



# Effectiveness and Safety of Switching Rapid-Acting Insulins to Insulin Glulisine in Patients with Diabetes: The Observational IGLU-S Study

Jochen Seufert · Martin Pfohl · Anja Borck · Peter Bramlage · Thorsten Siegmund

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## ABSTRACT

**Introduction:** The IGLU-S study assessed the effectiveness of insulin glulisine after switching from human insulin/other rapid-acting insulin analogues in patients with type 1 diabetes (T1DM) and type 2 diabetes (T2DM) in a real-world setting in Germany.

**Methods:** Open-label, prospective, multicentre, non-interventional study in Germany. The primary outcome was proportion of patients

reaching pre-defined glycosylated haemoglobin A1c (HbA1c) goal at 3, 6, 9 and 12 months. Secondary outcomes included absolute changes in HbA1c, rate of hypoglycaemia and 7-point blood glucose profiles.

**Results:** Overall, 432 (55 T1DM, 377 T2DM) patients were enrolled. Baseline HbA1c was 8.2% (T1DM) and 8.3% (T2DM); individual HbA1c targets were 6.8% and 6.9%, respectively. After insulin glulisine introduction, the proportion of patients achieving their individual HbA1c increased to 43.6% (T1DM) and 39.6% (T2DM) of patients at 12 months. At 12 months, mean HbA1c was reduced by  $0.86 \pm 1.03\%$  ( $p < 0.0001$ ) in T1DM and  $1.01 \pm 1.02$  ( $p < 0.0001$ ) in T2DM. The 7-point blood glucose profile showed a significant reduction in patients with T2DM ( $p < 0.0001$ ) and a non-significant reduction in T1DM patients. Confirmed symptomatic hypoglycaemia was 5.7% (T1DM) and 1.6% (T2DM). There were no cases of severe hypoglycaemia.

**Conclusion:** Switching prandial insulin to insulin glulisine resulted in improved effectiveness with 43.6% of T1DM and 39.6% of T2DM patients reaching their individual pre-defined HbA1c target within 1 year. Switching was safe and was associated with a low rate of hypoglycaemia and adverse events.

**Trial Registration:** <https://awbdb.bfarm.de>; Identifier: 6818; Date of registration: 23.06.2016

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J. Seufert (✉)  
Division of Endocrinology and Diabetology,  
Department of Medicine II, Faculty of Medicine,  
Medical Center, University of Freiburg, Freiburg,  
Germany  
e-mail: jochen.seufert@uniklinik-freiburg.de

M. Pfohl  
Department of Internal Medicine I, Evang.  
Bethesda-Hospital Duisburg, Duisburg, Germany

A. Borck  
Sanofi-Aventis Deutschland GmbH, Berlin,  
Germany

P. Bramlage  
Institute for Pharmacology and Preventive  
Medicine, Cloppenburg, Germany

T. Siegmund  
Division for Endocrinology, Diabetology and  
Metabolism, Isar Clinic, Munich, Germany

**Keywords:** Blood glucose; Diabetes; HbA1c; Hypoglycaemia; Insulin

### Key Summary Points

There is insufficient longer-term data in both patients with type 1 diabetes (T1DM) and type 2 diabetes (T2DM), on the performance of insulin glulisine in patients who are switched to insulin glulisine under real-world conditions.

The IGLU-S study documented the effectiveness of insulin glulisine when switching from regular human insulin or any other rapid-acting insulin analogues to insulin glulisine in patients with T1DM (in addition to any basal insulin) or T2DM (in addition to oral drugs or to basal insulin) in a real-world setting over a period of 52 weeks in Germany.

Switching from prandial insulin to insulin glulisine is an appropriate treatment option for patients with insufficiently controlled T1DM and T2DM.

Direct comparisons cannot be made with other rapid-acting prandial insulins or regular human insulins because of the one-armed observational nature of the study.

mealtime insulin requirements in patients with type 1 diabetes (T1DM) and type 2 diabetes (T2DM). Based on its zinc-free formulation, insulin glulisine has a faster onset of action compared with insulin lispro and insulin aspart [1–3].

Patients with T1DM are usually treated with intensified conventional insulin therapy (ICT) using either regular human insulin or insulin analogues [4]. In patients with T2DM, switching mealtime insulin to rapid-acting analogues as part of a supplementary insulin therapy (SIT), basal-insulin supported oral therapy with a single prandial dose of rapid-acting insulin (BOT Plus) or ICT may be considered after failure of previous insulin treatment [5]. Recent studies provide evidence that switching from another rapid-acting insulin analogue, e.g., insulin lispro, to insulin glulisine may improve glycosylated haemoglobin A1c (HbA1c) and patient satisfaction [6, 7]. There is insufficient longer term data, however, in both T1DM and T2DM, on the performance of insulin glulisine in patients who are switched to insulin glulisine under real-world conditions.

The objective of this non-interventional observational study was to document the effectiveness of insulin glulisine when switching from regular human insulin or any other rapid-acting insulin analogues to insulin glulisine in patients with T1DM (in addition to any basal insulin) or T2DM (in addition to oral drugs or to basal insulin) in a real-world setting over a period of 52 weeks.

## DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to <https://doi.org/10.6084/m9.figshare.13526510>.

## INTRODUCTION

Insulin glulisine is a rapid-acting insulin analogue with rapid absorption and onset of action after subcutaneous injection. It is used to cover

## METHODS

### Study Design

This was an open-label, prospective, multicentre, non-interventional 12-month observational study. Participating physicians were specialised diabetologists, internists, general practitioners and family physicians in Germany. The registry protocol was approved by the University of Freiburg, Germany, and was carried out in accordance with the Declaration of Helsinki and its amendments. Only patients who provided

written informed consent to participate were included.

### Patient Selection

Adult patients ( $\geq 18$  years) were eligible if they had either T1DM (intensified conventional treatment [ICT]) or T2DM (supplementary insulin therapy [SIT]; basal supported oral therapy [BOT] plus or ICT). Patients had to present with insufficient blood glucose control defined as an HbA1c  $> 7.0\%$  (53.0 mmol/mol) and  $\leq 10\%$  (85.8 mmol/mol), and the treating physician had to make a previous decision to replace current mealtime insulin with insulin glulisine no earlier than 2 weeks prior to the documentation. Further inclusion criteria were the ability and readiness to record a 7-point blood glucose profile and the provision of written informed consent. Patients with a contraindication for insulin glulisine, pregnancy, active cancer, alcohol or drug-abuse were excluded.

### Drug Treatment

Insulin glulisine was used as the mealtime insulin during ICT in patients with T1DM or as part of SIT, BOT plus or ICT in patients with T2DM. Mealtime insulin glulisine doses were recorded. Patients determined and adjusted insulin doses prior to each of the five study visits using a 7-point self-monitoring of blood glucose.

