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Efficacy and Safety of Self-Titration Algorithms of Insulin Glargine 300 units/mL in Individuals with Uncontrolled Type 2 Diabetes Mellitus (The Korean TITRATION Study): A Randomized Controlled Trial

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Background: To compare the efficacy and safety of two insulin self-titration algorithms, Implementing New Strategies with Insulin Glargine for Hyperglycemia Treatment (INSIGHT) and EDITION, for insulin glargine 300 units/mL (Gla-300) in Korean individuals with uncontrolled type 2 diabetes mellitus (T2DM).
Methods: In a 12-week, randomized, open-label trial, individuals with uncontrolled T2DM requiring basal insulin were randomized to either the INSIGHT (adjusted by 1 unit/day) or EDITION (adjusted by 3 units/week) algorithm to achieve a fasting self-monitoring of blood glucose (SMBG) in the range of 4.4 to 5.6 mmol/L. The primary outcome was the proportion of individuals achieving a fasting SMBG ≤5.6 mmol/L without nocturnal hypoglycemia at week 12.
Results: Of 129 individuals (age, 64.1±9.5 years; 66 [51.2%] women), 65 and 64 were randomized to the INSIGHT and EDITION algorithms, respectively. The primary outcome of achievement was comparable between the two groups (24.6% vs. 23.4%, P=0.876). Compared with the EDITION group, the INSIGHT group had a greater reduction in 7-point SMBG but a similar decrease in fasting plasma glucose and glycosylated hemoglobin. The increment of total daily insulin dose was significantly higher in the INSIGHT group than in the EDITION group (between-group difference: 5.8±2.7 units/day, P=0.033). However, body weight was significantly increased only in the EDITION group (0.6±2.4 kg, P=0.038). There was no difference in the occurrence of hypoglycemia between the two groups. Patient satisfaction was significantly increased in the INSIGHT group (P=0.014).
Conclusion: The self-titration of Gla-300 using the INSIGHT algorithm was effective and safe compared with that using the EDITION algorithm in Korean individuals with uncontrolled T2DM (ClinicalTrials.gov number: NCT03406663).

Keywords: Algorithms; Blood glucose self-monitoring; Diabetes mellitus, type 2; Hypoglycemia; Insulin glargine; Patient satisfaction; Pragmatic clinical trial; Randomized controlled trial

INTRODUCTION

Insulin glargine 300 units/mL (Gla-300) is a three-fold concentrated formulation of insulin glargine 100 units/mL (Gla-100) that can be calibrated in 1-unit increments up to 80 units per injection [1]. In euglycemic clamp studies, Gla-300 provid-

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ed more constant pharmacokinetic and pharmacodynamic profiles than Gla-100 in individuals with type 1 diabetes mellitus (T1DM) [2,3]. The EDITION program compared the efficacy and safety of Gla-300 and Gla-100 in individuals with type 2 diabetes mellitus (T2DM) [4-7] and T1DM [8,9]. In the EDITION 1–3 trials [4-6], the doses of Gla-300 and Gla-100 were self-titrated to increase 3 or 6 units and to decrease 3 units once weekly (but no more often than every 3 days) with fasting self-monitoring of blood glucose (SMBG) to achieve a target range of 4.4 to 5.6 mmol/L (the EDITION algorithm). In the EDITION JP 2 trial for Japanese patients [7], the insulin doses were self-titrated to increase 1.5 or 3 units and to decrease 3 units to achieve the same target range. Both the EDITION 2 [5] and the EDITION JP 2 [7] trials were conducted in individuals with T2DM using basal insulin plus oral antidiabetic drugs (OADs). At the end of the study, the EDITION JP 2 trial showed a lower total daily insulin dose (TDD) (0.3 to 0.4 units/kg/day vs. 0.8 to 0.9 units/kg/day) and lower insulin increments from baseline (0.1 units/kg/day vs. 0.2 to 0.3 units/kg/day) than the EDITION 2 trial [5,7]. However, hypoglycemia occurred more frequently in the EDITION JP 2 trial than in the EDITION 2 trial [5,7]. The changes in glycosylated hemoglobin (HbA1c) levels from baseline were similar between the two studies [5,7]. In the EDITION 2 trial, the participants were mainly Caucasians, with a body mass index (BMI) of 34.8 ± 6.4 kg/m^2 at baseline [5]. In contrast, in the EDITION JP 2 trial, all participants were Japanese, with a baseline BMI of 25.3 ± 3.8 kg/m^2 [7]. Asians develop T2DM at a lower BMI than Caucasians [10], and there are ethnic differences in β-cell function [11], insulin sensitivity [12,13], and the incretin effect [14]. Therefore, these findings suggest that for the Asian population, a smaller dose of basal insulin adjustment may be more suitable than the EDITION algorithm.

