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An observational, multicentre study on different insulin glargine U100 titration algorithms used in patients with type 2 diabetes in daily medical practice in Adriatic countries: The ADRESA study

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ABSTRACT

Aims: To compare the effectiveness of different titration algorithms for insulin glargine U100 used in everyday practice to achieve glycaemic targets in patients with type 2 diabetes mellitus (T2DM).

Methods: A total of 526 patients (278 in Slovenia, 248 in Croatia) with T2DM (aged ≥ 18 years) and treated with insulin glargine prior to inclusion were enrolled. Patients self-titrated insulin glargine according to physicians' guidance.

Results: Among the 524 patients included in the final analysis, the titration algorithm from the LANMET study was used most commonly (n = 368, 70.5% patients), followed by the Treat-To-Target (TTT) algorithm (n = 117, 22.4%). At the end of the study (6 months), 179 (34.3%) patients reached HbA1c ≤ 7%. There was no significant difference in the proportion of patients who reached their target HbA1c between the different algorithms at 6 months (35.6% using LANMET, 30.7% with TTT, and 32.4% with other algorithms; p = 0.611). HbA1c levels were more significantly reduced in patients using the TTT algorithm compared to LANMET (−2.31%, vs. −1.57%; p < 0.05). The proportion of patients with reported symptomatic hypoglycaemia did not differ significantly between the algorithms.

Conclusions: Continuous titration of insulin glargine U100 is a safe and efficient option for T2DM management, regardless of the titration algorithm applied.

Abbreviations: AE, adverse event; FPG, fasting plasma glucose; SAE, serious adverse event; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TTT, Treat-To-Target

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1. Introduction

Achieving and maintaining glycaemic targets represents a major challenge in the management of type 2 diabetes mellitus (T2DM). Initial intervention is largely based around lifestyle modification; pharmacologic intervention, including insulin therapy, becomes necessary as the progressive decline in cell function leads to deterioration in glycaemic control [1]. One of the key barriers for initiating and optimizing insulin therapy is hypoglycaemia [2,3]. Indeed, fear of hypoglycaemia often prevents subjects and physicians from reaching the targeted HbA1c levels defined by many national organizations [4–6]. Using intermediate-acting insulin such as NPH insulin, with its peak action profile [7] and large day-by-day variability in absorption after injection [8], might be a limitation for achieving appropriate glucoregulation in some patients. Long-acting (basal) insulin analogues, which show improved glycaemic control together with a lower risk of hypoglycaemia, are increasingly being considered in the treatment of type 1 diabetes mellitus (T1DM) and T2DM [1,9]. Therefore, long-acting insulin analogues are recommended by many international and national guidelines as a standard for treatment of T1DM and T2DM [4–6,10,11].

Insulin glargine was the first clinically available basal insulin analogue to show prolonged absorption and peakless long lasting activity [12]. Compared to NPH insulin, insulin glargine shows at least equivalent glycaemic control in T2DM patients [13,14] and has a lower incidence of hypoglycaemic episodes [15,16]. Therefore, insulin glargine can be used as part of a more intensive treatment algorithm aiming to achieve targeted values of HbA1c with a lower risk of hypoglycaemia [17]. Different titration algorithms for insulin glargine have shown proven efficacy in improving glycaemic control with a low incidence of severe hypoglycaemia in prospective randomized clinical trials including the Treat-To-Target (TTT) study [14], the LANMET study [17], and the AT.LANTUS trial [18].

The aim of this study was to document the comparative effectiveness of the different titration algorithms for insulin glargine U100 used in everyday clinical practice in Croatia and Slovenia when treating patients with T2DM, as well as to describe the most commonly used titration schemes among physicians in these countries.

2. Subjects and methods

2.1. Study design and protocol

This prospective, observational, multicentre, international study was conducted in Croatia and Slovenia from November 2010 to March 2014. Participating physicians were randomly selected from the initial list of specialists diabetologists; participation of university hospital centres and local hospitals ensured broad representation of management of T2DM patients on insulin therapy.