### Data Collection

Data were collected at baseline and after a follow-up of 3, 6, 9 and 12 months (with some flexibility according to clinical practice routines). Data were entered into an electronic case report form. A monitoring visit was performed at random for 5% of the trial sites. All adverse events (AEs), regardless of intensity and relationship to the study drug, were collected between baseline and 7 days after the last follow-up visit.

### Outcomes

The primary outcome was the proportion of patients reaching the pre-defined individual HbA1c target at each of the four follow-up visits for each diabetes type. Secondary outcomes were separately assessed by diabetes type: mean change from baseline in insulin glulisine dosing at each study visit, mean change from baseline in mean haemoglobin A1c (HbA1c) at each study visit, median time to reach individual HbA1c targets after starting insulin glulisine, median duration of response (duration until the individual target HbA1c was exceeded or insulin glulisine was switched), change from baseline in mean blood glucose profile at 12 months using 7-point self-monitoring blood glucose testing, change from baseline in bodyweight and change from baseline in blood lipid profile at 12 months. We recorded all AEs, including serious adverse events (SAEs) and the rate of symptomatic, confirmed (self-monitoring blood glucose [SMBG] value of  $\leq 70$  mg/dl [ $\leq 3.9$  mmol/l]), symptomatic, nocturnal (symptomatic or confirmed hypoglycaemia occurring approximately between 10 p.m. and 6 a.m., while the patient was asleep), severe (assistance of another person required or SMBG value of  $\leq 56$  mg/dl [ $\leq 3.0$  mmol/l]) and severe nocturnal hypoglycaemia.

### Statistical Analysis

Data are presented using descriptive statistics, with categorical variables expressed as frequencies and continuous variables as means  $\pm$  standard deviations (SD).

The Safety Analysis Set (SAS) included all patients with at least one dose of insulin glulisine administered. The Full Analysis Set (FAS) included all patients meeting the inclusion and exclusion criteria. The modified FAS (mFAS) group included all patients with any post-baseline data and the mFAS12 group all patients with 12-months follow-up.

For the primary outcome, response rates were calculated using frequency distribution with exact 95% confidence intervals (CI) according to Clopper-Pearson. The time to

response was analysed by Kaplan-Meier methods with reaching the pre-defined individual HbA1c goal for the first time being considered as the event. Median time to response and corresponding 95% CI were estimated using the Kaplan-Meier method. The duration of response was analysed using Kaplan-Meier. End of response was defined as first measurement of an HbA1c above the pre-defined individual HbA1c goal or switch to another form of insulin therapy (discontinuation of insulin glulisine). Median duration of response was analysed using Kaplan-Meier.

A  $p$  value of  $< 0.05$  was considered significant with no adjustment for multiple testing. All analyses were performed using Statistical Analysis System version 9.4.

## RESULTS

For this observational study, 81 sites in Germany collected data between May 2016 and September 2017 for a total of 432 patients, of whom 55 patients had T1DM (12.7%) and 377 patients had T2DM (87.3%). A breakdown of patient numbers into the Safety Analysis Set (SAS), the Full Analysis Set (FAS) and the modified full analyses of patients with a 12 months follow-up available (mFAS12) is displayed in Fig. 1. Efficacy results are presented for the FAS and, as a sensitivity analysis, the mFAS12 while safety results are based on the SAS.

### Baseline Characteristics and Drug Treatment

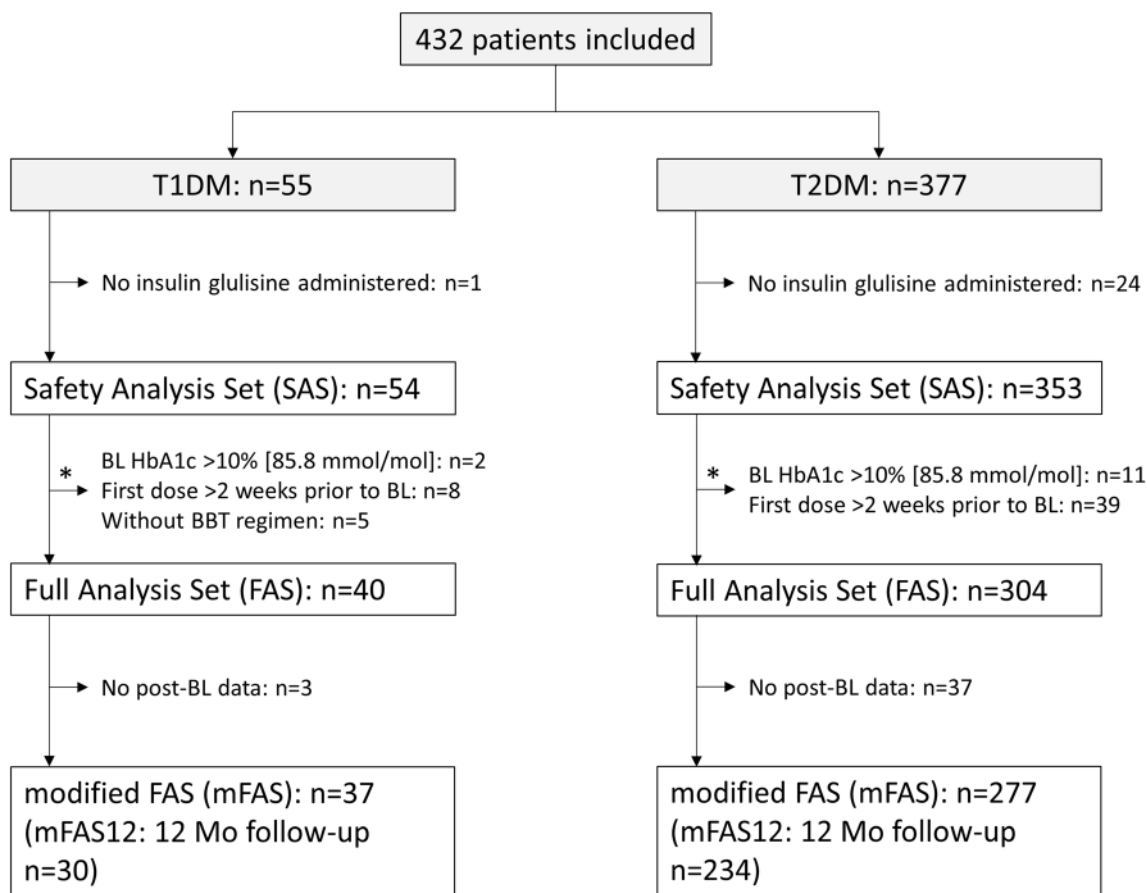
Patients with T1DM (FAS) had a mean age of 49.9 years, 47.5% were female, and the mean bodyweight was 79.0 kg (Supplementary Table 1). T1DM patients had a mean HbA1c value of 8.2% (66.1 mmol/mol) at baseline, and the mean individual HbA1c target was 6.8% (50.8 mmol/mol) at insulin glulisine initiation. The majority of patients received insulin glargine as long-acting insulin (100 units: 19 [47.5%] patients; 300 units: 9 [22.5%] patients) (Table 1). Patients started insulin glulisine at mean doses of 8.6, 7.3 and 8.0 units in the morning, at lunch time and in the evening,

respectively (Table 2). Basal insulin was applied at a mean dose of  $23.2 \pm 14.0$  units. Daily doses increased from 22.8 units at baseline to 32.9 units at 12 months ( $p = 0.5212$ ). Patients in the mFAS12 group had demographics and treatment patterns comparable to the FAS population.

