

# HbA1c target achievement in the elderly: results of the Titration and Optimization trial for initiation of insulin glargine 100 U/mL in patients with type 2 diabetes poorly controlled on oral antidiabetic drugs

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## ABSTRACT

**Objectives** To identify real-world, age-related trends in the use of insulin glargine 100 U/mL (Gla-100) as part of basal-supported oral therapy (BOT).

**Research design and methods** The prospective, observational Titration and Optimization registry enrolled patients with poorly controlled type 2 diabetes mellitus initiated on Gla-100 BOT. The primary outcome was the proportion of patients with capillary fasting blood glucose (FBG)  $\leq 110$  mg/dL on  $\geq 2$  occasions and/or who met their individual HbA1c target within 12 months.

**Results** 2462 patients were analyzed (<65 years: n=1122; 65–74 years: n=771;  $\geq 75$  years: n=569). Diabetes duration (6.8, 8.9, and 11.2 years,  $p < 0.0001$ ) and proportion of women (40.7%, 47.9%, and 55.7%,  $p < 0.0001$ ) increased with age. Baseline HbA1c was highest in <65-year-olds (8.6% vs 8.4% and 8.5%,  $p < 0.0001$ ). Gla-100 up-titration until 12 months was highest in <65-year-olds (+11.6 U/day), compared with 65–74 (+10.2 U/day) and  $\geq 75$  years (+8.8;  $p < 0.0001$ ) but similar by units per kilogram, as was the decrease in FBG (<65: –64.1 mg/dL; 65–74: –56.1 mg/dL;  $\geq 75$ : –53.4 mg/dL) and HbA1c (<65: –1.47%; 65–74: –1.31%;  $\geq 75$ : –1.22%,  $p < 0.0001$ ). At 12 months, 65.9% of participants met the primary endpoint, with no significant difference between age groups. The proportion achieving their individual HbA1c target was lower for <65-year-olds (46.0% vs 54.3% and 54.7%;  $p < 0.02$ ). Symptomatic hypoglycemia incidence was more common in the  $\geq 75$ -year-old group (3.4% vs 1.4% and 1.4%;  $p = 0.0126$ ).

**Conclusions** BOT with Gla-100 results in similar improvements of glycemic values with low risk of hypoglycemia across age groups. Given the link between HbA1c and long-term cardiovascular risk, ensuring appropriately stringent target-setting, intensification of basal insulin and making sure hypoglycemia is avoided is of paramount importance.

**Trial registration number** Database: <https://awbdb.bfarm.de>; Identifier: 1641; Date of registration: September 23, 2013

## Significance of this study

### What is already known about this subject?

- ▶ Guidelines emphasize the influence of age on appropriate HbA1c target-setting and insulin regimes in type 2 diabetes mellitus.

### What are the new findings?

- ▶ In this study, glycemic improvements after the initiation of insulin glargine 100 U/mL as part of basal-supported oral therapy were apparent in all age groups, and rates of symptomatic hypoglycemia were low.
- ▶ Nevertheless, suboptimal rates of glycemic target attainment were apparent for all groups, especially HbA1c target achievement was observed in less than 50% of participants in the <65-year-old group, indicating a particular need to improve glycemic control in this younger population.

### How might these results change the focus of research or clinical practice?

- ▶ These results foster research into the hurdles to overcome when aiming to find an optimal balance between glucose control and a low risk of hypoglycemia in elderly patients.

## INTRODUCTION

The global prevalence of type 2 diabetes mellitus (T2DM) is on the rise, with an additional 210 million individuals expected to have the disease in 2035 compared with 2013.<sup>1</sup> This is largely due to the aging of populations, with advanced age a known independent risk factor for both developing the disease and experiencing associated complications.<sup>2–4</sup>

Guidelines pertaining specifically to older patients with diabetes emphasize the influence of age on the appropriacy of treatment

regimens and the added importance of recognizing individual patient characteristics in this population.<sup>1 5 6</sup> Indeed, elderly patients tend to be more comorbid and have more atherosclerotic vasculature, poorer kidney function, and shorter life expectancy.<sup>7</sup> If the latter is shorter than 20 years, the cardiovascular advantages of stringent glycemic control may not have sufficient time to manifest,<sup>1</sup> and intensive treatment to reach low HbA1c targets may consequently be more harmful than beneficial.<sup>8</sup> Furthermore, patient mental state, functionality, and quality of support systems may dictate the feasibility of meeting such targets in elderly patients, especially where insulin administration is indicated. Therefore, guidelines suggest that individual glycemic targets may be relaxed as age increases (HbA1c 7.5%–8.0%; 58–64 mmol/mol), with prevention of hypoglycemia and quality of life particularly important aspects.<sup>5 6</sup> Conversely, younger patients with long life expectancies and lower rate of comorbidities may be assigned a more stringent target (HbA1c 6.0%–6.5%; 42–48 mmol/mol), given the potential protective effect of intensive glycemic control against long-term microvascular complications and cardiovascular events.<sup>9 10</sup>