Observations and data collections were done during two to three clinical visits for each patient: at enrolment (baseline visit), optionally at 3 months, and at 6 months (control visit) in a prospective follow-up manner.

Data was collected in paper form and included: anthropometric data, anamnestic data about diabetes duration and complications, glycaemic status and HbA1c at the time of insulin glargine initiation (further referred to as baseline HbA1c), insulin glargine treatment (treatment goals, means of titration, titration algorithm, and titration algorithm criteria), and concomitant diabetes treatment.

At the baseline visit, participating physicians were asked to record insulin glargine titration recommendation already given to patient. At the follow-up visit, adverse events and hypoglycaemic episodes since the previous visit were collected. After 6 months, physicians were asked to complete a questionnaire on their satisfaction with the insulin glargine treatment and reasons for not achieving therapy goals. Physicians participating in the study were also treating physicians i.e. those who initiated glargine treatment also gave recommendation on dose adjustments, followed the patients during routine clinical visits, etc.

2.2. Subjects

Patients with T2DM aged 18 years and older who had been initiated with insulin glargine treatment prior to the study inclusion and according to the reimbursement conditions in the respective countries were included. The vast majority of Croatian patients in this study were treated with insulin glargine as a part of a basal bolus regimen, while a significant proportion of Slovenian patients were prescribed insulin glargine in conjunction with oral therapy only.

Informed consent was obtained prior to the conduction of any study-related data collection procedures and prior to enrolment of patients. The study was approved by the Central Ethics Committees in the respective countries and by the Hospital Drugs Committees where requested.

As the study was non-interventional in nature, the choice of prescribed therapy and identification of patients for inclusion were completely at the physicians' discretion. This means that all the procedures for including patients and documenting the data did not affect the everyday clinical practice. The patients, in whom insulin glargine U100 therapy was initiated prior to and irrespective of study participation, were enrolled in the study if inclusion criteria were fulfilled.

2.3. Adverse events

Participating physicians were instructed to report adverse events (AEs). Each event that resulted in a patient's death or was life threatening, required hospitalization or prolonged hospitalization, resulted in permanent or significant disability/handicap, or caused foetal damage or congenital anomalies was considered a serious AE (SAE). Symptomatic hypoglycaemia was defined as causing symptoms that disappeared after food/carbohydrate intake or if measured glucose levels were lower than 3.9 mmol/L. Severe hypoglycaemia was defined as an event requiring help from another person and

glucose levels lower than 3.1 mmol/L, and as such, was reported as a SAE.

2.4. Outcome measures

The primary endpoint was to determine how many patients achieved the reference therapeutic goal values of HbA1c ≤ 7%. Secondary endpoints included analysis of HbA1c and fasting plasma glucose (FPG) changes, the incidence of hypoglycaemia, and patient satisfaction with the therapy. Weight gain was assessed by performing simple anthropometric measurements of weight, body mass index (BMI), and waist circumference.

2.5. Statistical analyses

Statistical analysis was performed using IBM SPSS Statistics software version 16.0.1 (2007). Depending on the type and number of examined parameters, the Chi squared test, Mantel–Haenszel test, Student's *t* test for independent or paired samples, Mann–Whitney *U* test (not Gaussian distribution), and ANOVA were used. In all tests, an alpha level of 0.05 ($p < 0.05$) was considered statistically significant.

Levene's test was used to assume Equality of Variances. The normal distribution of each variable was checked with the Kolmogorov-Smirnoff test. Missing data were presented in descriptive analysis with the valid percentage calculated; in other analysis, they were handled as missing data and excluded (note: no patients were lost to follow-up in this study). Continuous data are presented as mean values with standard deviations (SD). Categorical data are presented by absolute numbers with percentages and valid percentages. Under the assumption that 40% of patients would be at controlled (target) HbA1c of ≤7%, a total of 525 patients had to be included in the study to estimate this prevalence with $\alpha = 0.05$ (Z = 1.96) and a chosen precision of 4.5%.

