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Real-World Data Collection Regarding Titration Algorithms for Insulin Glargine in Patients With Type 2 Diabetes Mellitus

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Abstract

The primary objective of this study was to collect data regarding the effectiveness of different dose titration algorithms (TAs) for optimization or initiation of basal insulin supported oral therapy (BOT) in patients with type 2 diabetes. A total of 50 patients were enrolled in this trial (17 women, 33 men, age 63 ± 8 years, HbA1c 7.9 ± 0.8%). The investigator decided on an individual basis to apply any of 4 standard TAs: standard (S: fasting glucose target 90-130 mg/dL, n = 39), standard-fast titration (S-FT: 90-130 mg/dL, larger dose increments at FBG < 180 mg/dl, n = 1), less tight (LT: 110-150 mg/dL, n = 5), and tight (T: 70-100 mg/dL, n = 5). During the next 30 days daily contacts were used to adapt the insulin dose. The majority of all patients (70%) achieved a stable insulin glargine dose within 5 ± 6 days after initiation of the dose titration. HbA1c improved from 7.9 ± 0.8% to 7.5 ± 0.7% ($P < .001$). In total, 1300 dose decisions were made (1192 according to the TA and 108 by the physicians independently from the TA in 29 patients [58% of study population]). Reasons for TA-overruling dosing decisions were hypoglycemic events (14 mild/4 moderate) in 9 patients. In the majority of these cases (89.8%), the physician recommended continuation of the previous dose or a higher dose. The majority of FBG values were within the respective target range after 4 weeks. In conclusion, the insulin glargine TAs delivered safe dose recommendations with a low risk of hypoglycemia, which successfully led to a stable dose in the vast majority of patients.

Keywords

fasting blood glucose, basal insulin, titration algorithm

The current joint position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) emphasizes the individualization of both glycemic targets and the treatment approach for the management of type 2 diabetes mellitus (T2DM).[1] In this guideline, early combination of oral drugs and insulin is recommended, when treatment targets are not achieved within reasonable time periods. Addition of basal insulin to the existing oral drug regimen has become a well-accepted option for treatment intensification in many countries. Long-acting insulin analogs, such as insulin glargine, glargine U300, insulin detemir, and insulin degludec have a very flat time action profile. They offer the possibility to treat the patient to a fasting blood glucose (FBG) target, which is in the normal reference range, without major increase of the risk of nocturnal hypoglycemia.[2-5] The glucose target is best achieved by using a titration procedure, where the FBG level measured in the morning is used to determine the basal insulin dose in the following evening of the same day. In contrast to calculation of the prandial insulin dose, which considers the actual glucose value and the size of the planned meal, the basal insulin dose determination should consider the results from the previous basal doses. In consequence, dose changes are made in a much more conservative way to achieve a stable trend and finally reach the desired target blood glucose level over several days and weeks. This titration process is usually guided and supervised by the responsible health care professional. However, basal insulin titration is not really challenging, and patient-driven titration is a growing trend that can facilitate the introduction of BOT. Two clinical studies have been reported investigating the effectiveness and safety of a patient driven approach versus the physician

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directed titration. The AT.LANTUS and PREDICTIVE (Predictable Results and Experience in Diabetes through Intensification and Control to Target: An International Variability Evaluation) studies both clearly showed that patients can safely and effectively titrate their own basal insulin if given adequate instructions.[6,7]

In the AT.LANTUS study, patients using a self-titration algorithm achieved significantly larger reductions in their fasting glucose levels compared to patients using a physician-directed algorithm (−62 mg/dL vs −57 mg/dL; $P < .001$). They also experienced significantly larger HbA1c reductions of −1.22% (vs −1.08%; $P < .001$), but symptomatic hypoglycemia occurred at a significantly higher rate with the patient-driven algorithm. Differences in the rates of severe and nocturnal hypoglycemia were not statistically significant and weight gain was similar in the 2 treatment groups.[6] In the PREDICTIVE study, patients self-titrating their insulin dose also experienced significantly higher HbA1c reduction (−0.6% vs −0.5%; p< 0.01) and fasting glucose reductions (−34 mg/dL vs −22 mg/dL; $P < .0001$) compared to patients whose basal insulin doses were determined by a physician. The clinical relevance of the detected significant differences, however, may be negligible. Overall hypoglycemia frequency was higher among patients self-titrating their insulin dose (6.44 events/patient/year vs 4.95 events/patient/year), but severe hypoglycemic events were rare in both groups (0.26 events/patient/year vs 0.20 events/patient/year; ns).[7]

While it has been shown that patients, when well instructed may achieve similar results than health care professionals, modern technology also suggests use of treatment algorithm software programs, which may provide web-based or device-based support for basal insulin dose calculation, to facilitate the dose titration process in daily routine ("dose coach"). For the development of such software, it is important to understand the circumstances that may be associated with deviations between an algorithm-based basal insulin dose and the dose selected by a physician.