While the use of newer oral and non-insulin injectable antidiabetic drugs is on the rise, the Titration and Optimization (TOP) registry gathered data on patients with T2DM unsatisfactorily controlled on one or more oral antidiabetic drugs (OADs) who were being initiated on insulin glargine 100U/mL (Gla-100). This addition of once-daily long-lasting basal insulin to existing OAD treatment is known as basal-supported oral therapy (BOT),<sup>11–13</sup> and has been associated with greater target attainment and a lower risk of hypoglycemia compared with the addition of less-long-acting insulins (such as neutral protamine Hagedorn (NPH) and premixed insulin).<sup>14</sup> In a previous TOP analysis, BOT with Gla-100 was shown to effectively improve glycemic control, with approximately two-thirds of patients reaching their individual HbA1c targets and/or a capillary fasting blood glucose (FBG) level of  $\leq 110$  mg/dL.<sup>15</sup> In addition, a very low rate of hypoglycemia was observed. However, the effect of age on patient characteristics, titration behavior, and the associated degree of glycemic control has not been explored in this population. Such an analysis would shed further light on the impact of age in real-world T2DM treatment decisions and outcomes. In the present subanalysis of the TOP registry, we aim to evaluate the influence of age on Gla-100 treatment during the first 12 months after BOT initiation in patients with T2DM and to assess the corresponding effect on glycemic control, including hypoglycemia.

## MATERIALS AND METHODS

### Study design

The present study is a post hoc subanalysis of the prospective, observational TOP registry, which was carried out between October 2013 and October 2015 in Germany.

The registry enrolled people with T2DM poorly controlled on OADs or on basal insulin/OAD combination therapy who initiated or were switched to Gla-100 at the discretion of the treating physician in a hospital setting and followed over a period of 12 months. The methods and main results of the registry have been previously published.<sup>15</sup> A brief description is provided below.

### Patient selection

People were included in the present analysis if they fulfilled the following criteria: age >18 years; a diagnosis of T2DM; baseline HbA1c 7.5%–10% despite taking OAD medication ( $\pm$ insulin); physician decision to initiate insulin Gla-100 independently from the registry and also had precise age information available. People already receiving basal insulin plus mealtime insulin (basal-bolus therapy) were excluded. For the present analysis, participants were stratified into three age groups according to their age at inclusion: <65-year-olds; 65–74-year-olds;  $\geq 75$ -year-olds.

### Documentation

On the day of Gla-100 initiation (baseline), patient demographics, glycemic values (HbA1c and FBG), prior insulin treatment and OAD medications were documented. A personal HbA1c target was assigned by the treating physician based on their clinical judgment, independently from the registry. Throughout the 12-month follow-up period, FBG and HbA1c levels, hypoglycemia events, and any titration of a patient's Gla-100 were documented. At the final follow-up, changes to OAD medication since baseline were recorded.

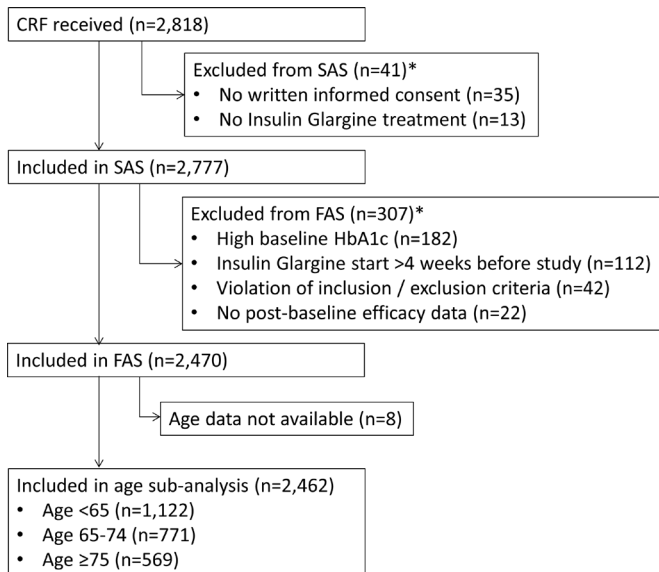
### Endpoints

Participants who achieved an FBG of  $\leq 110$  mg/dL on a minimum of two occasions and/or met their preassigned personal HbA1c target at least once during follow-up were considered to have met the primary efficacy endpoint. The proportions of people meeting these criteria in each age group were compared.

Secondary endpoints included changes to daily Gla-100 dosage over 12 months, absolute changes in HbA1c and FBG levels at 6 and 12 months, and requirement for a change of insulin therapy (ie, switching to an alternative basal insulin or insulin type) during the study. Rates of hypoglycemia (symptomatic; symptomatic and confirmed (blood glucose measurement of  $\leq 70$  mg/dL); nocturnal symptomatic or confirmed; severe symptomatic or confirmed (blood glucose measurement of  $\leq 56$  mg/dL); severe nocturnal symptomatic or confirmed) were also predefined secondary endpoints.