3. Results

3.1. Patient characteristics

A total of 526 patients with T2DM were enrolled by 53 participating physicians, 278 of which were in Slovenia and 248 in Croatia. A total of 524 patients completed the study (two were removed due to missing/uncorrected data). Patient characteristics at inclusion are presented in Table 1.

At inclusion, patients were a median age of 60.9 years, generally overweight or obese (mean BMI 30 kg/m^2) with mean waist circumference values of 101.5 cm, and had a mean duration of diabetes of 11.9 years.

At the time of initiation of insulin glargine U100 therapy, mean HbA1c was 9.15% (77 mmol/mol) and FPG was 10.8 mmol/L. Diabetic complications were already substantially present in the included population, with more than 30% of patients having diabetic neuropathy and 28.5% having nephropathy. The most prominent macrovascular complications reported were diabetic macroangiopathy (11.2%) and myocardial infarction (7.8%). Arterial hypertension was present in 75% of patients, and dyslipidaemia in 66% (Table 1). Among the included patients, 49.6% used biguanidines, 24.3% used sulphonylureas, and 32.1% used other concomitant oral antihyperglycaemic therapy (dipeptidyl peptidase 4 inhibitor or pioglitazone were most commonly reported).

3.2. Insulin glargine titration algorithms

In total, 180 (34%) patients were treated with basal insulin supported oral therapy (BOT scheme, Slovenia only), and 346 (66%) patients were in a basal-bolus scheme (mostly in Croatia). The most common titration algorithm selected in this study was LANMET, which was used in 368 patients (70.5%), followed by the TTT algorithm in 117 (22.4%) (Fig. 1). At the beginning of the study, the mean (±SD) dose of insulin glargine U100 used in the LANMET group was 23.18 ± 11.5 U/day compared to 19.16 ± 8.8 U/day in the TTT group.

The LANMET algorithm assumes insulin glargine dose increases by 2 IU if FPG is >5.5 mmol/L and by 4 IU if FPG is > 10 mmol/L on three consecutive mornings. The TTT algorithm assumes weekly insulin glargine dose adjustment based on self-monitored FPG values from the preceding 2 days based on the scheme presented in Table 2. Both schemes anticipate no increase in dosage in case of FPG ≤ 4 mmol/L, and indicate small insulin dose decreases (2–4 U/day) if severe hypoglycaemia or plasma-referenced glucose < 3 mmol/L were documented in the preceding week.

Physicians were given the opportunity to use their own titration algorithm, which was recorded in 7.1% of participants as "other" (Fig. 1). The most common criteria identified by physicians for selection of a certain algorithm was the simplicity of the algorithm for patients in 465 (88.4%) cases and minimal risk for hypoglycaemia in 307 (58.4%) cases (Table 3).

At the end of the study period (6 months), 179 (34.3%, 95% confidence interval [CI] 28.7–40.5) patients reached HbA1c ≤ 7% (53 mmol/mol). With regards to the titration scheme, 131/368 (35.6%) patients using the LANMET algorithm reached the target level, 36/117 (30.7%) with the TTT algorithm, and 12/37 (32.4%) with other algorithms. There was no significant difference in the proportion of patients reaching target HbA1c between different algorithms at the end of the study ($p = 0.611$).

