DISSERTATION

Glycaemic Management with a Clinical Decision Support System in the Hospital Setting

Quality analysis – Algorithm development– Evaluation of a computerised system

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A thesis submitted for the academic degree of
Doctor of Medical Science
(Dr. scient. med.)

2016

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STATUTORY DECLARATION

“I hereby declare that this thesis is my own original work and that I have fully acknowledged by name all of those individuals and organisations that have contributed to the research for this thesis. Due acknowledgement has been made in the text to all other material used. Throughout this thesis and in all related publications I followed the “Standards of Good Scientific Practice and Ombuds Committee at the Medical University of Graz“.

Graz, 2. Mai 2016 Katharina Maria Neubauer, eh

Please note that parts of this thesis are already published. Therefore, some chapters represent the original publications or parts of the publications that have been adapted. At the beginning of each chapter the relevant publications are listed and referenced again directly in the text. Journals and co-authors gave permission for using the publications within this doctoral thesis.

ACKNOWLEDGEMENTS

“…it is not joy that makes us grateful,

it is gratitude that makes us joyful.”

(David Steindl-Rast)

This thesis is the result of my work within the research group *GlucoTab* at the Medical University of Graz (Division of Endocrinology and Diabetology), Joanneum Research (HEALTH) and LKH-Univ.Klinikum Graz. The completion of my doctoral thesis is also a result of the commitment, motivation and creativity of all my colleagues in this research group. Thanks to all of you for your spirit and passion!

Furthermore, I thank my supervisors for being teachers and lighthouses on my way through the doctoral studies.

Last but not least I want to thank David, my family and friends for always being beside me - in successful but also in challenging times. I’m very happy having such brilliant people on my side.

ACKNOWLEDGEMENTS OF CONDUCTED STUDIES

I thank all co-authors and other colleagues for their support in the performance of the studies.

Study 1: Failure to control hyperglycaemia in non-critically ill diabetes patients despite standard glycaemic management in a hospital setting
Co-Authors: Schaupp L, Plank J, Augustin T, Mautner SI, Tschapeller B, Pieber TR

Study 2: Efficacy, usability and sequence of operations of a workflow-integrated algorithm for basal-bolus insulin therapy in hospitalised type 2 diabetes patients
Co-Authors: Mader JK , Schaupp L, Augustin T, Beck P, Spat S, Höll B, Treiber GM, Fruhwald FM, Pieber TR, Plank J
I thank all physicians and nurses at the Divisions of Endocrinology and Diabetology and Cardiology for their help in the performance of the study, B. Tschapeller for data management, A. Berghofer for data monitoring and S. Mautner for editorial assistance.

Study 3: Tablet-based workflow and decision support of in-hospital glycaemic management– perceptions of nurses and physicians
Co-Authors: Mader J, Aberer F, Schaupp L, Donsa K, Spat S, Hoell B, Augustin T, Beck P, Plank J, Pieber T

Study 3: Basal bolus insulin therapy in hospitalised patients with diabetes mellitus type 2 using two algorithms embedded in a tablet PC
Co-Authors: Mader JK, Schaupp L, Höll B, Spat S, Augustin T, Beck P, Buttinger M, Plank J, Pieber TR
I thank all physicians and nurses at the Division of Endocrinology and Diabetology for their help in the performance of the study, B. Tschapeller for data management and A. Berghofer for data monitoring.

Study 4: Standardised glycaemic management with a computerised workflow and decision support system for hospitalised patients with type 2 diabetes on different wards

Co-Authors: Mader JK, Höll B, Aberer F, Donsa K, Augustin T, Schaupp L, Spat S, Beck P, Fruhwald FM, Schnedl C, Rosenkranz AR, Lumenta DB, Kamolz LP, Plank J, Pieber TR

I acknowledge the critical review of the manuscript and the editorial assistance of B. Boulgaropoulos, the data management of B. Tschapeller, C. Krainer, and G. Schwagerle, the data monitoring of A. Berghofer, the technical implementation of support and software testing of F. Chiarugi and D. Manousos, and the mobile device security and user management of M. Enzmann and F. Franke. The author thanks the nurses and physicians of the Divisions of Endocrinology and Diabetology, Cardiology, Nephrology, and Plastic Surgery.

Study 5: Efficacy, safety and usability of a clinical decision support system for basal-bolus insulin therapy in hospital routine care

Co-Authors: Mader JK, Aberer F, Tuca A, Donsa K, Augustin T, Höll B, Schaupp L, Beck P, Plank J, Pieber TR

I thank all physicians and nurses at the Divisions of Endocrinology and Diabetology, Cardiology and Plastic Surgery for their help in the performance of the study, B. Tschapeller, C. Krainer and K. Moschik for data management, A. Berghofer and S. Bischof for data monitoring.

Study 6: Efficacy and safety of standardised glycaemic control in adult and geriatric hospitalised patients with type 2 diabetes mellitus

Co-Authors: Mader JK, Aberer F, Schaupp L, Donsa K, Augustin T, Beck P, Pieber TR, Plank J

Study 7: GlucoTab: Decision Support für Diabetes

Co-Authors: Tax C, Pieber TR

I thank J. Mader, J. Plank, M. Buttinger, B. Semlitsch, C. Kapeller, P. Beck for the critical review of the concept and B. Höll for GlucoTab mock ups.

CONTENT

LIST OF ABBREVIATIONS

BG	blood glucose
BZ	Blutzucker
BMG	Bundesministerium für Gesundheit
CGM	continuous glucose monitoring
MPG	Medizinproduktegesetz
OAD	oral antidiabetic drug
SEM	standard error of the mean
SD	standard deviation
TDD	total daily insulin dose
vs.	versus

SUMMARY

Hyperglycaemia is a complex and highly prevalent phenomenon in hospitals that has to be adequately treated by implementing standardised and evidence-based strategies. The overall aims of this doctoral thesis are to determine the quality of glycaemic management and to develop and evaluate a computerised workflow and decision support system for patients with diabetes in the hospital.

The **first chapter** provides background information, guideline recommendations and gaps in the research of glycaemic management in the hospital. Additionally, the detailed aims of the studies conducted are presented.

In the **second chapter** the general methodical approach, *Mode-2-Science,* and an overview of the studies (design, sample, setting, data collection and analysis) are illustrated.

Chapter three describes the methods and results of Study 1-7. In **Study 1** the quality of glycaemic management in 50 patients at two general wards (Endocrinology and Cardiology) was assessed retrospectively, considering most recent international recommendations. Glycaemic control was clearly above the recommended target (mean blood glucose (BG) values per population Endocrinology: 175 ± 62 mg/dl, Cardiology: 186 ± 68 mg/dl). When comparing the first to the second half of the hospital stay, no difference in glycaemic control (Endocrinology: 168 ± 32 vs. 164 ± 42 mg/dl, Cardiology: 174 ± 36 mg/dl vs. 170 ± 42 mg/dl) and insulin dose (Endocrinology: 15 ± 14 vs. 15 ± 13 units per day, Cardiology: 27 ± 17 vs. 27 ± 18 units per day), was found despite frequent BG measurements [1]. The quality analysis of glycaemic management demonstrated considerable glycaemic management effort, but also a lack of translation into an adequate insulin therapy. This gap in glycaemic management could be closed by implementing a basal-bolus insulin algorithm.

In the proof-of-concept **Study 2**, glycaemic control and usability of a paper-based algorithm for basal-bolus insulin therapy were evaluated to develop a decision support system. In this ward-controlled study, 74 patients with diabetes (24 female, age 68 ± 11 years, HbA1c 72 ± 3 mmol/mol, Body Mass Index 30 ± 7 kg/m^2) were assigned to either algorithm driven therapy or standard care. Mean BG values in the algorithm group were significantly reduced from 204 ± 65 (baseline) to 148 ± 32 mg/dl (last 24 hours) during a period of 7.5 ± 4.6 days (P<0.001). The algorithm group had a significantly higher percentage of BG values in the range 70-180 mg/dl compared to the standard group (73% vs. 53%, P<0.001). Health care professionals' adherence to the algorithm calculations was high (≥93%) [2]. These results supported the implementation of the algorithm in a computerised decision support system.

The aim of the feasibility **Study 3** was to evaluate the efficacy, safety and usability of two versions (part 1 and part 2) of the computerised algorithm (different distribution of daily bolus insulin) in 30 patients. The GlucoTab system provided automated workflow and insulin dosing support to nurses and physicians. The mean BG was 166 ± 34 mg/dl (algorithm in part 1) vs. 144 ± 27 mg/dl (modified algorithm in part 2). 1.7% and 1.5% of BG values were in the hypoglycaemic range below 70 mg/dl in part 1 and part 2 respectively. The feasibility implementation of the GlucoTab system was well accepted by health care professionals. The modified algorithm improved glycaemic control further.

The aim of the non-controlled **Study 4** was to investigate efficacy, safety and usability of the GlucoTab system in 99 patients with diabetes (41 female, age 67 ± 11 years, HbA1c 65 ± 21 mmol/mol, Body Mass Index 30.4 ± 6.5 kg/m^2) at different wards (Endocrinology, Cardiology, Nephrology, Plastic Surgery). Adherence to insulin dosing suggestions was high (96.5% bolus, 96.7% basal). Percentage of BG measurements from 70-140 mg/dl occurred in 50.2 ± 22.2% of all measurements. The overall mean BG was 154 ± 35 mg/dl. BG measurements <70 mg/dl occurred in 1.9% of all measurements. A regression analysis showed that acute admission at the Cardiology ward and pre-existing home insulin therapy had the strongest impact on mean BG. 91% of the health care professionals felt confident with GlucoTab, 89% believed in its practicability and 80% in its ability to prevent medication errors [3]. Based on the efficacious, safe and user-accepted

implementation at different wards, the GlucoTab was CE marked as a medical device which allowed GlucoTab use in routine care.

GlucoTab was implemented at three hospital wards. The use of GlucoTab in routine care was evaluated in **Study 5** according to MPG §40(5) (Austrian medical device law). By using the GlucoTab system in 92 patients in routine care, results of Study 4 concerning efficacy and safety were confirmed. The mean use per patient of the GlucoTab treatment during hospital stay was 72.5 ± 22.2%. In 17 patients GlucoTab was used for treatment during the complete length of hospital stay. The use of GlucoTab treatment during a patient's hospital stay demonstrated that decision and documentation support systems for alternative therapy types (e.g. basal only, prandial insulin therapy) are urgently needed in combination with personalised glycaemic targets.

The analysis of pooled patient data in **Study 6** aimed to investigate efficacy and safety of the GlucoTab system in 97 adult (<70 years) and 94 geriatric (≥70 years) patients. Insulin therapy was started with a total daily dose (TDD) of 0.5 units per kg bodyweight in adult patients and 0.3 units per kg bodyweight in geriatric patients or in patients with a serum creatinine value ≥2 mg/dl. The first provided TDD was 0.49 ± 0.16 vs. 0.37 ± 0.24 units per kg bodyweight in adult and geriatric patients, respectively. The overall mean daily BG value was 155 ± 33 mg/dl (adult patients) and 157 ± 31 mg/dl (geriatric patients). 69.6% vs. 71.7% of BG values were in the range 70-<180 mg/dl for adult and geriatric patients, respectively. 2.5% vs. 1.5% of BG values occurred in adult and geriatric patients in the range <70 mg/dl. 2.8% vs. 1.8% of BG values were in the hyperglycaemic range ≥300 mg/dl in adult and geriatric patients, respectively. Mean daily injected insulin dose during the study was lower in geriatric than in adult patients. After day six, geriatric patients received a higher proportion of bolus insulin than adult patients. The suggested insulin starting dose supported an efficacious and safe glycaemic control in both age groups [4].

The aim of **Study 7** was to develop a comprehensive concept for insulin therapy adjustments by nurses including workflow simplifications and how to react in critical situations. Based on the current legal regulations in Austria, a dialog with the Austrian Federal Ministry of Health (BMG) was started. The Federal Ministry

stated that insulin adjustment by nurses is permitted under certain conditions. These conditions are implemented into the GlucoTab feature *insulin adjustment by nurses*. This feature is an important milestone for the Austrian nursing profession. For the first time it is now legally allowed that nurses adjust insulin therapy when supported by technology.

Chapter 4 summarises and discusses the main results of this doctoral thesis. Ongoing projects and recommendations related to GlucoTab research are presented.