### Statistics

For the present analysis, endpoint assessment was based on the full analysis set (those complying with all study inclusion/exclusion criteria with Gla-100 initiation <4 weeks before enrollment and availability of 12-month follow-up data). Patients were divided into groups according to age at study start. Data are presented using



**Figure 1** Patient flow for inclusion. \*More than one reason could apply. CRF, case report form; FAS, full analysis set; SAS, safety analysis set.

descriptive statistics, with categorical variables expressed as frequencies and continuous variables as means plus SD. A one-way analysis of variance,  $\chi^2$  test or Fisher's exact test (for rare events) were used to identify any statistically significant differences between the three age groups. A paired t-test was used to compare within-group differences in Gla-100 dose, FBG, and HbA1c at different time points. For the primary endpoint and its components, significant differences were further explored through two-group comparisons using a  $\chi^2$  test. A p value of <0.05 was considered significant. All analyses were performed using SAS V.9.4.

## RESULTS

Of the 2470 eligible participants, 8 were excluded from this subanalysis owing to a lack of available age data. Most of the participants were found in the <65 years group (n=1122), followed by 65–74 years (n=771) and ≥75 years groups (n=569) (figure 1).

### Baseline characteristics

The mean age was 55.5±7.7 years in the <65 years group, 69.7±3.0 years in the 65–74 years group, and 79.3±3.9 years in the ≥75 years group (p<0.0001) (table 1). The proportion of women increased with increasing age group (40.7%, 47.9%, and 55.7%, respectively; p<0.0001), as did the diabetes duration (6.8±5.4, 8.9±6.1, and 11.2±7.2 years, respectively; p<0.0001). The inverse was observed for body mass index (32.0±5.6, 31.0±5.2, and 29.7±5.0 kg/m<sup>2</sup>, respectively; p<0.0001).

Those aged <65 years had the highest glycaemic values (186.5±41.2 mg/dL and 8.6%±0.8% (70±9 mmol/mol), respectively), followed by those aged ≥75 years (181.1±40.5 mg/dL and 8.5%±0.8% (69±9 mmol/mol)) and those aged 65–74 years (180.1±39.0 mg/dL and

8.4%±0.8% (68±9 mmol/mol)) (table 1). The mean physician-assigned HbA1c target was statistically lowest for <65-year-olds (6.8%±0.5% (51±5 mmol/mol)), followed by 65–74-year-olds (6.9%±0.4% (52±4 mmol/mol)) and ≥75-year-olds (7.1%±0.5% (54±5 mmol/mol); p<0.0001). However, in clinical terms, both baseline glycaemic values and targets were fairly similar.

### Antidiabetic medication at baseline

At baseline, the most common OAD was metformin, with the frequency of patients taking this medication falling across age groups (63.2%, 59.7%, and 53.3%, respectively; p=0.0004) (table 1). This trend was also seen for glucagon-like peptide-1 receptor agonists (GLP-1 RA; 2.1%, 0.8%, and 0.4%; p=0.0028). The inverse trend was true for DPP-4 inhibitors (DPP-4i) without metformin (23.7%, 28.3%, and 31.8%; p=0.0012) and sulfonylureas (13.2%, 18.7%, and 22.7%; p<0.0001). All other OADs were taken at low and comparable frequencies (<10%).

Prior to the decision to initiate Gla-100 therapy, the proportion of patients already on a basal insulin was low (8.7% overall) and did not differ between age groups (p=0.77; table 1). The most common basal insulin was NPH (5.2% overall) followed by insulin detemir (2.0% overall), with only 0.6% of all patients already taking insulin glargine. Prior use of rapid-acting insulin analogues only and premixed insulins were rare (<1% in each case) as per exclusion criterion.

### Antidiabetic therapy over the 12-month follow-up

In all age groups, the insulin dose increased substantially between Gla-100 initiation and 12-month follow-up (figure 2). When the dose was considered in units per day (U/d) (figure 2A), the mean increase was most pronounced in the <65 group (from 12.0±6.5 to 23.6±11.5 U/d;  $\Delta$ =+11.6±0.4 U/d), followed by the 65–74 group (from 11.6±6.3 to 21.7±11.1 U/d;  $\Delta$ =+10.2±10.0 U/d) and the ≥75 group (from 11.4±5.7 to 20.2±9.4 U/d;  $\Delta$ =+8.8±8.7 U/d; p<0.0001). However, when considered in units per kilogram of body weight (figure 2B), the 12-month dose was comparable between groups (0.26±0.12, 0.25±0.12, and 0.25±0.17 U/kg, respectively, across age groups; p=0.30) and the Gla-100 dose increments from baseline to 12 months were no longer significantly different (0.13±0.11, 0.12±0.11, and 0.11±0.17 U/kg, respectively; p=0.054). In all groups, the most rapid dose increase was seen within the first 4 months after baseline, with leveling out of the curve over time.

