




## ORIGINAL ARTICLE

# GlucoTab-guided insulin therapy using insulin glargine U300 enables glycaemic control with low risk of hypoglycaemia in hospitalized patients with type 2 diabetes

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**Aims:** To investigate efficacy, safety and usability of the GlucoTab system for glycaemic management using insulin glargine U300 in non-critically ill hospitalized patients with type 2 diabetes (T2D).

**Materials and Methods:** In this open, non-controlled single-arm pilot study, glycaemic control at the general ward of a tertiary care hospital was guided by a mobile decision support system (GlucoTab) for basal-bolus insulin dosing using the novel basal insulin analogue insulin glargine U300 for the first time. Glycaemic control was surveilled with capillary glucose measurements and continuous glucose monitoring (CGM). The primary endpoint was efficacy of glycaemic management, defined as the percentage of blood glucose measurements within the target range of 3.9 to 7.8 mmol/L.

**Results:** A total of 30 patients with T2D (12 female; age,  $67 \pm 11$  years; HbA1c,  $70 \pm 26$  mmol/mol; BMI,  $31.8 \pm 5.6$  kg/m<sup>2</sup>; length of study,  $8.5 \pm 4.5$  days) were included. In total, 894 capillary glucose values and 49 846 data points of CGM were available, of which 56.1% of all measured capillary glucose values and 54.3% of CGM values were within the target area (3.9–7.8 mmol/L). Overall capillary mean glucose was  $8.5 \pm 1.2$  and  $8.4 \pm 1.2$  mmol/L assessed by CGM. Time within glucose target improved continuously during the course of treatment, while time within hypoglycaemia (<3.9 mmol/L) decreased substantially. The GlucoTab-suggested total daily dose was accepted by staff in 97.3% of situations.

**Conclusions:** Treatment with GlucoTab using insulin glargine U300 in hospitalized patients with T2D is effective and safe.

## KEYWORDS

basal bolus insulin therapy, decision support system, inpatient diabetes management, insulin glargine U300, type 2 diabetes

## 1 | INTRODUCTION

Both, hypo- and hyperglycaemia are associated with poor clinical outcomes including prolonged hospitalization, complications and death.<sup>1–4</sup>

In general wards, current guidelines recommend a target glucose range of 7.8 to 10.0 mmol/L; for selected patients, more stringent targets (6.1–7.8 mmol/mol) can be applied if safely achieved without relevant hypoglycaemia.<sup>5</sup> Target ranges should preferentially be achieved by basal-bolus insulin therapy incorporating basal, nutritional and correctional components.<sup>5</sup> Recent suggestions express the need to develop

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and evaluate point-of-care computerized clinical decision tools to guide prescribers in implementing evidence-based guidelines.<sup>6</sup>

In studies investigating glycaemic control in the hospital setting, NPH insulin, insulin glargine U100 or insulin detemir were used as basal insulin.<sup>7–17</sup> To the best of our knowledge, novel basal insulin analogues, insulin glargine U300 or insulin degludec, have not yet been combined with automated basal-bolus insulin algorithms for the hospital setting. In previous studies GlucoTab, a mobile decision support (DSS) system for diabetes management that incorporates an automated basal-bolus algorithm, has proven to effectively and safely establish glycaemic control without increased risk of hypoglycaemia.<sup>12,14,18</sup> It can be assumed that, also in the hospital setting, insulin glargine U300 leads to comparable glycaemic control with reduced rates of hypoglycaemia at any time of the day as well as reduced rates of nocturnal hypoglycaemia in patients with type 2 diabetes mellitus (T2D) as shown in the outpatient setting.<sup>19–23</sup> Insulin glargine U300 provides predictable, evenly distributed 24-hour coverage as a result of lower variability and higher reproducibility in insulin exposure, and it appears to be an effective basal insulin.<sup>24</sup>

Thus, the aim of this pilot study was to evaluate the efficacy and safety of the mobile DSS, GlucoTab, using for the first time the novel basal insulin analogue glargine U300 in non-critically ill patients with T2D at the general ward of a tertiary care centre.