The Canadian Implementing New Strategies with Insulin Glargine for Hyperglycemia Treatment (INSIGHT) study compared the efficacy of adding Gla-300 with that of titrating and/or adding OADs in individuals with uncontrolled T2DM who were taking moderate doses of OADs or not taking OADs [15]. Participants assigned to Gla-300 started with 10 units of Gla-300 and adjusted the dose by 1 unit every day until a fasting SMBG reached ≤5.5 mmol/L (the INSIGHT algorithm). In this study, the addition of Gla-300 using the INSIGHT algorithm showed better glycemic control with no difference in hypoglycemia compared with the titration and/or addition of OADs [15].

Currently, international clinical practice guidelines provide recommendations on the initiation and adjustment of basal insulin therapy [16-19]. Nevertheless, there is insufficient evidence to support or contradict a specific insulin titration algorithm for the management of T2DM. The TITRATION study compared the efficacy and safety of the two titration algorithms, INSIGHT and EDITION, for Gla-300 in individuals with T2DM, mainly from a primary care setting in Canada [20]. In a 12-week, randomized trial, the INSIGHT algorithm was as effective as the EDITION algorithm, but had greater patient and healthcare provider (HCP) satisfaction [20]. However, the efficacy and safety of the two algorithms have not been evaluated in the Asian population. In this regard, we investigated the efficacy and safety of the INSIGHT and EDITION algorithms for Gla-300 in Korean individuals with uncontrolled T2DM.

METHODS

Study population and ethical statement

We included individuals who were aged ≥19 years and had been treated for T2DM with or without basal insulin on non-insulin antihyperglycemic agents (NIAHAs). They had either an HbA1c level >7% and ≤10% with basal insulin (Gla-300, Gla-100, neutral protamine Hagedorn [NPH] insulin, or insulin detemir) or an HbA1c level >7% and ≤11% without basal insulin (insulin-naïve). We excluded individuals who were diagnosed with T1DM, who were unwilling to inject insulin or to perform SMBG, who initiated NIAHAs or changed the dose of NIAHAs in the previous 3 months, who were not on stable doses (±20%) of basal insulin in the previous 3 months, who were treated with insulin other than basal insulin in the last 3 months prior to screening, who were pregnant or lactating, and who were night shift workers.

This study was conducted following the principles established in the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of Seoul National University Hospital (IRB No. 1708-078-878) and is registered at ClinicalTrials.gov (ClinicalTrials.gov number: NCT03406663). All study participants provided written informed consent before participating in any study-related activities.

Study design

This study was a 12-week, single-center, pragmatic, randomized, open-label, and treat-to-target trial. The participants were

randomly assigned to either the INSIGHT or EDITION algorithm (1:1 ratio, stratified by prior insulin use) using web-based randomization from the Medical Research Collaborating Center at Seoul National University Hospital. Treatment allocation was concealed until the algorithms were assigned. As in the Canadian TITRATION study [20], all participants received Gla-300 with or without NIAHAs. Insulin-naïve individuals started Gla-300 at 0.2 units/kg. Individuals receiving once-daily Gla-100, NPH insulin, or insulin detemir switched basal insulin to the same dose of Gla-300. Individuals receiving twice-daily NPH insulin or insulin detemir started Gla-300 at 80% of the previous daily dose. Gla-300 was administered once daily at the same time of the day. In the INSIGHT group, the participants self-titrated the dose of Gla-300 by 1 unit/day until achieving a fasting SMBG in the range of 4.4 to 5.6 mmol/L (Supplementary Table 1). In the EDITION group, the participants self-titrated the dose of Gla-300 according to the median SMBG values of the last 3 days at least once weekly but no more often than every 3 days to achieve the same target range (Supplementary Table 1). The participants continued taking NIAHAs at the same dose during the study period. Fasting SMBG values were measured using participants' glucometers before breakfast and the administration of insulin or NIAHAs. After the instruction for each algorithm, the participants were followed up under usual care conditions to mimic real-world clinical practice in this pragmatic trial. They were allowed to contact the study site if they had any episodes of hypoglycemia or wanted to discuss insulin dose adjustments between scheduled visits. The study flow is depicted in Fig. 1.

The primary outcome was the proportion of individuals achieving a fasting SMBG ≤5.6 mmol/L without nocturnal hypoglycemia at week 12 (Supplementary Table 2). The fasting SMBG value was measured with 7-point SMBG on one of the three days prior to the week 12 visit. The secondary outcomes were changes in 7-point SMBG, laboratory-measured fasting plasma glucose (FPG), and HbA1c from week 0 to week 12; the proportion of individuals with HbA1c ≤7.0% at week 12; changes in body weight and TDD from week 0 to week 12; the rate of hypoglycemic events (confirmed, symptomatic, or severe) (Supplementary Table 2) [21] during the study period; adherence and patient satisfaction to insulin titration algorithms. We evaluated treatment adherence with the proportion of patients adjusting the dose of Gla-300 according to each algorithm during the study period. Patient satisfaction was measured using the Korean version of the Diabetes Treatment Satisfaction Questionnaire-status (DTSQs) score, ranging from 0 (very dissatisfied/inconvenient/inflexible, none of the time, or definitely not recommend) to 6 (very satisfied/convenient/flexible, most of the time, or definitely recommend) [22,23].