Though the aforementioned trends in OADs across age groups at baseline were preserved at 12 months, the proportion of patients taking metformin had fallen in all groups (>65: –10.1%; 65–74: –9.4%; ≥75: –9.2%), the same being true for DPP-4i, sulfonylureas, and glinides (table 1). Changes in other OADs were minimal. At 12 months, the majority of patients were continuing Gla-100 treatment (85.8% overall), with no significant differences between groups (p=0.1204) (table 1). Very few patients had switched to an alternative basal insulin (0.4% overall)

**Table 1** Patient characteristics and diabetes therapy at baseline and 12 months

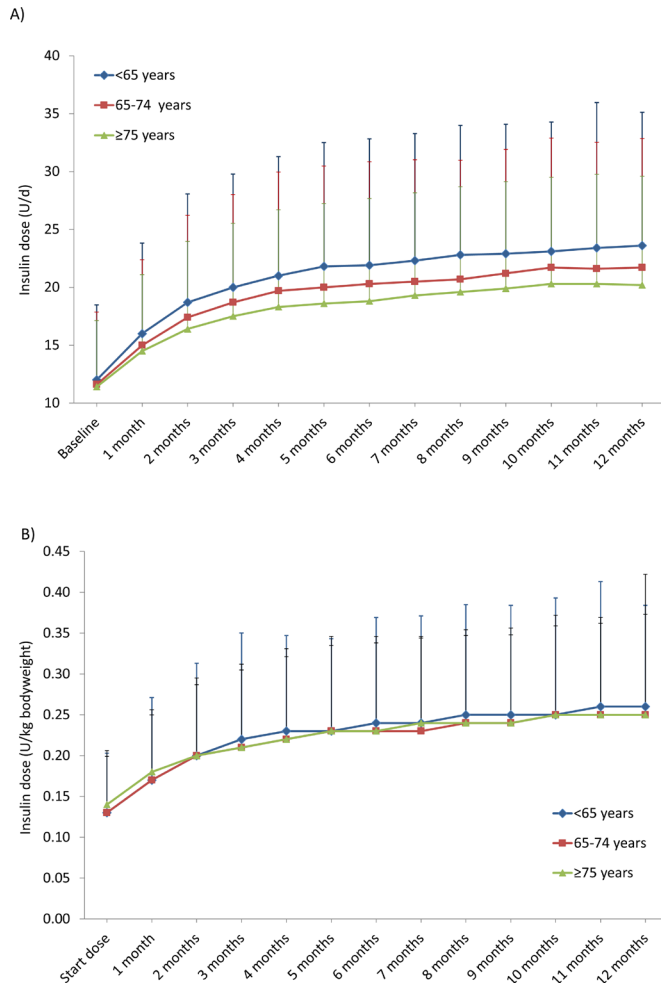
	Age <65 years N=1122 %/mean±SD	Age 65–74 N=771 %/mean±SD	Age ≥75 N=569 %/mean±SD	P value (<65 vs 65–74 vs ≥75)
Age (years)	55.5±7.7	69.7±3.0	79.3±3.9	<0.0001
Women*	41.0	48.4	56.0	<0.0001
Body weight (kg)	95.1±18.6	88.7±15.8	82.4±15.2	<0.0001
Body mass index (kg/m <sup>2</sup> )	32.0±5.6	31.0±5.2	29.7±5.0	<0.0001
Diabetes duration (years)	6.8±5.4	8.9±6.1	11.2±7.2	<0.0001
Baseline FBG (mg/dL)	186.5±41.2	180.1±39.0	181.1±40.5	0.0019
Baseline HbA1c (%/mmol/mol)	8.6±0.8/70±9	8.4±0.8/68±9	8.5±0.8/69±9	<0.0001
Individual target HbA1c (%/mmol/mol)	6.8±0.5/51±5	6.9±0.4/52±4	7.1±0.5/54±5	<0.0001
Diabetes therapy at baseline				
OADs				
Metformin†	63.2	59.7	53.3	0.0004
DPP-4i‡	23.7	28.3	31.8	0.0012
Sulfonylurea†	13.2	18.7	22.7	<0.0001
Glinide	5.4	5.2	9.5	0.0013
Glitazone†	2.2	1.0	0.9	0.0499
GLP-1 RA†	2.1	0.8	0.4	0.0028
SGLT-2 inhibitor†	3.6	3.4	1.6	0.0516
Acarbose	0.6	0.9	1.1	0.5689
Others†	0.4	0.3	0.0	0.2923
Insulin				
Basal insulin (any)	8.3	9.1	9.1	0.7744
NPH insulin	4.9	5.5	5.3	0.8528
Insulin detemir	2.0	2.3	1.8	0.7662
Insulin glargine	0.6	0.7	0.7	1.000
Short-acting analogues	0.2	0.3	0.5	0.4912
Premixed insulins	0.5	0.4	0.9	0.5060
Other insulins	0.4	0.1	0.0	0.4524
Diabetes therapy at 12 months				
OADs				
Metformin†	53.1	50.3	44.1	0.0022
DPP-4i‡	20.5	24.0	25.0	0.0643
Sulfonylurea†	6.4	13.0	15.6	<0.0001
Glinide	4.5	4.0	7.2	0.0224
Glitazone†	2.0	1.0	0.7	0.0811
GLP-1 RA†	1.5	0.9	0.5	0.1680
SGLT-2 inhibitor†	6.3	3.9	1.8	<0.0001
Acarbose	0.4	0.5	0.5	0.7925
Others†	0.8	0.5	0.5	0.7660
Insulin				
Continuation of Gla-100	87.3	85.3	83.7	0.1204
Change to other basal insulin	0.3	0.7	0.4	0.5042
Change insulin type	2.0	2.5	3.9	0.0688
Not stated	10.8	12.1	12.3	0.5605