## 2 | MATERIALS AND METHODS

This study was a prospective, monocentric, open, non-controlled, single-arm, interventional study in hospitalized patients with T2D or newly diagnosed hyperglycaemia and was performed at the Endocrinology and Diabetology general ward at a tertiary care centre, the Medical University of Graz. The study was approved by the ethical board of the Medical University of Graz (EC-No. 27-531 ex 14/15) and is registered at the German Clinical Trials Register (DRKS 00011487; <https://www.germanctr.de>). All patients were informed about the nature and objective of the study and the study procedures. Signed informed consent was obtained prior to any study procedure. The trial was conducted in full accordance with the principles of the Declaration of Helsinki. All nurses and physicians were trained with respect to study protocol, study-specific procedures, handling of the GlucoTab system and Good Clinical Practice guidelines prior to initiation of the study.

### 2.1 | Study procedure

The primary objective of this study was to investigate the efficacy in establishing glycemic control (target range, 3.9–7.8 mmol/L) of GlucoTab-driven basal-bolus therapy in combination with insulin glargine U300 as basal insulin in patients with T2D in a general ward. Secondary objectives included evaluation of the percentage of glucose values within different target ranges, the number of hypoglycaemic events and staff adherence to and acceptance of GlucoTab suggestions. Patients who were admitted to the Endocrinology and Diabetology ward from June to October 2016 and who required subcutaneous insulin therapy were eligible to participate in the study. Main inclusion

criteria were: age  $\geq$  18 years; T2D treated with diet, oral antidiabetic drugs, glucagon-like peptide 1 receptor agonists (GLP-1-RA), insulin or any combination of the above, or newly diagnosed hyperglycaemia requiring subcutaneous insulin therapy. Exclusion criteria comprised: type 1 diabetes mellitus, gestational diabetes, pregnancy, continuous parenteral nutrition or participation in another study that could interfere with this study. Patients admitted to the general ward who fulfilled all inclusion criteria and none of the exclusion criteria were enrolled for GlucoTab-guided basal-bolus insulin therapy. Sulfonylurea, glinides or glitazones were interrupted during GlucoTab treatment according to the intended use of the device; all other oral antidiabetic drugs (OAD) and GLP-1-RA were continued, interrupted or newly initiated according to the diabetologist in charge. GlucoTab treatment during hospital stay was continued as long as deemed necessary by the treating physician but was restricted to a maximum duration of 21 days. Antidiabetic treatment at discharge, including insulin therapy, was prescribed by the responsible physician.

Capillary glucose measurements were performed at least four times daily, pre-meal and bedtime, by the nurse on duty according to local standard procedures with a point of care testing device (Roche AccuChek Inform II System, Roche Diagnostics, Rotkreuz, Switzerland), which is integrated into the laboratory information system. In total, 894 capillary blood glucose (BG) values were collected during the study.

In order to understand and interpret the full effect of insulin glargine U300 when used with the decision support component of GlucoTab, patients were equipped with a continuous glucose monitoring system (CGM). To avoid influence of the CGM signal we used the blinded iPro2 system (Medtronic, Northridge, California). The device was retrospectively calibrated, four times daily, changed after a maximum of 6 days of use, and newly inserted according to the manufacturer's instructions as necessary (eg, in the case of an imaging procedure such as magnetic resonance or computed tomography). As CGM data were analysed retrospectively, treatment was not influenced by data acquired by CGM.

### 2.2 | GlucoTab-based glycaemic management

GlucoTab (Joanneum Research GmbH, Graz, Austria) is a workflow and decision support system for diabetes management in the hospital setting that is integrated into the hospital information system. One component of GlucoTab incorporates a basal-bolus insulin dosing algorithm that aims to achieve the recommended glycaemic target range of fasting and pre-meal BG values of 5.6 to 7.8 mmol/L.<sup>5</sup> Details of the algorithm, which was not specifically modified for this study, are described elsewhere.<sup>12</sup> In brief, an initial total daily insulin dose is calculated upon enrolment depending on patient age, renal function and body weight. The basal-bolus insulin dose is initiated with a proportion of 50%:50%. To date, all rapid-acting insulin analogues and insulin glargine U100 have been approved for use within the DSS component of GlucoTab. Within this study, insulin glargine U300 was used for the first time as basal insulin in the hospital setting with a DSS system. Insulin glulisine was used as bolus insulin (both insulins, Sanofi, Frankfurt/Main, Germany). Automated total daily dose suggestions are based on blood glucose (BG) values of the

previous 24 hours and must be confirmed once daily by the treating physician. At every time point (morning, noon, evening, bedtime), upon entering the current BG value and meal information (yes/no), the nurse receives a suggestion of insulin dose. Before each main meal (morning, noon, evening) and at bedtime, capillary glucose measurements were taken by the nurse in charge and were entered into GlucoTab and insulin therapy was administered according to the automated dose suggestion generated by GlucoTab. At any time, healthcare professionals could overrule the suggested insulin dose and perform additional BG measurements if deemed necessary.