We assessed the degree of pragmatism using the PRagmatic Explanatory Continuum Indicator Summary 2 (PRECIS-2) tool (Supplementary Table 3), scored from 1 (very explanatory) to 5 (very pragmatic) [24], and reported the results according to the Consolidated Standards of Reporting Trials (CONSORT) 2010 statement (Supplementary Table 4) [25].

Statistical analysis

The objective of the study is to provide descriptive statistics on the efficacy and safety of the two insulin titration algorithms in Korean individuals with uncontrolled T2DM. The initial planned number of participants was 180. The sample size was calculated, assuming that the proportion of individuals reaching the primary outcome was 30% with a 95% confidence interval and that the dropout rate was 10% in each group. How-

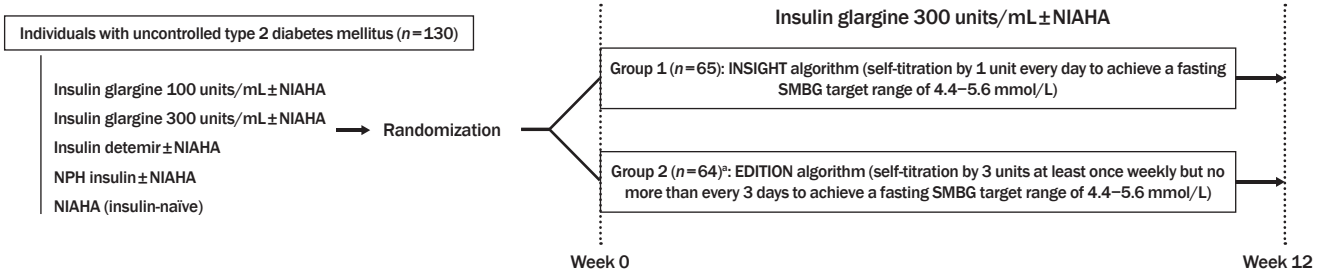

Fig. 1. Study design. The participants were randomly assigned to either the Implementing New Strategies with Insulin Glargine for Hyperglycemia Treatment (INSIGHT) or EDITION group and self-titrated the dose of insulin glargine 300 units/mL according to each algorithm for 12 weeks. NIAHA, noninsulin antihyperglycemic agents; NPH, neutral protamine Hagedorn; SMBG, self-monitoring of blood glucose. [a]In group 2, one individual was excluded owing to the withdrawal of informed consent.

ever, since this was a single-center study, some difficulties were encountered with timely patient recruitment. Based on the interim analysis, we amended the assumed proportion of individuals with the primary outcome and the dropout rate as 20% and 5%, respectively. As a result, 130 individuals were finally enrolled in this study.

Continuous variables are presented as the mean±standard deviation. Categorical variables are presented as numbers (%). All analyses were conducted according to the intention-to-treat principle. The primary outcome and the proportion of individuals with HbA1c ≤7.0% at week 12 were analyzed by the chi-square test. Changes in 7-point SMBG from week 0 to week 12 were analyzed using repeated measures analysis of variance (ANOVA). Changes in the area under the curve (AUC) of 7-point SMBG, FPG, HbA1c, body weight, TDD, and DTSQs scores from week 0 to 12 were analyzed using paired *t*-test. Adherence to each algorithm was analyzed by unpaired *t*-tests. All analyses were performed with GraphPad Prism version 8.4.3 (GraphPad Software Inc., San Diego, CA, USA). *P* values <0.05 were regarded as statistically significant.

RESULTS

Characteristics of the study participants

Of 130 individuals evaluated for this study, 129 (65 and 64 in the INSIGHT and EDITION groups, respectively) were included. One individual was excluded owing to the withdrawal of informed consent. The baseline characteristics of the participants are described in Table 1. The mean HbA1c level was 8.4%, and 90.7% of the participants had been using basal insulin. The mean body weight and TDD were 66.2 kg and 26.4 units/day, respectively. There were no significant differences between the two groups at baseline.

