Remote Accessibility to Diabetes Management and Therapy in Operational Healthcare Networks

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1 Executive summary

Diabetes is a common co-morbid condition in hospitalized patients. Poor glycaemic control during hospital stay is associated with poor clinical outcomes. Current guidelines recommend a pre-meal BG target of less than 140 mg/dL and the implementation of a standardised subcutaneous insulin basal-bolus therapy a key intervention. Thus, a stepwise approach was used to improve glycaemic management on the general ward. Two trials have already been completed; a third trial is still ongoing.

As a first step, we assessed the quality of physician-based glycaemic management in two general wards, considering the most recent recommendations for glycaemic control for non-critically ill patients (<140 mg/dL for premeal glucose).

The quality of glycaemic management in 50 patients in two wards (endocrinology, cardiology) was retrospectively assessed by analysing blood glucose levels, glycaemic management effort and an online questionnaire.

Glycaemic control was clearly above the recommended target (mean blood glucose levels: endocrinology: 175 ± 62 mg/dL; cardiology: 186 ± 68 mg/dL). When comparing the first to the second half of the hospital stay, we found no difference in glycaemic control (endocrinology: 168 ± 32 vs. 164 ± 42 mg/dL, P = 0.67; cardiology: 174 ± 36 mg/dL vs. 170 ± 42 mg/dL P = 0.51) and in insulin dose (endocrinology: 15 ± 14 IU vs. 15 ± 13 IU per day, P = 0.87; cardiology: 27 ± 17 IU vs. 27 ± 18 IU per day, P = 0.92), despite frequent blood glucose measurements (endocrinology: 2.7 per day; cardiology: 3.2 per day). A lack of clearly defined blood glucose targets was indicated in the questionnaire.

In both wards the recommended blood glucose target range was not achieved. Analysis of routine glycaemic management demonstrated considerable glycaemic management effort, but also a lack of translation into adequate insulin therapy. Implementation of corrective measures, such as structured treatment protocols, is therefore regarded as essential tools to improve this situation.

The aim of the second trial was to evaluate glycaemic control and usability of a workflow-integrated algorithm for basal-bolus insulin therapy in a proof-of-concept study to develop a decision support system in hospitalized patients with type 2 diabetes.

In this ward-controlled study, 74 type 2 diabetes patients (24 female, age 68±11 years, HbA1c 8.7±2.4%, BMI 30±7) were assigned to either algorithm-based treatment with a basal-bolus insulin therapy or to standard glycaemic management. Algorithm performance was assessed by continuous glucose monitoring and staff's adherence to algorithm-calculated insulin dose.

Average blood glucose levels (mg/dL) in the algorithm group were significantly reduced from 204±65 (baseline) to 148±32 (last 24h) over a period of 7.5±4.6 days (p<0.001). The algorithm group had a significantly higher percentage of glucose levels in the ranges from 100-140 mg/dL (target range) and 70-180 mg/dL compared to the standard group (33% vs. 23% and 73% vs. 53%, both p<0.001). Physicians´ adherence to the algorithm-calculated total daily insulin dose was 95% and nurses´ adherence to inject the algorithm-calculated basal and bolus insulin doses was high (98% and 93%). In the algorithm group significantly more glucose values <70 mg/dL were detected in the afternoon relative to other times (p<0.05), a finding mainly related to pronounced morning glucose excursions and requirements for corrective bolus insulin at lunch.

The workflow-integrated algorithm for basal-bolus therapy was efficacious in establishing glycaemic control and was well accepted by medical staff. Our findings support the implementation of the algorithm in an electronic decision support system.

The aim of the third trial is to investigate, safety, usability and efficacy of the tablet based workflow support system (GlucoTab system) used for glycaemic management of non-critically ill patients with type 2 diabetes at the general ward. The monocentric, open, non-controlled intervention pilot trial will include a total of 30 patients hospitalised with type 2 diabetes.

After successful testing of the GlucoTab system at the medical ward of Endocrinology, another trial is planned at other clinical wards to reduce any potential bias from experienced nurses and to prove its usability to support in hospital glycaemic management outside specialised wards.

2 Introduction

Diabetes is a common co-morbid condition in hospitalized patients. In the USA, 22% of the estimated 186 million hospital inpatient days occurred in patients with diabetes and 13% are caused by diabetes in 2007 (American Diabetes Association, 2008). Poor glycaemic control is associated with an increased risk of infection, disability after hospital discharge and death (Clement et al., 2004; Pomposelli et al., 1998; Umpierrez et al., 2002), and in the presence of diabetes, hospital stays are 50% longer (American Diabetes Association, 2008). In 2011, bedside data from more than 11,000 inpatients at 188 sites in England demonstrated that in almost 25% of diabetes inpatients insulin therapy was not adjusted when blood glucose (BG) was persistently higher than 200 mg/dL and a better glycaemic control would have been appropriate (National Health Service GB, 2011).

A recent systematic review and meta-analysis of randomized and observational studies that had evaluated the effect of intensive glycaemic control in the non-critical care setting, found a benefit in terms of a reduction in the risk of hospital-acquired infections (Murad et al., 2012). Current guidelines recommend a pre-meal BG target of less than 140 mg/dL and a random BG of less than 180 mg/dL for the majority of hospitalized patients with non-critical illness (American Diabetes Association, 2012; Umpierrez et al., 2012a). These guidelines consider the implementation of a standardised subcutaneous insulin basal-bolus therapy a key intervention and request the development of integrated decision support strategies and systems to guide medical staff in the glucose management process.

Thus, a stepwise approach was used to improve glycaemic management on the general ward (Figure 1).

(1) As a first step, a workflow analysis of glycaemic management was performed to determine in retrospect the quality of clinical glycaemic management in two internal medicine wards: endocrinology and cardiology.
(2) As a second step, the first clinical trial was performed on the endocrinology ward to assess the efficacy, workflow integration, and usability of a paper-based algorithm in hospitalized patients with type 2 diabetes. As a control glycaemic management on the cardiology ward was monitored.
(3) As a third step, we are currently doing a clinical pilot trial to investigate, the safety, usability and efficacy of the GlucoTab system used for glycaemic management of non-critically ill patients with type 2 diabetes on the general ward.
(4) As a fourth step, a clinical trial will be performed to investigate the performance and safety of the GlucoTab system used for glycaemic management of non-critically ill patients with type 2 diabetes at other clinical wards.

Each step is described in detail in the following chapters.

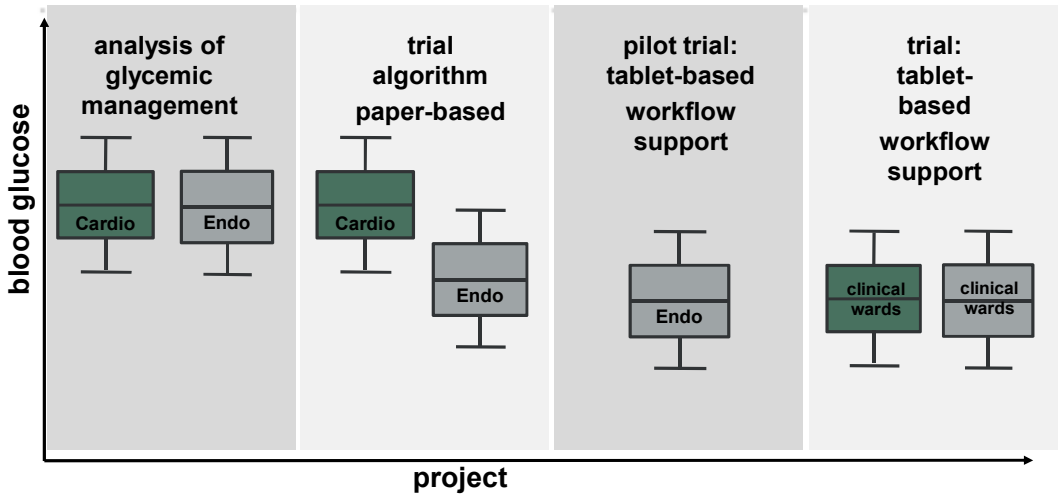


Figure 1: Stepwise approach of clinical evaluation of general ward clinical field trials

3 Workflow analysis of glycaemic management

3.1 Aim of the workflow analysis

The aim of this study was to determine in retrospect the quality of clinical glycaemic management in two internal medicine wards. Data from patients who had received diabetes treatment were analysed in the context of the most recent recommendations regarding BG levels. To further characterize the glycaemic management during the course of patients' hospital stays, parameters of glycaemic management effort, such as change of insulin dose, frequency of insulin injections and BG measurements were compared for the first and second half of the stay. In addition, nurses in both wards were asked to fill in a questionnaire regarding the current procedures of glycaemic control.