This study was performed as part of the development of the MyStar "Dose Coach" (Sanofi, Paris, France) with the primary objective to collect data regarding the effectiveness of different dose titration algorithms (TAs) for optimization or initiation of basal insulin glargine supported oral therapy (BOT) in patients with type 2 diabetes, when applied in daily routine practice and to understand the nature and reason of dose differences between software and health care professional. The development of the TAs was based on the current literature on basal insulin titration as summarized in Arnolds et al[8] and recent guidelines for insulin treatment of type 2 diabetes.[1]

Patients and Methods

This open-label, prospective, uncontrolled study was performed in accordance with the principles of the Declaration of Helsinki and good clinical practice and in compliance with national and local regulations (EUDRA-CT 2011-005806-32) . The protocol was approved by the responsible institutional review board, and patients gave written informed consent prior to any study procedure.

The primary objective was to collect data sets regarding the use of TAs for implementation of BOT with insulin glargine in patients previously treated with insulin glargine alone or for optimizing BOT by means of titration rules. The goal was to collect 50 well-documented individual patient cases with at least 50% of the necessary data sets (at least 13 insulin glargine dose and resulting FBG values). Secondary objectives included an assessment of effectiveness of the applied titration rules and the number of patients with stable glargine dose after 4 weeks. Also, the time to achieve a stable insulin glargine dose during the study period was evaluated. This was defined as the first time (first day) of reaching a stable insulin dose (no changes occurred regarding the taken insulin glargine dose on 10 consecutive days). Safety was addressed by monitoring the occurrence of adverse events, hypoglycemic events, that is, blood glucose values below the study specific limit (<70 mg/dL) or hypoglycemic symptoms reported by the patient. Vital signs and a potential pregnancy in women with childbearing potential were controlled at time of enrollment and at the final visit.

Participants were male and female patients with type 2 diabetes between 30 and 75 years of age and with a stable BOT therapy (insulin glargine combined with oral hypoglycemic agents) or insulin glargine alone currently achieving an HbA1c level between >6.5 to ≤9.5%, and with a body mass index ≤ 40 kg/m2. At enrollment, each patient was assigned by the physician to 1 of 4 available activation keys, which defined the rules for the insulin glargine TA. The activating investigator chose the activation key, which in his/her clinical opinion suited best the individual patient needs. The titration rules of the 4 TAs are provided in Table 1. Duration of study participation for 1 patient completing the study was approximately 35 days. After enrollment at V1 (–7 to 2 days before V2) and at V2 (activation of titration) baseline values were established with a constant insulin glargine dose, which was selected by the physician.

During the next 28 consecutive days, the patients had daily contact with the investigator either personally or by phone to discuss the blood glucose data, the finally injected dose of insulin glargine, and eventually any (serious) adverse event occurred since the last visit with special focus on hypoglycemic (<70 mg/dL) and hyperglycemic episodes (>250 mg/dL). During the visit, the patient received an adapted insulin glargine dosing recommendation. For this purpose, the rules engine used for this procedure was displayed in a flow chart to the physician, who checked, whether the dose recommendation derived from the rules engine was in accordance with his own dosing estimate for the patient. The measured FBG values, dosing recommendations given by the insulin glargine TA, and the investigator's approval or deviating dosing recommendation (with a reason for overruling the algorithm) were recorded. In case of any FBG measurement below the

Table 1. Titration Rules and Results of the 4 Activation Keys.

	Standard	S-FT	LT	70-100 target
Titration rules				
Target blood glucose	90-130 mg/dL (5.0-7.2 mmol/L)	90-130 mg/dL (5.0-7.2 mmol/L)	110-150 mg/dL (6.1-8.3 mmol/L)	70-100 mg/dL (3.9-5.6 mmol/L)
Up-titration	+2 IU every 3 days	+4 IU every 3 days if glucose value >180 mg/dL (10 mmol/L), then +2 IU every 3 days	+2 IU every 3 days	+2 IU every 3 days
Very low blood glucose value	70 mg/dL (3.9 mmol/L)	70 mg/dL (3.9 mmol/L)	70 mg/dL (3.9 mmol/L)	60 mg/dL (3.3 mmol/L)
Results				
n	40	1	5	4
Patients achieving a stable dose (n)	29 (73%)	0 (0%)	4 (80%)	2 (50%)
Time to first stable dose	6 ± 6 days	—	4 ± 6 days	2 ± 2 days
Duration of first stable dose period	18 ± 6 days	—	19 ± 4 days	17 ± 1 days
Insulin dose in stable patients	23 ± 10 IU	—	21 ± 5 IU	25 ± 4 IU
Insulin dose in instable patients	32 ± 9 IU	57 IU	42 IU	28 ± 7 IU