Table 1. Baseline characteristics of the study participants

Characteristic	INSIGHT (*n*=65)	EDITION (*n*=64)	*P* value
Age, yr	63.7±8.8	64.5±10.2	0.658
Range, yr	36–77	22–86	
Men/Women	35/30	28/36	0.332
Body weight, kg	67.3±10.5	65.1±11.3	0.255
Body mass index, kg/m^2	25.5±2.8	25.1±3.0	0.415
Range, kg/m^2	20.6–33.3	19.5–35.0	
Fasting plasma glucose, mmol/L	7.8±2.1	8.0±2.3	0.704
HbA1c, %	8.4±0.7	8.4±0.8	0.758
Prior basal insulin treatment	59 (90.8)	58 (90.6)	0.999
Total insulin dose, units/day	26.9±13.0	25.9±12.9	0.651
NIAHA			
Metformin	61 (93.8)	51 (81.2)	0.057
Sulfonylurea	35 (55.4)	35 (54.7)	0.999
Glinides	0	2 (3.1)	0.469
Thiazolidinediones	0	1 (1.6)	0.934
DPP-4 inhibitors	30 (46.2)	31 (48.4)	0.934
GLP-1 receptor agonists	3 (4.6)	2 (3.1)	0.999
SGLT2 inhibitors	5 (7.7)	6 (9.4)	0.979
α-Glucosidase inhibitors	1 (1.5)	1 (1.6)	0.999
Hypertension	44 (66.7)	43 (67.2)	0.999
Hyperlipidemia	52 (80.0)	55 (85.9)	0.508

Values are presented as mean±standard deviation or number (%).
INSIGHT, Implementing New Strategies with Insulin Glargine for Hyperglycemia Treatment; HbA1c, glycosylated hemoglobin; NIAHA, noninsulin antihyperglycemic agent; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT2, sodium-glucose cotransporter 2.

Glycemic control, insulin dosage, and body weight

The percentages of individuals achieving a fasting SMBG ≤5.6 mmol/L without nocturnal hypoglycemia at week 12 were 24.6% and 23.4% in the INSIGHT and EDITION groups, respectively (*P*=0.876) (Fig. 2). From week 0 to week 12, the corresponding differences in the mean 7-point SMBG values were –2.47 mmol/L (*P*<0.001) and –1.03 mmol/L (*P*=0.017) in the two groups. In the INSIGHT group, the SMBG values were significantly decreased at prebreakfast (*P*=0.001), postlunch (*P*=0.002), predinner (*P*<0.001), postdinner (*P*=0.001), and bedtime (*P*=0.001) (Fig. 3A). In the EDITION group, the SMBG values were significantly decreased only at prebreakfast (*P*=0.031) (Fig. 3A). The AUC of 7-point SMBG was significantly reduced in the INSIGHT group (–15.41±17.68 mmol·hr/L, *P*<0.001) but not in the EDITION group (–3.78±15.58 mmol·hr/L, *P*=0.107) during the same period (Fig. 3B). The INSIGHT and EDITION groups showed similar decreases in laboratory-measured FPG (–1.7±2.5 mmol/L vs. –1.5±2.6 mmol/L, *P*=0.568) and HbA1c (–0.7%±0.8% vs. –0.5%±0.9%, *P*=0.200) from week 0 to week 12. There was no difference in the proportion of individuals with HbA1c ≤7.0% at week 12 between the two groups (23.1% vs. 20.3%, *P*=0.703).

The TDD of Gla-300 was significantly increased from week 0 to week 12 in both the INSIGHT (12.7±19.0 units/day, *P*<0.001) and EDITION (6.8±10.5 units/day, *P*<0.001) groups

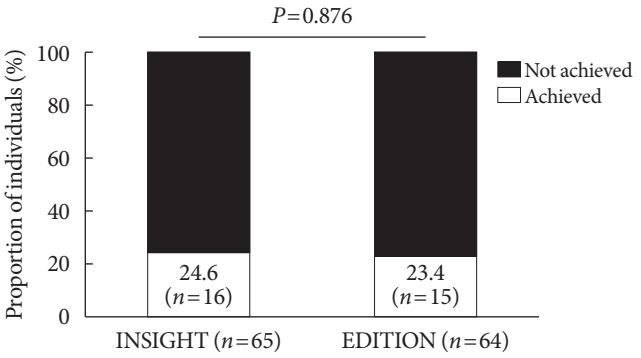

Fig. 2. The proportion of individuals with type 2 diabetes mellitus achieving a fasting self-monitoring of blood glucose value ≤5.6 mmol/L without hypoglycemia at week 12. Data are presented as proportion (%). The analysis was performed according to the intention-to-treat principle ($n=129$). P values <0.05 were regarded as statistically significant. INSIGHT, Implementing New Strategies with Insulin Glargine for Hyperglycemia Treatment.

(Fig. 4A). The increment of TDD was significantly higher in the INSIGHT group than in the EDITION group (between-group difference: 5.8±2.7 units/day, $P=0.033$). At week 12, body weight was not changed from baseline in the INSIGHT group (–0.5±7.2 kg, $P=0.576$). However, in the EDITION group, there was a small but significant increase in body weight (0.6±2.4 kg, $P=0.038$) (Fig. 4B). There was no significant change in BMI from baseline to week 12 in the INSIGHT (–0.3±3.8 kg/m^2, $P=0.487$) and EDITION (–0.1±3.6 kg/m^2, $P=0.857$) groups.

Hypoglycemia and adverse events

During the study period, there was no difference in the rate of hypoglycemic events between the INSIGHT and EDITION groups (0.8±1.8 events/person vs. 0.7±1.5 events/person, $P=0.785$). None of the participants experienced severe hypoglycemia. No treatment-emergent adverse events, except for hypoglycemia, were observed.