In the total cohort, the mean HbA1c values decreased from 9.15 ± 1.7% at inclusion to 7.7 ± 1.1% at 3 months, and 7.5 ± 1.1% at 6 months ($p < 0.01$). Overall, the mean HbA1c change was −1.65%. The greatest difference was observed in the group of patients using the TTT algorithm (n = 117), where the HbA1c level was reduced from the inclusion visit to the end of the study by −2.31%; this was followed by the LANMET algorithm (n = 368), in which the HbA1c reduction was −1.57%, and then the other titration algorithms (n = 37) with a HbA1c reduction of −1.5%. The General Linear Model "Univariate Analysis of Variance" showed an overall statistically significant difference in end-point HbA1c values between the different insulin titration algorithms once their means had been adjusted for baseline HbA1c values (LANMET 7.64 95% CI [7.53–7.79], TTT 7.39 95% CI [7.15–7.52], and other 7.80 95% CI [7.16–8.40]; $F = 40.1$, $p < 0.001$).

Overall, the mean FPG values decreased from 10.83 ± 3.8 mmol/L at inclusion to 7.7 ± 2.4 mmol/L at 3 months,

Table 1 – Patient characteristics and complications in the intent-to-treat population at inclusion.

Characteristic	Value
Male/female (%)	51.5/48.5
Age (years) (mean ± SD)	60.9 ± 11.1
Duration of T2DM (years) (mean ± SD)	11.9 ± 7.9
Body mass index (kg/m^2) (mean ± SD)	30.06 ± 5.6
Waist circumference (cm) (mean ± SD)	101.5 ± 13.9
Fasting plasma glucose (mmol/L) (mean ± SD)	10.83 ± 3.8
HbA1c (%) (mean ± SD)	9.15 ± 1.7
Complication	n (%)
Diabetic neuropathy	165 (31.4)
Diabetic retinopathy	150 (28.5)
Diabetic nephropathy	90 (17.1)
Diabetic macroangiopathy	59 (11.2)
Angina pectoris	40 (7.6)
Myocardial infarction	41 (7.8)
Diabetic cardiomyopathy	15 (4.6)
Transitory cerebral ischemia	24 (1.9)
Diabetic foot	13 (2.5)
Arterial hypertension	395 (75.1)
Dyslipidaemia	351 (66.7)
Smoking	100 (19)

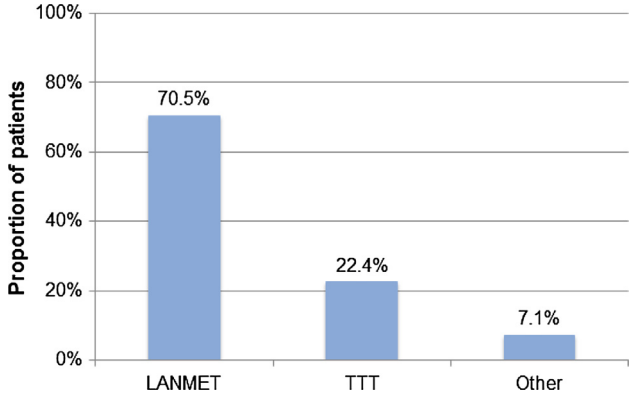

Fig. 1 – Proportion of patients using the different algorithm for insulin glargine titration. TTT: Treat-To-Target.

and 7.29 ± 2.2 mmol/L after 6 months ($p < 0.01$). Also, the mean administered daily dose of insulin glargine increased significantly from 20.1 ± 12.1 U at inclusion to 29.6 ± 16.2 during the study period ($p < 0.01$).

Table 2 – Scheme of weekly insulin glargine dose adjustment based on self-monitored fasting plasma glucose (FPG) values in the Treat-to-Target titration algorithm.

Mean of self-monitored FPG values from preceding 2 days	Increase of insulin glargine dosage (U/day)
≥10 mmol/L	8
7.8–10.0 mmol/L	6
6.7–7.8 mmol/L	4
5.6–6.7 mmol/L	2

Table 3 – The criteria for algorithm selection.

Criteria	n (%)
Minimal risk for hypoglycaemia	307 (58.4)
Simplicity of algorithm for patients	465 (88.4)
Fast reaching of necessary insulin dose	179 (34.0)
Simplicity of algorithm for physicians	131 (24.9)
Other	2 (0.4)

Changes in daily insulin glargine doses did not show significant differences among the different titration algorithm groups (Table 4). A total of 66.9% of patients self-titrated insulin glargine U100 according to recommendations previously received from a healthcare professional, while titration was done by physicians in 37.3% of patients (by phone or during the clinical visit).