### 2.3 | Statistical analysis

For analysis of efficacy parameters, insulin doses and adherence to suggestions for only complete 24-hour treatment days were included. To be eligible for analysis using CGM readings, at least 70% of the CGM measurements must have been available per day. Furthermore, CGM measurements for at least two eligible days must have been available per participant. CGM profiles were analysed based on recommendations for standardizing the analysis and presentation of glucose monitoring data.<sup>25</sup> Calculation of sample size was performed to test the study hypothesis by using a one-tailed one-sample t-test weighted by the total number of BG measurements per participant, with a 5% level of significance and a power of 80%, to test whether the mean percentage of capillary BG measurements in the target range of 3.9 to 7.8 mmol/L (primary outcome) was greater than that of a comparable best-practice study with the criterion threshold of 42%.<sup>16</sup> To ensure that calculation of the primary endpoint was based on BG data of at least 27 patients, the planned number of patients was increased to 30.

Prior to data analysis, all metric outcome variables were checked for normality by means of a Shapiro-Wilk's test. The level of significance was set to 5% for all tests. Statistical analysis was performed using R version 3.1.2 software.

## 3 | RESULTS

A total of 30 patients were included in the study. Baseline characteristics are indicated in Table 1. Time to inclusion was  $1.4 \pm 1.9$  days. Duration of treatment with the GlucoTab basal-bolus insulin algorithm was  $8.5 \pm 4.5$  days, which means that the GlucoTab treatment covered  $72.5\% \pm 22.2\%$  of the patients' total hospital stay.

### 3.1 | Glycaemic control achieved by GlucoTab

The overall mean percentage of capillary BG values in the target range (3.9–7.8 mmol/L) was  $56.1\% \pm 23.5\%$  which was significantly higher than the criterion value of 42% from a comparable best-practice study ( $P < 0.001$ ).<sup>16</sup> Time within the target range based on capillary BG was comparable, with 54.3% of glucose values within target as assessed by CGM. Time within the glucose target range improved continuously over the treatment period for capillary BG and CGM data (Figure 1A and B). Mean daily capillary BG improved in response to GlucoTab-guided insulin titration (Figure 2A). Mean total daily insulin dose was  $63.8 \pm 39.8$  U (bolus insulin dose,  $34.9 \pm 19.9$  U and basal insulin

**TABLE 1** Baseline characteristics of included patients

Patients (n)	30
Gender f/m (n)	12/18
Age (years)	$67.3 \pm 11.1$
BMI (kg/m <sup>2</sup> )	$31.8 \pm 5.6$
Weight (kg)	$92.5 \pm 22.2$
Ethnicity: Caucasian/African/Asian (n)	28/1/1
Serum Creatinine (mg/dL)	$1.3 \pm 0.5$
HbA1c (mmol/mol)	$78.8 \pm 26.1$
Diabetes duration (years)	$14.2 \pm 11.2$
Admission type: acute / scheduled n (%)	29 (96.7%) / 1 (3.3%)
<b>Diabetes therapy at admission n (%)</b>	
Diet only or newly diagnosed	2 (6.7%)
OAD only	7 (23.3%)
Insulin only	8 (26.7%)
Insulin and GLP1-RA	2 (6.7%)
OAD and GLP1-RA	1 (3.3%)
Insulin and OAD	10 (33.3%)