ZUSAMMENFASSUNG

Hyperglykämie ist ein komplexes und häufig auftretendes Phänomen im Krankenhaus, welches adäquat mittels der Implementierung standardisierter und evidenz-basierter Strategien behandelt werden muss. Die Hauptziele dieser Doktorarbeit sind die Qualitätserhebung des Blutzuckermanagements und die Entwicklung und Evaluierung eines elektronischen Workflow und Decision Support Systems (GlucoTab) für PatientInnen mit Diabetes im Krankenhaus.

Das **erste Kapitel** liefert Hintergrundwissen und beschreibt Empfehlungen von Guidelines und Forschungslücken zu Blutzuckermanagement im Krankenhaus. Abschließend werden detaillierte Ziele der durchgeführten Studien präsentiert.

Im **zweiten Kapitel** werden die allgemeine Forschungsmethodik (*Modus-2-Forschung)* und ein methodischer Überblick der Studien (Design, Stichprobe, Setting, Datensammlung und Analyse) beschrieben.

Kapitel drei stellt die Methoden und Ergebnisse der Studien 1-7 dar. In der **Studie 1** wurde die Qualität des Blutzuckermanagements von 50 PatientInnen zweier Stationen (Endokrinologie und Kardiologie) retrospektiv unter der Berücksichtigung neuester internationaler Empfehlungen erhoben. Die glykämische Kontrolle war eindeutig über dem empfohlenen Ziel (mittlerer Blutzucker (BZ) Endokrinologie: 175 ± 62 mg/dl, Kardiologie: 186 ± 68 mg/dl). Beim Vergleich der ersten und zweiten Aufenthaltshälfte konnte kein Unterschied der glykämischen Kontrolle per Population (Endokrinologie: 168 ± 32 vs. 164 ± 42 mg/dl, Kardiologie: 174 ± 36 vs. 170 ± 42 mg/dl) und Insulindosis (Endokrinologie: 15 ± 14 vs. 15 ± 13 Einheiten/Tag, Kardiologie: 27 ± 17 vs. 27 ± 18 Einheiten/Tag), trotz häufiger Blutzuckerkontrollen beobachtet werden [1]. Die Analyse zeigte, dass beträchtliche Bemühungen für das Blutzuckermanagement aufgewendet werden, obwohl die Umsetzung in eine adäquate Insulintherapie damit nicht erreicht wird. Dies könnte sich durch die Implementierung eines Basis-Bolus Insulinalgorithmus verbessern.

In der *Proof-of-Concept* **Studie 2** wurden die glykämische Kontrolle und die Benutzerfreundlichkeit eines papier-basierten Algorithmus für Basis-Bolus Insulintherapie überprüft, um ein *Decision Support System* zu entwickeln. 74 PatientInnen mit Diabetes (24 weiblich, Alter 68 ± 11 Jahre, HbA1c 72 ± 3 mmol/mol, Body Mass Index 30 ± 7 kg/m^2) wurden entweder zur Algorithmusbehandlung oder Standardversorgung zugeteilt. Mittlere BZ-Werte der Algorithmusgruppe reduzierten sich signifikant von 204 ± 65 (Start) auf 148 ± 32 mg/dl (letzten 24 Stunden) über 7.5 ± 4.6 Tage (P<0.001). Die Algorithmusgruppe hatte im Vergleich zur Standardgruppe einen signifikant höheren Prozentsatz der BZ-Werte im Ziel von 70-180 mg/dl (73% vs. 53%, P<0.001). Die Adhärenz der ÄrztInnen und Pflegepersonen zur Algorithmus-Berechnung war hoch (≥93%) [2]. Die Ergebnisse trieben die Integration des Algorithmus in ein elektronisches *Decision Support System* voran.

Das Ziel der **Pilotstudie 3** war die Evaluierung der Wirksamkeit, Sicherheit und Benutzerfreundlichkeit zweier Versionen des elektronischen Algorithmus (unterschiedliche Verteilung des täglichen Bolusinsulins) bei 30 PatientInnen. GlucoTab bietet dabei automatisierte Arbeitsprozess- und Insulindosierungs-Vorschläge für Pflegepersonen und ÄrztInnen an. Der mittlere BZ-Wert war 166 ± 34 mg/dl (Algo Teil 1) vs. 144 ± 27 mg/dl (Algo Teil 2). 1.7% (Teil 1) bzw. 1.5% (Teil 2) der BZ-Werte waren im hypoglykämischen Bereich unter 70 mg/dl. Die Pilotstudie des GlucoTab wurde von ÄrztInnen und Pflegepersonen sehr gut akzeptiert. Der geänderte Algorithmus verbesserte die glykämische Kontrolle weiter.

Das Ziel der nicht-kontrollierten **Studie 4** war die Wirksamkeit, Sicherheit und Benutzerfreundlichkeit des GlucoTab bei 99 PatientInnen mit Diabetes (41 weiblich, Alter 67 ± 11 Jahre, HbA1c 65 ± 21 mmol/mol, Body Mass Index 30.4 ± 6.5 kg/m^2) auf verschiedenen Stationen (Endokrinologie, Kardiologie, Nephrologie, Plastische Chirurgie) zu überprüfen. Die Adhärenz zu Insulindosis-Vorschlägen war hoch (96.5% Bolus, 96.7% Basis). 50.2 ± 22.2% aller Messungen lagen zwischen 70-140 mg/dl. Der mittlere BZ war 154 ± 35 mg/dl. BZ-Werte <70 mg/dl traten bei 1.9% der Messungen auf. Die Regressionsanalyse zeigte, dass akute Aufnahmen auf der Station Kardiologie und eine bestehende Insulintherapie den stärksten Einfluss auf den mittleren BZ hatten. 91% der ÄrztInnen und

Pflegepersonen fühlten sich sicher in der Anwendung von GlucoTab, 89% glaubten an dessen Praktikabilität und 80% an dessen Fähigkeit Medikationsfehler zu vermeiden [3]. Basierend auf dieser erfolgreichen Implementierung auf verschiedenen Stationen wurde das GlucoTab als Medizinprodukt CE gekennzeichnet, was die Benutzung des Systems in der Routine ermöglicht.

GlucoTab wurde auf drei Stationen im Krankenhaus implementiert. Die Anwendung des Systems in der Routine wurde in **Studie 5** nach MPG §40(5) überprüft. Bei der Routineanwendung des GlucoTab bei 92 PatientInnen, wurden die Ergebnisse der Studie 4 bestätigt. Die mittlere Anwendung der GlucoTab Behandlung während des Aufenthalts betrug 72.5 ± 22.2%. Bei 17 PatientInnen wurde das System während des gesamten Aufenthalts verwendet. Der Grad der Anwendung zeigt auf, dass weitere Lösungen für alternative Therapieformen in Kombination mit variablen BZ-Zielbereichen benötigt werden.

Das Ziel der **Studie 6** mit Patientendaten aus den Vorstudien war die Wirksamkeit und Sicherheit des GlucoTab bei 97 erwachsenen (<70 Jahre) und 94 geriatrischen (≥70 Jahre) PatientInnen zu überprüfen. Die Insulintherapie startete mit einer TDD von 0.5 Einheiten/kg bei erwachsenen und 0.3 Einheiten/kg bei geriatrischen PatientInnen oder PatientInnen mit einem Serum Kreatinin ≥2 mg/dl. Die erste TDD betrug 0.49 ± 0.16 bzw. 0.37 ± 0.24 Einheiten/kg bei erwachsenen und geriatrischen PatientInnen. Der mittlere BZ-Wert war 155 ± 33 mg/dl (<70 Jahre) und 157 ± 31 mg/dl (≥70 Jahre). 69.6% bzw. 71.7% der BZ-Werte waren im Bereich 70-<180 mg/dl bei erwachsenen und geriatrischen PatientInnen. 2.5% bzw. 1.5% der Werte lagen im Bereich <70 mg/dl. 2.8% vs. 1.8% der Werte traten im Bereich ≥300 mg/dl bei erwachsenen und geriatrischen PatientInnen auf. Die mittlere verabreichte TDD war bei geriatrischen PatientInnen niedriger als bei erwachsenen PatientInnen. Nach dem sechsten Studientag erhielten geriatrische PatientInnen einen höheren Anteil an kurzwirksamen Insulin als erwachsene PatientInnen. Die vorgeschlagene Startdosis unterstützte in beiden Altersgruppen eine wirksame und sichere BZ-Kontrolle [4].

Das Ziel der **Studie 7** war die umfassende Konzeptentwicklung zur Insulinanpassung durch Pflegepersonen, welches die Vereinfachung des Prozesses und Vorgehens bei kritischen Situationen beinhaltet. Basierend auf

dem gesetzlichen Rahmen von Österreich wurde eine Kooperation mit dem Gesundheitsministerium gestartet. Das Ministerium gab an, dass die Insulinanpassung durch die Pflege unter definierten Bedingungen erlaubt ist. Diese werden als Feature im GlucoTab implementiert. Dieses Feature erweist sich als relevanter Meilenstein der österreichischen Pflegeprofession, da erstmalig die Insulinanpassung durch Pflegepersonen mithilfe eines elektronischen Systems erlaubt ist.

Kapitel 4 fasst die Ergebnisse der Doktorarbeit zusammen und diskutiert diese. Fortlaufende Projekte und Empfehlungen zu zukünftigen Forschungsgebieten bezogen auf das GlucoTab System werden präsentiert.

CHAPTER 1

GENERAL INTRODUCTION

GENERAL INTRODUCTION

This chapter presents the general background information of this doctoral thesis. The research gaps and the overall aims are presented subsequently. Finally, the aims of the conducted studies and the outline of the doctoral thesis are illustrated.

GENERAL BACKGROUND

Diabetes as a common co-morbid condition in hospitalised patients places serious financial burden to hospital management costs and public health care systems. Approximately 22% of all patients being admitted to a hospital in the US, and up to 35% admitted in England have been previously diagnosed with diabetes. In the year 2014 up to 8% of all hospitalised patients at the hospital of the Medical University of Graz suffered from diabetes, making glycaemic management an important part of routine care in most hospital wards [5–8].

Hospitalised patients have been reported to experience hyperglycaemic events with BG values exceeding 200 mg/dl. Even in patients who are not admitted for elevated BG values, diabetes complications and suboptimal glycaemic management can lead to adverse clinical outcomes [5, 9, 10]. Patients with diabetes have an increased risk of infections [11], prolonged hospital stays and increased mortality. There is little agreement, as to whether these associations reflect either the effects of the quality of glycaemic management or rather the severity of illness [8, 12]. In 2014, hospitalised patients with diabetes compared with non-diabetes patients had a longer hospital stay (6.9 vs. 4.6 days) [7] and a higher mortality rate (1.93% vs. 1.20%), respectively at the hospital of the Medical University of Graz[1].

[1] Unpublished data are described in following internal report „Diab-Curve: Vergleich der Verweildauer von Patienten mit gleicher nicht diabetes relevanter Hauptdiagnose“ (Pak A, 03.07.2015, LKH-Univ.Klinikum Graz, Stabstelle Controlling)

In 2013, bedside data from more than 14,000 inpatients at 211 sites in England demonstrated that almost 28% of hospitalised patients with insulin therapy had at least one medication management error in the last 7 days of hospital stay. For example insulin therapy was not adjusted when BG was persistently higher than 200 mg/dl and a better glycaemic control would have been appropriate [6].

GUIDELINE RECOMMENDATIONS

A recent systematic review and meta-analysis of randomised and observational studies that had evaluated the effect of intensive glycaemic control in the non-critical hospital wards, found a benefit by reducing the risk of hospital-acquired infections [11]. This has led to growing interest in improving the quality of glycaemic management in hospitals [13, 14]. Glycaemic management in hospitalised patients with diabetes aims to avoid both hypo- and hyperglycaemic episodes and keep BG values within a certain range [15–19].

Guidelines have been developed to improve glycaemic management in hospitals. In general wards, most recent guidelines recommend a target range of less than 140 mg/dl for pre-meal BG and less than 180 mg/dl for a random BG for the majority of non-critically ill patients treated with insulin. These guidelines consider the implementation of a standardised subcutaneous insulin therapy as a key intervention. Target ranges should be achievable by scheduled subcutaneous insulin dosing with basal, nutritional and a correctional component [20, 21]. These recommendations were considered within this doctoral thesis. However, it should be noted that the American Diabetes Association recently recommended modified glycaemic target ranges for non-critically ill patients with diabetes in the hospital. A target range of 140-180 mg/dl for the majority of non-critically ill patients is recommended by using a basal plus a correctional bolus insulin therapy as the preferred method in patients with poor nutritional intake. An insulin therapy with basal, nutritional and correctional insulin is the preferred method for patients with good oral intake [22].