Patients with T2DM (FAS) had a mean age of 65.4 years, 45.4% were female, and the mean bodyweight was 94.4 kg. Patients had a mean HbA1c value of 8.3% (67.2 mmol/mol) at baseline and the mean individual HbA1c target was 6.9% (51.9 mmol/mol) (Supplementary Table 2). While non-insulin antidiabetic drugs were the most common antidiabetic treatment, many patients received long-acting insulin glargine (100 units: 100 [32.9%] patients; 300 units: 84 [27.6%] patients) (Table 1). Patients started insulin glulisine at mean doses of 13.1, 11.2 and 12.4 units in the morning, at lunch time and in the evening, respectively (Table 2). Basal insulin was applied at a mean dose of  $28.9 \pm 15.3$  units. Daily doses increased from  $34.6 \pm 21.2$  units at baseline to  $42.0 \pm 22.7$  units at 12 months ( $p < 0.0001$  vs. baseline). Patients in the mFAS12 population had a higher comorbidity burden and more frequently received regular human insulin at baseline, but were otherwise comparable to the FAS population.

### Achievement of Pre-Defined Individual HbA1c Target (FAS)

The primary outcome of this investigation was to determine the proportion of patients achieving their pre-defined individual HbA1c target at each of the four follow-up visits separately for T1DM and T2DM (Fig. 2a, c). In the FAS group, there was a steady increase from baseline in the proportions of patients who achieved their target HbA1c at each follow-up visit. Target HbA1c was reached by 43.6% of patients with T1DM and 39.6% of patients with T2DM at 12 months. While effects were in the same order for patients receiving regular human insulin, target achievement was blunted in patients switching from other analogues (Fig. 3a, c). Target achievement was slightly



**Fig. 1** Patient disposition. *BBT* basal-bolus therapy, *BL* baseline, *HbA1c* glycosylated haemoglobin A1c, *T1DM* type 1 diabetes, *T2DM* type 2 diabetes. Asterisk: multiple reasons for exclusion from a particular dataset possible

better in patients with a full 12-month follow-up (mFAS12) with rates of 50.0% for patients with T1DM and 44.9% for patients with T2DM at 12 months.

### Blood Glucose Control

There was a decrease in mean HbA1c from 8.21 to 7.53% (66.2–58.8) in T1DM ( $\Delta$  0.86% [9.4 mmol/mol];  $p < 0.0001$ ) and 8.27 to 7.29% (66.9–56.2) in T2DM ( $\Delta$  1.01% [11.0 mmol/mol];  $p < 0.0001$ ) (FAS, Fig. 2b, d). Effects were similar independent of the type of prior insulin used (Fig. 3b, d). The estimated median duration for reaching that response was 432 days in T1DM and 394 days in patients with T2DM (FAS, Fig. 4a, b). Once target HbA1c had been achieved, the estimated duration of

response was longer in patients with T2DM (median 301 days) than in those with T1DM (median 119 days). A total of 52.9% of T1DM and 29.1% of T2DM lost their HbA1c target response or switched from insulin glulisine (FAS, Fig. 4c, d). The 7-point blood glucose profile was significantly reduced at all time points in T2DM ( $p < 0.0001$ ), while reductions were not significant in patients with T1DM (FAS, Fig. 5a). Effects on blood glucose control were virtually identical between the FAS and the mFAS12 groups: HbA1c reductions were in the same order (Fig. 2b, d) as were reductions in the 7-point blood glucose profile (Fig. 4b, d).

**Table 1** Baseline antidiabetic therapies used prior to insulin glargine initiation (FAS/mFAS12)

	FAS		mFAS12	
	T1DM (N = 40)	T2DM (N = 304)	T1DM (N = 30)	T2DM (N = 234)
Rapid-acting insulin <sup>a</sup>				
Regular human insulin, %	24 (60.0)	172 (56.6)	19 (63.3)	144 (61.5)
Aspart/lispro, %	14 (35.0)	91 (29.9)	11 (36.7)	64 (27.4)
Other, %	1 (2.5)	14 (4.3)	0 (0.0)	6 (2.6)
Long-acting insulin <sup>b</sup>				
Insulin glargine 100 U/ml, %	19 (47.5)	100 (32.9)	14 (46.7)	76 (32.5)
Insulin glargine 300 U/ml, %	9 (22.5)	84 (27.6)	7 (23.3)	61 (26.1)
Insulin detemir, %	1 (2.5)	27 (8.9)	0 (0.0)	22 (9.4)
NPH insulin, %	2 (5.0)	25 (8.2)	2 (6.7)	24 (10.3)
Others, %	1 (2.5)	22 (7.2)	0 (0.0)	21 (9.0)
Non-insulin antidiabetic drugs <sup>b</sup>				
Metformin, %	2 (5.0)	172 (56.6)	2 (6.7)	130 (55.6)
DPP4 inhibitor, %	0 (0.0)	71 (23.4)	0 (0.0)	55 (23.5)
SGLT-2 inhibitor, %	0 (0.0)	22 (7.2)	0 (0.0)	18 (7.7)
Sulfonylurea, %	0 (0.0)	9 (3.0)	0 (0.0)	8 (3.4)
Glinides, %	0 (0.0)	4 (1.3)	0 (0.0)	3 (1.3)
Glucosidase inhibitors, %	0 (0.0)	2 (0.7)	0 (0.0)	1 (0.4)
GLP-1 analogues, %	0 (0.0)	14 (4.6)	0 (0.0)	12 (5.1)
Others, %	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Treatment regimen <sup>b</sup>				
BOT plus	n.a	109	n.a	84
SIT	n.a	37	n.a	22
ICT	40	158	30	128

*BOT* basal insulin supported oral therapy, *DPP4* dipeptidyl peptidase 4, *GLP-1* glucagon peptide 1, *ICT* intensified insulin treatment, *NPH* neutral protamine hagedorn, *SGLT-2* sodium glucose cotransporter 2, *SIT* supplementary insulin treatment, *T1DM* type 1 diabetes, *T2DM* type 2 diabetes

<sup>a</sup> Prior to baseline and before switch

<sup>b</sup> At baseline as concomitant treatment

### Effects on Bodyweight and Metabolism

There was no meaningful change in mean bodyweight among patients with T1DM (76.5 kg at baseline vs. 76.5 kg at 12 months;

$p = 0.7778$  mFAS). A small reduction in mean bodyweight was observed in patients with T2DM (94.3 kg at baseline vs. 92.5 kg at 12 months;  $p = 0.0005$ ).

