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Original Article

# Titration of basal insulin or immediate addition of rapid acting insulin in patients not at target using basal insulin supported oral antidiabetic treatment – A prospective observational study in 2202 patients

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ABSTRACT

*Aim:* Optimal treatment intensification strategies in patients with type-2 diabetes mellitus (T2DM) receiving basal insulin supported oral antidiabetic therapy (BOT) remain controversial. The objective of the present study was to compare outcomes of BOT-intensification by either the uptitration of long-acting insulin glargine or by the immediate addition of a rapid acting insulin analogue (RAIA).
*Methods:* This was a prospective, observational, 24-week study in T2DM patients with BOT using insulin glargine and baseline glycated hemoglobin (HbA1c) between 7.0 and 8.5%. Patients were stratified by their physicians to one of the following treatment intensification strategies: Basal insulin titration to target with discretionary subsequent addition of RAIA at weeks 12 or 24 (GLAR), or immediate addition of RAIA at baseline (GLARplus).
*Results:* A total of 3266 patients were prescreened of whom 2202 fulfilled the selection criteria. Of these, 1684 patients were documented in the GLAR group and 518 in the GLARplus group. In the GLAR group, in 91 (5.5%) and 21 patients (1.3%) RAIA was added at weeks 12 and 24, respectively. The groups displayed similar baseline characteristics; except, mean diabetes duration was slightly shorter in the GLAR group (8.7 *vs.* 9.4 years). During the study, insulin glargine dose was increased from 18.7 to 26.4 U (plus 7.7 U) in GLAR and from 24.9 to 27.3 U (plus 2.4 U) in GLARplus patients. Mean RAIA dose was $9.6 \pm 4.7$ U at the final visit. After 24 weeks, HbA1c was reduced by 0.8 and 0.9% in the GLAR and GLARplus groups, respectively (both $p < 0.001$). An HbA1c of $\leq$7.0% was achieved in 49.2% of GLAR and 48.5% of GLARplus patients. In both groups, we observed improvements in cardiovascular risk factors such as lipids and blood pressure. The rates of symptomatic (1.6 *vs.* 1.7%) and severe (0.18 *vs.* 0.19%) hypoglycemic episodes were low and comparable in both groups.
*Conclusion:* These findings provide evidence that treatment intensification in patients with type 2 diabetes not at glycemic target on BOT with insulin glargine is equally safe and effective using either long-acting insulin titration alone or the addition of a rapid-acting insulin analogue.


*Abbreviations:* ADA, American Diabetes Association; BMI, body mass index; BOT, basal insulin supported oral antidiabetic therapy; EASD, European Association for the Study of Diabetes; FBG, fasting blood glucose; GLAR, basal insulin group; GLARplus, basal insulin with immediate addition of short acting insulin analogue; HbA1c, glycated hemoglobin; LDL, low-density lipoprotein; PPBG, postprandial blood glucose; RAIA, rapid acting insulin analogue; T2DM, type-2 diabetes mellitus.

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## 1. Introduction

Effective glycemic control in patients with type 2 diabetes mellitus (T2DM) is necessary for preventing the onset and progression of microvascular complications [1–4]. Therefore, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) have recommended a glycated hemoglobin (HbA1c) target of around 7% with individualized treatment goals based on patient characteristics [5,6]. The progressive nature of T2DM requires continuous treatment intensification to achieve and maintain the individualized HbA1c target. As an effective treatment intensification strategy, insulin glargine [7,8], is frequently added when HbA1c goals are not met in patients exclusively using oral antidiabetic drugs [9], and several clinical trials have supported the efficacy of this basal insulin supported oral antidiabetic therapy (BOT) [10–12].

While basal insulin therapy can help to control fasting plasma glucose (FPG), elevations in postprandial blood glucose (PPG) also significantly contribute to the overall daily hyperglycemia of patients with T2DM. Therefore, treatment intensification strategies targeting PPG in addition to FPG may hold the potential of more effective control of glucose excursions. For the control of prandial glucose excursions, various rapid acting insulin analogs (RAIA) have been introduced (*e.g.*, glulisine, lispro, and aspart) [8]. These insulin preparations were developed to overcome the slow and prolonged absorption associated with regular human insulin in order to mimic more closely the physiological postprandial insulin levels [13–16]. Moreover, RAIA have demonstrated beneficial safety and efficacy profiles [17–20]. While the use of these agents has been advocated as a potential add-on therapy for intensifying BOT in T2DM patients [21–23], there is little "real life" evidence for efficacy and safety of a BOTplus regimen. The value of this approach in comparison to uptitrated BOT remains to be fully elucidated in clinical practice.