The guidelines also suggest the development and evaluation of evidence-based computerised decision support systems, including computerised insulin and BG data display that will not only improve glycaemic control but also workflow aspects and communication among health care professionals. Integrated decision support

strategies and systems should guide health care professionals in the glycaemic management process [12].

RESEARCH GAPS

Five gaps in the research of glycaemic management in the hospitals were identified before the thesis was started and are summarised as follows:

1. Many studies reported hyperglycaemia in patients with diabetes in the hospital setting [23, 24]. However, in Austrian hospitals and at the hospital of the Medical University of Graz (LKH-Univ.Klinikum Graz) the quality of glycaemic management was not yet assessed.

2. Standardised interventions, e.g. paper-based algorithms for basal-bolus insulin therapy, in the hospital setting were developed. These algorithms increased the quality of glycaemic control and reduced hospital complications in patients with type 2 diabetes [25–27]. Based on these results, international guidelines recommend the implementation of a standardised basal-bolus insulin therapy regime [20, 21]. Such algorithms have not yet been implemented at the LKH-Univ.Klinikum Graz [1].

3. International guidelines recommend the development and evaluation of computerised decision support systems to guide health care professionals in glycaemic management processes in the hospital setting [12]. However, user-friendly clinical decision support systems for health care professionals have not yet been developed and implemented in routine care at general hospital wards.

4. International guidelines recommend glycaemic target ranges depending on patient's age and health status. In addition, guidelines highlight that the prevention of hypoglycaemic events is the most important treatment goal in geriatric patients [22]. The evaluation of the efficacy and safety of well-established basal-bolus insulin algorithms in patients with diabetes in different age groups was missing.

5. In Austria, nurses *(Angehörige des gehobenen Dienstes für Gesundheits- und Krankenpflege)* were so far not legally allowed to perform insulin therapy adjustments [28]. A strategy should be developed enabling nurses to legally perform insulin therapy adjustments by using standardised protocols.
These are the research gaps which this doctoral thesis attempts to close with the studies performed at the hospital of the Medical University of Graz, Austria.

AIMS OF THIS DOCTORAL THESIS

The overall aims of the doctoral thesis are

(1) to determine the **quality of state of the art** of glycaemic management in the hospital,
(2) to evaluate a **paper-based algorithm** for basal-bolus insulin therapy in hospitalised patients with type 2 diabetes,
(3) to evaluate **a computerised clinical decision support system** (GlucoTab system) in patients with type 2 diabetes at a general hospital ward for the first time,
(4) to evaluate the **GlucoTab system** in patients with type 2 diabetes at **different general wards**,
(5) to evaluate the **GlucoTab system** in patients with type 2 diabetes in hospital **routine care**,
(6) to evaluate the GlucoTab in patients **with different age groups** and
(7) to develop a concept for **insulin therapy adjustment by nurses**.

Based on each aim, the following goals/studies were deduced and defined to guarantee a continuous development and evaluation process. The aims are the focus of seven studies, which were carried out within the framework of two research projects (EU project REACTION, FP7 248590; FFG project: Research Studio Austria *GlucoTab*, 844737). The detailed aims of the studies conducted are demonstrated below and in Figure 1.

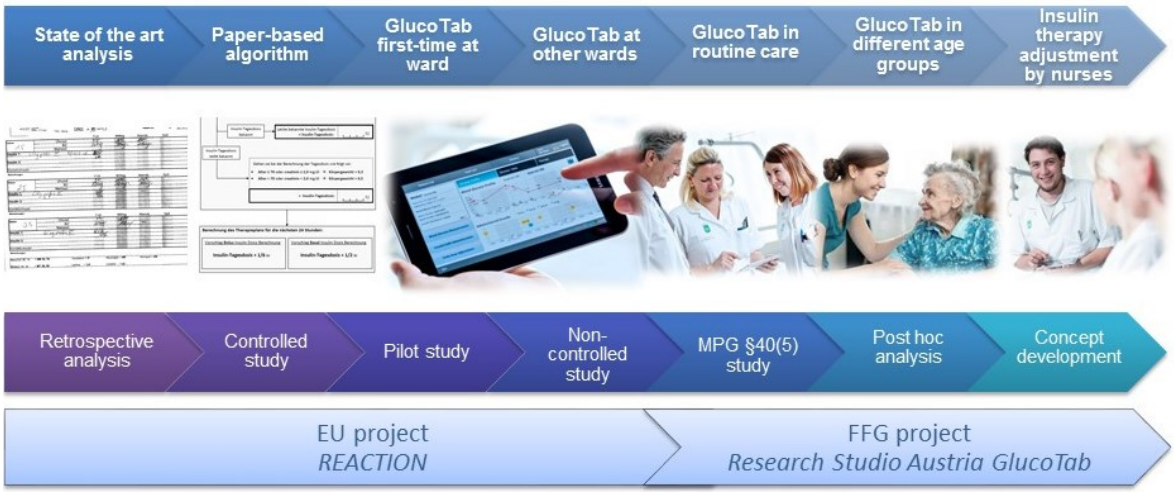

Figure 1 Overall aims of the conducted studies

Study 1: State of the art analysis

The aim of this retrospective study was to determine the current quality of clinical glycaemic management at two internal medicine wards (Endocrinology and Cardiology) at the Medical University of Graz. Data from patients who had received diabetes treatment were analysed in the context of the most recent international recommendations regarding BG values. Additionally, 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 hospital stay [1].

Study 2: Paper-based algorithm

The aim of the proof-of-concept study was to assess the efficacy, workflow integration, and usability of a paper-based algorithm in hospitalised patients with type 2 diabetes. As a first step, a previously published insulin dosing algorithm for basal-bolus therapy [25–27] was customised to account for complex processes during inpatient care and was then integrated into the workflow of a general internal medicine ward [2].

Study 3: First-time GlucoTab in clinical practice

Within this study, the GlucoTab system was used in clinical practice for the first time. Therefore, the primary aim of the feasibility study was to evaluate the performance (safety) of the GlucoTab system by investigating the percentage of actions the GlucoTab system supported either to capture BG values or provide insulin dose suggestions according to the algorithm.
Secondary aims of the feasibility study were to compare the efficacy and safety of two versions of the computerised algorithm for basal-bolus insulin therapy for glycaemic management in hospitalised patients with type 2 diabetes and to assess the usability of the GlucoTab system [29, 30].

Study 4: GlucoTab at general wards

The aim of this study was to investigate the efficacy, safety and usability of standardised glycaemic management with the GlucoTab system for non-critically ill patients with type 2 diabetes. The final mobile version of the GlucoTab system was used for the first time to guide the glycaemic management process at four different general wards in divisions of internal medicine and surgery [3]. This study was the basis for the CE marking of the GlucoTab system as a medical device.

Study 5: GlucoTab in routine care

The GlucoTab system was implemented for standardised glycaemic management in routine care at three general wards for the first time. The aim of the study was to investigate risks of the routine use of the GlucoTab system, assessed by the percentage of BG values <70 mg/dl and ≥300 mg/dl, for glycaemic management in non-critically ill patients with type 2 diabetes at general wards. To further evaluate the GlucoTab in hospital routine care efficacy, safety and usability parameters were analysed.

Study 6: GlucoTab in different age groups

The aim of this analysis was to investigate the efficacy and safety of the standardised glycaemic management supported by the computerised algorithm of the GlucoTab system in adult (<70 years) and geriatric (≥70 years) patients with diabetes in the hospital [4].

Study 7: Insulin therapy adjustment by nurses

The aim was to develop a comprehensive concept for insulin therapy adjustments by nurses including workflow simplifications and how to react in critical situations of glycaemic management in the hospital. The feature insulin adjustment by nurses should simplify the workflow of glycaemic management, reduce the time required and reduce workflow and medication errors by minimising interfaces between health care professionals.

STRUCTURE OF THE DOCTORAL THESIS

The doctoral thesis consists of four chapters. Chapter two provides an overview of the methodological aspects of the studies conducted. Chapter three includes the studies according to the seven research aims. These chapters have been published, accepted or submitted as scientific journal publications or abstracts for international conferences. Chapter four provides a general discussion, reflects the findings of the prior described studies and presents ongoing projects and recommendations related to GlucoTab research.

CHAPTER 2

GENERAL MATERIALS AND METHODS

GENERAL MATERIALS AND METHODS

This chapter provides a general overview of the *Mode-2-Science* method and the methodical approach of the different studies. The design, sample, setting, data collection and analysis of the studies are described in Table 1. A detailed description of the methodical approach of the studies can be found in Chapter 3.

All studies were prepared and conducted in a multidisciplinary research team including engineers, researchers, nurses and physicians of three institutions (Medical University of Graz, Joanneum Research, and LKH-Univ.Klinikum Graz). The principles of cooperation are based on *Mode-2-Science*, a new approach to knowledge production [31], to fulfill the aims of the project.

MODE-2-SCIENCE – THE GENERAL METHODICAL APPROACH

Mode-2-Science suggests that new knowledge is always produced in the context of an application, in this case the hospital setting, and that different professions and experts work together to solve complex research questions in a complex setting. Therefore, *Mode-2-Science* is not limited to researchers who ask specific academic questions but it can also be applied to problems in routine care which are described in Chapter 1 [31, 32]. In this thesis, a multidisciplinary team from the fields of clinical research and clinical practice worked together to identify and characterise a problem (poor glycaemic management in the hospital) and to find an appropriate solution.

The implementation of the specific characteristics of *Mode-2-Science* is illustrated below:

Application orientation: A flexible research strategy is defined by scientific problems which arise in the context of an application. *Mode-2-Science* considers producing knowledge which is practical und useful for routine care [31, 32]. Additionally, results should be socially distributed. In Studies 1 to 7, health care professionals were invited to participate in research meetings to identify requirements and problems in routine care of glycaemic management in the hospital.

Transdisciplinarity: *Mode-2-Science* brings together different disciplines in a temporary nature of a *Mode-2* working style. The transdisciplinary knowledge of *Mode-2-Science* is based on the expertise of individual researchers but also on the whole research team. The transdisciplinary research team is motivated to find consensus in the context of the specific application. Individual professions and institutional differences of the Medical University of Graz, Joanneum Research and LKH-Univ.Klinikum Graz are no longer relevant. Transdisciplinarity includes the application-oriented development, which guides the process of problem solving. In addition, transdisciplinary teams are able to use individualised and innovative structures, research methods, terminologies and dissemination strategies. Transdisciplinarity is dynamic and needs active and intensive communication between the different professions – in our case the researchers, engineers and health care professionals [31, 32].

Heterogeneity: Another characteristic of *Mode-2-Science* is heterogeneity which is not only defined by the multidisciplinary research team which combines different experiences, knowledge and skills but also the heterarchic and transient structure of research teams. Research results are produced in collaboration and together with different institutions [31, 32].

Reflectivity: The *Mode-2-Science* approach is highly reflective by changing the role of knowledge in social relations. The application-oriented approach increases the sensibility of social consequences of research results due to the cooperation with health care professionals. Additionally, requirements and wishes of different professions and institutions are known during *Mode-2-Science* and change

awareness of problem solving and responsibility. This positively influences the scientific reflection of the research team [31, 32].

Quality control: Novel forms of quality control are used based on the application-oriented approach. Not only scientific peers, but also users and target groups perform quality control. The quality is characterised based on results and consequences. Novel types of quality controls can also include for example public institutions [31, 32] (e.g. usability test and questionnaires with health care professionals Gesundheitsfonds Steiermark: Salus 2015- Steirischer Qualitätspreis für Gesundheit).