Changes in lipid values over time in the FAS did not reach statistical significance for

**Table 2** Mean dose for rapid-acting insulin treatment (FAS, mFAS12)

	FAS			mFAS12		
	Prior to visit 1	Visit 1	Visit 5	Prior to visit 1	Visit 1	Visit 5
<b>T1DM</b>						
Rapid-acting insulin (units)	23.5 ± 15.5	22.8 ± 15.8	32.9 ± 17.9*	22.4 ± 14.7	22.0 ± 14.6	32.9 ± 17.9
Morning (units)	8.7 ± 6.0	8.6 ± 6.0	12.6 ± 4.5	8.2 ± 5.6	8.4 ± 5.3	12.6 ± 4.5
Lunch (units)	7.5 ± 4.8	7.3 ± 4.9	10.0 ± 5.7	7.1 ± 4.7	6.9 ± 4.6	10.0 ± 5.7
Evening (units)	7.6 ± 5.3	8.0 ± 5.1	11.7 ± 6.7	7.5 ± 5.2	7.7 ± 4.8	11.7 ± 6.7
Basal insulin (units)	n.a	23.2 ± 14.0	25.1 ± 13.0	n.a	22.2 ± 14.6	25.1 ± 13.0
<b>T2DM</b>						
Rapid-acting insulin (units)	34.5 ± 22.6	34.6 ± 21.2	42.0 ± 22.7**	33.8 ± 22.6	34.4 ± 21.4	42.0 ± 22.7
Morning (units)	13.8 ± 8.4	13.1 ± 7.6	15.4 ± 9.2	14.0 ± 8.7	13.1 ± 7.8	15.4 ± 9.2
Lunch (units)	12.0 ± 9.0	11.2 ± 6.9	13.0 ± 6.9	11.7 ± 7.3	11.2 ± 7.0	13.0 ± 6.9
Evening (units)	12.7 ± 8.0	12.4 ± 7.9	14.3 ± 7.9	13.0 ± 8.1	12.6 ± 8.0	14.3 ± 7.9
Basal insulin (units)	n.a	28.9 ± 15.3	31.3 ± 14.7	n.a	29.4 ± 16.0	31.3 ± 14.7

n.a. not applicable, T1DM type 1 diabetes, T2DM type 2 diabetes

\* $p = 0.5212$  vs. baseline

\*\* $p < 0.0001$  vs. baseline

triglycerides or high-density lipoprotein (HDL) cholesterol. Low-density lipoprotein (LDL) cholesterol was nominally but non-significantly increased among patients with T1DM at 12 months (108.7 mg/dl at baseline vs. 125.5 mg/dl at 12 months;  $p = 0.412$ ). Significant reductions at 12 months were seen for LDL cholesterol (123.3 mg/dl at baseline vs. 112.5 mg/dl at 12 months;  $p = 0.0010$ ) and total cholesterol (199.3 mg/dl vs. 184.7 mg/dl;  $p < 0.0001$ ) in T2DM.

### Incidence of Hypoglycaemia

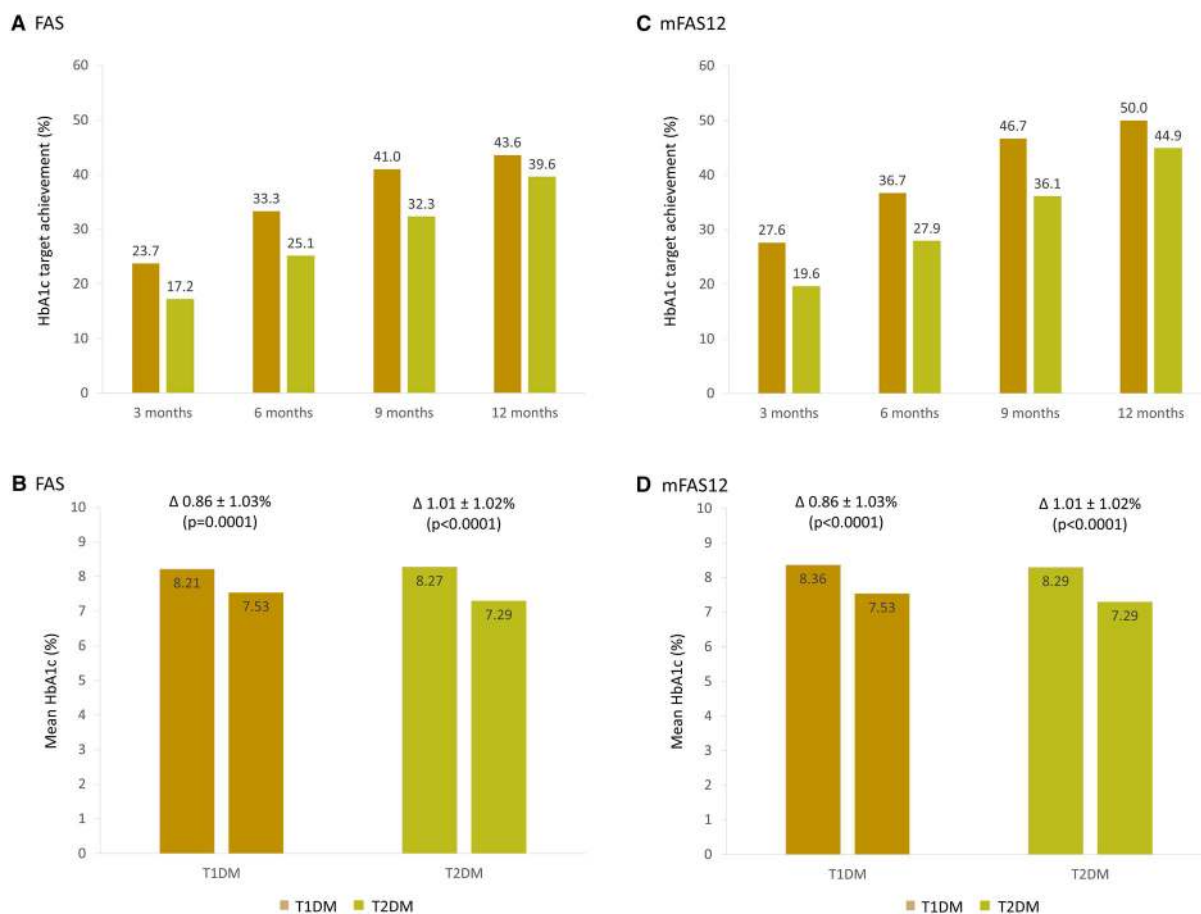
The rate of symptomatic hypoglycaemia was 5.7% (95% CI 1.2–15.4) in patients with T1DM and 1.6% (95% CI 0.5–3.6) in patients with T2DM (Table 3). All of these events were confirmed. Nocturnal hypoglycaemia was recorded in 0.3% of patients with T2DM (95% CI 0.0–1.7) and no patients with T1DM. No cases of

severe hypoglycaemia were recorded. Rates of hypoglycaemia were numerically lower in patients that completed the 12-month follow-up (mFAS12) with 3.3% of patients with T1DM and 1.3% of patients with T2DM suffering from (confirmed) symptomatic hypoglycaemia, respectively.