3.2 Methods

The study was approved by the Ethical Committee of the Medical University of Graz. Data from 50 non-critically ill patients who were consecutively admitted to the general medical endocrinology and cardiology wards of the Medical University of Graz were included in this study. Patients were assigned to the wards according to their medical diagnosis. Since both wards are general wards at the Department of Internal Medicine no critically ill patients or patients with scheduled surgery were admitted but on both wards invasive procedures occurred as part of the standard medical care. All patient data were retrospectively included in this study if any form of glycaemic management for BG control was required during hospital stay. Data were only included when patients were not transferred to a different ward during the study period. The two wards had a similar structure and used physician-based standard care regarding glycaemic control, but neither ward had standardised diabetes therapy protocols in place. BG levels were measured by the standardised POCT device Roche Accu Chek® Inform System (Roche Diagnostics, Switzerland) with additional quality control feedback from the hospital laboratory system. All data regarding glycaemic management were extracted from patient records and entered into the electronic data management software (Open Clinica®, OpenClinica, LLC, USA). Nurses in both wards were asked to fill in an online questionnaire about current glycaemic management.

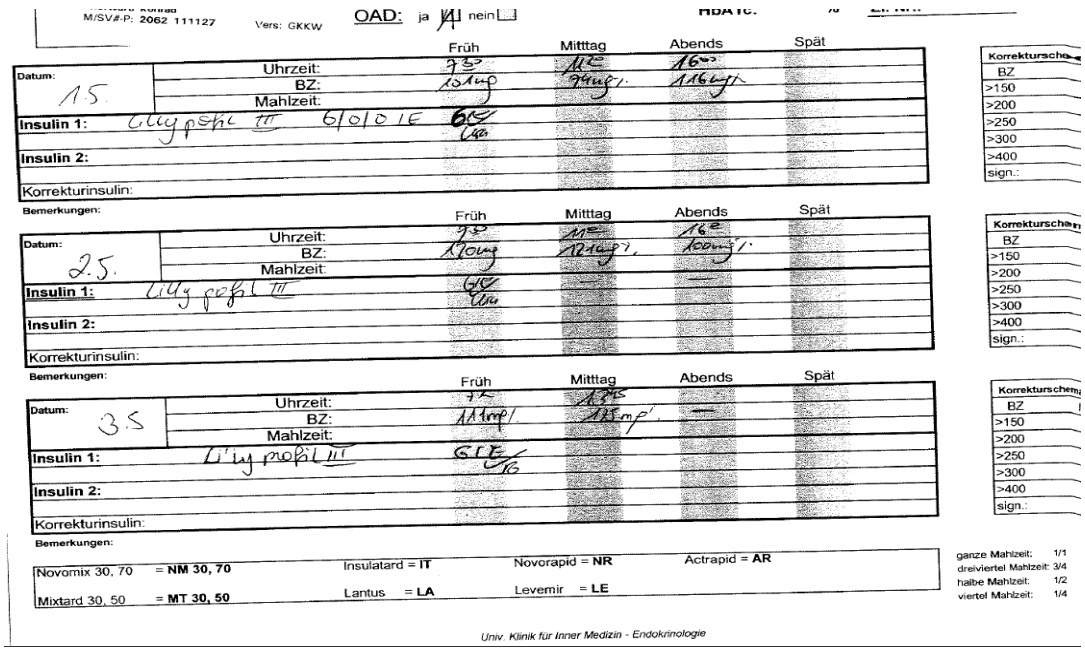


Figure 2: Documentation of glycaemic management

3.2.1 Data analysis

Patient data were analysed retrospectively in terms of mean BG values and the percentage of BG levels in the following ranges: <70 mg/dL (hypoglycaemic events), 70-140 mg/dL, 70-180 mg/dL, >180 mg/dL, >300 mg/dL (hyperglycaemic events). All data were analysed per population (data per ward), per patient-day (data per calendar day for each patient) and per patient-stay (data per patient) using

the standardised and validated *glucometrics* method for analysing in-hospital BG data (Goldberg et al., 2006). In order to analyse changes in glycaemic control and glycaemic management effort (mean number of BG measurements, mean number of insulin injections and mean insulin dose administered per patient) during the hospital stay, we compared the first half of each patient's hospital stay to the second half with respect to glycaemic management effort, but no comparison was attempted between the two wards.

Data are presented as mean ± SD if not stated otherwise. Since most of the data did not follow a normal distribution, we used Wilcoxon signed rank tests for statistical analyses. P <0.05 was considered to be significant. All statistical analyses were performed by using the software R 2.13.1.(R Development Research Group, 2008a)

3.3 Results

Records of 50 consecutively admitted patients were analysed over a four-month period. Demographic, admission, insulin therapy and discharge data for all patients are given in Table 1.

3.3.1 Glycaemic control

The mean BG values for patients in both wards were clearly above the recommended target of 140 mg/dL for premeal measurements and remained above the target until the end of the hospital stay (Figure 3).

When comparing several different glucometrics analyses (Table 2), 20 to 32% of BG values were found within the target range of 70-140 mg/dL, and 49 to 64% within the range of 70-180 mg/dL. For both wards, relatively few BG values were in the hypoglycaemic range (<70 mg/dL), whereas a significant proportion of values were above the limits of 180 and 300 mg/dL.

There was no significant difference in the mean BG levels of patients in either of the wards when comparing the first half to the second half of the hospital stay (endocrinology: 168 ± 32 vs. 164 ± 42 mg/dL, P = 0.67; cardiology: 174 ± 36 mg/dL vs. 170 ± 42, P = 0.51).

Most patients in the endocrinology ward (n=21) had BG ≥140 mg/dL in the first half of stay (Table 3). Standard glycaemic management did not result in a lowered BG level to the recommended target range for 16 of these 21 patients. Similarly, in the cardiology ward, 17 out of 21 had BG levels of ≥140 mg/dL in the first half of stay that remained ≥140 mg/dL in the second half of stay. Furthermore, glycaemic control (<140 mg/dL within first half) deteriorated in one patient in each ward.

Table 1: Demographic, admission, insulin therapy and discharge data for 50 diabetic patients

ward	endocrinology (n=25)	cardiology (n=25)
age (years)	70 ± 15	72 ± 9
BMI (kg/m^2)	28.5 ± 5.4	28.2 ± 6.5
sex (f)	14	14
diabetes type: 2/1	22/3	25/0
HbA1c (%)	8.1 ± 1.8	7.5 ± 0.8
outpatient diabetes therapy (%) at admission		
insulin	64	80
insulin + other anti-diabetic drugs	36	16
diet	0	4
diabetes therapy (% of patients) during hospital stay		
any insulin therapy	100	96
bolus insulin	64	60
premixed insulin	52	60
basal insulin	16	24
premixed & bolus insulin	12	32
basal & bolus insulin	12	16
sulfonylureas	16	4
metformin	28	16
admission diagnosis (n)		
cardiovascular	10	22
endocrine	8	0
infectious	4	2
pulmonary	1	1
gastrointestinal	1	0
nephrology	1	0
hospital stay (days)	10 ± 5	11 ± 8
discharge to (n)		
home	23	19
nursing home	2	0
transfer to other hospital	0	6

