlarU100 (-1.52 ± 2.08% *vs.* -1.30 ± 2.12%; p=0.003) [14]. In the present study, the FBG and HbA1c levels of 174 patients were followed up over the two-year follow-up period and the FBG values of 54 and 48 patients and the HbA1c levels of 54 and 43 patients in the IGlarU300 and IDegAsp groups were measured until month 12, respectively. The measurements indicated that both FBG and HbA1c levels decreased significantly in the IGlarU300 group both in all patients (p<0.001 for both) and in the patients that were followed up until month 12 (p=0.012 and p=0.002, respectively). In

our study, unlike in phase III trials, the administration of IGlarU300 decreased the frequency of hypoglycemia and also achieved a better control over blood sugar. A previous retrospective study evaluated T2DM patients that were switched from basal insulin to IGlarU300 and, in a similar way to our study, found a significant decrease in HbA1c levels and also a reduction in documented hypoglycemia. In the same study, a significant decrease was observed in the insulin doses administered in the patients (p=0.02), whereas no significant change occurred in the insulin doses administered in our patients (p=0.86) [15].

In the IDegAsp group, in a similar way to the IGlarU300 group, both FBG and HbA1c levels decreased significantly both in all patients and in the patients that were followed up until month 12 (p<0.001 for all). IDegAsp has been reported to be more effective than basal insulin in the regulation of PPG [16]. However, Ozcelik et al. found no significant change in FBG and HbA1c levels after switching from intensive insulin to IDegAsp [9]. By contrast, Kawaguchi et al. used a blood glucose monitoring system showed that basal-bolus therapy (IGlarU300 + insulin glulisine) was superior to IDegAsp in terms of efficacy and safety [13]. Tsimikas et al. reported that the administration of IDegAsp once- to twice-daily injection showed similar efficacy in insulin intensification therapy when compared to multiple injection (basal + bolus) therapy [12].

Taken together, our results indicated that IGlarU300 was mostly preferred in patients with higher BMI values and higher hypoglycemia incidence rates who previously received basal + bolus therapy, used high-dose insulin, and had a higher frequency of

retinopathy. By contrast, IDegAsp was mostly used in older age individuals who had lower hypoglycemia incidence rates and used simpler insulin regimens despite having higher FBG and Hba1c levels.

The use of higher insulin doses and injection numbers seems to be the disadvantage of the IGlarU300 ± bolus group. Additionally, IDegAsp led to a significant increase in both total insulin dose and the ratio of total dose of injected insulin to weight (unit/kg/day). This finding could be associated with the higher proportion of patients using basal ± OAD in the IDegAsp group and the higher requirement of insulin for reaching the target in this patient group. On the other hand, a significant weight gain was observed in both groups, which could be explained by the increased insulin use in the IDegAsp group and by the high proportion of patients in the IGlarU300 group who had a history of hypoglycemic events and administered their insulin injections without reducing or withholding any doses after their fear of hypoglycemia was reduced.

Systolic blood pressure (SBP) and ALT levels also decreased in both groups. However, the decreased ALT values despite increased weight gain in our patients cannot be explained by decreased hepatosteatosis. Therefore, further studies are needed to elucidate this phenomenon.

CONCLUSION

The present study evaluated the efficacy of transition from all insulin regimens used in daily practice to IGlarU300 and IDegAsp. The results indicated that both insulins led to a reduction in hypoglycemia and a significant reduction in FBG and HbA1c levels. Accordingly, both twice-daily IDegAsp±bolus insulin and IGlarU300+bolus insulin therapies are effective and safe treatment modalities.

Limitations

Not all the patients completed the 24-month follow-up period and thus the measurements obtained during their last clinical visit were accepted as final measurements.

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Disclosure

The authors declare no conflict of interest.

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Figure Legends

Figure 1. Reasons for switching to IDegAsp.

Figure 2. Reasons for switching to IGlarU300.

Figure 3. Comparison of baseline and 12-month values with regard to the effect of treatment.

Table 1. Demographic and baseline clinical characteristics.

Variable		Groups IGlarU300 (n=84)	Groups IDegAsp (n=90)	p
Age (year) †		58.7 ± 9.5	62.7 ± 9.1	0.005*
Sex ‡				
Male		21 (25)	36 (40)	0.035***
Female		63 (75)	54 (60)	
Weight (kg) †		91 ± 18.8	87.9 ± 13.2	0.205*
BMI (kg/m^2) †		35.1 ± 6.7	33 ± 5	0.021*
Duration of diabetes (years)		13 [2 – 36]	11.5 [1 – 46]	0.548**
Hypertension	Yes	76 (90.5)	79 (87.8)	0.568***
	No	8 (9.5)	11 (12.2)	
Macrovascular complications		41 (48.8)	39 (43.3)	0.469***
Microvascular complications	Retinopathy	43 (62.3)	26 (40)	0.010***
	Neuropathy	44 (52.4)	40 (44.4)	0.295***
	Nephropathy	42 (50)	45 (50)	0.999***
Previous hypoglycemia events		48 (57.1)	32 (35.6)	0.004***
Fasting blood glucose (mg/dL) ¥		175.5 [72 – 555]	193.5 [57 – 393]	0.070**
HbA1c (%)¥		9 [5.1 – 14.4]	9.4 [6 – 14.5]	0.092**
Previous bolus insulin dose (unit)		44 [16 – 130]	30 [8 – 60]	<0.001**
Previous basal insulin dose (unit)		37 [8 – 100]	32 [10 – 66]	0.020**

†: mean ± standard deviation, ‡: n (%), ¥:median [min-max]
*. Independent Samples t-test
**: Mann-Whitney U test
***. Pearson Chi-Square test

Table 2. Baseline treatment details.