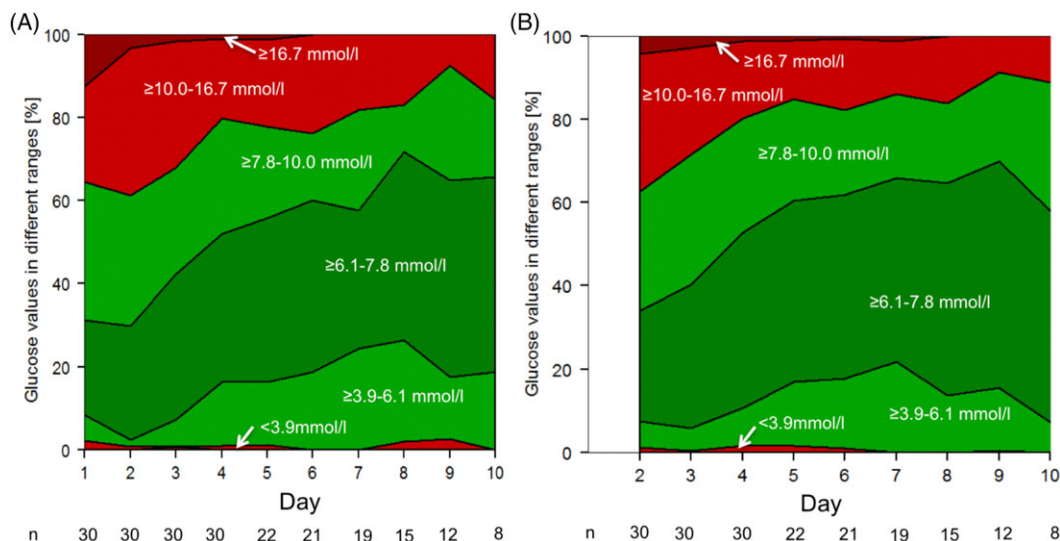
Data are given as mean  $\pm$  SD if not indicated otherwise.

dose,  $29.0 \pm 21.0$  U) (Figure 2B). We observed a difference in mean daily insulin dose between genders, with insulin dose for males being one third higher: men,  $74.6 \pm 47.0$  U vs women,  $47.6 \pm 17.2$  U. Furthermore, the increase in insulin dose over time was also higher in men than in women: men,  $+0.18 \pm 0.37$  U/kg vs women,  $+0.15 \pm 0.18$  U/kg. This was despite an absence of difference in BMI (men,  $31.9 \pm 6.4$  kg/m<sup>2</sup> vs women,  $31.7 \pm 4.4$  kg/m<sup>2</sup>). Mean glycaemic control over the entire treatment period is shown in Figure 3A: time within target, 3.9 to 10.0 mmol/L: 80.2%). Overall glycaemia assessed by capillary BG and CGM data was  $8.5 \pm 1.5$  mmol/L and  $8.4 \pm 1.2$  mmol/L, respectively. Pre-existing therapy affected glycaemia during hospitalization as follows: pre-existing insulin therapy (n = 20; 8.3 [7.2; 8.9] mmol/L); combination of insulin therapy and oral agents (n = 12; 8.3 [7.2; 8.5] mmol/L); or insulin therapy only (n = 8; 8.9 [7.8; 9.3] mmol/L). Patients with no pre-existing insulin therapy had higher mean blood glucose than the participants in the other groups (n = 10; 9.8 [7.7; 10.2] mmol/L). On average, glucose target was achieved on Day 4 of GlucoTab treatment (Figure 2A).

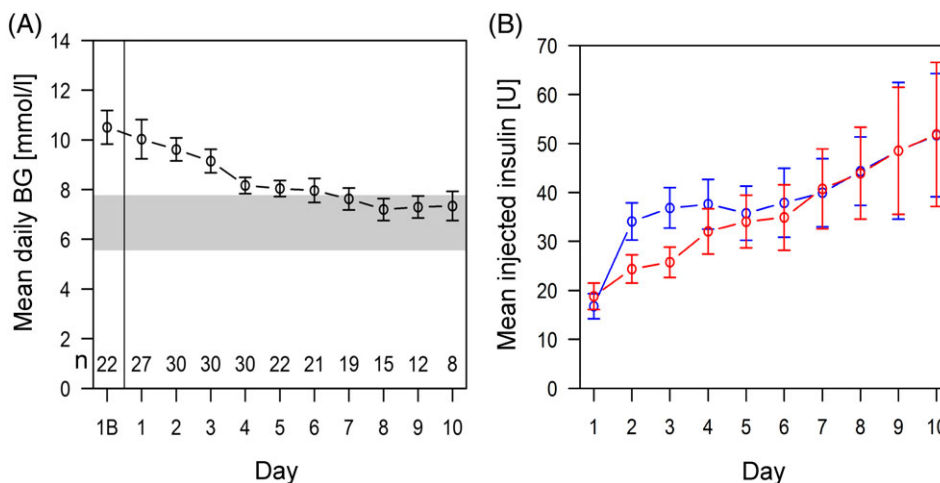
Mean glycaemic control, as represented by mean pre-meal and bedtime values, improved from the first full 24 hours (time within target, 3.9–10.0 mmol/L: 61.8%) (Figure 3B) to the last full 24-hour treatment day (time within target, 3.9–10.0 mmol/L: 85.2%) (Figure 3C). CGM data were available for 29 patients with eligible treatment days (>70% data/d), resulting in a total of 49 846 CGM readings covering 79.2% of the study duration. Concomitant to improvement in glycaemic control, a reduction in glycaemic variability was seen (coefficient of variation [CV], 36.1% vs 31.4% vs 28.9%; Days 1 vs 4 vs 7, respectively). Four-day intervals were chosen, as a three to four day period is considered necessary to achieve steady-state for insulin glargine U300.<sup>26</sup>