\*17 patients missing this information (<65: 6 patients; 65–74: 8 patients; ≥75: 3 patients). Values are stated as percentages or mean±SD.

†Alone or in combination with any other OAD(s).

‡Alone or in combination with any other OAD(s) except metformin.

DPP-4i, dipeptidyl peptidase-4 inhibitor; FBG, capillary fasting blood glucose; GLP-1 RA, glucagon-like peptide-1 receptor agonist; NPH, neutral protamine Hagedorn; OAD, oral antidiabetic therapy; SGLT-2, sodium-glucose cotransporter-2.



**Figure 2** Insulin dose in U/d (A) and U/kg body weight (B) over 12 months. Final doses were significantly different between groups when considered in U/d ( $p < 0.0001$ ), but not U/kg body weight ( $p = 0.297$ ).

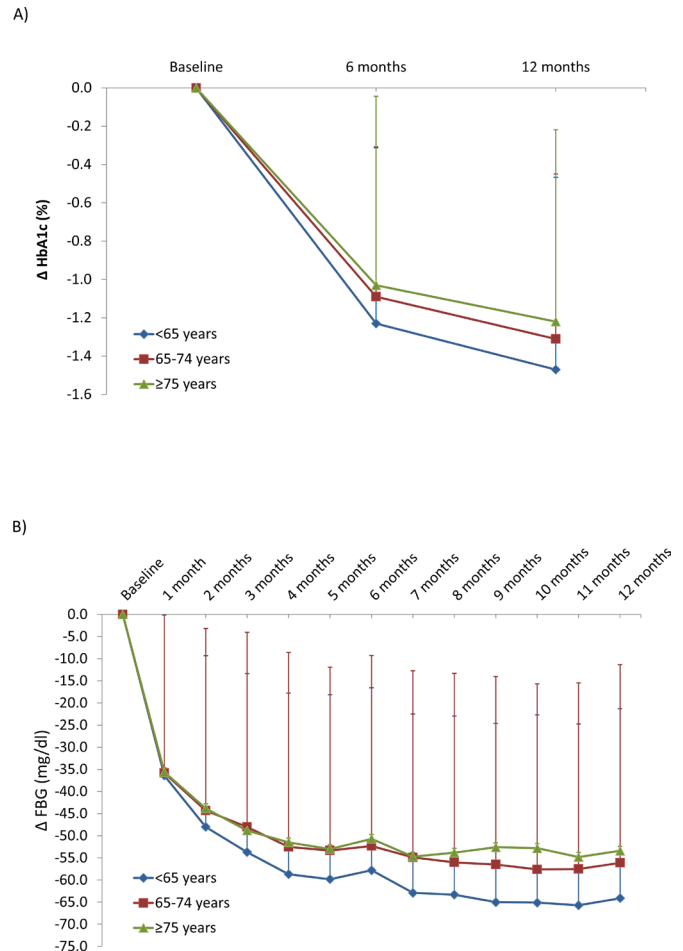
or changed the type of insulin therapy (2.6% overall). The change was not documented for the remainder.

### Glycemic control over the 12-month follow-up

While the FBG and HbA1c levels dropped between baseline and 12 months in all age groups, the magnitudes of the reductions were greater in the <65 group ( $\Delta = -64.1 \pm 44.2$  mg/dL and  $-1.47 \pm 1.00\%$  ( $-16 \pm 11$  mmol/mol)) followed by the 65–74 group ( $\Delta = -56.1 \pm 42.8$  mg/dL and  $-1.31 \pm 0.86\%$  ( $-14 \pm 9$  mmol/mol)) and the  $\geq 75$  group ( $\Delta = -53.4 \pm 44.8$  mg/dL and  $-1.22 \pm 1.00\%$  ( $-13 \pm 11$  mmol/mol);  $p < 0.0001$  for both glycemia measures) (figure 3A and B). FBG levels decreased considerably in the first month (<65:  $\Delta = -36.4 \pm 38.9$  mg/dL; 65–74:  $\Delta = -35.8 \pm 36.2$  mg/dL;  $\geq 75$ :  $\Delta = -35.5 \pm 39.3$  mg/dL;  $p = 0.904$ ), however, did not markedly change anymore between 6 and 12 months in all age groups. Similar findings were observed for HbA1c (figure 3B).