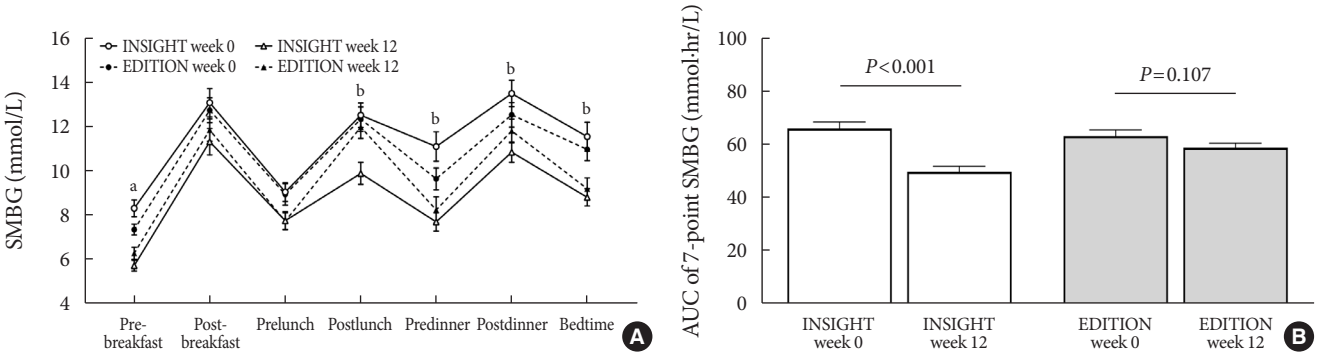

Fig. 3. Changes in (A) 7-point self-monitoring of blood glucose (SMBG) values and (B) the area under the curve (AUC) from week 0 to week 12. Data are presented as mean and standard error of the mean. The analysis was performed according to the intention-to-treat principle ($n=129$). P values <0.05 were regarded as statistically significant. INSIGHT, Implementing New Strategies with Insulin Glargine for Hyperglycemia Treatment. There was a significant decrease in SMBG levels from week 0 to week 12 in [a]the abovementioned groups and the [b]INSIGHT group.

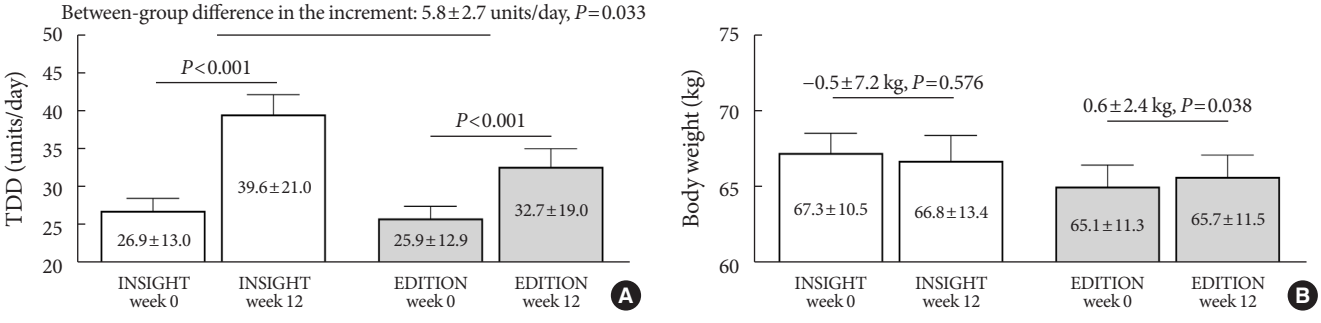

Fig. 4. Changes in (A) total daily insulin dose (TDD) and (B) body weight from week 0 to week 12. Data are presented as mean and standard error of the mean. The analysis was performed according to the intention-to-treat principle ($n=129$). P values <0.05 were regarded as statistically significant. INSIGHT, Implementing New Strategies with Insulin Glargine for Hyperglycemia Treatment.

Adherence and patient satisfaction

Adherence to the insulin titration algorithms during the entire study period tended to be higher in the INSIGHT group than in the EDITION group (45.7%±35.0% vs. 35.3%±33.7%, P=0.088). Patient satisfaction, measured by the DTSQs scores, was significantly increased in the INSIGHT group (2.5±7.6, P=0.014) but significantly decreased in the EDITION group (–0.1±7.5, P=0.020).

DISCUSSION

This 12-week, pragmatic, randomized trial compared the efficacy and safety of the two insulin titration algorithms, INSIGHT and EDITION, for Gla-300 in Korean individuals with uncontrolled T2DM. The proportion of individuals achieving a fasting SMBG ≤5.6 mmol/L without nocturnal hypoglycemia at week 12 was comparable between the two groups. The INSIGHT group showed a greater reduction in 7-point SMBG than the EDITION group. The changes in laboratory-measured FPG and HbA1c and the proportion of individuals with HbA1c ≤7.0% at week 12 were similar in the two groups. Compared with the EDITION group, the INSIGHT group had a significantly higher increment of Gla-300 dose but showed less weight gain and no difference in hypoglycemia. Patient satisfaction was greater in the INSIGHT group than in the EDITION group, along with nominally higher treatment adherence.