very low limit as defined for each algorithm (see Table 1), a dose reduction of 2 IU, 4 IU, or 10% in case of doses > 40 IU per day was immediately enforced.

The primary and secondary efficacy variables were analyzed by means of descriptive statistics: mean value, standard deviation, minimum value, 1st quartile, median, 3rd quartile, maximum value, number of nonmissing values for continuous variables and counts per category, percentages per category, and number of nonmissing values for categorical variables were calculated and listed. The collected data were analyzed in an exploratory sense with inferential statistics: Continuous variables, which were measured at 2 different visits were compared by applying a 2-sided paired *t* test or alternatively Wilcoxon signed rank test if a normal distribution was not met. In addition, Pearson product–moment correlation coefficient or alternatively Spearman's correlation coefficient was used. A P value < .05 was considered statistically significant.

Results

A total of 54 patients were screened and 51 could be enrolled into this protocol. One patient needed to be excluded from the analysis because of major protocol violation (noncompliance with the dosing recommendations), and 50 patients could be finally included into this analysis (17 female, 33 male, age [mean ± SD]: 63 ± 8 years, BMI: 30.1 ± 5.0 kg/m², HbA1c: 7.9 ± 0.8%). Patients were either treated with insulin glargine alone (12 patients) or with additional oral drugs or oral drug combinations (metformin: 80%, sulfonylurea: 10%, pioglitazone: 8%, DPPIV inhibitors: 8%). Activation key 1 (standard) was selected for 40 patients (standard-faster titration: 1 patient, less-tight target: 5 patients, 70-100 target: 4 patients). The primary objective to collect 50 well-documented individual patient cases with at least 50% of the necessary data sets (at least 13 insulin glargine dose and resulting FBG values) was achieved. A minimum of 26 dose and FBG pairs for each patient could be obtained. This was the basis for the subsequent analysis of the usability of the TA for implementation of a BOT with insulin glargine in patients previously treated with insulin glargine alone or for optimizing of BOT by means of titration rules.

Different topics, for example, the time to achieve a stable insulin glargine dose within the titration phase, the duration of this phase, and how many patients had a stable dose after 4 weeks were investigated. The majority of all patients (70%) achieved a stable insulin glargine dose during the titration phase, which was reached early with a mean of 5 ± 6 days after initiation of the dose adaption. The proportion of patients who achieved a stable dose differed between the 4 allocation groups. Most of the patients in the "standard" and the "less-tight target" activation key group reached this goal (72.5% and 80%, respectively). The other groups were too small to perform a thorough analysis. Two of the 4 patients in the stringent "70-100 target" key group (50%) achieved a stable dose and the single patient in the "standard-fast initial titration" key failed to reach a stable dose during the dose adaption period (see Table 1).

During the 28 day titration phase the FBG values were about half of the time (14.6 ± 6.24 days) within the respective target range for all patients. There were better results for the "standard" and "less tight target" groups compared to the other 2 small groups. In total, 57.1% of all patients were within the target range of their respective activation key. 58.8% of patients allocated to the "standard" (n = 34), 0% of the "standard-fast initial titration" (n = 1), 50% of the "less-tight target" (n = 4) and 66.7% of the 70-100 target" (n = 3) activation key were at target at the end of the titration phase. Typical examples for dose up-titration and corresponding