At the end of the study, insulin glargine therapy was evaluated by participating physicians as effective in 88.7% of patients and as tolerable in 98.1% of patients. The most common reasons for inefficiency according to physicians' opinion were poor compliance with dietary measures or with patients not following the titration algorithm instructions. One of the main reasons for inadequate basal insulin dose adjustment was fear of hypoglycaemia as reported by 13.9% of patients.

3.3. *Safety of insulin glargine treatment*

The majority of patients (98.1%) tolerated insulin glargine U100 well. During the course of the study, a total of 6 SAE were documented, including 2 cases of severe hypoglycaemia. However, there was no treatment discontinuation because of the SAE.

Table 4 – Changes in insulin glargine daily doses according to titration algorithms.

U/day	LANMET	Treat-To-Target	Other
Introduction	23.2 ± 11.5[a]	19.2 ± 8.8	20.8 ± 17.7
Visit 1	28.1 ± 15.7[b]	24.2 ± 9.5[b]	25.1 ± 19.1[b]
Visit 2	30.2 ± 16.3[b]	30.9 ± 13.0[b]	27.8 ± 17.3

[a] Mann–Whitney *U* test: $p < 0.05$ vs. Treat-To-Target.
[b] Wilcoxon signed-rank test: $p < 0.01$ vs. previous visits within the same titration algorithm All data are shown as mean ± SD.

Hypoglycaemic events were evaluated from patient diaries. The proportion of patients with ≥1 event of symptomatic hypoglycaemia at the 3 month and 6 month visit was 14.7% and 12.9%, respectively, with no significant differences among the titration algorithms. The rate of overall symptomatic hypoglycaemia was 2.47, and 1.07 nocturnal events occurred per patient year at the end of the study.

3.4. *Analysis of parameters influencing treatment outcome*

In patients who did not reach glycaemic targets, the two main reasons for inadequate basal insulin dose adjustment, according to physicians, were either non-compliance with dietary recommendations in 87 (17.0%) patients and fear of hypoglycaemia in 71 (13.9%) patients.

The patient titration compliance was poor. The reason for non-compliance in 71 patients (13.9%) was fear of hypoglycaemia, and in 87 patients (17.0%), it was inadequate diet.

4. Discussion

We found the commonly used titration algorithm in Slovenia and Croatia was the one based on the scheme used in the LANMET study (70.5% of patients), followed by the TTT algorithm (22.4% of patients). Our findings indicate that, irrespective of the titration scheme used, titrated insulin glargine can significantly decrease FPG and consequently contributes to HbA1c reduction. This is in accordance with previous findings documented in large randomized clinical trials [14,17,18].

In our study, due to the observational design, dose adjustment of concomitant antihyperglycaemic therapy was at the participating physicians' discretion. However, the doses were changed only in a minority of patients during the course of the study, i.e., in 11.9% of patients using oral antihyperglycaemic therapy and in 14.3% of patients using short-acting insulins.

In the present study, patients using the TTT algorithm had a larger HbA1c reduction from baseline compared to LANMET (the difference was statistically significant when baseline mean HbA1c had been adjusted). Interestingly, patients treated with the TTT algorithm presented with higher mean baseline HbA1c. A possible explanation for this finding could be that the TTT algorithm, with larger possible dose increments, is considered a more ambitious titration scheme by prescribers, and therefore used in patients with prominent inadequate glycaemic status.

Patients in our study were not *insulin naïve* prior starting insulin glargine treatment (one of the inclusion criteria was that insulin glargine is prescribed according to reimbursement limitations). Data about previous insulin therapy was not recorded, but taking into account limitations, patients were suboptimally treated either with NPH or premixed insulin prior to initiating insulin glargine.