Table 1 Overview of the methodical approach of the studies (topic, design, setting, sample, data collection, data analysis)

	Topic	Design	Setting	Sample	Data collection	Data analysis
Study 1	State of the art analysis	Retrospective analysis of patient records	Hospital, 2 general wards (Endocrinology, Cardiology)	50 patients with diabetes	Review of patient records during hospital stay (BG values, glycaemic management effort), online questionnaire for nurses	Descriptive statistics
Study 2	Evaluation of paper-based algorithm	Ward-controlled study	Hospital, 2 general wards (Endocrinology: algorithm group, Cardiology: control group)	74 patients with type 2 diabetes	Patients were allocated per ward Algorithm group: study was performed during hospital stay, questionnaire for nurses Control group: data from patient record during hospital stay	Descriptive statistics
Study 3	Evaluation of performance of GlucoTab for the first time at ward	Feasibility study	Hospital, general ward (Endocrinology)	30 patients with type 2 diabetes	Patients were treated with the GlucoTab system during hospital stay, data were collected with the GlucoTab and in patient record, questionnaire for health care professionals	Descriptive statistics
Study 4	Evaluation of efficacy, safety and usability of the GlucoTab at general wards	Non-controlled study	Hospital, four general wards (Endocrinology, Cardiology, Nephrology, Plastic Surgery)	99 patients with type 2 diabetes	Patients were treated with the GlucoTab system during hospital stay, data were collected with the GlucoTab and in patient record, questionnaire for health care professionals	Descriptive statistics, Regression model
Study 5	Evaluation of efficacy, safety and usability of GlucoTab in routine care	MPG §40(5) study	Hospital, three general wards (Endocrinology, Cardiology, Plastic Surgery)	92 patients with type 2 diabetes	Patient records during hospital stay were collected	Descriptive statistics
Study 6	Evaluation of the efficacy and safety of the GlucoTab in different age groups	Post hoc analysis	Hospital, four general wards (Endocrinology, Cardiology, Nephrology, Plastic Surgery)	191 patients with type 2 diabetes	Patient data of Study 3, 4 and 5 were collected	Descriptive statistics
Study 7	Concept development of insulin therapy adjustment by nurses	Concept development	Hospital	nurses	Cooperation with *Bundesministerium für Gesundheit*, nursing head of LKH-Univ.Klinikum Graz	-

CHAPTER 3

RESULTS – FINDINGS

The following chapter includes detailed information of study 1-7.

STUDY 1 – STATE OF THE ART ANALYSIS

Main results were published in a scientific peer-reviewed journal.

Failure to control hyperglycaemia in non-critically ill diabetes patients despite standard glycaemic management in a hospital setting

Neubauer KM, Schaupp L, Plank J, Augustin T, Mautner SI, Tschapeller B, Pieber TR

Published in: J Diabetes Sci Technol 2013, 7:402–409

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STATE OF THE ART ANALYSIS OF GLYCAEMIC MANAGEMENT

Successful control of hyperglycaemia has been shown to improve clinical outcomes for patients with diabetes in the hospital [25–27]. Glycaemic target ranges and specific recommendations of glycaemic management in the hospital provide a first guideline to improve glycaemic control in general hospital wards. However, to identify the need for improvement, an analysis of the current glycaemic management process has to be individually performed for each ward [1].

AIM OF STATE OF THE ART ANALYSIS

The aim of this study was to determine the quality of clinical glycaemic management at two internal medicine wards at the Medical University of Graz retrospectively. Data from patients who had received diabetes treatment were analysed in the context of the most recent international recommendations regarding BG values. To further characterise the glycaemic management during 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 hospital stay. In addition, nurses at both wards were asked to fill out a questionnaire regarding the current procedures of glycaemic management [1].

METHODICAL APPROACH OF STATE OF THE ART ANALYSIS

This retrospective study was approved by the ethical board of the Medical University of Graz (protocol number EK-No. 21-485 ex 09/10) and performed by using data from 50 non-critically ill patients with diabetes consecutively admitted to the Endocrinology and Cardiology wards of the Medical University of Graz. The two wards had a similar structure and used a physician-based routine care regarding glycaemic management, but neither ward had standardised processes of glycaemic management in place. Capillary BG values were measured by using a point-of-care testing device (Accu-Chek® Inform System, Roche Diagnostics, Rotkreuz, 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 out an online questionnaire about current glycaemic management [1].

Statistical analysis

Patient data were analysed retrospectively regarding mean BG values and the percentage of BG values in the following ranges: <70 mg/dl (hypoglycaemic events), 70-140 mg/dl (target range), 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 G*lucometrics* method for analysing in-hospital BG data [33]. 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, the first half of each patient's hospital stay to the second half was compared with respect to glycaemic management effort, but no comparison was attempted between the two wards [1].

Data are presented as mean ± SD if not stated otherwise. Since most of the data did not follow a normal distribution, Wilcoxon signed rank tests were used for statistical analyses. The level of significance was set to 5%. Statistical analysis was performed using R version 2.13.1 [1, 34].

RESULTS OF STATE OF THE ART ANALYSIS

Patient records of 50 consecutively admitted patients with diabetes were analysed over a four-month period. Clinical characteristics, insulin therapy, admission and discharge data for all patients with diabetes are shown in Table 2 [1].

Efficacy and safety of glycaemic control

The mean BG values for patients with diabetes at Endocrinology and Cardiology wards were clearly above the recommended target of 140 mg/dl for pre-meal measurements. The mean BG values remained above the target from admission until hospital discharge (Figure 2) [1].

When comparing several different *Glucometrics* analyses [33] (Table 3), 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, 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 [1].

There was no significant difference in the mean BG values of patients with diabetes in either ward 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 vs. 170 ± 42 mg/dl, P=0.51) [1].

Most patients with diabetes at the Endocrinology ward (n=21) had BG ≥140 mg/dl in the first half of hospital stay (Table 4). Standard glycaemic management did not result in a lowered BG value to the recommended target range for 16 of these 21 patients with diabetes. Similarly, at the Cardiology ward, 17 out of 21 had BG values of ≥140 mg/dl in the first half of hospital stay that remained ≥140 mg/dl in the second half of hospital stay. Furthermore, glycaemic control (<140 mg/dl within first half) deteriorated in one patient in each ward [1].

Table 2 Clinical characteristics of the study population - 50 patients with diabetes [1]

Ward	**Endocrinology (n=25)**	**Cardiology (n=25)**
Gender, female (n/%)	14/56	14/56
Ethnicity, Caucasian (n)	25	25
Age (years)	70 ± 15	72 ± 9
Body Mass Index (kg/m^2)	28.5 ± 5.4	28.2 ± 6.5
Diabetes type: 2/1	22/3	25/0
HbA1c		
mmol/mol	65 ± 4	58 ± 15
%	8.1 ± 1.8	7.5 ± 0.8
Pre-admission diabetes therapy (n/%)		
Diet only	0/0	1/4
Insulin only	16/64	20/80
Insulin, other antidiabetic drugs	9/36	4/16
Diabetes therapy during stay (% of patients)		
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 type		
Planned	3	12
Acute	22	13
Admission diagnosis (n)		
Cardiovascular disease	10	22
Endocrine disease	8	0
Infectious disease	4	2
Pulmonary disease	1	1
Gastrointestinal disease	1	0
Nephrological disease	1	0
Length of hospital stay (days)	10 ± 5	11 ± 8
Discharge to (n)		
Home	23	19
Nursing home	2	0
Transfer to other hospital	0	6

Mean ± SD

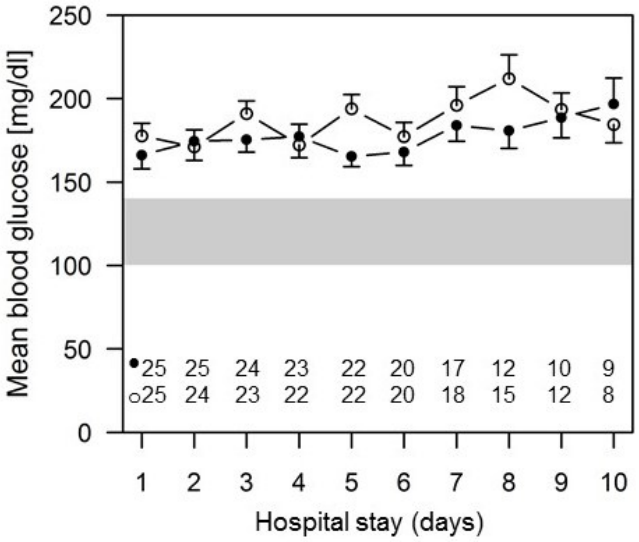


Figure 2 Mean BG ± SEM (standard error of the mean) per day in patients with diabetes at Endocrinology (•) and Cardiology (○). Grey range indicates BG limits 100 mg/dl and 140 mg/dl.

Table 3 *Glucometrics* analyses of BG values analysed per population, per patient-day and patient-stay following Goldberg et al. 2006 [1, 33]

Glucometrics analyses	**Per popluation**		**Per patient-day**		**Per patient-stay**	
Ward	**Endo**	**Cardio**	**Endo**	**Cardio**	**Endo**	**Cardio**
Sample size (n)	646	832	240	264	25	25
Mean BG measurements	-	-	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
BG in different ranges (%)						
<70 mg/dl	0.9	0.6	2.9	0.8	0.0	0.0
70-140 mg/dl	31.7	27.3	24.2	20.5	20.0	20.0
70-180 mg/dl	56.7	50.6	59.6	48.5	64.0	56.0
>180 mg/dl	42.4	48.8	37.5	50.8	36.0	44.0
>300 mg/dl	4.2	4.9	1.3	1.1	0.0	0.0

Mean ± SD (standard deviation)

Table 4 2x2 table showing the number of patients with diabetes with mean BG values above and within the 140 mg/dl target range during the first and the second half of hospital stay [1]

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

Glycaemic management effort

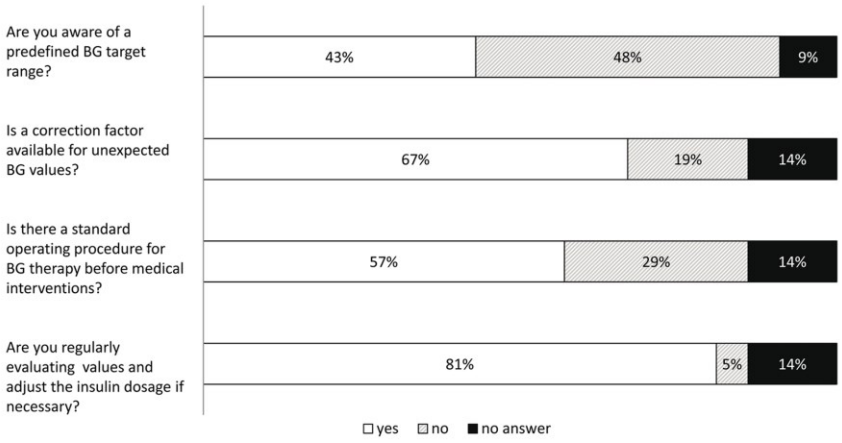
All but one patient received insulin therapy during the hospital stay (Table 2). At both wards, the use of bolus and premixed insulin was predominant, whereas a combination therapy of basal or premixed insulin together with flexible prandial insulin was used less often. Insulin dosage in both wards did not differ between first half and second half of hospital stay (Endocrinology 15 ± 14 vs. 15 ± 13 units insulin per day, *P*=0.87, Cardiology 27 ± 17 vs. 27 ± 18 units insulin per day, *P*=0.92). Additionally, there was no difference in the mean number of insulin injections per day neither in the Endocrinology ward (1.4 ± 1.0 vs. 1.3 ± 0.8, *P*=0.42) nor in the Cardiology ward (1.5 ± 0.7 vs. 1.4 ± 0.8, *P*=0.46) but a tendency for less BG measurements was observed between first and second half of hospital stay (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) [1].

In 16 patients with diabetes (Endocrinology: seven patients, Cardiology: nine patients) with hyperglycaemic values (mean BG per 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 of stay 25.1 ± 18.5 vs. second half of stay 26.6 ± 18.1 units, *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 with diabetes [1].

Questionnaire about state of the art glycaemic management

21 nurses of both wards completed an online anonymous questionnaire. More than 80% of the nurses reported that BG values and insulin therapy are regularly evaluated. Standardised processes regarding glycaemic management in case of "nothing per mouth" orders were familiar to 57% of the nurses. Although two-thirds stated that correctional insulin doses for higher BG values are prescribed, less than 50% could specify the glycaemic target range for the correctional scheme. Moreover, the stated target ranges for a specific type of BG measurements (average, fasting, pre-meal) showed high variability (Figure 3) [1].