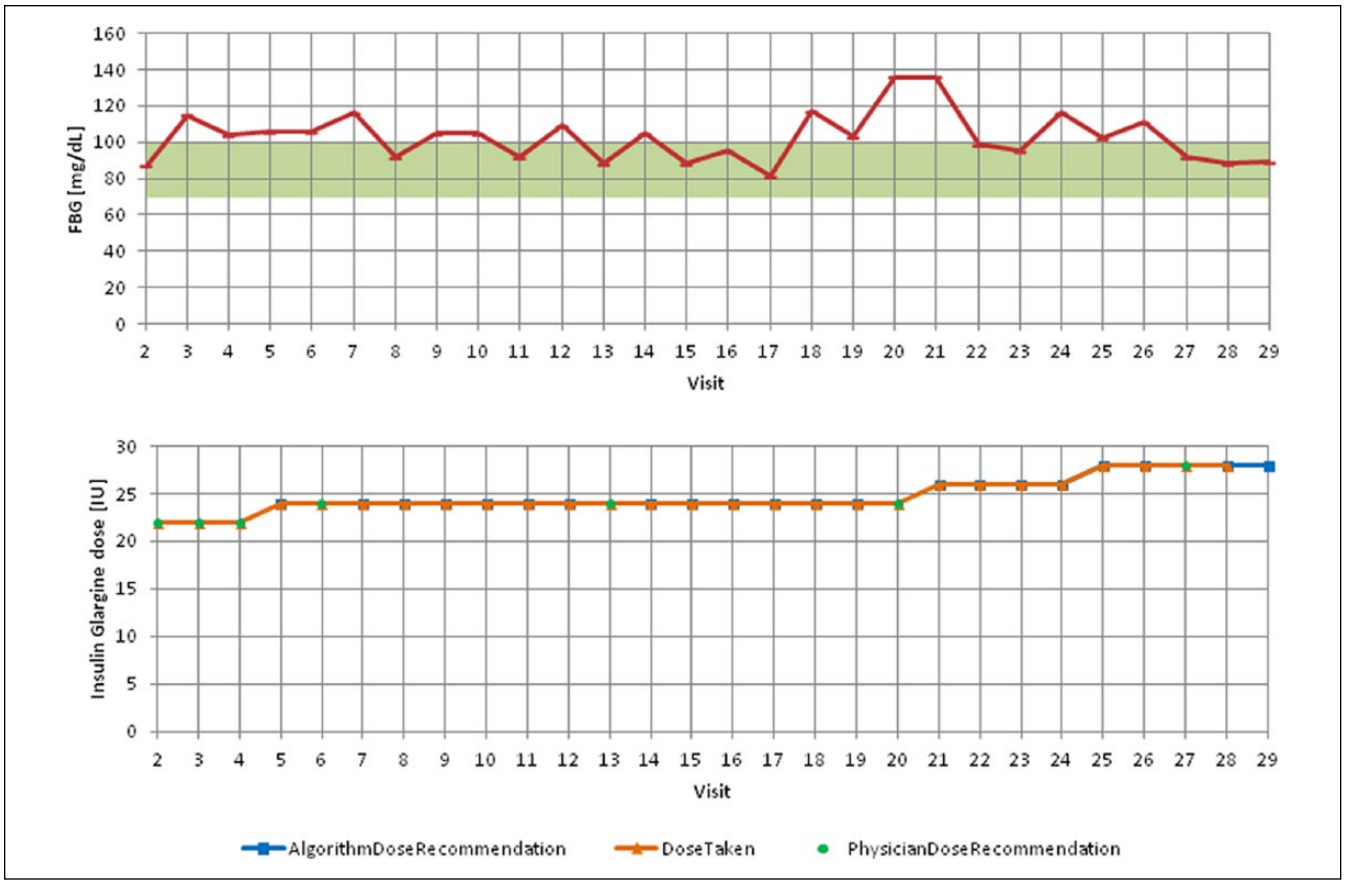

Figure 1. Patient example: Slow down titration into target range with algorithm reaction to increasing insulin requirements starting on day 17.

fasting glucose levels are provided in Figures 1 and 2. The titration results from patients with more variable blood glucose values are provided in Figures 3 and 4.

In total, 1300 dose decisions were made (1192 according to the TA and 108 by the physicians independently from the TA in 29 patients (58% of study population). In 23 cases, the reason for a dose decision by the investigator was missing or incomplete data. Other reasons for overruling the TA included hypoglycemic events (14 mild and 4 moderate) in 9 patients, while the other 41 patients (82%) did not experience any hypoglycemic event. In 11 cases, the physician decided for a lower dose than indicated by the TA. In the majority of the physician-derived doses, however, the physician recommended a continuation of the previous dose (63 cases) or a higher dose (34 cases) while the TA suggested a lower different dose.

A total of 80 adverse events occurred during the study, which were reported for 18 patients. No serious adverse event (SAE) was reported. Eighteen of these events (22.5%) were hypoglycemic events reported for 9 patients. These hypoglycemic events were classified as "mild" (n = 14) or "moderate" (n = 4). No severe hypoglycemic event occurred during the study period. Other most frequently seen adverse events were appetite disorders (6 events), dizziness (5 events), headache (5 events), and fatigue (4 events).