### Adverse Events (SAS)

Four patients with T1DM (7.4%) reported 9 adverse events and 37 patients with T2DM (10.5%) reported 81 adverse events (Table 4). Adverse events were considered by the investigator to be drug related in one patient with T1DM and in eight patients with T2DM, none of which were serious. During the follow-up period, two patients with T2DM died: one had a fatal stroke and one died of pneumonia. Both deaths were not considered drug related. Rates in patients with a complete 12 months follow-





**Fig. 2** HbA1c target achievement at 3, 6, 9 and 12 months (upper panels **a**, **c**). Mean HbA1c at baseline and at 12 months and absolute change (lower panels **b** and **d**). *HbA1c* haemoglobin A1c, *T1DM* type 1 diabetes,

*T2DM* type 2 diabetes. Differences in panels **c**, **d** could only be calculated for those with a follow-up which results in identical differences

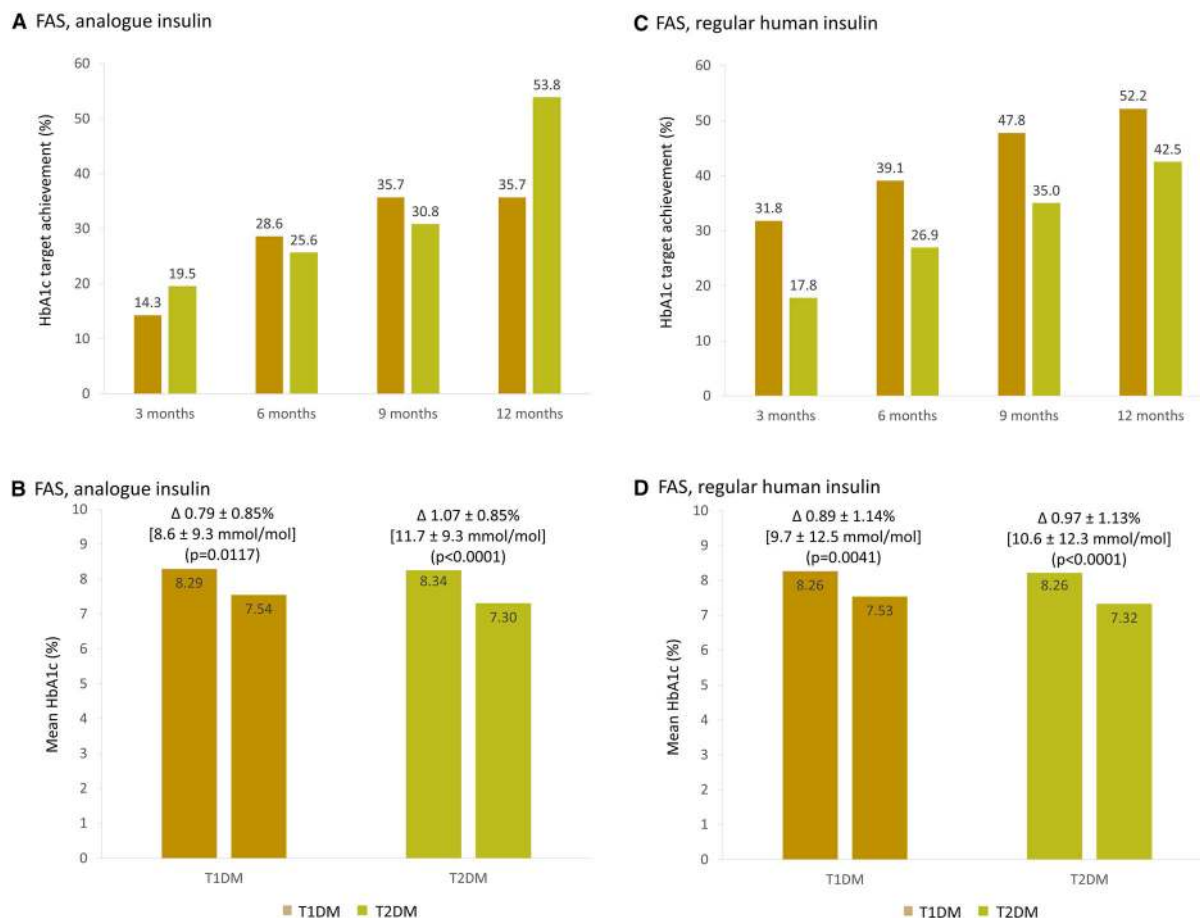
up (mFAS12) were in the same order than in the FAS.

## DISCUSSION

This was an observational study of patients and their care providers who had already made the decision to switch to insulin glulisine and were allowed to continue taking concomitant antidiabetic medications. Upon switching to insulin glulisine and modifying/increasing the dose of the long-acting insulin, target HbA1c was reached by 43.6% of patients with T1DM and 39.6% of patients with T2DM at 12 months with higher rates in prior regular human insulin users. There was a concomitant decrease in the

mean HbA1c by 0.86% (9.4 mmol/mol) in T1DM and 1.01% (11.0 mmol/mol) in T2DM, mostly independent of the prior insulin type used. While it took about 420 days (432 T1DM, 394 T2DM) to achieve the individual treatment target more than half of T1DM patients and one-third of the T2DM patients lost their HbA1c target achievement during follow-up. The 7-point blood glucose profile was significantly reduced at all time points in T2DM ( $p < 0.0001$ ), while reductions were not significant in patients with T1DM. The use of insulins is often associated with an increase in body-weight, and it was reassuring that, in our study, this was not observed with insulin glulisine and that there were no changes in plasma lipid





**Fig. 3** HbA1c target achievement (upper panel), HbA1c at baseline, 12 months and absolute change (lower panel) (FAS) by insulin type prior to baseline. *HbA1c*

haemoglobin A1c, *T1DM* type 1 diabetes, *T2DM* type 2 diabetes. Patients that could not be grouped into either group were excluded

levels. Symptomatic hypoglycaemia was observed in 5.7% and 1.6% of patients with T1DM and T2DM, respectively, with very low rates of nocturnal hypoglycaemia. Rates of adverse events were usually not drug related and none of the drug-related events were serious.