### 3.2 | Safety of GlucoTab

In total, eight hypoglycaemic episodes below 3.9 mmol/L in five patients (all male; two undergoing concomitant oral antidiabetic



**FIGURE 1** Mean percentage of BG values (A) and mean percentage of continuous glucose monitoring data (B) in different glycaemic ranges during GlucoTab treatment with U300. Numbers above the x-axis are total patient numbers



**FIGURE 2** Mean daily blood glucose ( $\pm$  standard error of the mean) (A) as a function of treatment day. Day 1B refers to baseline BG values on study Day 1. Numbers above the x-axis are total patient numbers. Alterations of mean injected bolus (blue) and basal (red) insulin ( $\pm$  standard error of the mean) (B) per treatment day

therapy), assessed by capillary BG, occurred. This is 0.9% of the total of 894 BG measurements that were performed throughout the study. Considering CGM data, 0.77% of values were  $<3.9$  mmol/L. Episodes of hypoglycaemia below 3.9 mmol/L (1.2% vs 0.6%) decreased over time (first vs last full treatment day, assessed by CGM). There was one severe hypoglycaemic event with a capillary BG level below 2.2 mmol/L. Of note, this event occurred in a patient for whom insulin initiation as suggested by GlucoTab was overruled by the treating physician and a clinically relevant higher starting dose was administered (52 U vs 23 U total daily dose). Five mild and moderate adverse events occurred during the trial, all of which were not related to GlucoTab. No severe adverse event was observed during the study.