Discussion

Self-adjustment and titration of the basal insulin dose is becoming common practice in patients with type 2 diabetes, who however need to be well educated on the dosing scheme to achieve targets with a similar effectiveness than health care professionals as shown in the AT.LANTUS and PREDICTIVE studies.[6,7] Another multinational, 24-week, randomized study compared patient-led with physician-led titration of once-daily insulin glargine in Asian patients with uncontrolled type 2 diabetes who were on 2 oral glucose-lowering agents. Like in the other studies, patient-led insulin glargine titration achieved better results with respect of glycemic control for the price of a slight increase in nonsevere nocturnal hypoglycemic events.[9] A different approach to achieve effective up-titration of basal insulin doses with less resource requirements is the use of modern communication technologies, such as text messaging via mobile phones. In a recent pilot study, 61 patients were randomized to either perform regular physician visits to obtain their dose recommendations or to use text messages for the same purpose. The mobile phone intervention was as feasible as the doctor visits and patients were highly satisfied with their treatment. The intervention was cost saving in terms of time for patients, who were able to have their insulin titrated

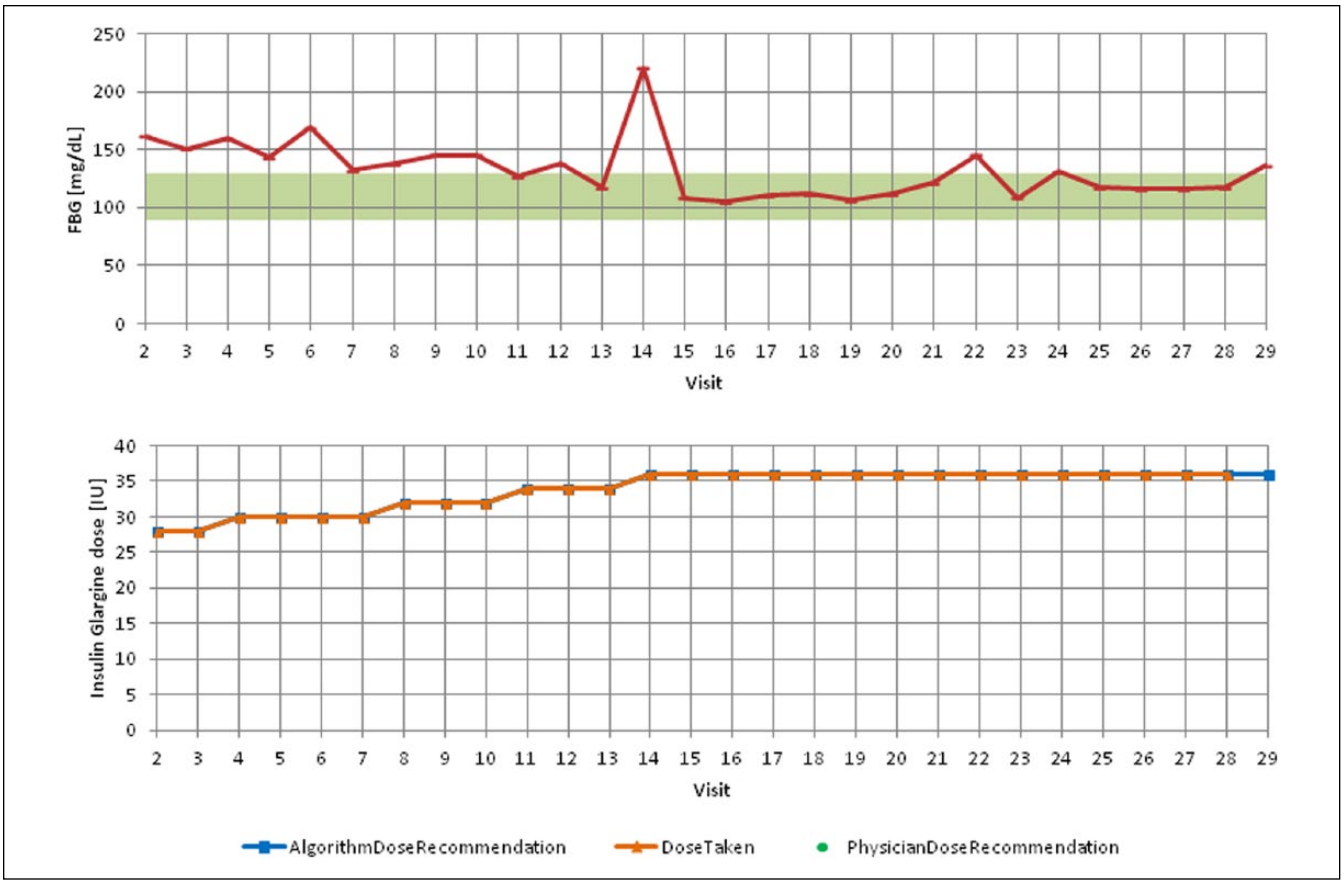

Figure 2. Patient example: Steady titration until reaching the fasting blood glucose target, showing that algorithm does not react to 1 isolated outlier result.

without multiple clinic appointments.[10,11] However, this approach still needs a health care professional on the other side to identify and communicate back the right dose.

The goal of our algorithm development was to define the specifications of a future software tool that is capable to guide patients safely and effectively through an insulin glargine up-titration phase until a stable dose has been reached. The development was based on common standards of basal insulin titration found in a review of 22 randomized controlled trials which evaluated different TAs directed by either the clinician or the patient. It was found that the majority of studies used 10 units of basal insulin per day as starting dose and a FBG target of 100 mg/dL. Most algorithms had incremental steps of 2 units with a titration frequency of twice per week or every 3 days. Patients were found to be as good as physicians in titration.