The progressive nature of T2DM necessitates insulin therapy in addition to NIAHAs in many patients, particularly in those with longer disease durations [26]. Insulin therapy should also be considered when patients have evidence of catabolic features such as weight loss and ketosis or have severe and symptomatic hyperglycemia [17]. Basal insulin with or without NIAHAs is usually preferred, and, if the treatment fails, prandial or bolus insulin needs to be added [27]. However, both patients and HCPs often delay treatment initiation or intensification owing to barriers to insulin therapy, including clinical inertia, burdensome regimens, and fear of hypoglycemia or weight gain [28]. Therefore, a simple, effective, and safe insulin regimen is needed to improve glycemic control in individuals with T2DM.

The INSIGHT group, which used a simpler self-titration of Gla-300, showed similar glycemic responses with significant improvement in 7-point SMBG values compared with the EDITION group. Insulin dose optimization using the INSIGHT algorithm improved postprandial hyperglycemia accompanied by a decrease in fasting or preprandial glucose levels, leading to improvement in the AUC of 7-point SMBG. In both groups, the participants adjusted the dose of Gla-300 based on fasting SMBG values. Previous studies demonstrated that the self-titration of basal insulin was superior to physician-led titration in terms of HbA1c reduction [29,30]. In our study, the INSIGHT group showed no difference in HbA1c reduction despite the improvement of 7-point SMBG values compared with the EDITION group. These findings were probably because the duration of improvement in the SMBG values was not enough to lower HbA1c levels in the INSIGHT group. A longer duration of follow-up would have revealed a greater HbA1c reduction in the INSIGHT group than in the EDITION group. In addition, individuals in our study were more likely to achieve the primary endpoint of a fasting SMBG ≤5.6 mmol/L without nocturnal hypoglycemia at week 12 than those in the Canadian TITRATION study (24.6% vs. 19.4% for the INSIGHT group; 23.4% vs. 18.3% for the EDITION group) [20]. In summary, patient-led insulin titration according to the INSIGHT algorithm would also be suitable for Korean individuals with uncontrolled T2DM.

The TDD of Gla-300 was significantly increased from week 0 to week 12 in the INSIGHT (0.4 to 0.6 units/kg) and EDITION (0.4 to 0.5 units/kg) groups. Treat-to-target trials [31,32] often used a higher TDD of basal insulin than observational studies [33,34]. In our study, the increase in the Gla-300 dose was significantly higher in the INSIGHT group than in the EDITION group. However, there was no difference in hypoglycemic events (confirmed, symptomatic, or severe) between the two groups, and weight gain, albeit very small in amount, was observed only in the EDITION group. Despite advances in insulin therapy, it was reported that many individuals with T2DM using basal insulin did not achieve individualized HbA1c targets in a real-world setting [35]. Concerns regarding hypoglycemia and weight gain are important factors leading to suboptimal insulin titration by both patients and HCPs [28,36-38]. However, optimizing insulin therapy with timely intensification could reduce hyperglycemia without worsening hypoglycemia or weight gain [39]. Furthermore, in line with our findings, the simple self-titration of Gla-100 increased the insulin dose but significantly improved glycemic control with a low incidence of severe hypoglycemia compared with physician-led titration [30]. Therefore, our results indicated that the INSIGHT algorithm could result in the optimal dosing of basal insulin without an increase in hypoglycemia and body weight

compared with the EDITION algorithm.

In the present study, adherence to the insulin titration algorithms tended to be higher in the INSIGHT group than in the EDITION group. As our study was a pragmatic trial conducted under routine clinical practice, treatment adherence to each algorithm was lower than that in the Canadian TITRATION study (45.7%±35.0% vs. 94.2%±16.2% for the INSIGHT group; 35.3%±33.7% vs. 96.1%±11.1% for the EDITION group) [20]. Adherence to insulin therapy is affected by various factors related to patients, HCPs, and treatments [40]. In the Canadian TITRATION study [20], investigators assessed the treatment responses weekly and determined the insulin dose adjustment for the EDITION group. Moreover, investigators could contact participants at any time to ensure that they titrated insulin by the SMBG results in both groups [20]. On the other hand, in our study, the participants were allowed to call the study site if they had hypoglycemia or would like to discuss insulin titration, but no actual contact was made during the study period. A retrospective cohort study showed that medication nonadherence, defined as the proportion of days covered <80%, was associated with an increase in HbA1c, hospitalization, and mortality in patients with diabetes mellitus (DM) [41]. Furthermore, in patients with T2DM taking insulin, medication nonadherence, defined as ≥1 missing visit or provider code for not taking medications, was associated with an increased risk of all-cause mortality [42]. Consequently, the INSIGHT algorithm may enhance treatment adherence, thereby improving clinical outcomes in patients with T2DM who require insulin therapy.