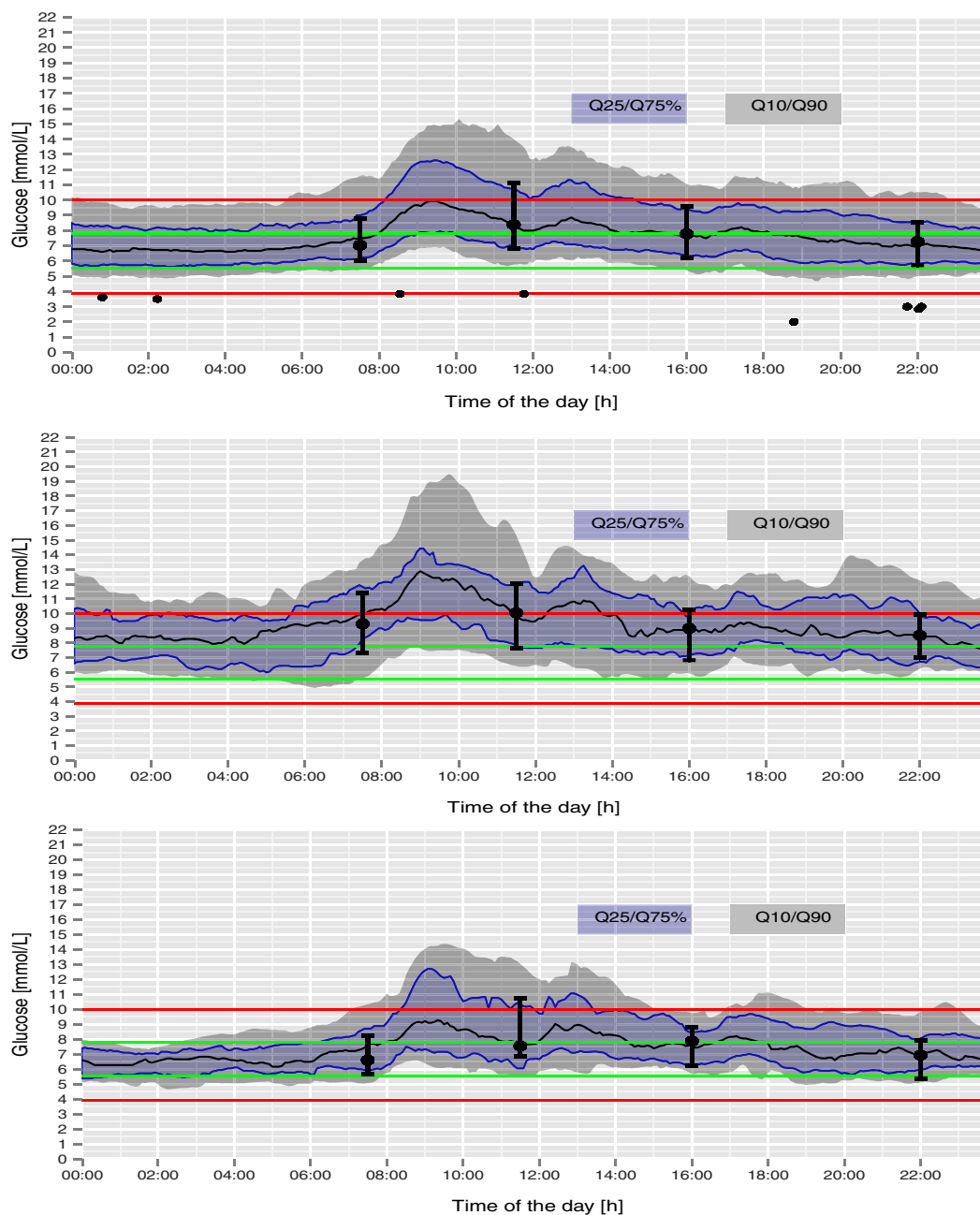
### 3.3 | Adherence to GlucoTab advice

The adherence of physicians in accepting GlucoTab suggestions concerning total daily insulin dose was 97.3%. Nurses adhered 99.1% of

the time to suggestions concerning basal insulin dose and 95.5% of the time to suggestions concerning bolus insulin dose. If adjustments to suggestions were undertaken by healthcare professionals, the changes were small:  $-0.2 \pm 1.4$  U for bolus insulin suggestions and no adjustments were undertaken concerning basal insulin suggestions. The nursing staff performed 98.7% of bolus insulin injections and 100% of basal insulin injections. Additionally, 99.1% of all requested BG measurements ( $n = 776$ ) were performed and 33 additional measurements were taken beyond the four mandatory measurements.

## 4 | DISCUSSION

We report the results of the first clinical trial using insulin glargine U300 in a basal-bolus insulin algorithm provided by an electronic DSS, GlucoTab, in patients with T2D hospitalized in a general ward. GlucoTab was previously tested for the use of insulin glargine U100 in



**FIGURE 3** Overall median sensor curve during (A) the entire treatment period, the first (B) and the last treatment day (C). CGM data are presented as median, interquartile ranges, 10% and 90% percentiles. Reference blood glucose values are indicated as black closed circles for the four mandatory time points (morning, noon, evening, bedtime) plus any hypoglycaemic event. Area between green lines indicates the 5.6 to 7.8 mmol/L target range; area between red lines indicates the 3.9 to 10 mmol/mol target range

combination with short-acting insulin analogues. In the present study insulin glargine U300 was used for the first time as basal insulin for treatment according to GlucoTab, without modifications of the underlying algorithm. To our knowledge basal-bolus therapy with insulin glargine U300 has not been used previously in combination with an electronic DSS. Our study indicates that insulin glargine U300 could be used safely and efficaciously when titrated by GlucoTab without increased risk of hypoglycaemia.

Current guidelines suggest that insulin therapy should be initiated during hospitalization in the case of persistent hyperglycaemia above 10.0 mmol/L, striving for a target of 7.8 to 10.0 mmol/L in the majority of patients. More stringent targets (5.6–7.8 mmol/L) are

appropriate only if they can be achieved without the risk of hypoglycaemia.<sup>27</sup> Our data indicate that a target range of 3.9 to 10.0 mmol/L can be achieved safely using the GlucoTab algorithm in combination with insulin glargine U300 as basal insulin, with a low rate of hypoglycaemia. Previous best-practice studies using basal-bolus insulin therapy in the hospital setting achieved 42% of values within target.<sup>16</sup> In our present study, using the unmodified GlucoTab algorithm for the first time with insulin glargine U300, we were able to achieve an even higher percentage of BG values within target (56.1%;  $P < 0.001$ ). Compared to GlucoTab performance using insulin glargine U100 in 99 hospitalized patients at four different general wards, we show superior performance with regard to time within target (56.1% vs