[8] Our standard TA has been shown to be superior to other algorithms with respect to hypoglycemia risk in a recent study comparing clinical outcomes using 3 initiation and TAs for insulin glargine in 1380 insulin-naive patients with T2DM receiving both metformin and sulfonylurea (SU) at baseline.[12] In our trial, we directly compared dose titration decisions for normalizing FBG values with insulin glargine in a BOT regimen, when made by an individually selected dose TA or by the responsible physician on a daily basis over 28 days. We achieved the study goal to collect complete data sets from 50 patients, who were using 4 different sets of activation keys and analyzed the decisions made by these algorithms with the decision made by the physician. The dose finally provided was the one chosen by the health care professional. In the overall majority of the cases, the physician confirmed and approved the dose suggested by the TA (91.7%). With respect to the deviating decisions, the overall majority of the finally injected doses was higher than the dose recommended by the algorithm. The algorithm therefore was more conservative in up-titration than the health care professional. The majority of the patients reached their FBG target within almost a week and the doses remained stable also in 70% of the study participants. A stable dose was defined as the same dose applied for at least 10 consecutive days. The rationale for this definition was based on the algorithm rules. Every 3 days a possible dose increase was evaluated by the algorithm. A 10-day assessment period not only covered 3 regular titration periods lasting 3 days each but also allowed to capture a possible extension of 1 day, a missing value, or an outlier value in 1 of these 3 periods without violating the titration schedule.

The amount of insulin glargine was lower in the patient category with a stable dose after 4 weeks compared to the