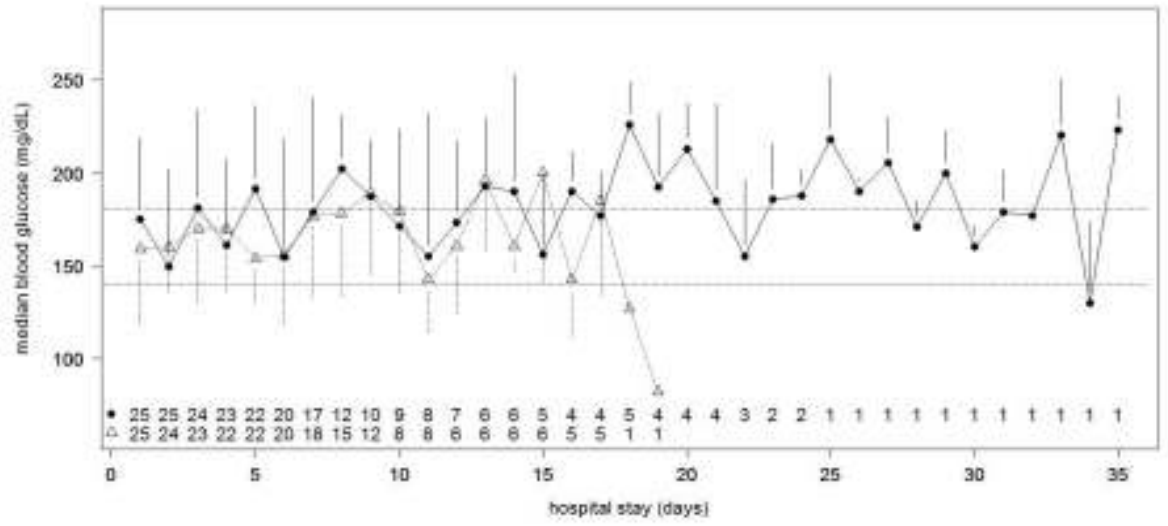


Figure 3: Median BG per day in endocrinology (Δ) and cardiology (•). Error bars are differences between upper quartiles and medians (upper bars), and differences between medians and lower quartiles (lower bars), respectively. Horizontal lines indicate BG limits

Table 2: Glucometrics analyses of blood glucose data analysed per population, per patient-day and patient-stay following Goldberg et al. 2006

glucometrics analyses	per population		per patient-day		per patient-stay	
sample size	endo n=646	cardio n=832	endo n=240	cardio n=264	endo n=25	cardio n=25
mean BG measurements	n.a.	n.a.	2.7	3.2	25.8	33.3
mean BG ± SD (mg/dL)	175 ± 62	186 ± 68	168 ± 54	180 ± 48	172 ± 31	175 ± 34
% BGs in 70-140 mg/dL range	31.7	27.3	24.2	20.5	20.0	20.0
% BGs in 70-180 mg/dL range	56.7	50.6	59.6	48.5	64.0	56.0
% hypoglycaemic events (<70 mg/dL)	0.9	0.6	2.9	0.8	0.0	0.0
% hyperglycaemic events (>180 mg/dL)	42.4	48.8	37.5	50.8	36.0	44.0
% hyperglycaemic events (>300 mg/dL)	4.2	4.9	1.3	1.1	0.0	0.0

Table 3: 2x2 table showing the number of patients with mean BG values above and within the 140 mg/dL target during the first and the second half of the hospital stay

endocrinology (n=25)	2nd period <140 mg/dL	2nd period ≥140 mg/dL	∑
1st period <140 mg/dL	3	1	4
1st period ≥140 mg/dL	5	16	21
∑	8	17	25
cardiology (n=25)	2nd period <140 mg/dL	2nd period ≥140 mg/dL	∑
1st period <140 mg/dL	3	1	4
1st period ≥140 mg/dL	4	17	21
∑	7	18	25

3.3.2 Glycaemic management effort

All but one patient received insulin therapy during the hospital stay (Table 1). In both wards, the use of bolus and premixed insulin formulation was predominant, whereas a combination therapy of basal or premixed insulin together with flexible prandial insulin was used less often. Insulin dosage in both wards did not differ between first half and second half (endocrinology: 15 ± 14 IU vs. 15 ± 13 IU insulin per day, $P = 0.87$; cardiology: 27 ± 17 IU vs. 27 ± 18 IU insulin per day, $P = 0.92$). In addition, there was no difference in the mean number of insulin injections per day in either the endocrinology ward (1.4 ± 1.0 vs. 1.3 ± 0.8, $P = 0.42$) or in the cardiology ward (1.5 ± 0.7 vs. 1.4 ± 0.8, $P = 0.46$) but we observed a tendency for less BG measurements in the second half (endocrinology: 2.9 ± 0.8 vs. 2.5 ± 0.7, $P = 0.06$; cardiology: 3.0 ± 0.8 vs. 2.7 ± 0.8, $P = 0.11$).

In 16 patients (endocrinology: 7, cardiology: 9) with hyperglycaemic levels (mean BG/day ≥180 mg/dL) no insulin dosing was performed in 6.7% of days with hyperglycaemia (BG ≥180 mg/dL) despite an average of 3.0 ± 0.7 BG measurements per day. Both, the mean daily insulin dose (first half 25.1 ± 18.5 IU vs. second half 26.6 ± 18.1 IU, $P = 0.69$) and the mean number of insulin injections per day (1.5 ± 0.6 vs. 1.7 ± 0.7, $P = 0.53$) did not significantly increase in these patients.

3.3.3 Questionnaire

More than 80% of the nurses stated that glycaemia and insulin therapy are regularly evaluated (Figure 4). Procedures regarding glycaemic management in case of “nothing per mouth” orders were familiar

to 57%. Although two-thirds indicated that corrective insulin doses for higher glucose levels are prescribed, less than 50% could specify the target range for these corrective measures. Moreover, both the stated target ranges and the type of target glucose showed high variability (Figure 4).

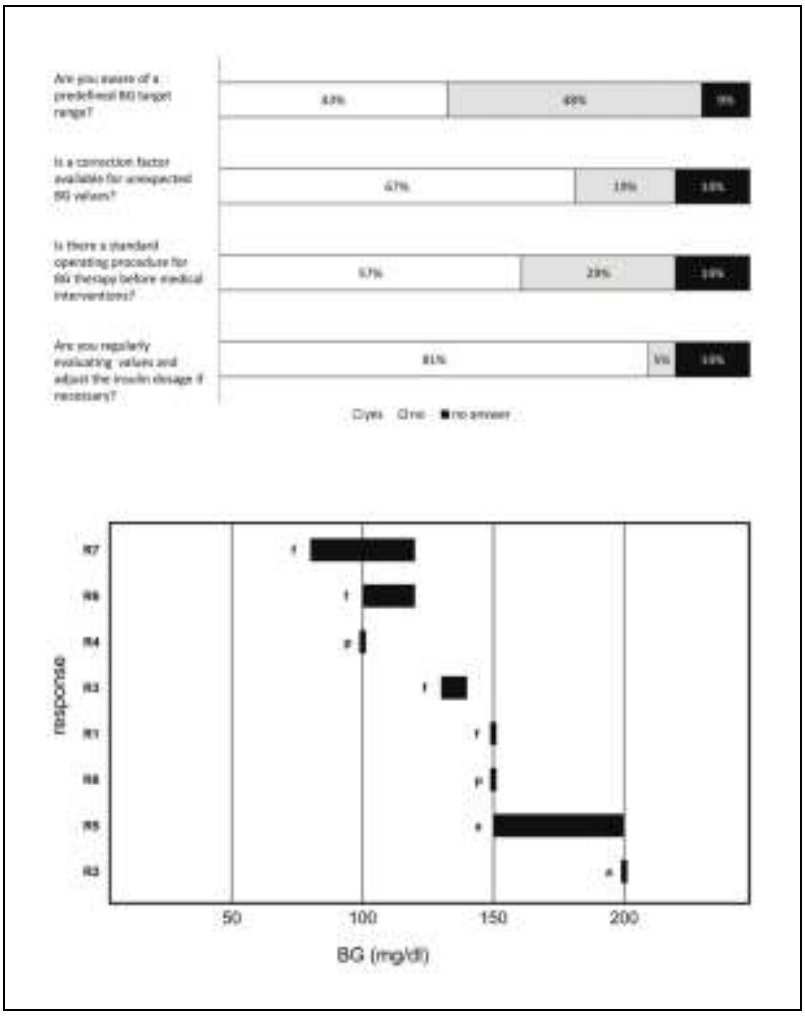


Figure 4: a) Results of an online anonymous questionnaire about current glycaemic management filled in by 21 nurses in both wards. (b) BG ranges stated by 8 nurses in the online questionnaire defining the type of target glucose level either as fasting (f), average (a) or premeal (p).

3.4 Discussion of workflow analysis

In this study we retrospectively assessed the effects of physician-based standard glycaemic management in two general hospital wards and analysed glycaemic management effort in relation to standard glycaemic care parameters. In both wards approximately two-thirds of patients' BG values remained >140 mg/dL, indicating failure to control hyperglycaemia regarding recent recommendations for glycaemic control of non-critically ill diabetic patients (American Diabetes Association, 2012; Umpierrezet al., 2012a).