A



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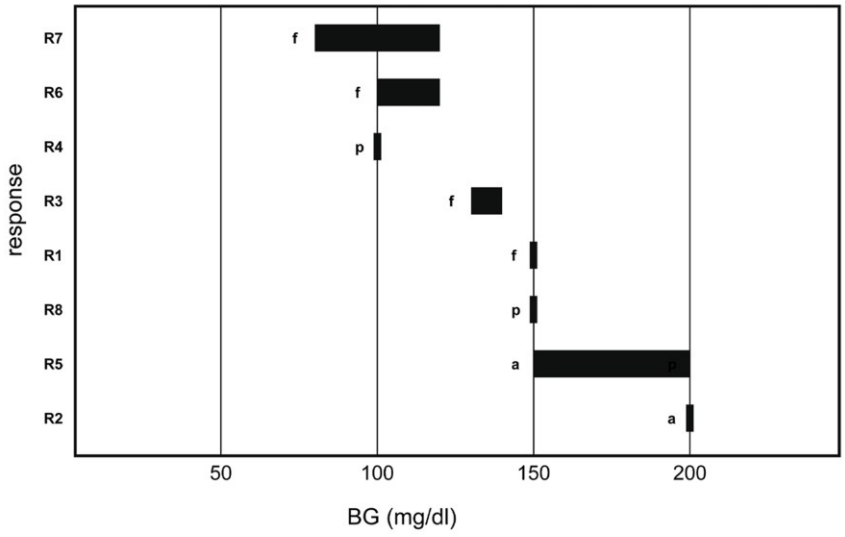

Figure 3 (A) Results of the questionnaire about current glycaemic management. (B) BG target ranges stated by eight nurses defining the type of BG measurement either as fasting (f), average (a) or pre-meal (p) [1]

SUMMARY OF STATE OF THE ART ANALYSIS

Successful control of hyperglycaemia has been shown to improve outcomes for patients with diabetes in the hospital. Glycaemic target ranges provide a first guideline to improve glycaemic control. However, to identify the need for improvement, a review of patients' record of the current glycaemic management has to be performed individually at each hospital ward.

In Study 1, the quality of a physician-based glycaemic management was assessed retrospectively in 50 patients with diabetes at two general wards (Endocrinology, Cardiology) considering the most recent guideline recommendations for glycaemic control in non-critically ill patients with diabetes. BG values, glycaemic management effort and an online questionnaire for nurses were analysed.

BG values were clearly above the recommended glycaemic target range. When comparing the first and the second half of hospital stay, no difference in glycaemic control and insulin dose was found, despite frequent BG measurements per day at both wards. A lack of clearly defined BG target ranges was demonstrated in the nurses' questionnaire.

At Endocrinology and Cardiology ward the recommended BG target range was not achieved. Results of Study 1 demonstrated considerable glycaemic management effort, but also a lack of an adequate insulin therapy. Therefore, the implementation of a standardised glycaemic management strategy (including correctional schemes, structured treatment protocols, target ranges etc.) is essential.

STUDY 2 – PAPER-BASED ALGORITHM

Main results were published in a scientific peer-reviewed journal.

Efficacy, usability and sequence of operations of a workflow-integrated algorithm for basal-bolus insulin therapy in hospitalised type 2 diabetes patients

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*these authors contributed equally to this study

Published in: Diabetes Obes Metab 2014, 16:137–146

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PAPER-BASED ALGORITHM FOR GLYCAEMIC MANAGEMENT

Considerable efforts are made to improve glycaemic management regarding BG measurements in the hospital. However, an adequate insulin therapy in hospital routine care is still lacking in many hospitals [1, 12].

Developed paper-based algorithms for basal-bolus insulin therapy in the hospital setting increase the quality of glycaemic control and reduce hospital complications in patients with type 2 diabetes [25–27]. Therefore, guidelines recommend the implementation of a standardised basal-bolus insulin therapy as a key intervention [20, 21].

AIM OF STUDY 2: PAPER-BASED ALGORITHM

The aim of the proof-of-concept study was to assess the efficacy, workflow integration and usability of a paper-based algorithm in hospitalised patients with type 2 diabetes. As a first step, a previously published insulin dosing algorithm for basal-bolus therapy [25–27] was customised to account for complex processes during inpatient care and was then integrated into the workflow of a general internal medicine ward [2].

METHODICAL APPROACH OF EVALUATION OF PAPER-BASED ALGORITHM

The controlled study was conducted at two general wards at the hospital of the Medical University of Graz, Austria. At both wards the state of the art analysis (Study 1) found comparable and sustained BG values around 180 mg/dl in patients with diabetes independent of antidiabetic treatments [1]. In Study 2, a basal-bolus insulin algorithm-based treatment was implemented at one ward (Endocrinology) and compared to glycaemic management in routine care at another ward (Cardiology). Treatment allocation was not randomised to avoid biased treatment by algorithm trained health care professionals (physicians and nurses) [2].

Any patient admitted to either ward was eligible to be included in Study 2. Inclusion criteria were history of type 2 diabetes for at least three months (treated with diet, oral antidiabetic drugs (OADs), non-insulin injected antidiabetic drugs, insulin or any combination of the four therapies), age between 18 and 90 (both inclusive), BG in the range 140-400 mg/dl prior to inclusion and 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 [2].
For both groups, the study ended with hospital discharge, the transfer of the patient to another ward, or after 21 days of study duration. The study was approved by the ethical board of the Medical University of Graz (NCT01407289, EK-No. 23-351 ex 10/11) 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 had been explained and before any study-related activities were started [2].

Algorithm group (Endocrinology)

For the algorithm group, insulin therapy adjustment was performed according to a paper-based workflow-integrated algorithm. The paper-based algorithm, which

aims for fasting and pre-meal BG values in the range of 100-140 mg/dl, is based on a previously published algorithm by Umpierrez et al. [25–27] and has been further customised for future deployment in a clinical 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 health care professionals at a general ward. All health care professionals were trained in the correct use of the algorithm [2].

The paper-based algorithm was used to calculate the initial TDD based on patient's weight, age and renal function: 0.5 units per kg bodyweight in patients <70 years and with a serum creatinine value <2.0 mg/dl, the dose was reduced to 0.3 units per 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 antidiabetic 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 hours which was then confirmed by the attending physician during morning rounds (Figure 4A). The algorithm calculated the new TDD based on the dinner BG the day before and that day's breakfast BG following a new scheme for all possible combinations of BG values (Figure 4A, middle panel) [2].

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 (Figure 4A, lower panel). At noon, the basal insulin dose (i.e. the half of the calculated TDD) was administered as the long-acting insulin analogue (insulin glargine, Sanofi-Aventis, Frankfurt am Main, Germany). The bolus insulin dose (insulin aspart, NovoNordisk, Bagsværd, Denmark) was further divided into three equal doses (suggested bolus dose) that were administered at breakfast, lunch and dinner. 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 [2].

In case pre-meal BG values were out of target range the paper-based algorithm adjusted the suggested bolus dose further by using insulin sensitivity and the current BG value (corrective bolus dose, Figure 4B). Insulin sensitivity (sensitive,

normal, resistant) was assessed by the attending physician during each morning round [2]. At any time nurses were able to modify the paper-based algorithm-calculated insulin dose. If patients were placed on nothing per mouth orders, bolus insulin was withheld and only basal insulin was administered [2].

Routine care group (Cardiology)

Glycaemic management in the routine care group was performed by the attending health care professionals using OADs, insulin or a combination of both [2].

initial TDD	TDD: **48 units**	yesterday lunch (units)	yesterday dinner (units)	yesterday bedtime (units)	today breakfast (units)
	basal insulin (TDD/2)	**24**			
	bolus insulin (TDD/2/3)	**8**	**8**		**8**
	BG (mg/dl)	166	138	142	191

		breakfast: **191** mg/dl			
dinner: **138** mg/dl	BG range (mg/dl):	70-100	101-140	141-180	>180
	70-100	-10%	± 0%	± 0%	± 0%
	101-140	± 0%	± 0%	± 0%	+ 10%
	141-180	± 0%	± 0%	+ 10%	+ 10%
	>180	± 0%	+ 10%	+ 10%	+ 20%
	if BG ≤70mg/dl reduce next 24 hours TDD by 20%				

new TDD	next 24 hours TDD: **52** units	today lunch (units)	today dinner (units)	today bedtime (units)	tomorrow breakfast (units)
	basal-insulin (TDD/2)	**26**			
	bolus-insulin (TDD/2/3)	**9 (8 + 1)**	**8**		**9 (8 + 1)**

Figure 4 Sequence of operations of the paper-based workflow-integrated algorithm [2]

(A) Calculation of the suggested insulin dose (example): The physician uses the algorithm to calculate a TDD based on yesterday's dinner (138 mg/dl) and today's breakfast (191 mg/dl) BG values. In the example, the TDD is increased by 10%, resulting in a TDD of 52 units for the next 24 hours. The TDD is then split into half basal dose (26 units) and half bolus dose (26 units). The bolus dose is then divided into three equal parts (8 units, suggested dose). Any remaining bolus insulin units are added consecutively to the breakfast or lunch bolus (+1 unit to breakfast and +1 unit to lunch). If any BG value is <70 mg/dl, the TDD is reduced by 20% irrespective of the other BG values

Insulin sensitivity	O sensitive	O normal	O resistant
<70 mg/dl	no bolus insulin		
70–100 mg/dl	reduce suggested bolus insulin dose by 50%		
101–140 mg/dl	0	0	0
141–180 mg/dl	2	4	6
181–220 mg/dl	4	6	8
221–260 mg/dl	6	8	10
261–300 mg/dl	8	10	12
301–350 mg/dl	10	12	14
351–400 mg/dl	12	14	16
>400 mg/dl	14	16	18

(B) Calculation of corrective bolus insulin dose: Before each bolus insulin dose is administered, the nurse uses the algorithm to correct for insulin sensitivity and the current BG value (calculated bolus insulin dose=suggested dose + corrective dose). Insulin sensitivity is assessed as *sensitive*, *normal* or *resistant* by the physician during morning rounds. At bedtime only a corrective bolus dose will be calculated.

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 (Accu-Chek® Inform System, Roche Diagnostics, Rotkreuz, Switzerland) integrated into the hospital information system. Additionally, glycaemia in the algorithm group was monitored with a blinded continuous glucose monitoring system (CGM, iPro^{TM}2, Medtronic, Northridge, CA). 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 six days to allow CGM 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 calibrated retrospectively using the four daily capillary BG measurements [2].

In order to assess usability, 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 paper-based algorithm, attending nurses in the algorithm group completed a questionnaire regarding efficacy and usability of the algorithm at the end of the study [2].

Statistical 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 [26] and on the retrospective state of the art analysis, which was conducted at the two wards [1]. For sample size determination, it was anticipated that with algorithm treatment, the mean daily BG per treatment day could 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 correct for a drop-out rate of ~10% [26], 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 normal distribution 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. Wilcoxon's signed rank test was used 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 [2, 34].

RESULTS OF EVALUATION OF PAPER-BASED ALGORITHM

From July 2011 to April 2012, 1015 patients who were admitted to the two wards (545 patients at the ward of the algorithm group, 470 at the routine care ward), were assessed for eligibility. Out of 296 patients with BG values >140 mg/dl, 102 had no previously established diagnosis of diabetes, 29 had an expected hospital stay <48 hours, twelve had type 1 diabetes and two had steroid-induced diabetes, two patients had BG values >400 mg/dl, nine had advanced kidney or liver disease, five were older than 90 years, sixteen were mentally not able to give informed consent, three were terminally ill, nineteen were participating in another study and another seventeen were admitted to the wards at times when no staff for assessment or inclusion visits was present. Of the remaining 80 eligible patients, six did not give informed consent and, finally, 74 were included in the study. The algorithm and the routine group were well matched with a similar number of patients with pre-existing insulin therapy in both groups (Table 5). 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 routine care group (P=0.5). No patient died during hospital stay [2].