### Achievement of the primary endpoint at 12 months

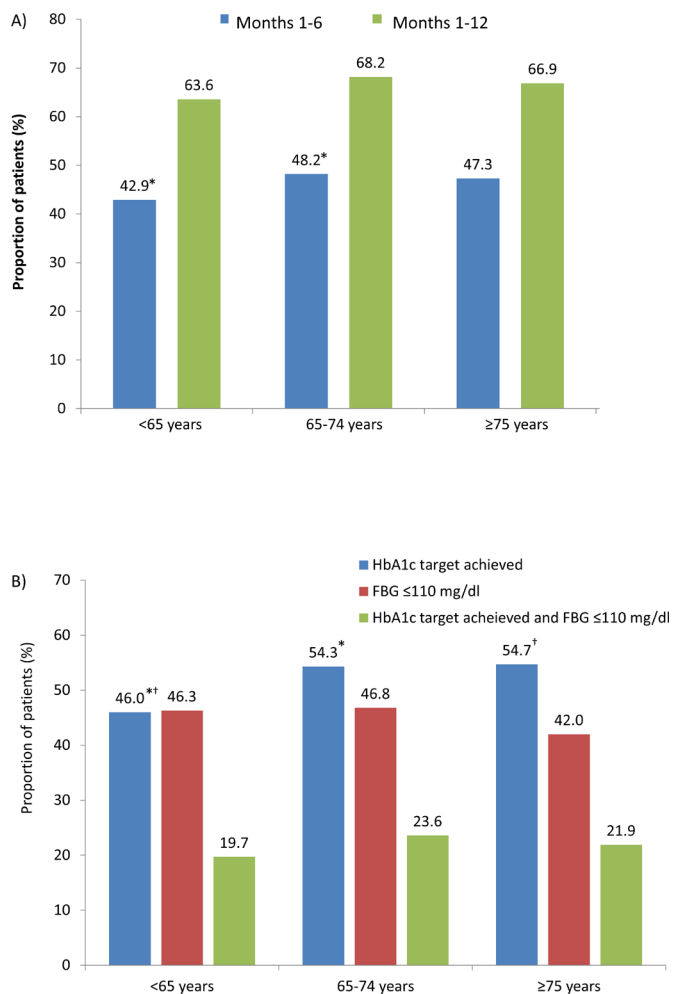
The proportion of patients who met the primary endpoint (achievement of an individual HbA1c target



**Figure 3** Change in HbA1c (A) and capillary fasting blood glucose (FBG) (B) levels over 12 months. At 6 and 12 months, the within-group change in both HbA1c and FBG vs baseline was significant for all groups ( $p < 0.0001$  in all cases).

and/or FBG  $\leq 110$  mg/dL on two occasions) was significantly lower in the <65 age group compared with the 65–75 age group at 6 months (42.9% vs 48.2%;  $p = 0.023$ ) (figure 4A). However, no significant differences were evident between groups at 12 months, with 65.9% of all patients achieving their individual HbA1c target and/or an FBG of  $\leq 110$  mg/dL.

Regarding the separate components of the primary endpoint (figure 4B), the proportion of patients who achieved their individual HbA1c target at 12 months was significantly lower in the <65 age group (46.0%) compared with those in the 65–74 group (54.3%;  $p < 0.02$ ) and  $\geq 75$  group (54.7%;  $p < 0.02$ ). Endpoint rates were substantially lower when a combination of both endpoint components (achievement of an individual HbA1c target and FBG  $\leq 110$  mg/dL on two occasions) was investigated with rates of 19.7%, 23.6%, and 21.9% in the three age groups (from youngest to oldest age group), respectively. No significant differences in the proportions of patients who attained FBG  $\leq 110$  mg/dL or met both HbA1c and FBG endpoint criteria at 12 months were seen between groups.



**Figure 4** (A) Primary endpoint achievement at 6 and 12 months. Primary endpoint is defined as achievement of individual HbA1c target and/or fasting blood glucose (FBG) ≤110mg/dL on two occasions. Values are percentages of all patients with available data. The only significant difference was between <65 and 65–74-year-olds at 6 months (\* $p=0.023$ ). (B) Components of the primary endpoint at 12 months. HbA1c target achievement was significantly different between <65 and 65–74-year-olds (\* $p\leq 0.02$ ) and <65 and ≥75-year-olds († $p\leq 0.02$ ). No other comparisons were significant.