Very few hypoglycaemic events <70 mg/dL occurred, whereas a substantial proportion of hyperglycaemic events >300 mg/dL were documented. These results are similar to other retrospective studies of glycaemic control which reported that hyperglycaemia was common in a clinical setting, but hypoglycaemic events were rare. Retrospective and prospective studies shared the same difficulties even when a higher BG level of 180 mg/dL had been set as the target (Boord et al., 2009; Knecht et al., 2006; Schnipper et al., 2009).

We also assessed whether persistent hyperglycaemia might have been caused by insufficient glycaemic management effort or heavy workload (Knecht et al., 2006; Schnipper et al., 2006). Neither ward reported a significant change from first to second half, neither in the number of BG measurements per day, the number of insulin injections per day nor the insulin dose adjustments.

Basal-bolus insulin therapy, which is considered a key intervention by recent guidelines, was not routinely used and although insulin dosing was adjusted individually, it did not result in a significant overall improvement of glycaemic control.

While many studies reported similar levels of hyperglycaemia in a clinical setting independent of the glycaemic management protocols, it is difficult to find a common explanation. The failure to adhere to BG target levels and avoid hyperglycaemia is most likely caused by a number of factors, such as lack of training, clinical personnel fears of hypoglycaemic events, reluctance to use insulin, preference to administer oral medication, individuality of patients, unfamiliarity with inpatient diabetes management strategies, clinical inertia and hesitant institution wide changes (Schnipper et al., 2006; Trujillo et al., 2008). Often, physicians are aware of diabetes at admission, but during hospitalization this diagnosis is often overlooked (Knecht et al., 2006). Scepticism about the benefit of tighter glycaemic control also contributes to this problem (The ACE/ADA task force on inpatient diabetes, 2006).

BG target ranges of <140 mg/dL recommended in recent guidelines may not be appropriate for some patient groups such as terminally ill, geriatric or paediatric patients, and glycaemic target ranges should be modified accordingly (Qaseem et al., 2011; Umpierrez et al., 2012a). As a consequence of the mean age of 70 years in our study population the recommended target range may not have been applicable to some patients and contributed to some extent to the overall elevated glycaemia. The wide spectrum of admission diagnosis as well as intensified medical treatment might have influenced individual BG measurements but are unlikely to have affected the average BG values on each ward. However, in the absence of documented individual BG goals it is difficult to adjust individual target ranges. As indicated by results of the questionnaires, there is a lack of well-defined target ranges and standardised procedures, which results in highly variable individual glycaemic management.

Although we were not able to identify a single underlying reason for the lack of improvement from the first to the second half of patients' stays, our findings provide a starting-point on how to assess and improve glycaemic management in hospitalized non-critically ill patients. Awareness must be increased in physicians and nurses about the importance of individual goal setting and documentation. Educational training should lead to adequate insulin adjustments in response to previous BG values and individual targets to improve glycaemic management (Fowler & Rayman, 2010; Hermayer et al., 2008; Trujillo et al., 2008; Umpierrez et al., 2012a).

Electronic decision support systems could also help to achieve a structured treatment protocol. New supportive technologies can make glycaemic management processes more effective by reducing prescription errors, thereby increasing effective insulin use, and minimizing the length of patients' stays. Possible electronic implementation approaches are validated alerts and guidelines on the prescription of antidiabetic medication, especially insulin (Ali et al., 2011; Bates & Gawande, 2003; Klonoff, 2011; Nirantharakumar et al., 2012a; Schnipper et al., 2009).

In summary, our results show insufficient control of hyperglycaemia of non-critically ill hospitalized patients with diabetes despite considerable glycaemic management efforts. While the data indicate substantial glycaemic management effort in the care of diabetic patients, it did not result in appropriate glycaemic control according to recent guidelines. Baseline data must be analysed to provide a starting point for the evaluation of new interventions in order to improve glycaemic management in hospitalized non-critically ill diabetic patients.

4 Clinical trial of a paper-based algorithm

4.1 Aim of the clinical trial

The aim of this proof-of-concept study was to assess the efficacy, workflow integration, and usability of a paper-based algorithm in hospitalized patients with type 2 diabetes. As a first step, a previously published insulin dosing algorithm for basal-bolus therapy (Umpierrez et al., 2007, 2009, 2011) was customized to account for complex processes during inpatient care and was then integrated into the workflow of a general internal medicine ward.

4.2 Methods

The controlled study was conducted at the two general wards at the Department of Internal Medicine (Medical University of Graz, Austria). At both wards a recently performed study found comparable and sustained BG levels around 180 mg/dL in diabetic patients independent of anti-hyperglycaemic treatments (Neubauer et al., 2012, Neubauer et al., 2013). In the present study, algorithm-based treatment was implemented on one ward and compared to standard glycaemic management on the other ward. Treatment allocation was not randomized to avoid biased treatment by algorithm trained medical staff.

Any adult patient admitted to either ward was eligible to be included in the study. Inclusion criteria were history of type 2 diabetes for at least 3 months treated with diet alone, and/or with any oral or injectable anti-hyperglycaemic therapy and/or insulin, age range between 18 and 90 (both inclusive), BG in the range 140-400 mg/dL prior to inclusion, expected hospital stay longer than 48 hours. Main exclusion criteria were the following: hyperglycaemia without known history of type 2 diabetes, severely impaired renal function (serum creatinine ≥3.0 mg/dL), clinically relevant hepatic disease, pregnancy, presence or history of diabetic ketoacidosis, incapability to provide informed consent and terminal illness.

For both groups, the study ended with hospital discharge, the transfer of the patient to a different ward, or after 21 days. The study was approved by the local ethics committee and performed in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. Patients gave written informed consent after the purpose, nature, and potential risks of the study were explained and before any study-related activities were started.

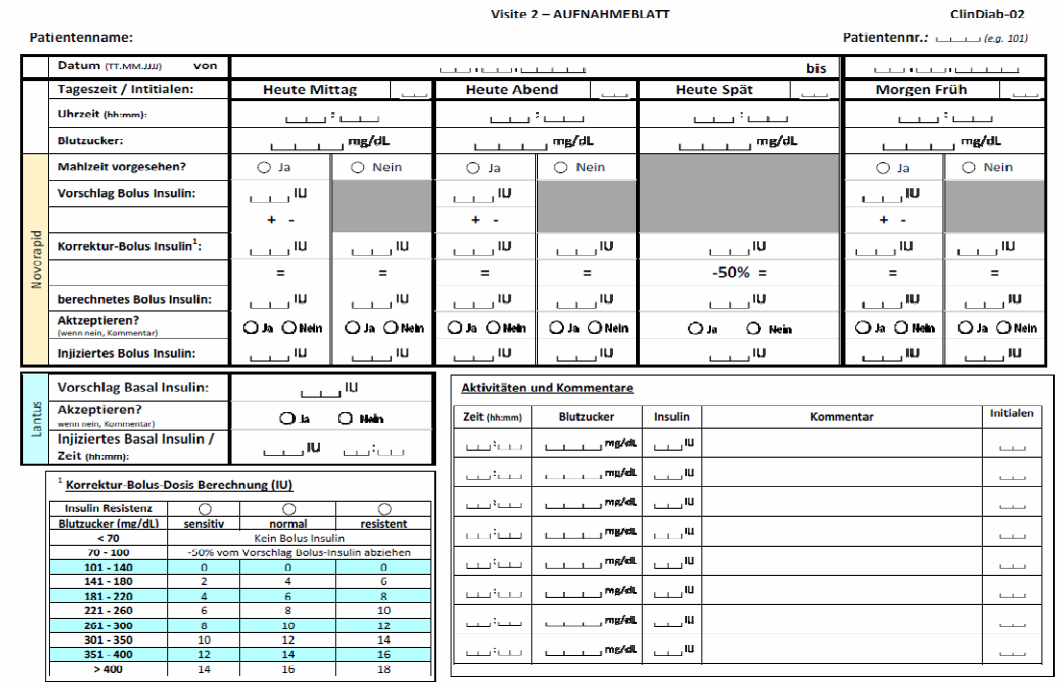


Figure 5: paper-based algorithm documentation of glycaemic management

4.2.1 Algorithm group

For the algorithm group, insulin therapy adjustment was performed according to a paper-based workflow-integrated algorithm. The algorithm, which aims for fasting and pre-meal levels in the range of 100-140 mg/dL, is based on a previously published algorithm (Umpierrez et al., 2007, 2009, 2011) and has been further customized for future deployment in a decision support system. In particular, this algorithm is able to take into account all possible combinations of pre-meal BG values when calculating the total daily insulin dose (TDD). The algorithm-based basal-bolus insulin therapy was integrated into daily routine of physicians and nurses. All personnel were trained in the correct use of the algorithm.