Table 5 Clinical characteristics of population of Study 2 (adapted from Mader et al. 2013 [2])

Patients (n)	**Algorithm Group (n=37)**	**Routine Group (n=37)**
Gender, female (n/%)	11/30	13/35
Ethnicity (Caucasian/other)	35/2	37/0
Age (years)	70 ± 12	67 ± 9
Body Mass Index (kg/m^2)	29.7 ± 6.8	30.5 ± 6.6
Weight (kg)	84 ± 19	88 ± 21
Serum creatinine (mg/dl)	1.5 ± 0.5	1.2 ± 0.4
HbA1c		
mmol/mol	76 ± 7	67 ± 4
(%)	9.1 ± 2.8	8.3 ± 1.8
Diabetes duration (years)	14 ± 12	12 ± 7
Pre-admission diabetes therapy (n/%)		
Diet only	5/13.5	4/10.8
OADs only	12/32.4	13/35.1
Insulin only	18/48.7	12/32.5
Insulin, OADs	2/5.4	8/21.6
Concomitant disease (n)		
Cerebrovascular disease	32	37
Infectious diseases	10	8
Renal disease	19	14
Other	1	1

All comparisons algorithm vs. routine care group n. s. except serum creatinine (P<0.01), not tested for discharge therapy, mean ± SD

Table 6 Efficacy and safety of patients in algorithm and routine care group (adapted from Mader et al. 2013 [2])

Patients per group (n)	Algorithm Group (n=37)	Routine Group (n=37)
Length of hospital stay (days)	13.6 ± 8.5	9.8 ± 5.9
Length of study (days)	7.5 ± 4.6	7.0 ± 4.4
Time to inclusion (days)	1.8 ± 2.4	2.0 ± 1.6
BG on inclusion (mg/dl)	204 ± 65	191 ± 41
Efficacy and safety		
Mean daily BG (mg/dl)	155 ± 46	184 ± 49
Mean pre-breakfast BG (mg/dl)	138 ± 21	163 ± 26
Mean pre-lunch BG (mg/dl)	190 ± 40	213 ± 49
Mean pre-dinner BG (mg/dl)	147 ± 41	191 ± 44
Mean bedtime BG (mg/dl)	144 ± 37	173 ± 43
BG in different ranges (%)		
70-<100 mg/dl	15	3
100-140 mg/dl	34	23
70-180 mg/dl	73	53
180-300 mg/dl	23	43
≥300 mg/dl	1	4
BG values in hypoglycaemic ranges (n)	1038	914
BG <70 mg/dl		
Number of patients (%)	11 (29.7)	1 (2.7)
Number of readings (%)	31 (3.0)	1 (0.1)
BG <60 mg/dl		
Number of patients (%)	5 (13.5)	0 (0.0)
Number of readings (%)	9 (0.9)	0 (0.0)
BG <40 mg/dl		
Number of patients (%)	1 (2.7)	0 (0.0)
Number of readings (%)	1 (0.1)	0 (0.0)
Antidiabetic therapy		
First calculated TDD (units)	43 ± 41	-
First TDD/kg of bodyweight (units)	0.49 ± 0.37	

Number of patients with BG <70 mg/dl (P<0.01), number of BG readings <60 mg/dl (P<0.01) and <70 mg/dl (P<0.001); length of study n.s., not tested for BG values/BG in different ranges/antidiabetic therapy; *the first and last study day is excluded for each patient, mean ± SD

Efficacy of paper-based algorithm

The percentage of BG values in the target range (100-140 mg/dl) was significantly higher in the algorithm group (34%) compared with the routine care group (23%, *P*<0.001). Similarly, a significantly higher percentage of patients in the algorithm group had BG values between 70-180 mg/dl (73% vs. 53%, *P*<0.001). The percentage of BG values in the different ranges can be found in Table 6 and Figure 5 [2].

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). 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 6). None of the events was associated with unconsciousness or required intravenous glucose infusion. In the routine care group no BG value was <60 mg/dl. For the entire study population no hypoglycaemia related adverse outcomes were reported [2].

A Algorithm group **B Routine group**

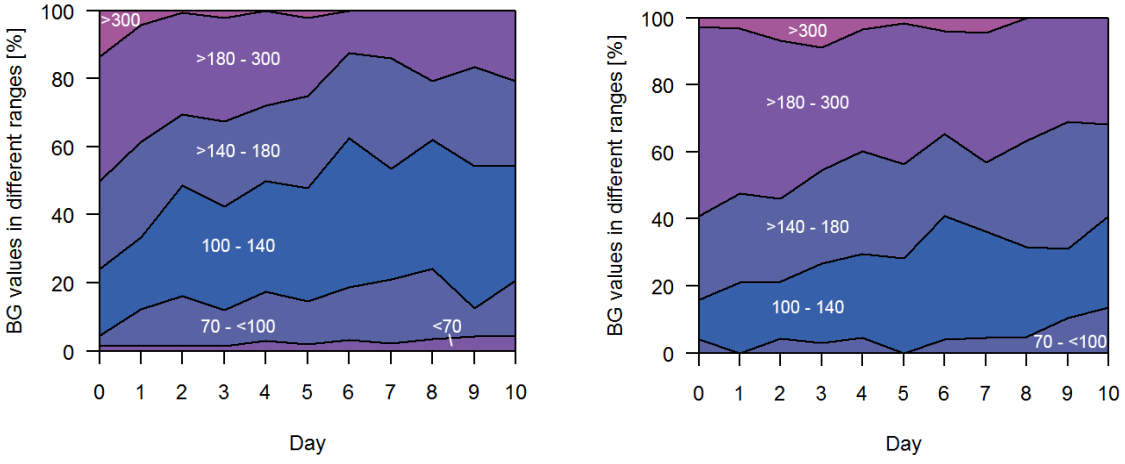


Figure 5 Distribution of BG values in different ranges during the study treatment [2]

Antidiabetic therapy

In the algorithm group the mean TDD was 41 ± 30 units. The mean daily bolus insulin dose (23 ± 16 units) was significantly higher than the mean daily basal insulin dose (19 ± 14 units, P<0.001, Figure 6B). In the routine care group 24 patients were on OAD during the hospital stay. The mean daily insulin dose was 20 ± 16 units in 28 patients receiving any insulin therapy during the hospital stay (Figure 6C). In the routine care group no basal insulin was given to patients without pre-existing insulin therapy at any time (Figure 6C, right panel) [2].

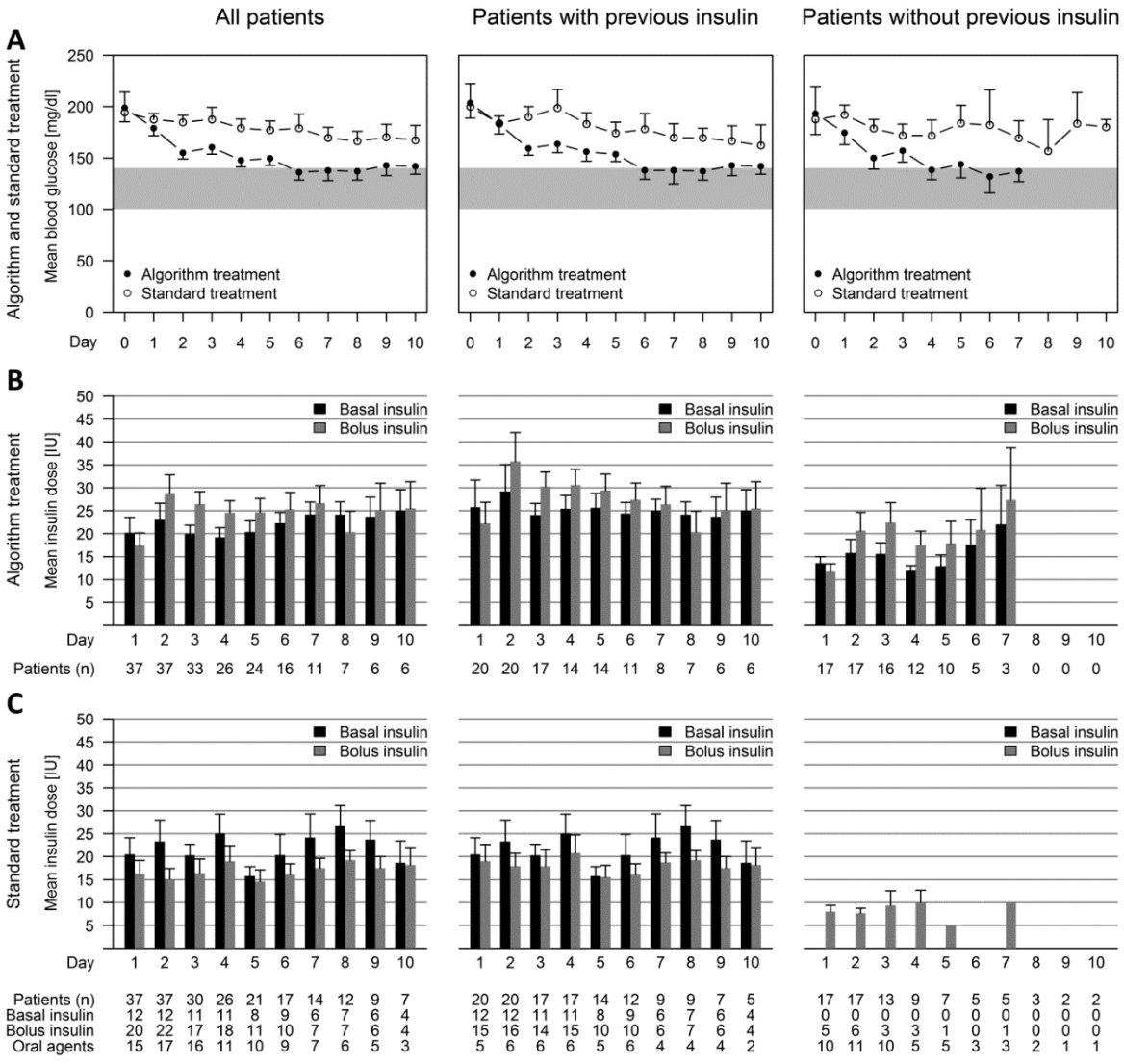


Figure 6 (A) Mean daily BG values during 10 days of hospital stay. (B) Mean daily administered basal and bolus insulin dose in the algorithm group. (C) Mean daily administered basal and bolus insulin dose and number of OAD in the routine care group [2]

All patients (left), patients with pre-existing insulin therapy (middle) and patients without pre-existing insulin therapy (right); all data are mean ± SEM

There was a 95% physicians' adherence to the algorithm-calculated TDD and a 98% nurses' adherence to the algorithm-calculated basal dose and 93% nurses' adherence to the algorithm-calculated bolus dose. High adherences were observed during the whole treatment period and there were no differences, when the first half of stay was compared to the second half (*P*>0.05) (Figure 7) [2].

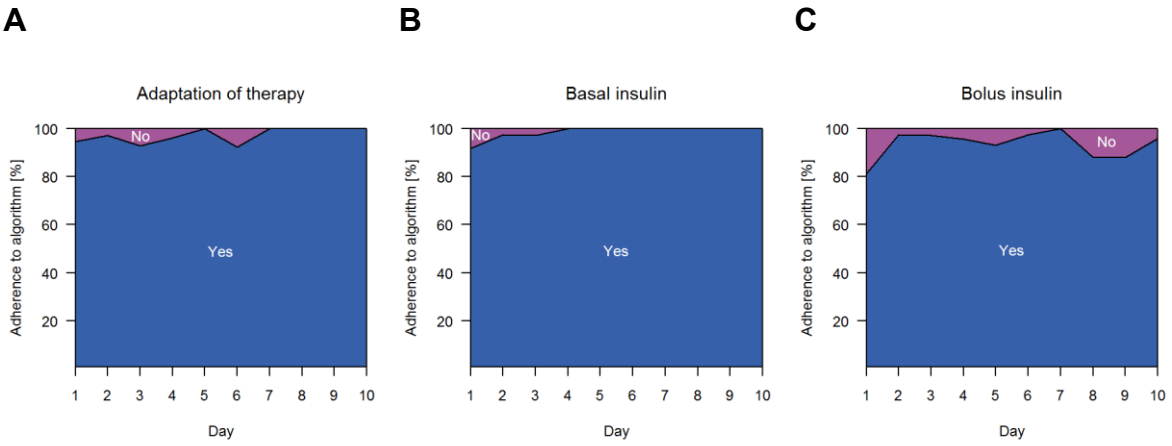


Figure 7 Health care professionals' adherence to paper-based algorithm. (A) Physicians' adherence to algorithm calculated TDD. (B) Nurses' adherence to calculated basal insulin dose. (C) Nurses' adherence to calculated bolus insulin dose [2]

24 hour CGM profile

In the algorithm group 32 out of 37 patients (86%) were monitored using CGM. Two of the five patients without CGM data were not willing to use a CGM (two patients lacked subcutaneous adipose tissue, one patient lost the sensor during the study period). 88.2% of the study period (in total 5132 hours) were monitored with CGM. 24 hours CGM profiles and bolus BG values showed pronounced breakfast BG excursions and subsequently higher lunch BG values (Figure 8A) [2]. 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 8A). 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 vs. 15:30-17:00, *P*<0.05).

Algorithm application

The administered bolus insulin doses as calculated by the paper-based algorithm (suggested and corrective component) are given in Figure 8B [2].

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) [2].