### Hypoglycemia during the 12 months of follow-up

The proportion of patients who experienced one or more symptomatic hypoglycemia events during the 12-month study was higher in the ≥75 years group (3.4%) compared with the <65 and 65–74 groups (both 1.4%;  $p=0.0126$ ) (online supplementary table 1). No significant differences in any of the other predefined types of hypoglycemia were found between groups.

### DISCUSSION

In patients with T2DM being initiated on BOT therapy with Gla-100, advancing age is associated with slightly more lenient HbA1c target-setting, less aggressive insulin titration, and a lesser absolute reduction in glycemic values. However, in this study, glycemic improvements

were apparent in all age groups, and although rates of symptomatic hypoglycemia were slightly higher in ≥75-year-olds, they were still low. These findings support the safe and efficacious use of Gla-100 in elderly patients. Nevertheless, suboptimal rates of glycemic target attainment were apparent for all groups, indicating that there is scope for more intensive antidiabetic treatment while considering the risk of hypoglycemia, regardless of age. HbA1c target achievement was observed in less than 50% of participants in the <65-year-old group, indicating a particular need to improve glycemic control in this younger population.

### Effect of age on patient characteristics and target-setting

The number of patients enrolled decreased across age groups, with almost half the number of ≥75-year-olds starting insulin therapy compared with <65-year-olds. This may be reflective of a general unwillingness to initiate insulin therapy in elderly patients due to an age-related increase in the risk of hypoglycemia and the perceived complexity of dosing regimens.<sup>16 17</sup> In terms of Gla-100, this may be misplaced, given that its activity is nearly peak-free and long-lasting (approximately 24 hours),<sup>18</sup> reducing the likelihood of hypoglycemia and minimizing the burden of complex injection regimes.

The proportion of women rose across ascending age groups. This is logical, given that life expectancy in Germany is longer for women than for men (currently 83.6 vs 78.7 years).<sup>19</sup> This may, in part, explain the decrease in body weight across age groups, given that women are generally lighter than men. In addition, advancing age is associated with muscle wastage and a decrease in bone density,<sup>20</sup> which are also key contributors. Weight is of note as it is sometimes considered when establishing basal insulin doses in clinical practice.<sup>21</sup> Indeed, when insulin doses in the present study were calculated in units per kilogram of body weight, the magnitude of up-titration and final dose at 12 months were both comparable between age groups. Whether or not this was intentional cannot be answered with the present data and merits further investigation.

A longer diabetes duration was seen in older patients.<sup>22</sup> This has been identified as an independent risk factor for hypoglycemia.<sup>23</sup> Accordingly, guidelines state that stringent HbA1c targets (6.0%–6.5%) should only be considered for patients with a shorter diabetes duration and long life expectancy, while older patients with longer diabetes durations nearing the end of their lives may have a more relaxed target and higher risks of comorbidities such as impaired renal function and potential side effects to aggressive therapies.<sup>1</sup> While targets must also take into account factors such as comorbidities, microvascular complications, and functional status, it follows that the youngest age group in the present study had the most stringent targets. This is despite them having higher HbA1c and FBG values at baseline, demanding a greater improvement in glycemic control. However, although statistically different, the mean group targets were

reasonably similar in magnitude from a clinical perspective (6.8%–7.1%). Considered in the context of guideline recommendations,<sup>1</sup> this is surprising. It is possible that physicians were more lenient with the younger age group because of their high glycemic values at baseline and the wish to set a realistic target. Indeed, setting unrealistically low glycemic targets has been suggested to be counterproductive for long-term motivation in patients with type 1 diabetes,<sup>6</sup> and this is likely to extrapolate to patients with T2DM.

### Age and antidiabetic medication

All patients were taking at least one OAD at baseline, though the type was distributed differently across age groups. While a higher proportion of younger patients were taking metformin, sulfonylureas and DPP-4 without metformin were more common with advancing age. This may partly be explained by the higher frequency of contraindications to metformin (eg, renal impairment, hypoxia, or dehydration<sup>7</sup>) found in older patients and the additional concern over its gastrointestinal side effects in frail patients with poor appetite.<sup>24</sup> Use of any type of insulin was uncommon at baseline (<11% in each group), despite all group mean HbA1c values being above 8%. This suggests an inappropriate delay in starting insulin therapy, given that several studies have outlined the greater improvement in glycemic control to be gained from its early initiation.<sup>25 26</sup>

During follow-up, there was a drop in the use of antidiabetic drugs as can be seen in [table 1](#): metformin, glinides, and sulfonylurea were all used less often after 12 months, potentially as a result of treatment adjustment based on either the fear of hypoglycemia (eg, sulfonylurea) or merely to reduce the number of drugs used (metformin, glinides). This needs to be kept in mind when interpreting the level of target achievement and hypoglycemic side effects.