50.2%) with less time in hyperglycaemia above 16.7 mmol/L (1.7% vs 2.7%). Bally et al. recently applied artificial pancreas (AP) technology to establish euglycaemia in hospitalized patients with T2D in a general ward, that is, in a similar patient group. AP performance was comparable to that of GlucoTab with regard to mean glucose ( $8.5 \pm 1.6$  vs.  $8.4 \pm 1.2$  mmol/L).<sup>28</sup>

Time within glucose target assessed by CGM (3.9–10 mmol/L) improved continuously during the course of treatment (61.8% vs 85.2%; first vs last treatment day) while time within hypoglycaemia (1.2% vs 0.6%; first vs last treatment day) substantially decreased. These data are superior to the CGM data seen with insulin glargine U100 in a comparable setting. Schaupp et al. report an increase in time within target (3.9–10.0 mmol/mol) from 67.7% to 77.5%, whereas hypoglycaemia rates were stable throughout treatment (2.6% vs 2.8%; first vs last treatment day). Thus, the use of insulin glargine U300 in combination with GlucoTab leads to superior glycaemic control, with reduced rates of hypoglycaemia as compared to those with insulin glargine U100 in the hospital setting. As treatment during hospitalization is brief, safe early-phase insulin titration is important and insulin glargine U300 might be a safe approach for this purpose. This hypothesis is supported by findings from the BRIGHT study in which insulin glargine U300 showed low hypoglycaemia rates during the titration phase while achieving glycaemic control similar to that of insulin degludec.<sup>29</sup>

Adherence to GlucoTab dose suggestions was high (97% for TDD; 99% for basal; 96% for bolus suggestions) and, if users modified the dose, only minimal changes were made. These data are in line with previous studies concerning GlucoTab in which suggestions for basal, bolus and total daily dose were accepted without modification more than 90% of the time. The high acceptance rate of dose suggestions indicates that users are confident and trust the algorithm. As GlucoTab facilitates insulin titration without requiring expert user input in the course of the treatment, it can be speculated that such a device could contribute to safely establishing glycaemic control in other fields of medicine such as surgery or neurology where other diseases are the main focus and diabetes is considered an inconvenient comorbidity. In a previous study in which GlucoTab was used on different general wards including surgery, the high acceptance rate on the part of staff, accompanied by good glycaemic control, was demonstrated.<sup>12</sup> Acceptance rates and the mean glucose values achieved exceeded those seen in internal medicine wards where physicians interfered more with therapy. Of note, the only severe hypoglycaemic event (BG 2.0 mmol/L) that occurred during the study was the result of manual insulin overdosing by a physician who assumed that the GlucoTab suggested dose of insulin was too low and manually increased the initial total daily dose (52 U vs 23 U; physician's discretion vs GlucoTab suggestion, respectively).

The frequency of hypoglycaemic events was comparable or even lower than that shown in published data of inpatient investigations. Umpierrez et al. reported a higher percentage of patients who experienced hypoglycaemia during hospitalization while undergoing pre-existing insulin therapy as compared to insulin-naïve patients (22% vs 10%;  $P = 0.01$ ); these findings are in line with our results (20% vs 10%).<sup>16</sup> The overall incidence and prevalence of in-hospital hypoglycaemic events varies, depending on the inpatient setting and the

glycaemic thresholds used for the definition. Umpierrez et al. reported 2.0% of values in the hypoglycaemic range ( $<3.9$  mmol/L) during basal-bolus therapy using insulin glargine U100 in surgical patients.<sup>17</sup> In a previous study using GlucoTab-guided basal-bolus therapy in combination with insulin glargine U100 in 99 inpatients, only 1.5% of all BG measurements were less than 3.9 mmol/L.<sup>12</sup> In the present study using insulin glargine U300 with an otherwise unchanged basal-bolus algorithm, we showed even lower rates of hypoglycaemia (0.9% of all capillary BG measurements). Of note, in the present trial, this lower number of hypoglycaemic episodes was achieved; however, patients in the present trial can be considered to be at higher risk than those in other inpatient trials as they had a longer duration of diabetes, with a large proportion of patients undergoing pre-existing insulin therapy. Both factors are well known to be associated with increased risk of hypoglycaemia.<sup>30–32</sup>