An important observation in the present study was that two thirds of patients self-titrated insulin, proving the simplicity of basal insulin dose adjustment. Again, this is in line with findings from randomized clinical trials comparing these two treatment algorithm approaches where patient-led titration has proven to be safe and sometimes more efficient than physician-led titration [18]. This indicates that insulin glargine treatment algorithms could be oriented toward patient's titration with less need for physician's interventions.

Although the insulin glargine dose was steadily adjusted during the course of the study, analysis revealed no significant difference in daily basal insulin dose increase among titration subgroups. Regardless the applied algorithm, the daily insulin glargine dose reached at the end of our study is still lower compared those reached in previous randomized clinical trials [14,17,18]. As more than half of the patients in our study did not reach their glycaemic targets, the need for further dose increase should be considered in patients not at risk of hypoglycaemia (which is a possible limiting factor for further optimal insulin dose increase).

The proportion of patients experiencing overall and nocturnal hypoglycaemia was comparable to literature data, regardless of the titration algorithm [15]. A trend towards a higher rate of nocturnal hypoglycaemia was documented at the 3-month visit compared to the 6-month visit. However, the average duration of titration in this study was only 31.15 days, which is shorter than the titration duration of prior randomized control trials [14,17,18], but in line with observations from a large meta-analysis [15].

At the end of this study, insulin glargine treatment was evaluated as efficient and well tolerated in the majority of patients. For those still not reaching glycaemic targets, the main obstacle for proper titration compliance was the "fear of hypoglycaemia" recognized by both physicians and patients.

5. Study limitations

A limitation of our prospective cohort study was the lack of randomization. Due to the open-label, non-comparative nature of the study, the results could have been influenced by sequence effects or physician and/or patient bias. Furthermore, this study did not provide standardized diaries; therefore many reported hypoglycaemic episodes lacked the appropriately measured plasma glucose values. Finally, the method of data collection for hypoglycaemic episodes and adverse events was based on patient recording, which could present underreporting. Despite the abovementioned limitations, data on local practices of insulin glargine titration schemes used in routine clinical care and their related effectiveness is important complementary information to the already reported findings from randomized clinical trials.

6. Conclusion

In summary, this study provides insight into widely applicable insulin glargine U100 titration algorithms that are used in everyday clinical practice by Slovenian and Croatian diabetologists. Results show that regardless of the algorithm applied, insulin glargine titrated to targeted fasting plasma glucose allows unregulated T2DM patients from diverse clinical settings to safely improve their glycaemic control. While all titration algorithms were safe and well tolerated, the TTT scheme should be considered as the first choice due to its statistically significant better results regarding reduction of HbA1c values. Although the advantage of a lower incidence of hypoglycaemia is linked with insulin analogue therapy, "fear of hypoglycaemia" is still recognized as a major barrier that prevents optimized titration.

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Conflict of interest

This study was sponsored by Sanofi Aventis.

M.K. received honoraria from Sanofi Aventis, NovoNordisk, Elly Lilly, MSD, Takeda, Novartis, Boehringer Ingelheim, Lifescan, and Astra Zeneca as a speaker and for attendance at advisory boards. I.M. received honoraria from Astra Zeneca, Novo Nordisk, MSD, AMGEN, Roche, Boehringer Ingelheim, Eli Lilly, Novartis, Sanofi as occasional speaker and for the advisory board attendance.

M.K., I.M. and D.R. received honoraria from Sanofi Aventis as investigators in ADRESA study. M.S. received honoraria from Roche as a speaker and does not have any financial or other interest with Sanofi Aventis. Author does not have any conflicts of interest associated with this research. NG is Sanofi employee.

Author's contributions

MK, IM and DR contributed to conception and design, acquisition of data, analysis and interpretation of data, drafting the article, critical revision and final approval of the version to be published. MS contributed to interpretation of data, drafting the article, critical revision and final approval of the version to be published.

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