		Overall ‡	Groups	
			IGlarU300 (n=84) ‡	IDegAsp (n=90) ‡
Metformin, *yes*		126 (72.4)	60 (71.4)	66 (73.3)
Insulin secretagogues, *yes*		10 (5.7)	2 (2.4)	8 (8.9)
DPP-4 inhibitors, *yes*		41 (23.6)	18 (21.4)	23 (25.6)
SGLT-2 inhibitors, *yes*		9 (5.2)	8 (9.5)	1 (1.1)
GLP-1 receptor agonists, *yes*		6 (3.4)	3 (3.6)	3 (3.3)
Basal insulin	Insulin Glargin	88 (50.6)	46 (54.8)	42 (46.7)
	Insulin detemir	55 (31.6)	33 (39.3)	22 (24.4)
	NPH insulin	3 (1.7)	1 (1.2)	2 (2.2)
Bolus insulin	Insulin aspart	51 (29.3)	34 (40.5)	17 (18.9)
	Insulin glulisine	16 (9.2)	12 (14.3)	4 (4.4)
	Insulin lispro	21 (12.1)	15 (17.9)	6 (6.7)
	Regular insulin	3 (1.7)	3 (3.6)	0 (0)
IDegAsp bolus	Insulin aspart	16 (17.6)	0 (0)	16 (19.5)
IGlar + bolus	Insulin aspart	38 (44.7)	38 (45.2)	0 (0)
	Insulin glulisine	15 (17.6)	14 (16.7)	1 (100)
	Insulin lispro	15 (17.6)	15 (17.9)	0 (0)
	Regular insulin	0 (0)	0 (0)	0 (0)
Mixed insulin	Lispro/lisproprotamin	15 (8.6)	3 (3.6)	12 (13.3)
	Aspart/ Aspartprotamin	13 (7.5)	1 (1.2)	12 (13.3)

‡: n (%) DPP-4 : Dipeptidyl peptidase-4 , SGLT-2 : Sodium-glucose cotransporter-2,
GLP-1 : Glucagon-like peptide-1

Table 3. Prestudy treatment regimens.

Treatment	Overall ‡	Groups	
		IGlarU300 (n=84) ‡	IDegAsp (n=90) ‡
Basal insulin ± metformin ± other OADs	45 (81.8)	14 (87.5)	31 (79.5)
Basal insulin only	10 (18.2)	2 (12.5)	8 (20.5)
Basal + bolus insulin ± metformin ± other OADs	68 (74.7)	47 (73.4)	21 (77.8)
Basal + bolus insulin only	23 (25.3)	17 (26.6)	6 (22.2)
Mixed insulin ± metformin ± other OADs	24 (85.7)	4 (100)	20 (83.3)
Mixed insulin only	4 (14.3)	0 (0)	4 (16.7)

‡: n (%) OAD (Oral antidiabetics): Sulfonylurea ± DPP-4 inhibitors ± SGLT-2 inhibitors ± GLP-1 agonists

Table 4. OAD requirement during the treatment.

	Groups		*p*
	IGlarU300 (n=84)	IDegAsp (n=90)	
Metformin ‡			
Baseline	60 (71.4)	66 (73.3)	0.779***
After new insulin	56 (66.7)	66 (73.3)	0.337***
Secretagogues ‡			
Baseline	2 (2.4)	8 (8.9)	0.101****
After new insulin	0 (0)	0 (0)	-------
DPP-4 inhibitors ‡			
Baseline	18 (21.4)	23 (25.6)	0.522***
After new insulin	24 (28.6)	25 (27.8)	0.907***
SGLT inhibitors ‡			
Baseline	8 (9.5)	1 (1.1)	0.015****
After new insulin	9 (10.7)	4 (4.4)	0.116***
GLP-1‡			

Baseline	3 (3.6)	3 (3.3)	1.000****
After new insulin	2 (2.4)	0 (0)	0.232***

‡: n (%)
***. Pearson Chi-Square
****. Fisher's Exact Test
OAD: Oral antidiabetic drugs, DPP-4: Dipeptidyl peptidase-4, SGLT: Sodium-glucose co-transporter, GLP-1: Glucagon-like peptide-1

Table 5. Baseline and final clinical and laboratory parameters.