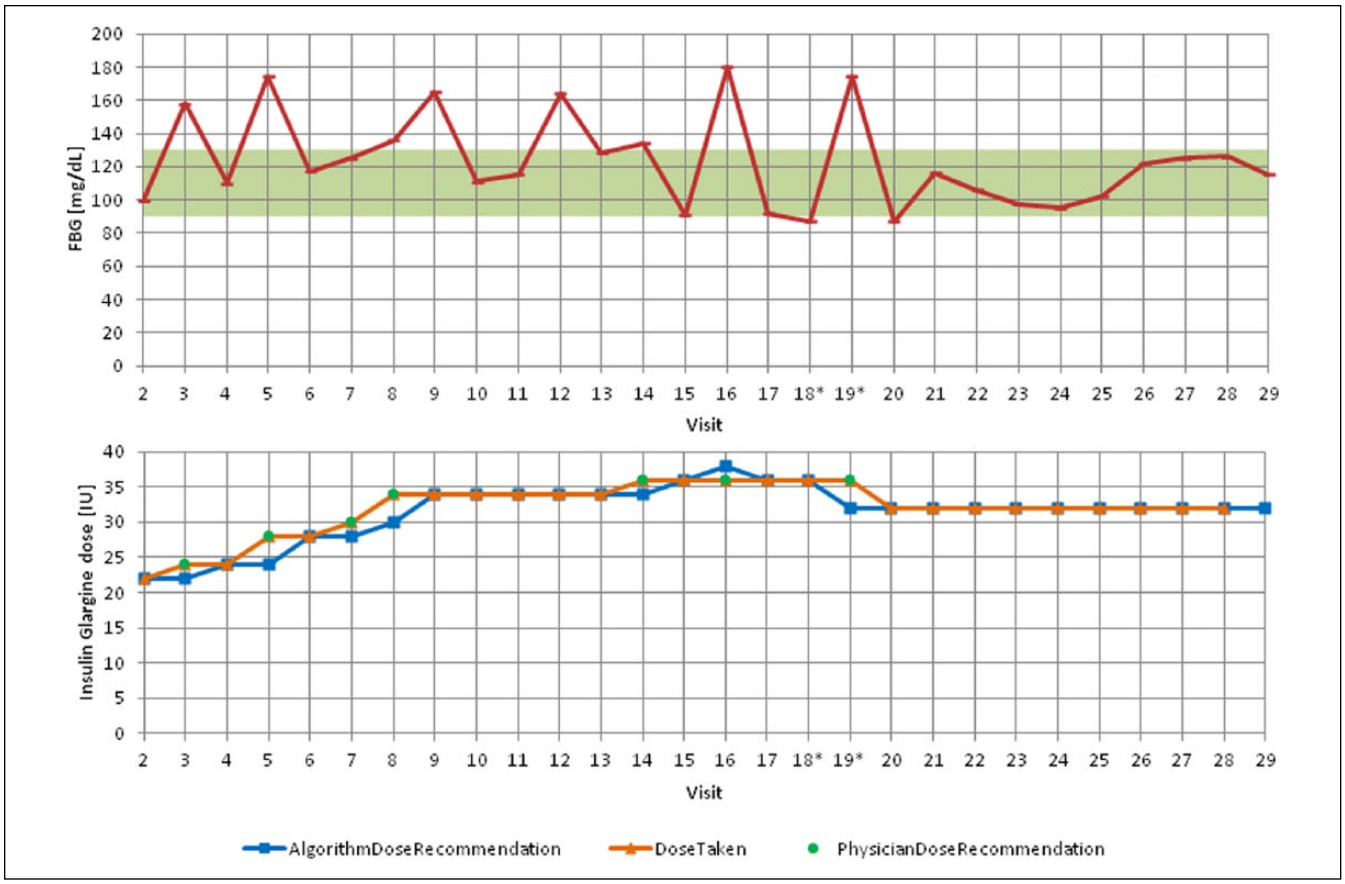

Figure 3. Patient example: Titration in a patient with initial high fasting blood glucose variability. Algorithm recommendations were more conservative than physician decisions overruling the algorithm recommendations.

patients with an unstable dose at the end for all available comparisons in the individual activation key groups. The size of the insulin glargine dose may therefore be of importance for an effective application of the TA to achieve the outcome of a stable dose, no matter if the absolute dose or the dose per kg body weight is considered. In general, insulin resistance may be an important issue in the further evaluation of the success of the applied insulin glargine TA.

Moving forward, all differences, variabilities and individual confounding factors found in the collected data set of 50 T2DM patients should be evaluated carefully for the fine-tuning of the insulin glargine TA. The possibility to ignore or overrule a dose recommendation because of a known reason for a recommendation differing from the prior dose or prospectively in case of planned activities or other confounding situations should be taken into consideration for the further development of the algorithm. In our study, the insulin glargine TA currently under development was tested in a preliminary version as a paper-based protocol instead of a final software to receive first results to evaluate the feasibility of future electronic version built into devices or used in Internet platforms for daily life (MyStar Dose Coach). A major limitation of the study is the unbalanced distribution of the used algorithms favoring the standard algorithm in 80% of the patients. This result was not foreseen when the study was started, but in turn confirms usability of this standard algorithm for the majority of the patients.

No serious adverse event or other severe conditions took place in any of the study participants during the study period. The hypoglycemic events, which should have led to a dose reduction as recommended by the algorithm were often overruled by the physician, which shows that only singular and mild hypoglycemic events occurred not even requiring a dose reduction. Exact consideration of time of the day the hypoglycemic events occurred will be useful for further assessment. In general, if the recommendation by the algorithm was modified by the investigator, only slight changes by 2 IU p to 4 IU were applied. This implies that the administered doses, which were mainly based on the recommendations of the insulin glargine TA, were generally safe.

In conclusion, the insulin glargine TAs delivered safe dose recommendations with a low risk of hypoglycemia, which successfully led to a stable dose within the 4-week dose adaption period in the vast majority of patients. Further investigation of the reaction of the algorithm to hypoglycemic episodes will be a key objective for future clinical studies in the development process.