Patient satisfaction was significantly increased in the INSIGHT group but significantly decreased in the EDITION group. Previous studies with injectable therapies have shown that a simplified regimen improves patient satisfaction in patients with T2DM [43,44]. From psychosocial and behavioral perspectives, diabetes-related distress, including the burden of treatment and worries about adverse consequences, can influence treatment satisfaction and health outcomes in patients with DM [45]. In insulin-naïve patients with T2DM, those who were ambivalent or unwilling to start insulin had more negative perceptions and diabetes-related stress than willing patients [46]. In a cross-sectional study in Europe, treatment satisfaction in patients with T2DM on insulin therapy was also associated with diabetes education, perceived and actual hyperglycemia, and macrovascular complications [47]. In our study, the INSIGHT algorithm revealed similar glycemic control without hypoglycemia and weight gain compared with the EDITION algorithm. Simple titration adjusting basal insulin 1 unit/day might turn every fasting SMBG data point into actionable data for patients struggling with burdensome regimens [28]. In addition, although not evaluated in our study, HCPs also preferred the INSIGHT algorithm over the EDITION algorithm in the Canadian TITRATION study [20].

This study has several limitations. First, this study was an open-label trial. As the investigators and participants were aware of the treatment allocation, this might cause bias in the assessment or reporting of outcomes. However, because the investigators did not intervene other than instructing the titration algorithm, it would have been minimized in this pragmatic, randomized trial. Second, since the duration of the study was short, the long-term effects of the INSIGHT algorithm on diabetes-related outcomes could not be evaluated compared with the EDITION algorithm.

In conclusion, the self-titration of Gla-300 using the INSIGHT algorithm was effective and safe, with similar glycemic control, less weight gain, and greater patient satisfaction, in Korean individuals with uncontrolled T2DM compared with that using the EDITION algorithm. Further research is needed to ascertain whether overcoming barriers to insulin therapy using the INSIGHT algorithm results in sustained glycemic control and improvement in diabetes-related outcomes in patients with T2DM.

SUPPLEMENTARY MATERIALS

Supplementary materials related to this article can be found online at https://doi.org/10.4093/dmj.2020.0274.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Conception or design: J.H.B., Y.M.C.
Acquisition, analysis, or interpretation of data: J.H.B., C.H.A., Y.S.Y., S.J.M., S.H.K., H.S.J., K.S.P., Y.M.C.
Drafting the work or revising: J.H.B., Y.M.C.
Final approval of the manuscript: J.H.B., C.H.A., Y.S.Y., S.J.M., S.H.K., H.S.J., K.S.P., Y.M.C.

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Supplementary Table 1. Insulin dose titration algorithms

Group 1 (INSIGHT algorithm)
• Patients are instructed to adjust the dose of insulin glargine 300 units/mL (Gla-300) by 1 unit per day until achieving a fasting self-monitoring of blood glucose (SMBG) in the range of 4.4–5.6 mmol/L.
• When fasting SMBG values are in the range of
1. >5.6 mmol/L, increase 1 unit of Gla-300 dose
2. ≥4.4 and ≤5.6 mmol/L, no change
3. <4.4 mmol/L, decrease 1 unit of Gla-300 dose
Group 2 (EDITION algorithm)
• Patients are instructed to adjust the dose of Gla-300 once weekly based on the median SMBG values of the last 3 days (including the current day) but no more than every 3 days to achieve a fasting SMBG in the range of 4.4–5.6 mmol/L.
• When fasting SMBG values are in the range of
1. ≥7.8 mmol/L, increase 6 units of Gla-300 dose
2. >5.6 and <7.8 mmol/L, increase 3 units of Gla-300 dose
3. ≥4.4 and ≤5.6 mmol/L, no change
4. ≥3.3 and <4.4 mmol/L, decrease 3 units of Gla-300 dose
5. <3.3 mmol/L, or the occurrence of ≥2 symptomatic or ≥1 severe hypoglycemic episodes in the preceding week, decrease 3 units of Gla-300 dose or at the discretion of the investigator
Both groups (INSIGHT and EDITION algorithms)
• Participants are allowed to contact the study site if they have any episodes of hypoglycemia or want to discuss insulin dose adjustments between scheduled visits.

INSIGHT, Implementing New Strategies with Insulin Glargine for Hyperglycemia Treatment.