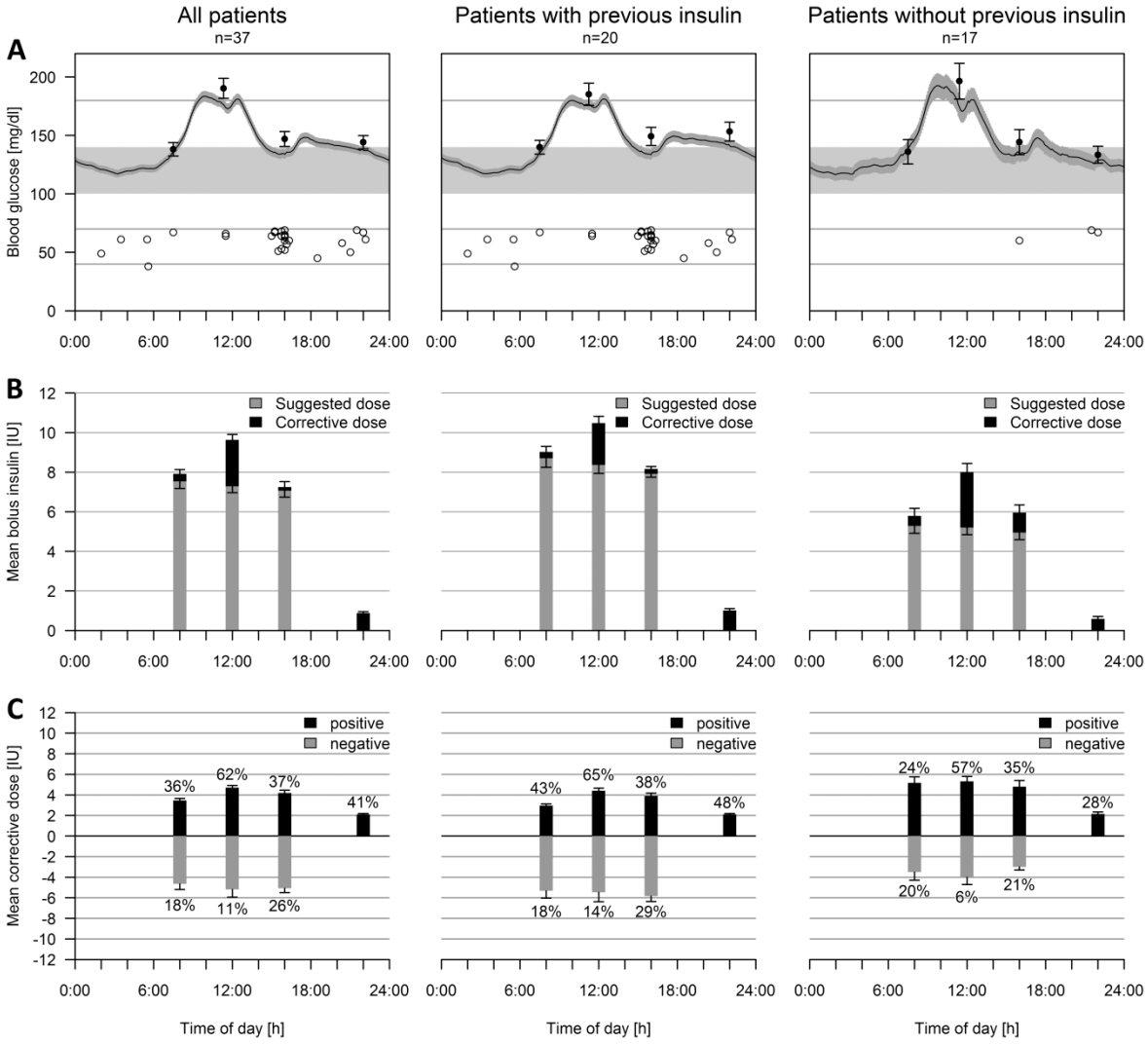
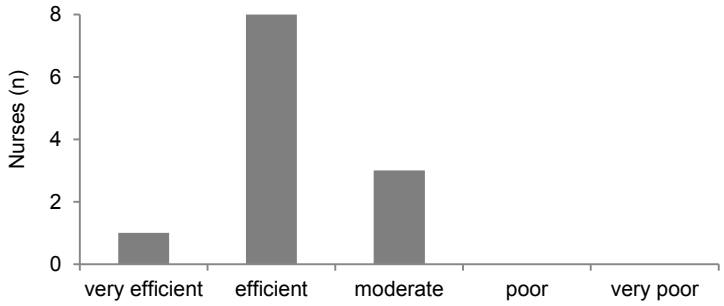


Figure 8 (A) Mean daily CGM profile, mean pre-meal BG values (solid circles) and hypoglycemic events (open circles). (B) Mean daily administered breakfast, lunch, dinner and bedtime bolus insulin dose shown as the algorithm-suggested dose (grey bar) and the total mean insulin correction based on insulin 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 patients (left), patients with pre-existing insulin therapy (middle) and patients without pre-existing insulin therapy (right); all data are mean ± SEM [2]

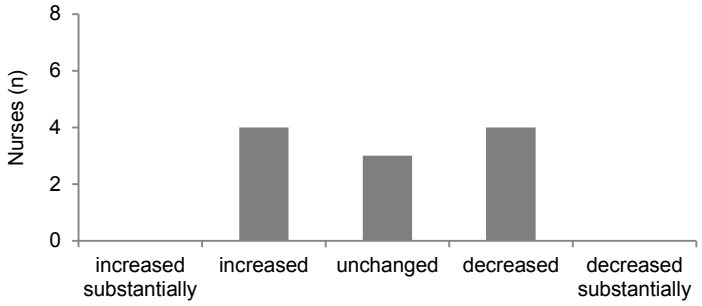
Usability of paper-based algorithm

At the end of the study, twelve of the fourteen nurses in the algorithm group completed an anonymous questionnaire (Figure 9). All nurses felt confident using the paper-based algorithm. 73% confirmed that the algorithm had improved the quality of glycaemic control including error prevention and 75% of the nurses reported to have achieved the glycaemic target range when using the paper-based algorithm in patients with type 2 diabetes. When using the algorithm, four nurses indicated a workload increase, four a workload decrease and another three indicated no change in workload of glycaemic management (one did not answer) [2].

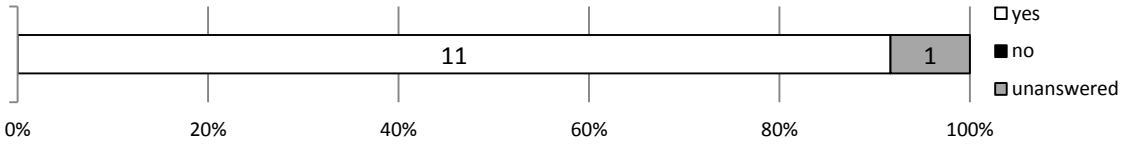
A Target glycaemic control (100-140 mg/dl) as established by the algorithm



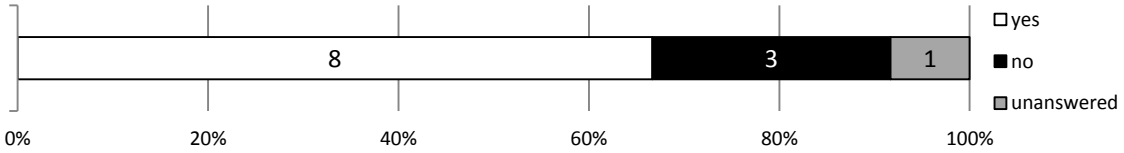
B Workload when using the algorithm (1 unanswered)



C Glycaemic control with algorithm is more efficient as compared to routine care?



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



E Did you feel confident using the paper-based algorithm?

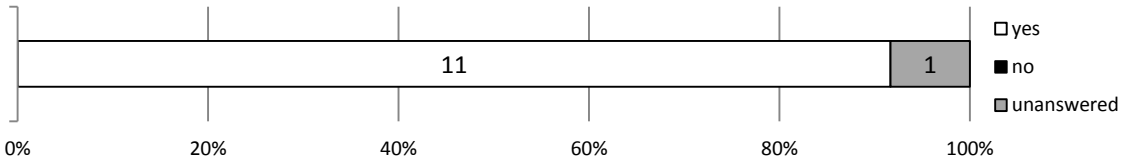


Figure 9 Nurses' questionnaire regarding the efficacy and usability of the paper-based algorithm [2]

SUMMARY OF EVALUATION PAPER-BASED ALGORITHM

Recent clinical studies have shown that the implementation of paper-based algorithms for basal-bolus insulin therapy in hospitalised patients with type 2 diabetes improves glycaemic control and reduces hospital complications.

The aim of Study 2 was to evaluate glycaemic control and usability of a workflow-integrated algorithm for basal-bolus insulin therapy in hospitalised patients with type 2 diabetes. In this ward-controlled study, 74 patients with type 2 diabetes were assigned to either the algorithm group with a basal-bolus insulin therapy or to routine care group.

The workflow-integrated algorithm for basal-bolus therapy was efficacious in establishing glycaemic control on hospitalised patients with type 2 diabetes. The mean BG values in the algorithm group were significantly reduced from 204 ± 65 mg/dl (baseline) to 148 ± 32 mg/dl (last 24 hours) during a period of 7.5 ± 4.6 days in the hospital (P<0.001). Furthermore, the paper-based algorithm was well accepted by health care professionals. These findings support the implementation of the paper-based algorithm in an electronic clinical decision support system.

STUDY 3 – FIRST-TIME GLUCOTAB IN CLINICAL PRACTICE

Parts of the study results were presented at scientific conferences and published in abstract form.

Tablet-based workflow and decision support of in-hospital glycaemic management– perceptions of nurses and physicians

Neubauer KM, Mader JK, Schaupp L, Höll B, Spat S, Augustin T, Beck P, Buttinger M, Plank J, Pieber TR

Abstract published in: Diabetes Technol Ther 2014; 16(S1):A140

© 2012 Mary Ann Liebert, Inc.

Basal bolus insulin therapy in hospitalised patients with diabetes mellitus type 2 using two algorithms embedded in a tablet PC

Mader J, Neubauer K, Aberer F, Schaupp L, Donsa K, Spat S, Hoell B, Augustin T, Beck P, Plank J, Pieber T

Abstract published in: Endocr Abstr 2014, 35:P488

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FIRST-TIME GLUCOTAB IN CLINICAL PRACTICE

Recent guidelines recommend the development and evaluation of evidence-based clinical decision support systems that will not only improve glycaemic control but also support workflow processes for health care professionals [12].
In Study 2, a paper-based insulin dosing algorithm for patients with type 2 diabetes was modified and successfully evaluated to comply with daily workflow requirements of a general hospital ward [2]. This modified paper-based algorithm was then implemented in a computerised workflow and decision support system (GlucoTab system) for basal-bolus insulin therapy in hospitalised patients with type 2 diabetes. This computerised decision support systems might improve the quality of inpatient glycaemic management.

AIM OF STUDY 3: FIRST-TIME GLUCOTAB IN CLINICAL PRACTICE

Within this study, the GlucoTab system was used in clinical practice for the first time. Therefore, the primary aim of the feasibility study was to evaluate the performance (safety) of the GlucoTab system by investigating the percentage of actions the GlucoTab system supported either to capture BG values or provide insulin dose suggestions according to the algorithm.
Secondary aims of the feasibility study were to compare the efficacy and safety of two versions of the computerised algorithm for basal-bolus insulin therapy for glycaemic management in hospitalised patients with type 2 diabetes and to assess the usability of the GlucoTab system [29].

METHODICAL APPROACH OF THE FEASIBILITY STUDY

This study was a mono-centric, open, non-controlled intervention study in patients with type 2 diabetes. The study included in total 30 patients hospitalised at the Endocrinology ward at the Medical University of Graz. All patients gave written informed consent after the purpose, nature, and potential risks of the study had been explained and before any study-related activities were started.
The study was approved by the ethical board of the Medical University of Graz (NCT01766752, EK-No. 24-510 ex 11/12) and performed in accordance with the "Declaration of Helsinki" and the principles of Good Clinical Practice.

Patient characteristics

This study included patients with type 2 diabetes (treated initially with OADs, non-insulin injected antidiabetic drugs, insulin, diet or any combination of the four), who were hospitalised for any condition at the Endocrinology ward and who were in the age range of 18-90 years. Main exclusion criteria were the following: impaired renal function (serum creatinine ≥3.0 mg/dl), pregnancy, any mental condition rendering the patient incapable of giving his consent and terminal illness. The demographic and clinical characteristics of included patients are presented in Table 7.
Study 3 was conducted in two parts with fifteen patients, respectively. First, the implemented algorithm of the GlucoTab system was the same as in the paper-based Study 2 [2]. In the second part of the feasibility study, an algorithm with a modified distribution of insulin doses was evaluated.