This low rate of hypoglycaemia, while achieving good glycaemic control, might be attributed to the combination of insulin glargine U300 in a DSS driven basal-bolus algorithm. Insulin glargine U300 features a reduced redissolution rate following subcutaneous injection as compared to insulin glargine U100 and, thereby, has a more prolonged duration of pharmacokinetic effect. Additionally, insulin glargine U300 provides predictable, evenly distributed 24-hour coverage as a result of low fluctuation and high reproducibility in insulin exposure.<sup>33</sup>

High glycaemic variability in the long-term is associated with an increase in cardiovascular morbidity and mortality.<sup>34–36</sup> To our knowledge, the glycaemic variability of insulin glargine U300 based on CGM data was never assessed in the titration phase but only after steady state had been achieved. It is assumed that 3 to 4 days are needed to achieve steady state conditions for insulin glargine U300.<sup>26</sup> Luchi et al. showed reduced glycaemic variability when comparing insulin glargine U300 and insulin glargine U100 after a 4-week titration period (CV, 26.8% vs 25.3%).<sup>37</sup> In our study, CV was 36.1% on Day 1 compared to 31.4% on Day 4 and 28.9% on Day 7 of titration, thus showing comparable glycaemic variability for insulin glargine U300 even early in the titration phase. As compared to previous studies using insulin glargine U100 with either an electronic DSS or a paper-based algorithm, BG target was reached earlier when using a DSS with insulin glargine U300, on Day 4 vs Day 5 or 6.<sup>10,12,16</sup>

The GlucoTab algorithm is a basal-bolus algorithm that provides a once daily suggestion for the total daily dose for the following 24 hours. Bolus insulin distribution according to the algorithm was adjusted in previous studies to better fit meal-related insulin requirements but was used without changes in the current study.<sup>10,12,14</sup> The algorithm can be used when switching from insulin glargine U100 to insulin glargine U300 without further modifications. In the current study, the still-existing increase in lunchtime BG is less pronounced than that when using insulin glargine U100.<sup>12</sup> Data from the present trial indicate that the GlucoTab algorithm can be safely and efficaciously used in its current design in combination with insulin glargine U300.

Several limiting factors must be acknowledged. First of all, the study was a single-arm study without a direct comparator, as the primary purpose was to show that the GlucoTab algorithm can be used without modifications in combination with insulin glargine U300. The sample size was rather small as previous studies have indicated that

15 to 30 patients can provide deep insight into 24-hour glycaemia when using CGM.<sup>10,12,38</sup> Furthermore, this trial was performed in an endocrinology ward with highly experienced staff that was already familiar with GlucoTab. In summary, basal-bolus insulin therapy using GlucoTab in combination with insulin glargine U300 can be safe and efficacious without an increase in hypoglycaemia.

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Parts of this study were presented at the International Hospital Diabetes Meeting, Atlanta, Georgia, 19 to 20 May 2017 and at the American Diabetes Association's 77th Scientific Session, San Diego, California, 9 to 13 June 2017.

## CONFLICTS OF INTEREST

T. R. P. is a member of the advisory board of Novo Nordisk A/S, a consultant for Roche Diabetes Care, Novo Nordisk A/S, Eli Lilly & Co, Infineon, Carnegie Bank and serves on speakers bureaus for Novo Nordisk A/S and Astra Zeneca. J. P. has received speaker honoraria from NovoNordisk A/S. J. K. M. is a member of the advisory board of Sanofi, Eli Lilly and Boehringer Ingelheim, and has received speaker honoraria from Abbott Diabetes Care, Astra Zeneca, Eli Lilly, Nintamed, NovoNordisk A/S, Roche Diabetes Care, Servier and Takeda. F. A. has received speaker honoraria from Astra Zeneca and Boehringer Ingelheim. K. D., P. B., T. R. P. and J. K. M. are shareholders in decide Clinical Software GmbH. P. B. and B. H. are employees of decide Clinical Software GmbH. The remaining authors have no relevant conflicts of interest to disclose.

## Author contributions

J. K. M., J. P., F. A., K. L. and P. B. designed and performed the study, interpreted data and contributed to discussions. K. M. L., F. A. and J. K. M. drafted the manuscript. K. D. designed the study and performed statistical analysis. E. S. performed the study and was responsible for data management. J. S. and O. M. performed the study, interpreted data and contributed to discussions. T. R. P. interpreted data and contributed to discussions. B. H. was responsible for technical support related to the GlucoTab system. J. K. M. supervised the project and is the guarantor of this work. All authors critically revised the article and approved the final version of the manuscript.

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