The algorithm was used to calculate the initial TDD based on patient weight, patient age and renal function: 0.5 IU/kg bodyweight in patients <70 years and with a serum creatinine level <2.0 mg/dL; the dose was reduced to 0.3 IU/kg in patients ≥70 years or with a serum creatinine level ≥2.0 mg/dL. For patients already on insulin therapy the pre-existing TDD was used. Any other anti-glycaemic therapy was discontinued before the initial TDD was calculated. According to the sequence of operations every subsequent day, the algorithm was used to calculate a new TDD for the next 24 h which was then confirmed by the attending physician during morning rounds. The algorithm calculated the new TDD based on the dinner BG the day before and today's breakfast BG according to a new scheme for all possible combinations of BG values.

Then, the calculated TDD was divided into a 50% basal and a 50% bolus insulin dose. If the calculated basal or bolus dose resulted in a fraction, it was rounded to the next lowest integer. At noon, the basal insulin dose (i.e. the half of the calculated TDD) was administered as the long-acting insulin analogue (Lantus®, Sanofi-Aventis, Germany). The bolus insulin dose (NovoRapid®, NovoNordisk, Denmark) was further divided into three equal doses (suggested bolus dose). If the bolus dose was not a multiple of three, the remaining insulin units were added first to breakfast bolus or to lunch bolus insulin dose.

In case pre-meal glucose values were out of target range the algorithm adjusted the suggested bolus dose further by using insulin sensitivity and the current BG value. Insulin sensitivity (sensitive, normal, resistant) was assessed by the attending physician during each morning round.

At any time nurses were able to modify the algorithm-calculated insulin dose. If patients were placed on non per os orders, bolus insulin was withheld and only basal insulin was administered.

4.2.2 Standard group

Glycaemic management in the standard group was performed by the attending physicians and nurses using oral agents, insulin or a combination of both.

4.2.3 Measurements

In both groups, glycaemic control was assessed by four daily BG measurements (three pre-meal and one bedtime value) using a point of care testing device (Roche Accu Chek® Inform System, Roche Diagnostics, Switzerland) integrated into the hospital information system. Additionally, glycaemia in the algorithm group was monitored with a blinded continuous glucose monitoring system (CGM, iPro2, Medtronic-Minimed, USA). CGM sensor insertion was performed according to manufacturer's instructions on the first study day. If a patient's participation in the study exceeded the manufacturer specified sensor lifetime a new sensor was inserted every 6 days to allow continuous monitoring throughout the study period. CGM was only temporarily discontinued when patients had to undergo diagnostic procedures (e.g. computed tomography, magnetic resonance imaging). Data made anonymous were downloaded using the Medtronic Carelink software. Sensor data were retrospectively calibrated using the four daily BG measurements.

In order to assess compliance, physicians´ adherence to the algorithm-calculated TDD was documented and nurses´ adherence to the basal and bolus insulin dose calculations and any deviation from calculated to administered insulin doses were recorded. To evaluate user acceptance of the algorithm, attending nurses in the algorithm group completed a questionnaire regarding efficacy and usability of the algorithm at the end of the study.

4.2.4 Data analysis

The primary endpoint was defined as the mean daily BG, calculated by using the four daily pre-meal and bedtime BG values per patient. The power analysis was based on a study by Umpierrez et al.

2011 (Umpierrez et al., 2011) and on a pretest chart review, which was conducted on the two wards (Neubauer et al., 2012). For sample size determination, we anticipated that with algorithm treatment, the mean daily BG per treatment day can be reduced from 170 ± 40 mg/dL (baseline) to an outcome of 145 ± 35 mg/dL. A one-tailed matched pairs t-test with 2.5% level of significance, power of 80% and a correlation between paired measurements (corresponding to the beginning and the end of treatment) of 0.15 would require a total of 33 patients. To also correct for a drop-out rate of ~10% (Umpierrez et al., 2011), the number of patients was increased to 37. Analysis was based on the intention to treat population. For the remaining analyses Pearson's chi-squared tests were used to analyse nominal data. Fisher's exact test was computed when a table had a cell with an expected frequency <5. Prior to data analysis, all metric outcome variables were checked for normality by means of a Shapiro-Wilk's test. Normally distributed metric variables were tested with Student's t-test. In case of not normally distributed metric variables, nonparametric tests were applied. We used Wilcoxon's signed rank test for matched samples, and the Mann-Whitney U test for independent observations. The level of significance was set to 5% for all tests. The statistical analysis was performed using R.2.13.1 (R Development Research Group, 2008b)

4.3 Results

From July 2011 to April 2012, 1015 patients who were admitted to the two wards (545 patients on the ward of the algorithm group, 470 on the standard care ward), were assessed for eligibility. Out of 296 patients with BG levels >140 mg/dL, 102 had no previously established diagnosis of diabetes, 29 had an expected hospital stay <48 h, 12 had type 1 diabetes and 2 had steroid-induced diabetes, 2 patients had BG values >400 mg/dL, 9 had advanced kidney or liver disease, 5 were older than 90 years, 16 were mentally not able to give informed consent, 3 were terminally ill, 19 were participating in another study and another 17 were admitted to the wards at times when no staff for assessment or inclusion visits was present. Of the remaining 80 eligible patients, 6 did not give informed consent and, finally, 74 were included in the study. The algorithm and the standard group were well matched with a similar number of patients with pre-existing insulin therapy in both groups (Table 4). One patient in the algorithm group felt that he did not respond to BG lowering treatment with the algorithm and withdrew informed consent on day four. The average length of treatment was 7.5 ± 4.6 days in the algorithm group and 7.0 ± 4.4 days in the standard care group (p=0.5). No patient died during their hospital stay.

4.4 Glycaemic control

The percentage of BG values in the different BG target ranges can be found in Figure 6. The percentage of bolus BG values in the target range (100-140 mg/dL) was significantly higher in the algorithm group (34%) compared with the standard care group (23%, p<0.001). Similarly, a significantly higher percentage of patients in the algorithm group had BG levels between 70 - 180 mg/dL (73% vs. 53%, p<0.001).

Mean daily BG (primary endpoint) in the algorithm group decreased significantly from baseline to the last 24 hours of hospital stay (from 204 ± 65 mg/dL to 148 ± 32 mg/dL, p<0.001, Figure 7A). In the algorithm group, nine BG values in a total of five patients (14%) were <60 mg/dL (0.9% of all measurements), including one event <40 mg/dL (Table 4). None of the events was associated with unconsciousness or required intravenous glucose infusion. In the standard care group no BG value was <60 mg/dL. For the entire study population no hypoglycaemia related adverse outcomes were reported.

Table 4: Clinical characteristics on admission, pre-existing diabetes therapy, admission diagnosis, and hypoglycaemic events during treatment

	algorithm group	**standard group**
n	37	37
gender, f (%)	11 (30%)	13 (35%)
age (years)	70 ± 12	67 ± 9
BMI (kg/m^2)	29.7 ± 6.8	30.5 ± 6.6
weight (kg)	84.0 ± 19.1	88.3 ± 21.1
race (Caucasian/other)	35/2	37
serum creatinine (mg/dL)	1.5 ± 0.5	1.2 ± 0.4
HbA1c (%)	9.1 ± 2.8	8.3 ± 1.8
diabetes duration (years)	14 ± 12	12 ± 7
diabetes therapy (n)		
diet alone	5	4
oral agents alone	12	13
insulin alone	18	12
insulin and oral agents	2	8
BG on inclusion (mg/dL)	204 ± 65	191 ± 41
time to inclusion (days)	1.8 ± 2.4	2.0 ± 1.6
concomitant disease		
cerebrovascular disease	32	37
infectious diseases	10	8
renal disease	19	14
other	1	1
hypoglycaemia		
number of BG tests	1038	914
BG <40mg/dL		
number of patients (%)	1 (2.7)	0 (0.0)
number of readings (%)	1 (0.1)	0 (0.0)
BG <60mg/dL		
number of patients (%)	5 (13.5)	0 (0.0)
number of readings (%)	9 (0.9)	0 (0.0)
BG <70mg/dL		
number of patients (%)	11 (29.7)	1 (2.7)
number of readings (%)	31 (3.0)	1 (0.1)