	Groups		*p*
	IGlarU300 (n=84)	IDegAsp (n=90)	
Systolic blood pressure (mmHg) ¥			
Baseline	139 [90 – 200]	130 [105 – 220]	0.594**
Final	130 [90 – 190]	130 [100 – 175]	0.401**
p€	0.015	0.002	
Diastolic blood pressure (mmHg) ¥			
Baseline	80 [60 – 130]	80 [50 – 110]	0.233**
Final	80 [60 – 110]	80 [60 – 120]	0.865**
p€	0.009	0.127	
Total dose of injected insulin (unit) ¥			
Previous	76 [8 – 230]	46 [12 – 115]	<0.001**
Final	69 [6 – 236]	54 [16 – 138]	<0.001**
p€	0.860	<0.001	
Bolus insulin dose¥			
Previous	44 [16 – 130]	30 [8 – 60]	<0.001**
Final	38 [4 – 132]	10 [3 – 64]	<0.001**
p€	0.146	0.050	
IGlarU300 dose¥			
Starting	40 [8 – 116]	-------	------
Final	42 [6 – 112]		
p€	0.113		
IDegAsp dose¥			
Starting	-------	38.5 [8 – 88]	------
Final		50 [12 – 122]	
p€		<0.001	
Injection number (n) ¥			
Previous	4 [1 – 5]	2 [1 – 5]	<0.001**
Final	4 [1 – 5]	2 [1 – 3]	<0.001**
p€	0.494	0.142	
Ratio of total dose of injected insulin to weight (unit/kg/day) ¥			
Previous	0.9 [0.1 – 2.0]	0.5 [0.1 – 1.3]	<0.001**
Final	0.8 [0.1 – 2.1]	0.6 [0.2 – 1.6]	<0.001**
p€	0.875	0.001	
Alanine aminotransferase (IU/L) ¥			
Baseline	23 [6 – 132]	19.5 [2 – 137]	0.033**
Final	21 [6 – 84]	15 [2 – 132]	0.027**
p€	0.007	0.001	
Low density lipoprotein (mg/dL) ¥			
Baseline	105.5 [42 – 210]	109.5 [21 – 226]	0.378**
Final	98 [25 – 203]	95 [32 – 186]	0.987**
p€	0.531	0.039	
Creatinine (mg/dL) ¥			
Baseline	0.8 [0.4 – 7.7]	0.79 [0.5 – 2.1]	0.798**
Final	0.9 [0.5 – 7.6]	0.81 [0.4 – 7.8]	0.722**
p€	0.169	0.047	
Glomerular filtration rate (ml/min) ¥			

Baseline	83.5 [7 – 133]	91 [27 – 124]	0.579**
Final	83 [7 – 120]	88.5 [7 – 121]	0.637**
p€	0.053	0.007	
Proteinuria (mg/mL) ¥			
Baseline	10 [0 – 875]	10 [0 – 700]	0.709**
Final	10 [0 – 2355]	10 [0 – 300]	0.366**
p€	0.690	0.681	

¥: Median [min-max]
**. Mann-Whitney U
€. Wilcoxon test

Table 6. Prevalence of hypoglycemic events.

	Groups					
	Total n	IGlarU300 n (%)		Total n	IDegAsp n (%)		
Hypoglycemic events			*p* (*vs.* baseline)*			*p* (*vs.* baseline)*	*p*
Baseline	84	48 (57.1)		90	32 (35.6)		0.004**
0-3 months	83	32 (38.6)	<0.001	87	11 (12.6)	<0.001	
3 months	78	24 (30.8)	<0.001	84	10 (11.9)	<0.001	
6 Months	72	21 (29.2)	<0.001	77	5 (6.5)	<0.001	
9 Months	66	18 (27.4)	<0.001	62	7 (11.3)	0.001	
12 Months	54	19 (35.2)	0.013	50	6 (12.0)	0.057	

*. McNemar Test
**. Pearson Chi-Square

Table 7. Intra- and inter-group analysis of the effect of treatment on body weight, FBG, and HbA1c levels.

	Groups		*p*
	IGlarU300 (n=84)	IDegAsp (n=90)	
Body weight (kg) †			
Baseline	91.0 ± 18.8	87.5 ± 12.8	0.208*
Final	92.6 ± 19.1	88.9 ± 12.9	0.138*
p***	0.015	0.007	
FBG (mg/dL) ¥			
Baseline	175.5 [72 – 555]	193.5 [57 – 393]	0.070**
Final	138.5 [72 – 428]	141.5 [64 – 380]	0.530**
p****	<0.001	<0.001	
HbA1c (%) ¥			
Baseline	9.0 [5.1 – 14.4]	9.4 [6.0 – 14.5]	0.092**

Final	7.8 [5.5 – 12.0]	8.2 [5.2 – 13.1]	0.207**
p****	<0.001	<0.001	

†: mean ± standard deviation, ‡: n (%),¥:median [min-max]
*. Student t-test
**. Mann-Whitney U
***. Paired t-test
****. Wilcoxon Test
FBG: Fasting blood glucose