In the present study, we have compared two simple therapeutic intensification strategies involving either long-acting insulin glargine titration (GLAR) or immediate additional use of a RAIA at baseline (GLARplus).

## 2. Methods

### 2.1. Study design and patients

This is an observational, prospective, multicenter study conducted over a 24 week period comparing two treatment intensification arms. Patients were enrolled at office-based general practitioners or internists across Germany. This study was conducted in accordance with the Declaration of Helsinki. It was approved by the local Ethical committee, and all patients provided written informed consent prior to study participation.

### 2.2. Patient population

Patient eligibility was based on the following criteria: Age between 18 and 75 years, with T2DM and treated with oral antidiabetic drugs and basal insulin glargine (BOT) for ≥6 months, HbA1c ≥7.0 and ≤8.5%, and the possibility of blood glucose self-measurement. Patients were excluded if they had any contraindications as to the summary of product characteristics of insulin glargine or the respective RAIA, known alcohol or drug abuse, dementia or the inability to comply with study requirements.

### 2.3. Treatment intensification

Physicians stratified (at their own discretion) patients into treatment groups based on two therapeutic intensification strategies: (1) Insulin glargine was titrated to achieve an FPG ≤130 mg/dl in the GLAR group. There was a discretionary option to add RAIA at week 12 or 24 in case there was no sufficient control of blood glucose achieved by insulin glargine titration alone (i. e. HbA1c ≥7%). (2) In the second group of patients, RAIA was immediately added at baseline once daily to the meal with the highest excursion of post-prandial blood glucose (GLARplus group). The titration of the RAIA was at the discretion of the treating physician. Patient characteristics, treatment related variables and safety information were recorded at baseline and after 12 and 24 weeks.

### 2.4. Objectives and endpoints

The primary objective was to document changes in HbA1c from baseline to 12 and 24 weeks, respectively. Secondary evaluation criteria were treatment target achievement for HbA1c (≤6.5% and ≤7.0%) and FPG ≤100 mg/dl (5.5 mmol/l); mean doses (U/day and U/kg bodyweight) of insulin glargine in those with FPG ≤100 mg/dl (5.5 mmol/l); proportion of patients with PPBG ≤135 mg/dl (7.5 mmol/l) 2 h after the meal with the highest PPBG increase; mean dose of insulin glargine and RAIA in patients with PPBG at target; time of insulin glargine and time of RAIA application. In addition, the tolerability and safety of as well as the rate of confirmed hypoglycaemia with either treatment strategy was documented. Non-severe hypoglycaemia was defined as documented blood glucose between 56 and 72 mg/dl (3.1–4.0 mmol/l), and it was recorded whether it occurred during the night or the day. Severe hypoglycaemia was defined as blood glucose equal or smaller than 56 mg/dl (3.1 mmol/l). When patients with severe hypoglycaemia required help or needed hospitalization this was also indicated.

### 2.5. Statistical analysis

Continuous variables are presented as means with standard deviations, whereas categorical data are shown as percentages. Changes after 12 or 24 weeks from baseline within each group were analyzed using Wilcoxon signed rank tests. P-values $<0.05$ were considered to be statistically significant.

## 3. Results

Overall 3266 patients were screened, of whom 2202 were eligible based on the selection criteria, and were recruited into the trial (Fig. 1). Of these, 1684 subjects were assigned to the GLAR group and 518 to the GLARplus group. In the GLAR group, 91 (5.4%) and 21 (1.2%) patients had added RAIA therapy after 12 and 24 weeks, respectively. In the GLARplus group, insulin-glulisine represented the most frequently prescribed RAIA (77.6%), followed by insulin lispro (13.7%), and insulin aspart (7.5%). In 6 patients (1.2%), the type of RAIA was not reported in the primary source data.

### 3.1. Patient demographics and baseline characteristics

Demographic and baseline characteristics of the GLAR and GLARplus groups are summarized in Table 1. More than half of the subjects within each group were male. Patients in the GLAR and GLARplus treatment groups displayed similar characteristics with regard to age, body weight, body mass index (BMI), Hb1Ac, and FPG at baseline. However, mean diabetes duration was slightly shorter in the GLAR group (8.7 *vs.* 9.4 years).

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