Supplementary Table 2. Definition of hypoglycemic events

Nocturnal hypoglycemia
• Defined as hypoglycemia, confirmed by typical symptoms or self-monitoring of blood glucose (SMBG) ≤3.9 mmol/L, occurring 1. Between bedtime and the administration of insulin glargine 300 units/mL (Gla-300) or noninsulin antihyperglycemic agents (NIAHAs) in case they are administered in the morning. 2. Between bedtime and measurement of fasting SMBG in case Gla-300 or NIAHAs are administered after the morning.
Confirmed hypoglycemia
• An event during which typical symptoms of hypoglycemia are accompanied by an SMBG value or a measured plasma glucose level ≤3.9 mmol/L.
Symptomatic hypoglycemia
• Mild hypoglycemia: Neurogenic symptoms, such as palpitations, tremors, and arousal/anxiety (adrenergic), or sweating, hunger, and paresthesia (cholinergic), are present. The individual can treat hypoglycemia by oneself without the assistance of another person. • Moderate hypoglycemia: Neurogenic (see mild hypoglycemia) and neuroglycopenic (such as behavioral changes, fatigue, confusion to seizure, and loss of consciousness) symptoms are present. The individual can treat hypoglycemia by oneself without the assistance of another person.
Severe hypoglycemia
• An event requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. SMBG or plasma glucose measurements may not be available during an event, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose level.

Supplementary Table 3. PRECIS-2 scores for nine domains

Domain	Score	Rationale
Eligibility—To what extent are the participants in the trial similar to those who would receive this intervention if it was part of usual care?	5	We included patients with type 2 diabetes mellitus who required insulin therapy and who were willing to inject insulin or to use self-monitoring of blood glucose (SMBG) under usual care conditions.
Recruitment—How much extra effort is made to recruit participants over and above what would be used in the usual care setting to engage with patients?	4	In routine clinical practice, the participants were recruited if they wanted to be engaged in the study during scheduled visits.
Setting—How different are the settings of the trial from the usual care setting?	5	The settings of the trial were not different from usual care except that the participants were recommended to adjust insulin doses according to assigned algorithms.
Organization—How different are the resources, provider expertise, and the organization of care delivery in the intervention arm of the trial from those available in usual care?	5	The number of healthcare providers or other professionals was not changed above the levels available in usual care.
Flexibility (delivery)—How different is the flexibility in how the intervention is delivered and the flexibility anticipated in usual care?	4	The participants adjusted insulin doses by assigned algorithms that were similar to usual care.
Flexibility (adherence)—How different is the flexibility in how participants are monitored and encouraged to adhere to the intervention from the flexibility anticipated in usual care?	5	The participants adjusted insulin doses based on fasting SMBG values. Fasting SMBG values were measured using participants' glucometers.
Follow-up—How different is the intensity of measurement and follow-up of participants in the trial from the typical follow-up in usual care?	5	After the initial visit (at week 0), the participants were followed up at week 12 under usual care conditions.
Primary outcome—To what extent is the trial's primary outcome directly relevant to participants?	5	The primary outcome was directly relevant to the participants.
Primary analysis—To what extent are all data included in the analysis of the primary outcome?	5	All analyses were conducted according to the intention-to-treat principle.

Scoring each domain can be done using a 5-point Likert scale: 1, very explanatory; 2, rather explanatory; 3, equally pragmatic and explanatory; 4, rather pragmatic; 5, very pragmatic.
PRECIS-2, PRagmatic Explanatory Continuum Indicator Summary 2.

Supplementary Table 4. CONSORT 2010 checklist

Section/Topic	Item no.	Checklist item	Reported on page no.
Title and abstract			
	1a	Identification as a randomized trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4, 5
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel and factorial), including allocation ratio	6, 7, Fig. 1
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	8
Participants	4a	Eligibility criteria for participants	5, 6
	4b	Settings and locations where the data were collected	6, 7
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6, 7, Supplementary Table 1
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	7
	6b	Any changes to trial outcomes after the trial commenced, with reasons	Not applicable
Sample size	7a	How sample size was determined	8
	7b	When applicable, explanation of any interim analyses and stopping guidelines	Not applicable
Randomization:			
Sequence generation	8a	Method used to generate the random allocation sequence	6
	8b	Type of randomization; details of any restriction (such as blocking and block size)	6
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	6
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, and those assessing outcomes) and how	Not applicable
	11b	If relevant, description of the similarity of interventions	7, Supplementary Table 1
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	8
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	Not applicable

(*Continued to the next page*)

Supplementary Table 4. Continued

Section/Topic	Item no.	Checklist item	Reported on page no.
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	9, Fig. 1
	13b	For each group, losses and exclusions after randomization, together with reasons	9, Fig. 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	Not reported
	14b	Why the trial ended or was stopped	Not applicable
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analyzed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	9
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	9, 10
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Not applicable
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Not applicable
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	10
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	14
Generalizability	21	Generalizability (external validity and applicability) of the trial findings	10–14
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	10–14
Other information			
Registration	23	Registration number and name of trial registry	3, 6
Protocol	24	Where the full trial protocol can be accessed, if available	Not applicable
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	15

Adapted from Schulz et al. [25].
CONSORT, Consolidated Standards of Reporting Trials.