### Individual HbA1c Targets and Blood Glucose Control

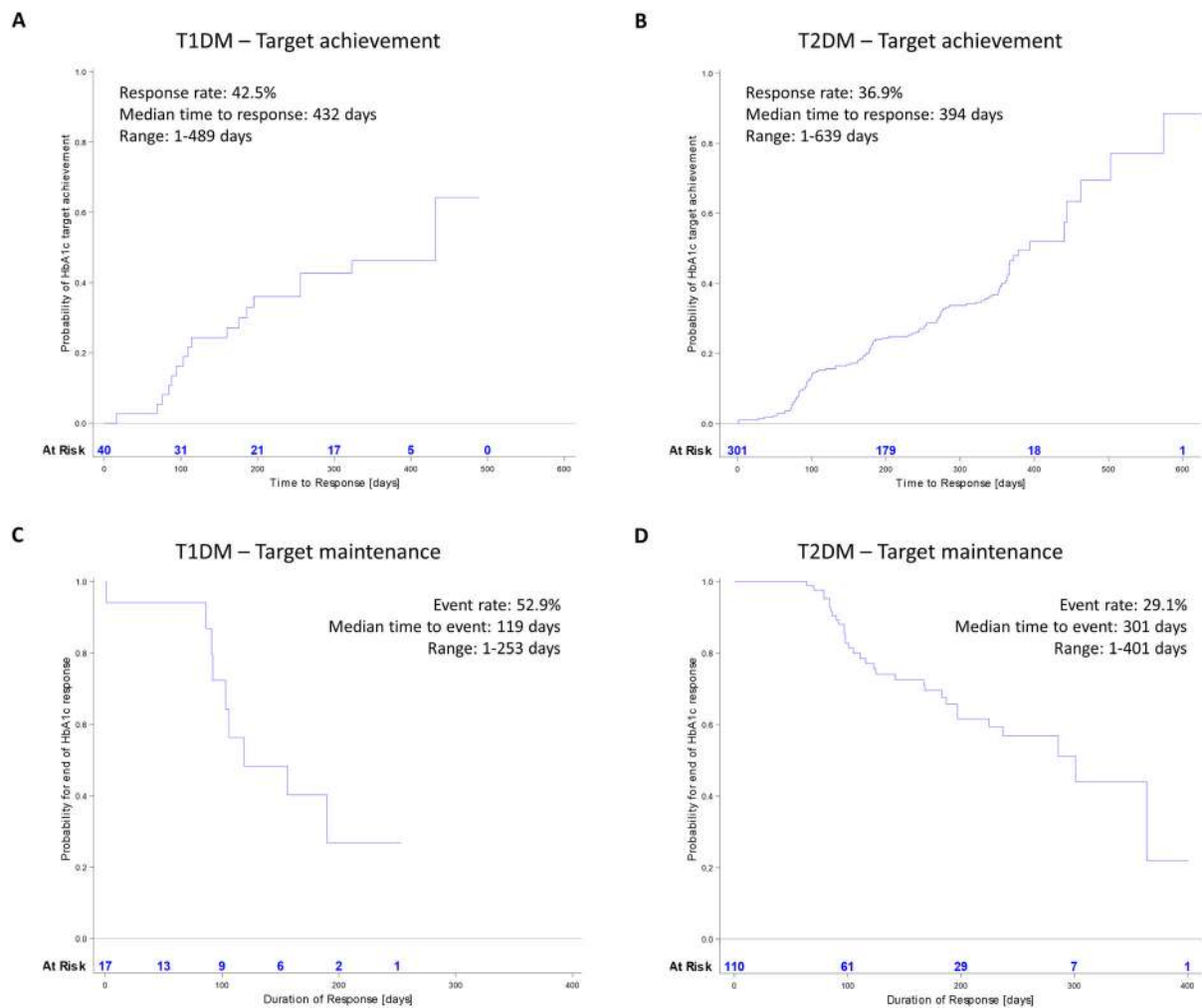
We showed that about 40% of the patients with insufficient HbA1c control at baseline met their individual HbA1c target within the 12 months after the initiation of insulin glulisine (T1DM > T2DM). The reductions in the

observed HbA1c levels achieved with insulin glulisine in our study are higher than those reported from prior controlled studies [8, 9]. Fullerton et al. [8] reported a mean difference of  $-0.15\%$  (95% CI  $-0.21; -0.08$ ) [ $-1.64$  mmol/mol (95% CI  $-2.29; -0.87$ )] from nine direct comparisons of rapid-acting insulin analogues with regular human insulin in patients with T1DM. Improvements were larger for lispro ( $-0.20$ ) than for aspart ( $-0.14$ ); none of the trials reported on differences of glulisine vs. regular human insulin. Similar results were obtained by Melo et al. [10] from a meta-analysis of randomised controlled trials, where the use of insulin analogues was associated with lower HbA1c levels (mean difference  $-0.13\%$  (95% CI  $-0.16$  to  $-0.10$ ) [ $-1.42$  mmol/mol

(95% CI  $-1.74$ ;  $-1.09$ )). Differences of rapid-acting insulin and insulin analogues were smaller in T2DM ( $-0.03$  (95% CI  $-0.16$ ;  $0.09$ ) [ $-0.32$  mmol/mol (95% CI  $-1.74$ ;  $-0.98$ )], which did not reach statistical significance when subgroups of insulin analogues were analysed individually or were combined (lispro  $+0.09\%$  [ $+0.98$  mmol/mol]; glulisine  $-0.08$  [ $-0.87$  mmol/mol]; aspart  $-0.07$  [ $-0.76$  mmol/mol]) [9]. It is encouraging, therefore, that our findings showed greater reductions in HbA1c levels than those previously reported with other rapid-acting insulin analogues.