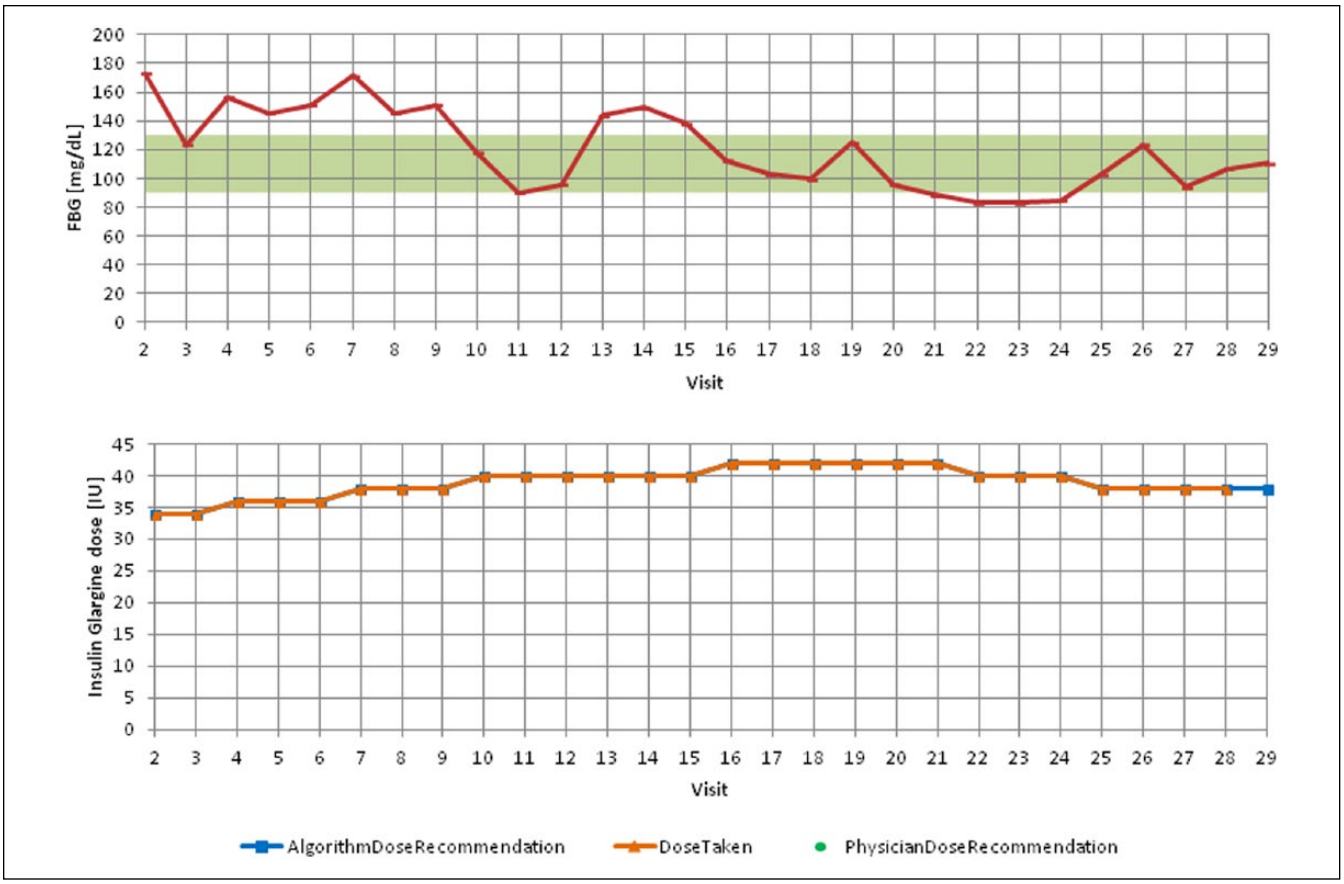

Figure 4. Patient example: Algorithm driven up titration of dose followed by down titration when achieving per protocol too low fasting blood glucose levels.

Abbreviations

ADA, American Diabetes Association; BOT, basal insulin supported oral therapy; EASD, European Association for the Study of Diabetes; FBG, fasting blood glucose; HbA1c, hemoglobin A1c; IU, international unit; LT, less tight (titration); S, standard (titration); SAE, serious adverse event; S-FT, standard-fast titration; SD, standard deviation; T, tight (titration); TA, titration algorithm; T2DM, type 2 diabetes mellitus.

Declaration of Conflicting Interests

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