### Effect of age on dosing and glycemic control

At 6 and 12 months, the magnitudes of absolute FBG and HbA1c reductions were greater in younger patients. These changes were concurrent with the more aggressive Gla-100 titration seen in younger age groups. Indeed, the magnitude of titration was evidently age dependent, with younger patients being treated more aggressively. However, overall, treatment intensification was slow and mainly occurred in the first few months, with only small increments seen after 4 months. Indeed, the 12-month dose in the <65 group was just 21.7 U/day, representing a mean up-titration of only +10.2 units over 12 months. According to the Fritsche and Davies algorithms for Gla-100 titration in patients with T2DM, an FBG of >110 mg/dL demands a minimum of a 2 U/d up-titration every 3–5 days.<sup>27 28</sup> This would correspond to an increase of anything up to 72 U/d (extremely unlikely and for illustrative purposes only) if a patient still had a FBG >110 mg/dL at 6 months. Considering that less than 50% of patients had achieved the primary endpoint in

each group at 6 months, it appears that such algorithms are not being adhered to, and that physicians are taking a more cautious approach. Such caution is likely due to the aforementioned concerns over hypoglycemia, also explaining the reduction in the proportions of patients taking concomitant OADs at 12 months. While this may be appropriate in more frail patients of advanced age, it is unlikely to be justifiable in younger patients. As such, a fear of hypoglycemia is hard to discriminate from an actual increase in the risk of hypoglycemia in an individual patient. A further explanation for the leveling off of doses may be physician satisfaction with less-than-optimal glycemic values, supported by a survey which found over 35% of general practitioners, internists, and endocrinologists to consider any FBG below 130 mg/dL as good glycemic control.<sup>29</sup> While the appropriacy of titrations must be established on an individual basis taking into account multiple patient factors, our findings suggest that there is scope for greater treatment intensification across age groups. This is especially true for younger patients with longer life expectancies, given the association between elevated HbA1c and microvascular complications, and a reported 42% reduction in cardiovascular events over the long term with intensive glycemic control.<sup>9 10</sup>

Increased rates of hypoglycemia are commonly seen in elderly patients as a result of polypharmacy, comorbidities, decreases in renal function, and reduced perception of hypoglycemic warning signs.<sup>30 31</sup> They are also more concerning, given that they are a known risk factor for falls in this population.<sup>32</sup> Concurrently, the proportion of patients who experienced  $\geq 1$  symptomatic hypoglycemia event during the 12-month study was highest in the  $\geq 75$  group, with no difference between <65 and 65–74-year-olds. However, this rate was low, at 3.5%. Indeed, when all of the hypoglycemia types were combined, only 5.3% of the  $\geq 75$ -year-old group had any kind of event. This is much lower than the 17.2% and 5.3% of older patients ( $\geq 65$ ; mean 71.9 years) who experienced daytime and nocturnal hypoglycemia, respectively, in the PREDICTIVE study with insulin detemir.<sup>22</sup> However, it should be noted that non-symptomatic events are included in PREDICTIVE values, and direct comparisons stratified by age groups are needed before any conclusive benefit can be established. It is also important to consider that the rate of hypoglycemia may have been underestimated in our older groups, given the reduced perception and reporting typical of geriatric patients. Nevertheless, the low incidence of hypoglycemia also in people with T2DM  $\geq 75$  years may encourage physicians to use Gla-100 more frequently in the elderly population.<sup>33</sup>

The majority of patients were continuing Gla-100 therapy at 12 months with no significant difference between groups, suggesting a high rate of tolerance and persistence. This is encouraging, as there is evidence for an association between interruption/discontinuation of basal insulin within the year after initiation and higher rates and costs of hospitalization.<sup>34</sup>

## Limitations

Due to the observational nature of the study, imbalances in group sizes and non-age-related factors were present at baseline. These may have had considerable impact when comparing outcomes, particularly in terms of hypoglycemia. Furthermore, there is no control group which would have interesting to explore the clinical benefits of Gla-100. However, our data offer valuable insight into the real-world situation in Gla-100 initiation and ongoing treatment in populations of different age. The large samples used in the present study are advantageous in terms of statistical power, though occasionally resulted in statistically significant differences with relatively low clinical relevance. Due to the study design, reporting of symptomatic hypoglycemia is likely to have been subject to recall bias and must be interpreted with care.

## CONCLUSIONS

Overall, the addition of Gla-100 to oral antidiabetic therapy resulted in a significant and clinically relevant improvement in glycemic control with low rates of hypoglycemia across all age groups, including those aged  $\geq 75$  years. Almost half of patients failed to meet their HbA1c targets which was particularly apparent in those aged  $< 65$  years, who failed to meet their (relatively lenient) targets in more than 50% of cases. Given the link between HbA1c and long-term cardiovascular risk, ensuring appropriately stringent target-setting, intensification of basal insulin, and making sure hypoglycemia is avoided is of paramount importance, particularly in younger patients.

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