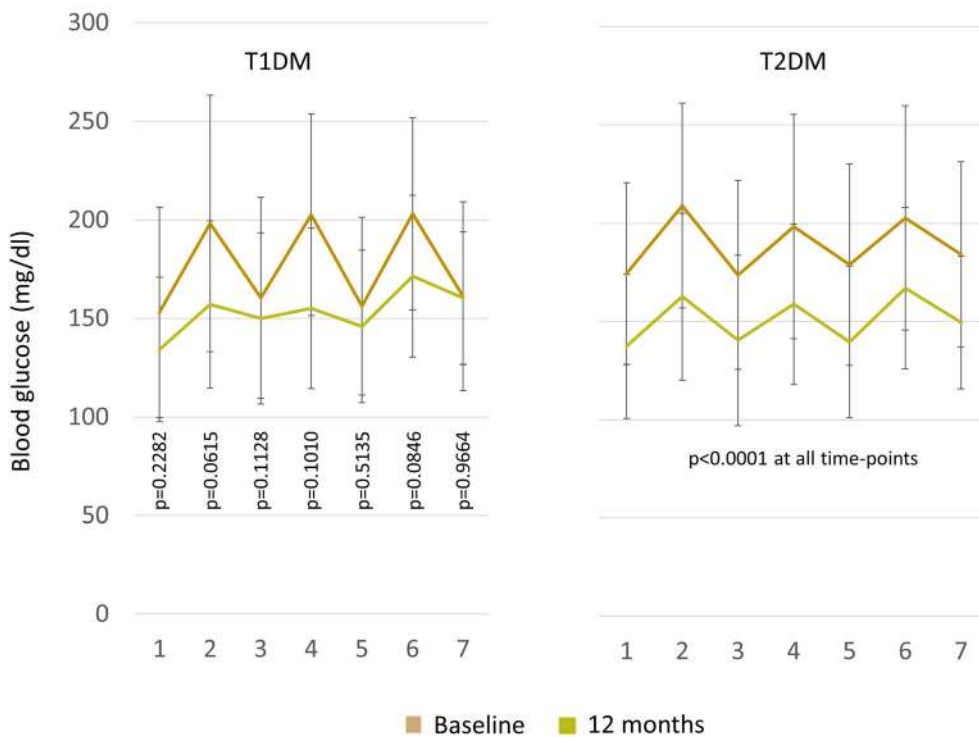
**Fig. 5** Mean blood glucose using a 7-point blood glucose profile (FAS, upper panel **A**; mFAS 12, lower panel **B**). T1DM, type 1 diabetes; T2DM, type 2 diabetes. 1. Prior to breakfast; 2. Two hours after breakfast; 3. Prior to lunch; 4. Two hours after lunch; 5. Prior to dinner; 6. Two hours after dinner; 7. Bedtime

An improved glycaemic control after switching from insulin lispro to insulin glulisine has also been reported by a study performed in Japan (BANDRA) [6], where patients with different diabetes types experienced a reduction of the HbA1c from 8.26 to 7.71% (66.8–60.8 mmol/mol;  $p < 0.01$ ) using a

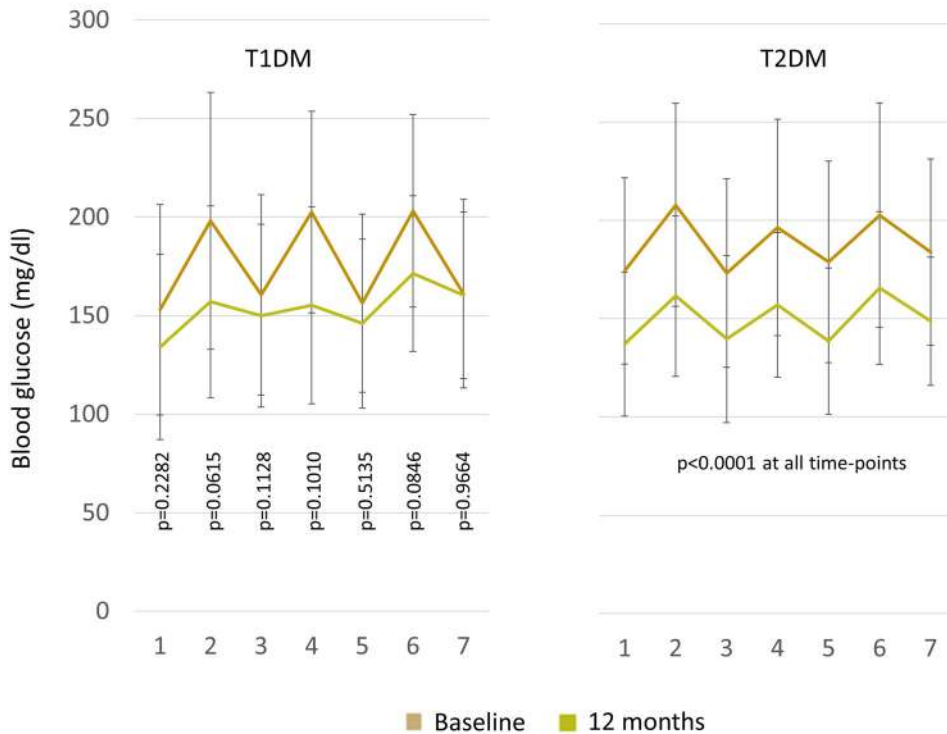


**Fig. 4** Kaplan-Meier estimates of median time to individual HbA1c target (upper panels) and duration of response (lower panels) (FAS). T1DM type 1 diabetes, T2DM type 2 diabetes

**A FAS**



**B mFAS12**



**Table 3** Hypoglycaemia (SAS, mFAS12)

	SAS		mFAS12	
	T1DM ( <i>N</i> = 54) % (95% CI)	T2DM ( <i>N</i> = 353) % (95% CI)	T1DM ( <i>N</i> = 30) % (95% CI)	T2DM ( <i>N</i> = 234) % (95% CI)
Symptomatic hypoglycaemia, %				
Patients	5.7 (1.2–15.4)	1.6 (0.5–3.6)	3.3 (0.1–17.2)	1.3 (0.3–3.7)
Rate per patient-year	0.08 (0.02–0.21)	0.14 (0.10–0.19)	0.03 (0.00–0.17)	0.14 (0.10–0.20)
Confirmed (blood glucose $\leq$ 70 mg/dl/ $\leq$ 3.9 mmol/l) symptomatic hypoglycaemia, %				
Patients	5.7 (1.2–15.4)	1.6 (0.5–3.6)	3.3 (0.1–17.2)	1.3 (0.3–3.7)
Rate per patient-year	0.08 (0.02–0.21)	0.14 (0.10–0.19)	0.03 (0.00–0.17)	0.14 (0.10–0.20)
Nocturnal hypoglycaemia, %				
Patients	0.0 (0.0–6.7)	0.3 (0.0–1.7)	0.0 (0.0–11.6)	0.4 (0.0–2.4)
Rate per patient year	0.0 (0.00–0.08)	0.00 (0.00–0.02)	0.0 (0.00–0.11)	0.0 (0.00–0.02)
Severe hypoglycaemia (in need of help and/or blood glucose $\leq$ 56 mg/dl/ $\leq$ 3.1 mmol/l), %				
Patients	0.0 (0.0–6.7)	0.0 (0.0–1.2)	0.0 (0.0–11.6)	0.0 (0.0–1.6)
Severe nocturnal hypoglycaemia (in need of help and/or blood glucose $\leq$ 56 mg/dl/ $\leq$ 3.1 mmol/l), %				
Patients	0.0 (0.0–6.7)	0.0 (0.0–1.2)	0.0 (0.0–11.6)	0.0 (0.0–1.6)

*T1DM* type 1 diabetes, *T2DM* type 2 diabetes

glulisine titration algorithm. Furthermore, Yanagisawa et al. [7] reported on the outcomes of a study in 49 T1DM and 10 T2DM patients whose treatment was switched from basal insulin in combination with aspart, lispro or regular human insulin to a combination of basal insulin and insulin glulisine. After 24 weeks and with an essentially unchanged rapid-acting insulin dose, HbA1c was significantly decreased.