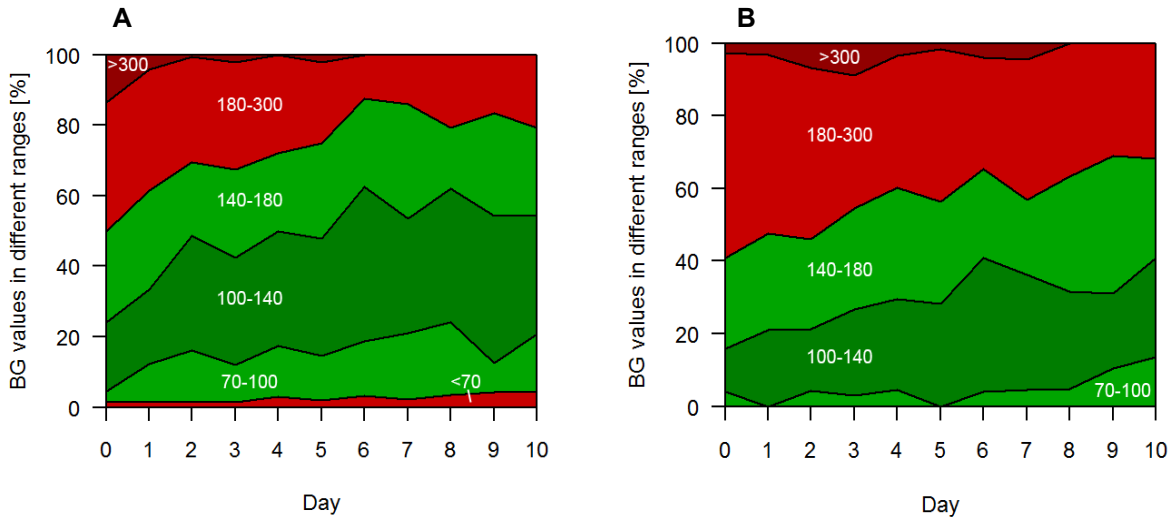


Figure 6: Distribution of BG values in predefined BG ranges during the treatment period. **A** Algorithm group **B** Standard group

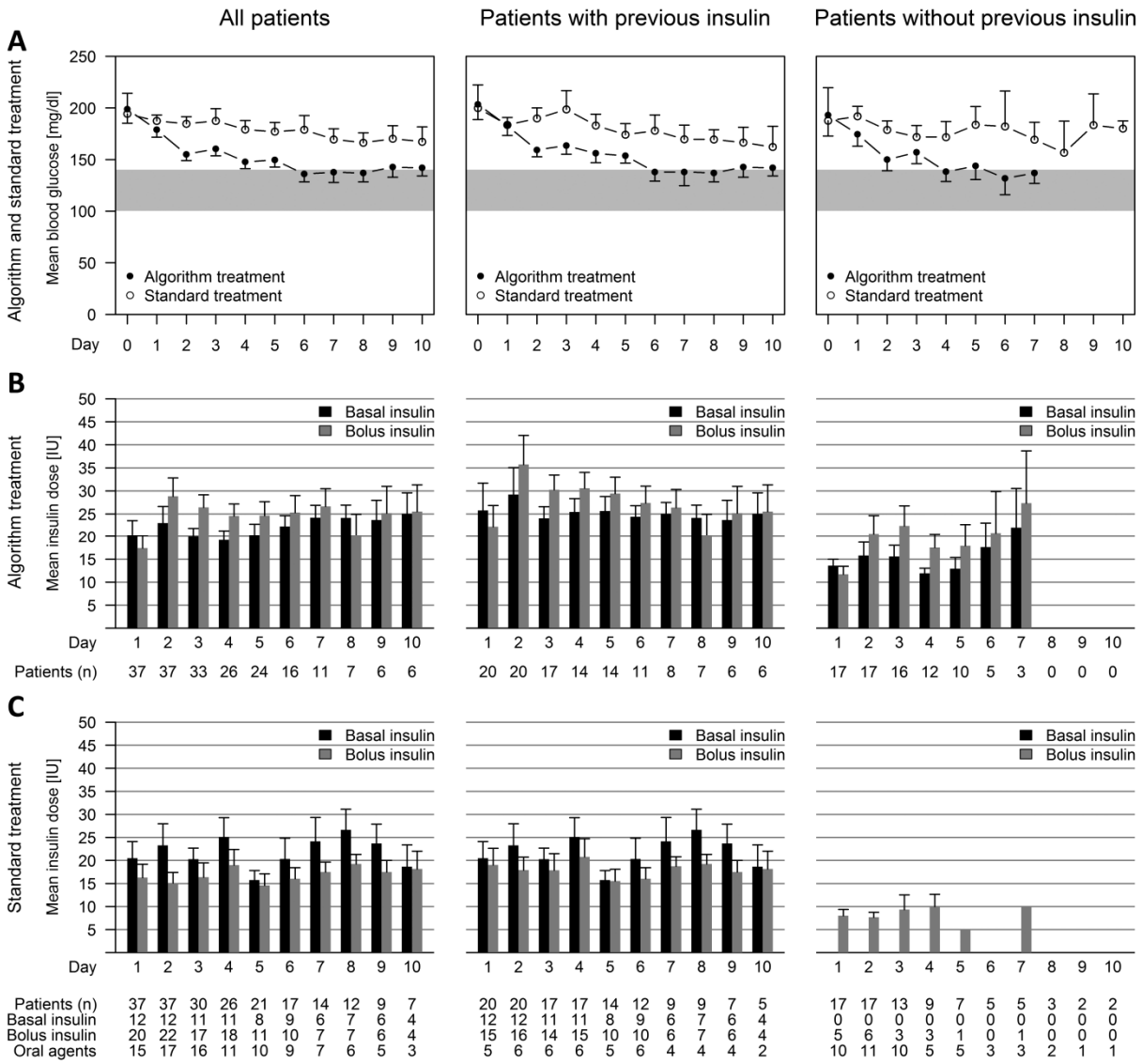


Figure 7: **A** Mean daily BG levels during 10 days of hospital stay for all patients (left), patients with pre-existing insulin therapy (middle) and patients without pre-existing insulin therapy (right). **B** Mean daily administered basal and bolus insulin dose in the algorithm group **C** Mean daily administered basal and bolus insulin dose and number of oral agents in the standard group. All data are mean ± SE.

4.4.1 Glycaemic management

In the algorithm group the mean TDD was 41 ± 30 IU. The mean daily bolus insulin dose (23 ± 16 IU) was significantly higher than the mean daily basal insulin dose (19 ± 14 IU, $p<0.001$, Figure 7B). In the standard care group 24 patients were on oral agents during the hospital stay. The mean daily insulin dose was 20 ± 16 IU in 28 patients receiving any insulin therapy during the hospital stay (Figure 7C). In the standard care group no basal insulin was given to patients without pre-existing insulin therapy at any time (Figure 7C, right panel).

There was a 95% physicians' adherence to the algorithm-calculated TDD and a 98% nurses' adherence to the algorithm-calculated basal dose and 93% adherence to the algorithm-calculated bolus dose. A high level of adherence was observed during the whole treatment period. There was no difference when the first half of stay was compared with the second half ($p>0.05$).

4.4.2 24 hour glucose profile and algorithm application

In the algorithm group, 32 out of 37 patients (86%) were monitored using CGM. 2 of the 5 patients without CGM data were not willing to use a CGM, 2 patients lacked subcutaneous adipose tissue and 1 patient lost the sensor during the study period. 88.2% of the study period (in total 5132 h) were

monitored with CGM. 24 h CGM profiles and bolus BG values showed pronounced breakfast BG excursions and subsequently higher lunch BG values (Figure 8A).

BG values <70 mg/dL indicated numerous hypoglycaemic events in the late afternoon in patients with pre-existing insulin therapy and few events in patients without pre-existing insulin therapy (Figure 5A). The post-hoc statistical analysis of hypoglycaemia identified the highest risk for hypoglycaemia in the late afternoon (15:30-17:00, n=14/237) relative to breakfast (7:00-8:30, n=1/234), lunch (10:30-12:00, n=2/223) or bedtime periods (21:30-23:00, n=4/241) (all comparisons versus 15:30-17:00, $p<0.05$). The administered bolus insulin doses as calculated by the algorithm (suggested and corrective component) are given in Figure 8B.

Mean corrective pre-meal doses (Figure 8B) are a result of positive and negative corrections (Figure 8C). At each of the three daily pre-meal BG values, the suggested bolus insulin dose had to be increased more often than it had to be reduced (Figure 8C). The highest mean bolus insulin dose correction was required at noon relative to both breakfast and dinner ($p<0.01$, Figure 8B).

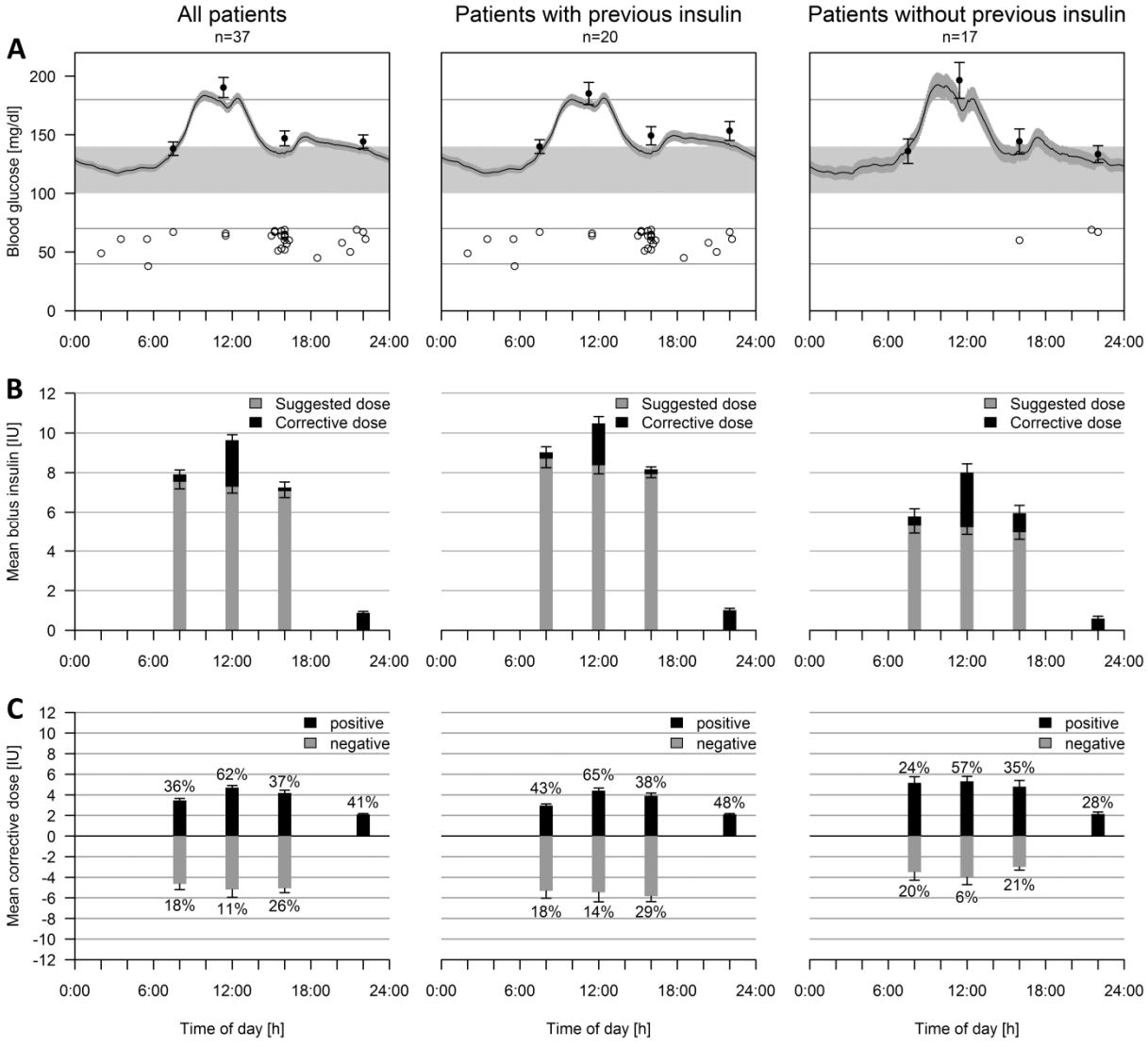
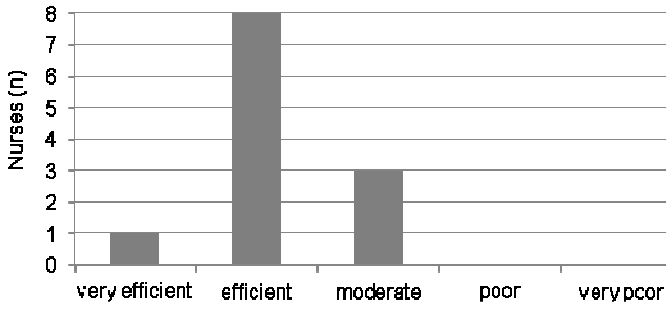


Figure 8: **A** Mean daily CGM profile, mean pre-meal BG values (solid circles) and hypoglycaemic events (open circles) for all patients (left), patients with pre-existing insulin therapy (middle) and patients without pre-existing insulin therapy (right). **B** Mean daily administered breakfast, lunch, dinner and bedtime bolus insulin dose shown as the algorithm-suggested dose (grey bar) and the total mean insulin correction (Figure 5C) based on insulin sensitivity and current BG levels (black bar). **C** Mean positive and negative corrective dose (IU) of each bolus insulin dose and the correction frequency (%). All data are mean ± SE.

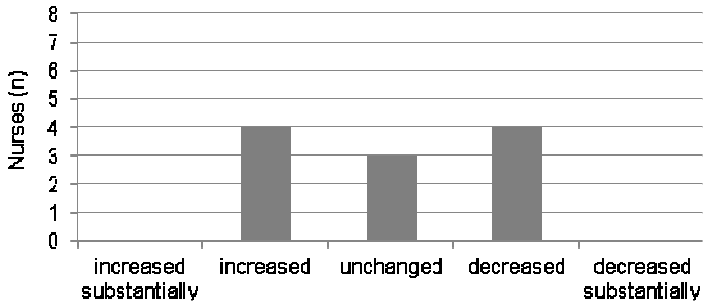
4.4.3 Usability

At the end of the study, 12 of the 14 nurses in the algorithm group completed a questionnaire (Figure 9). All nurses felt confident using the algorithm. 73% confirmed that the algorithm had improved the quality of glycaemic control including error prevention and 75% reported to have achieved the glycaemic target range. When using the algorithm, four nurses indicated a workload increase, four a workload decrease and another three indicated no change in workload (one did not answer).

A Target glucose control (100-140 mg/dL) as established by the algorithm

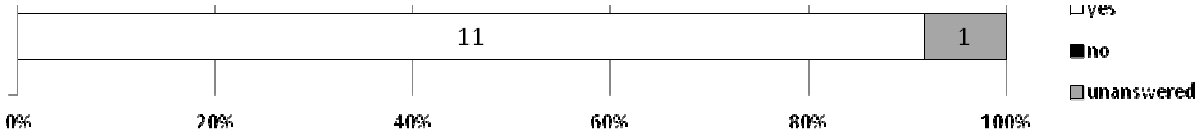


B The workload by the use of the algorithm *

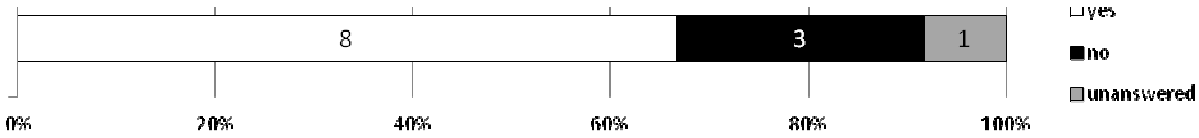


* 1 unanswered

C Glucose control by the use of the algorithm is more efficient as compared to standard routine care?



D Do you think that the algorithm will help to prevent error in the glycaemic management process?



E Did you feel confident using the algorithm based therapy?

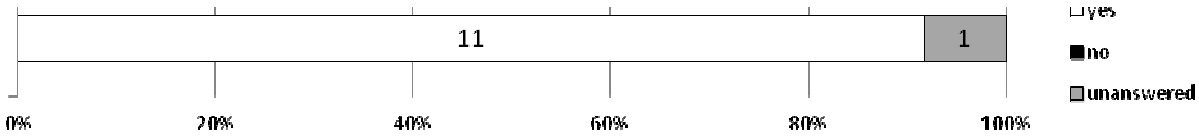


Figure 9: Nurses' questionnaire regarding the efficacy and usability of the algorithm. **A** Glucose control **B** Workload **C** Algorithm efficacy **D** Error prevention **E** User confidence

4.5 Discussion

Our data demonstrate that the use of a workflow-integrated algorithm for basal-bolus insulin therapy was efficacious in establishing glycaemic control in hospitalized patients with type 2 diabetes. Moreover, rigorous evaluation of the workflow indicated that physicians and nurses had a high adherence rate to the algorithm-based insulin therapy.