As such, the results of the present study show that switching the insulin analogue to insulin glulisine in patients with insufficient HbA1c control is an effective option to improve glycaemic control in patients with both T1DM and T2DM. While this may hypothetically be attributed to an improved efficacy of insulin glulisine per se, also enhanced efforts to reach

the HbA1c target using higher rapid-acting insulin doses likely contributed to this observation.

### Blood Glucose Profile

Patients were only able to enter the study when they were able and ready to perform a 7-point blood glucose profile. The patients had not been required to record their blood glucose profile prior to the study, however, so this analysis tool could have been newly introduced. Upon entering the study and switching to insulin glulisine, we saw a substantial improvement of the 7-point blood glucose profile in patients with both T1DM and T2DM, although the difference only reached statistical significance in

**Table 4** Adverse events (SAS, mFAS12)

	SAS		mFAS12	
	T1DM (N = 54)	T2DM (N = 353)	T1DM (N = 30)	T2DM (N = 234)
Adverse events				
Patients	4 (7.4)	37 (10.5)	2 (6.7)	22 (9.4)
Number of events	9	81	6	42
Drug-related events				
Patients	1 (1.9)	8 (2.3)	0 (0.0)	5 (2.1)
Number of events	2	10	0	6
Serious adverse events				
Patients	0 (0.0)	15 (4.2)	0 (0.0)	8 (3.4)
Number of events	0	20	0	12
Patients with drug-related serious adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Deaths	0 (0.0)	2 (0.6)	0 (0.0)	0 (0.0)

T1DM type 1 diabetes, T2DM type 2 diabetes

those with T2DM. This was likely due to the lower number of patients with T1DM ( $n = 40$ ) compared to T2DM ( $n = 304$ ). Both the introduction of insulin glulisine [6, 7] and its up-titration upon a switch [6], as well as the performance of a 7-point blood glucose profile [11, 12], have been demonstrated to improve glycaemic control in patients with diabetes. As such, these two changes to patient care likely contributed to the observed effects on glycaemic control and potentially should be implemented in parallel in practice.

### Hypoglycaemia and Adverse Events

Over the course of the year, few patients suffered from confirmed hypoglycaemia events and none reported severe or nocturnal hypoglycaemia. While no comparisons were possible to the rates of hypoglycaemia with the rapid-acting insulin used prior to baseline, the results are in line with a number of clinical studies, which have been summarised in recent meta-analyses [8–10, 13]. For patients with T1DM,

Fullerton et al. [8] found a modest but not statistically significant reduction (OR 0.89; 95% CI 0.71–1.12) in the rate of severe hypoglycaemia with the use of insulin analogues compared with regular human insulin. Reinforcing this observation, in a meta-analysis of randomised controlled trials in patients with T1DM, Melo et al. [10] found that rapid-acting insulin analogues were associated with a decrease in total hypoglycaemic episodes (risk rate 0.93), nocturnal hypoglycaemia (risk rate 0.55) and severe hypoglycaemia (risk rate 0.68) compared to regular human insulin. Differences between the three insulin analogues appear to be small. Fullerton et al. [8], on the one hand, reported no differences between lispro and aspart and no data were available for glulisine. On the other hand, Lak et al. [13] suggested lower rates of hypoglycaemia among glulisine users at a comparable HbA1c lowering among insulin analogues. Data for T2DM are much less abundant. Fullerton et al. [9] reported no clear difference between the insulin analogues and regular human insulin. The reduced rates of non-severe hypoglycaemia with regular human

insulin were only borderline significant ( $p = 0.05$ ), with no clear differences among the insulin analogues lispro, glulisine and aspart.

### Sensitivity Analyses

As we lost about 25% of the patients with T1DM and 22% of the patients with T2DM, we conducted a series of analyses to explore potential differences in the effectiveness and safety of insulin glulisine between the full analysis set (FAS) and the subset of patients with a full 12-months follow-up available (mFAS12). Patient characteristics were largely comparable between the two groups with a slightly higher comorbidity burden of T2DM patients in the mFAS12 than the FAS group. They also received regular human insulin prior to baseline more frequently. Target achievement was slightly higher in the mFAS12 group with rates of 50.0% for patients with T1DM (43.6% in the FAS) and 44.9% for patients with T2DM (39.6% in the FAS group) at 12 months. Effects on blood glucose control were virtually identical between the FAS and the mFAS12 groups with the HbA1c reduction being in the same order as were reductions in the 7-point blood glucose profile. Adverse events including hypoglycaemia were in the same order for patients in the FAS and mFAS12 groups.

### Limitations

This was a one-armed observational study so no direct comparisons can be made with other rapid-acting prandial insulins or regular human insulins. There were significantly fewer patients with T1DM enrolled compared to the number of patients with T2DM. As such, statistical significance was not observed for some end points in the T1DM group because of the small number of enrolled patients. We did not assess patient quality of life before or after initiating insulin glulisine. Our study was also too short to assess long-term outcomes relevant to patients, such as long-term diabetic complications, all-cause mortality and micro- or macrovascular complications. Further studies should be performed to

confirm our hypothesis and to address these limitations.

### Interpretation and Generalisability

A patient-centred approach is necessary for treatment of T1DM and T2DM, considering the patient's age, lifestyle, hypoglycaemic risk and comorbid conditions. Nearly all the patients who were screened were eligible to be included in the study, thereby demonstrating that our inclusion and exclusion criteria allowed for a true representation of patients with either T1DM or T2DM and illustrating real-world experience in Germany. As such, switching to rapid-acting insulin glulisine from other rapid-acting insulins or human insulin analogues in patients with T1DM, or adding insulin glulisine to an anti-diabetic regimen in patients with T2DM is a viable treatment strategy for patients with inadequate glucose control.

## CONCLUSIONS

Switching the prandial insulin to insulin glulisine, supported by dose adjustments/increases and the performance of the 7-point blood glucose profile, can be recommended based on 43.6% of T1DM and 39.6% of T2DM patients reaching their individual pre-defined HbA1c target within 1 year after its introduction at a low rate of hypoglycaemia and adverse events.

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**Compliance with Ethics Guidelines.** The registry protocol was approved by the University of Freiburg, Germany, and was carried out in accordance with the Declaration of Helsinki and its amendments. Only subjects who provided written informed consent to participate were included in this study. Patient consent for publication was not required.

**Data Availability.** The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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