In the algorithm group, the mean achieved BG levels were significantly more often within target range and well comparable to BG levels established in previous trials using basal-bolus algorithms (Umpierrez et al., 2007, 2009, 2011). For the first time, we have used a CGM system to closely monitor BG levels and retrospectively assess efficacy of the algorithm. Furthermore, the integration of the algorithm in the daily workflow of a general ward was assessed by thorough documentation. Such a detailed workflow analysis will enable us to support future development of a decision support system for in-hospital glucose management.

CGM profiles were stable overnight. Lunch glucose peaks were frequently outside the target range most likely caused by an elevated morning glucose excursion which was not sufficiently controlled by the administered morning insulin dose. Alternatively, since the basal insulin was administered at lunch to fit in the workflow of the ward, the fading basal insulin action could have contributed to that finding (Hamann et al., 2003). Elevated lunch BG values required higher bolus insulin doses at lunch and could have caused hypoglycaemic events in the afternoon.

Patients without pre-existing insulin therapy had a lower rate of hypoglycaemic events which is comparable to the incidence rate seen in insulin-naïve type 2 diabetes patients under basal-bolus therapy (Umpierrez et al., 2007). In hospitalized patients with type 2 diabetes on subcutaneous insulin therapy, patient age and insulin regimen (basal-bolus vs. sliding scale) were identified as independent predictors of inpatient hypoglycaemia (Farrokhi et al., 2012). Not only the type of insulin regimen, but also the application type may play a role in the occurrence of hypoglycaemia in hospitalized patients, besides the classical risk factors such as impaired kidney function, high total daily insulin requirements or increased age (Boucai, Southern, & Zonszein, 2011; Farrokhi et al., 2012; Rubin et al., 2011). A recent study of two different weight-based dose levels of a basal-bolus regimen in hospitalized patients with diabetes and impaired kidney function showed that a lower insulin dosing reduced the frequency of hypoglycaemia by 50% without compromising the control of hyperglycaemia (Baldwin et al., 2012). While our study lacks confirmation from a larger sample of patients, the analysis also indicates that the occurrence of hypoglycaemia in the late afternoon in patients with pre-existing insulin therapy could have been caused by inadequate timing of the basal insulin dose in combination with insufficient bolus insulin. Strategies, such as shifting more units of the daily bolus insulin to the morning dose or later administration of the basal insulin will be tested to minimize this risk of hypoglycaemia in the further development.

This study, which is applying a paper-based algorithm, is an intermediate step in the design of a computerized decision support system. Across a variety of clinical settings, the implementation of such systems has been shown to improve performance by an increased adherence to guidelines, reduced prescription errors, and enhanced monitoring of patients (Ammenwerth et al., 2008; Chaudhry et al., 2006; Eslami, de Keizer, & Abu-Hanna, 2008; Garg et al., 2005; Rothschild, 2004). Although the use of electronic prescriptions has been cited in diabetes care guidelines as key strategy to provide an efficient inpatient management (American Diabetes Association, 2012), a recent review of clinical decision support systems found only two cluster-randomized trials applying such systems in inpatient diabetes care (Nirantharakumar et al., 2012a). One study that had used an electronic order template for basal-bolus insulin at acute general medical wards found a significant reduction of the mean BG levels relative to standard insulin treatment (Wexler et al., 2010). However, glucose control was rather moderate (algorithm group: 195 ± 66 mg/dL vs. standard group: 224 ± 57 mg/dL) and the use of basal insulin at any time did not exceed 61% and 65% in the algorithm and the standard group, respectively.

The other study implemented an insulin order set into the hospital´s computer system, but found no difference in the use of basal insulin in patients with BG levels >180 mg/dL for the algorithm vs. the standard group (76% vs. 63%) (Schnipper, 2010). Hence, providing a computerized order set in daily routine does not guarantee efficient implementation of the electronic assistance (Moxey et al., 2010) as not all advices seem to be adhered to (Phansalkar et al., 2010). In order to increase the use by healthcare providers, it is important to consider organizational and contextual characteristics when designing a computerized decision support system (Nirantharakumar et al., 2012a). However, a recognised difficulty with such systems is that the apparent gain may not be due to the system alone but the learning of the system rules by clinical staff. Once learnt they become more effective and confident in their clinical decisions.

The high adherence of staff to the algorithm-calculated dose and the positive response rate in the questionnaire indicate a good integration into daily routine. Nevertheless, we acknowledge the limitation that our study was a single centre study and other hospital settings need to be examined before generalizing these results.

In conclusion, we successfully demonstrated the implementation of a paper-based workflow-integrated algorithm for basal-bolus insulin therapy in hospitalized patients with type 2 diabetes by means of adequate glycaemic control and high user acceptance rate. The occurrence of hypoglycaemic events in the afternoon requires further investigation. Overall, our findings support the implementation of the algorithm in an electronic decision support system.

5 Clinical pilot trial of tablet based workflow support system

5.1 Aim of the clinical trial

The aim of this trial is to investigate, safety, usability and efficacy of the tablet based workflow support system (GlucoTab system) used for glycaemic management of non-critically ill patients with type 2 diabetes at the general ward.

5.2 Methods

The mono-centric, open, non-controlled intervention pilot trial was conducted at Department of Internal Medicine (Division of Endocrinology) at Medical University Graz in patients with type 2 diabetes. The study will include a total of 30 patients hospitalised with type 2 diabetes.

The insulin therapy of the first 15 patients was performed according to the paper-based workflow-integrated algorithm. The calculated TDD was divided into a 50% basal and a 50% bolus insulin dose. The bolus insulin dose was further divided into three equal doses (33% at breakfast, 33% at lunch, 33% at dinner).

Due to the lunch glucose peaks (Figure 8A) were frequently outside the target range most likely caused by an elevated morning glucose excursion which was not sufficiently controlled by the administered morning insulin dose, the bolus insulin dose was divided into 45% at breakfast, 25% at lunch and 30% at dinner. This distribution of bolus insulin dose is currently investigated for glycaemic management of additional 15 patients.

The inclusion criteria are: Informed consent obtained after being advised of the nature of the study; age range between 18 and 90 (both inclusive); type 2 diabetes treated with diet, oral agents, non-insulin injected anti-diabetic medicine, insulin therapy or any combination of the four. Exclusion criteria are the following: impaired renal function (serum creatinine ≥3.0mg/dL), any disease or condition which the investigator or treating physician feels would interfere with the trial or the safety of the patient, pregnancy, any mental condition rendering the patient incapable of giving his consent, terminally ill patients, participation in a trial within 3 months prior to this trial, known or suspected allergy to insulin.

The study has been approved by the local ethics committee and the performance is in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice.

5.2.1 Investigational system

The GlucoTab system supports the glycaemic management of non-critically ill patients with type 2 diabetes at the general ward. The GlucoTab system is a software system to improve the treatment workflow of clinical professionals (nurses, doctors) for managing patients with diabetes type 2 at the general ward. In addition, the software supports clinical professionals in finding the proper insulin dose for patients with diabetes type 2. Medical (blood glucose, creatinine), physiological (age, weight) and demographic (age) data entered manually by clinical professionals or received automatically from the hospital information system is used by the clinical protocol to calculate the insulin dose. Visualization of BG values and medication is provided for usability, and the workflow is supported by a task management feature which automatically displays outstanding tasks. The decision support consists of therapy adjustment (directed to physician) and correction bolus (directed to nurse).

Figure 10: Tablet-based glycaemic management

5.3 Results of 30 subjects

The data analysis of the clinical pilot trial is currently going on.

6 Clinical trial of investigation of the GlucoTab System

After successful testing of the GlucoTab system at the medical ward of Endocrinology, another trial is planned at other clinical wards to reduce any potential bias from experienced nurses and to prove its usability to support in-hospital glycaemic management outside specialised wards.

6.1 Aim of the clinical trial

The aim of the clinical trial will be to investigate the performance and safety of the GlucoTab system used for glycaemic management of non-critically ill patients with type 2 diabetes at other clinical wards.

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