Feasibility implementation of the GlucoTab system

Two GlucoTab tablet-PCs were installed at the Endocrinology ward. The GlucoTab back-end was installed at a virtual server at the KAGes (hospital IT provider). The user front-end devices accessed the backend via Wi-Fi. The user frontend device was located at the central place of the ward. Patients' treatment with the GlucoTab system was performed at the point-of-care.

Table 7 Demographic and clinical characteristics of patients in the feasibility study

Patients	Patients of part 1 (n=15)	Patients of part 2 (n=15)
Gender, female (n/%)	4/26.7	7/46.7
Ethnicity, Caucasian (n)	15	15
Age (years)	69 ± 10	73 ± 11
Body Mass Index (kg/m²)	29.1 ± 5.6	30.1 ± 6.8
Weight (kg)	84 ± 20	91 ± 23
Serum creatinine (mg/dl)	1.3 ± 0.5	1.4 ± 0.6
HbA1c		
mmol/mol	76 ± 30	62 ± 18
%	9.1 ± 4.9	7.8 ± 3.8
Diabetes duration (years)	14 ± 9	17 ± 16
Pre-admission diabetes therapy (n/%)		
Diet only	0	2/13
OADs only	9/60	6/40
Insulin only	4/27	2/13
Insulin, OADs	2/13	5/34
Discharge diabetes therapy (n/%)		
Diet only	0	1/7
OADs only	2/13	4/27
Insulin only	11/74	6/39
Insulin, OADs	2/13	4/27
Admission type (n/%)		
Planned	3/20.0	2/13.3
Acute	12/80.0	13/87.7
Admission diagnosis (n/%)		
Hematological disease	0/0	1/7
Endocrine disease	7/47	3/20
Cardiovascular disease	6/40	4/27
Infectious disease	2/13	7/47
Discharge to (n)		
Home	14	9
Nursing home	1	0
Transfer to other hospital	0	5
Unknown	0	1

Mean ± SD

Glycaemic management with GlucoTab

GlucoTab is a mobile computerised clinical decision support system for subcutaneous insulin therapy that supports nurses and physicians in glycaemic management of hospitalised patients in two main tasks: First, it assists clinical health care professionals in organising the treatment workflow of patients with type 2 diabetes by providing automated workflow support, including display for open tasks, facilitating documentation and providing visualisation of BG values, nutrition and insulin doses (Figure 10, Figure 11, Figure 12). Second, it provides two standardised recommendations based on a basal-bolus insulin titration protocol [25–27] for

1) the TDD which is prescribed by the treating physician during the ward round (Figure 13) and
2) insulin dose suggestions for individual insulin administrations before each meal, at bedtime and after intermediate BG measurements, if required (Figure 14). After confirmation of the suggested insulin dosage, the insulin is injected subcutaneously by an authorized nurse [3].

The overall glycaemic management process is presented in Figure 10.

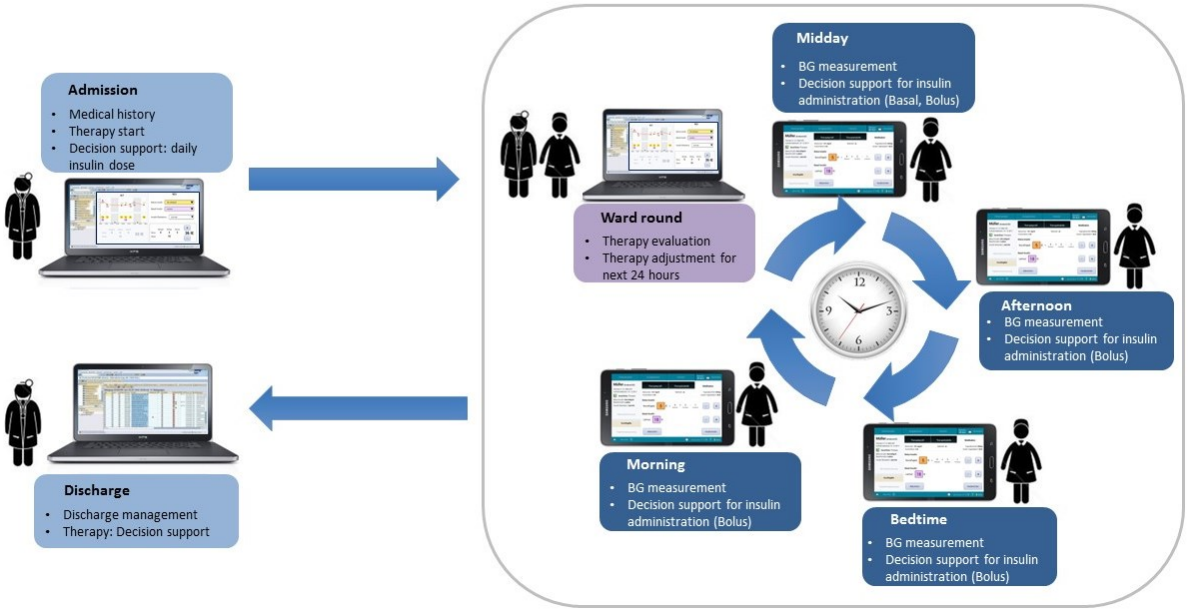

Figure 10 Process of glycaemic management with the GlucoTab system during hospital stay

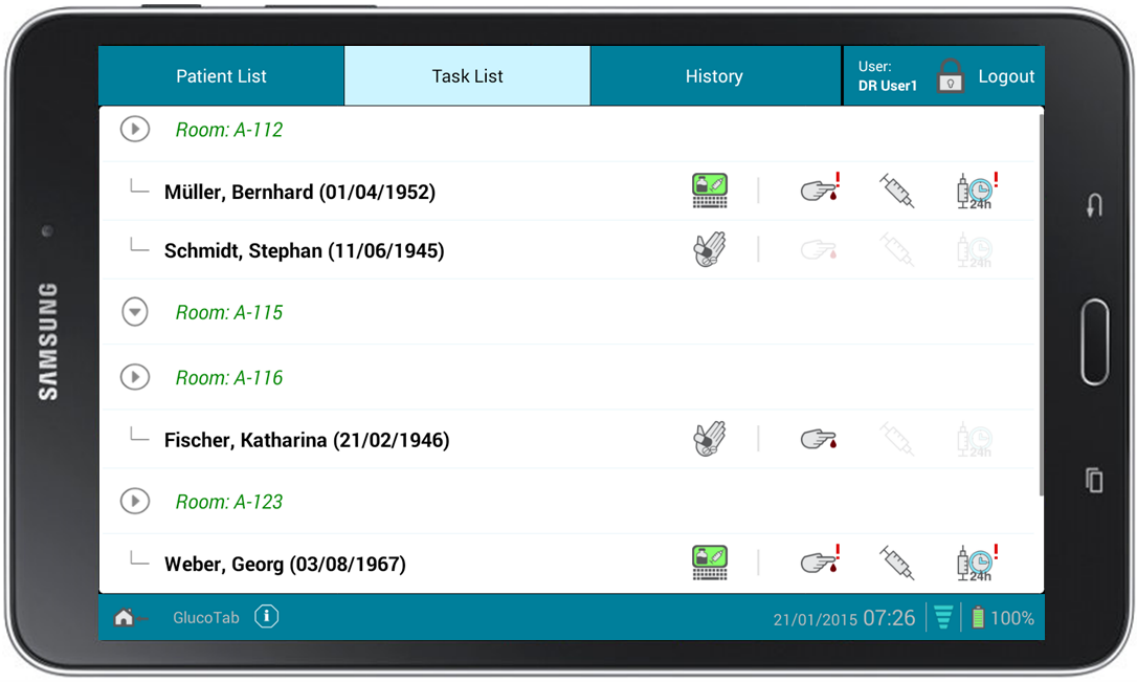

Figure 11 Workflow support for standardised glycaemic management with the GlucoTab

The standardised recommendations for insulin dose calculation, based on the modified basal-bolus insulin titration protocol [2, 25–27] consist of a daily dose of basal insulin (insulin glargine, Sanofi-Aventis, Frankfurt am Main, Germany), bolus insulin (insulin aspart, NovoNordisk, Bagsværd, Denmark) before each meal and a correctional dose at bedtime to achieve fasting and pre-meal BG values of less than 140 mg/dl [20, 21]. Insulin therapy was started with a TDD of 0.5 units per kg bodyweight. The initial TDD was reduced to 0.3 units per kg bodyweight in patients ≥70 years of age and/or serum creatinine values ≥2.0 mg/dl. In case the patient had already been on insulin therapy, the protocol allowed to use the former TDD as the initial dose, which could be adjusted by the treating physician. One half of the TDD was administered as basal insulin once a day before lunch. The other half was administered as bolus insulin three times a day [3].

Study 3 was conducted in two parts with fifteen patients, respectively. In the first part, the implemented algorithm of the GlucoTab system was the same as described in the paper-based Study 2 [2]. In the second part of the feasibility study, an algorithm with a modified distribution of insulin doses was implemented in the GlucoTab system and evaluated. In part 1 of the feasibility study the total daily bolus insulin dose was equally divided into three doses (33% breakfast bolus,

33% lunch bolus, 33% dinner bolus). In part 2 of the study a modified distribution of bolus insulin dosing was evaluated (45% breakfast bolus, 25% lunch bolus, 30% dinner bolus).

The TDD was adjusted by the treating physician during the ward round. Therefore, basal insulin was administered after the ward round at lunch time (Figure 10) [3].

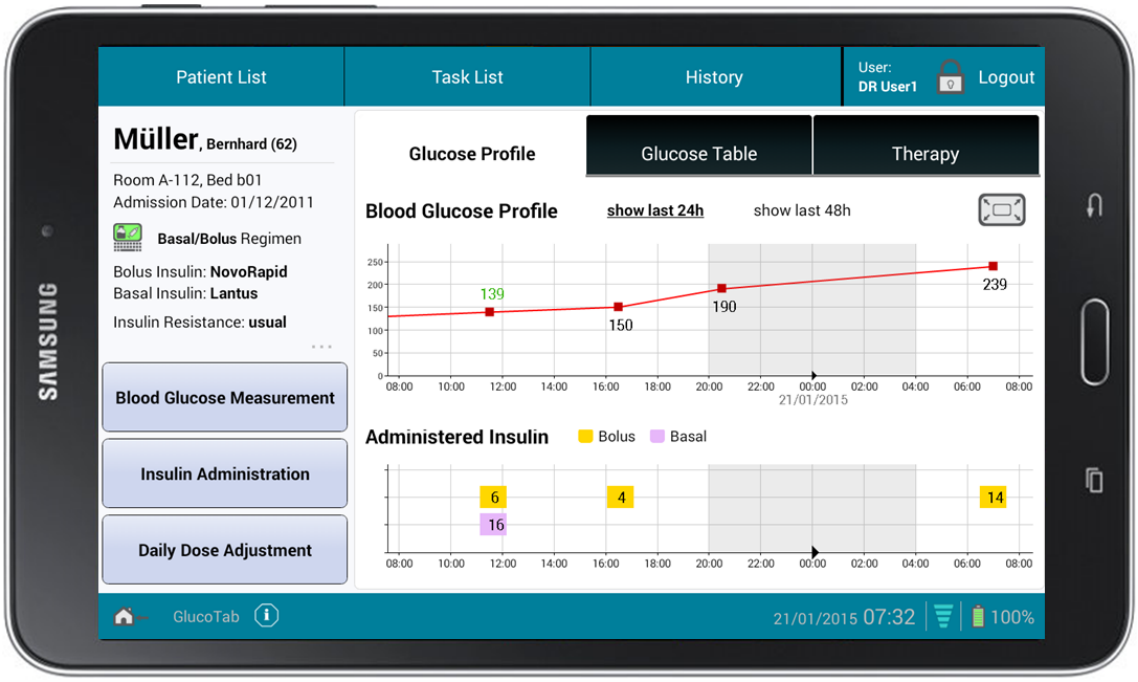

Figure 12 Computerised visualisation of patient's BG values, nutrition and insulin doses

The following safety features were implemented into the GlucoTab system: if a patient would not eat, basal insulin was administered, but the prescribed bolus insulin was withheld and correctional bolus doses were administered for the regulation of particular BG values if required. At any time, the health care professionals could overrule the suggested insulin dose and perform additional BG measurements [3].

At the end of Study 3, health care professionals were invited to fill out an anonymous questionnaire.

Figure 13 Decision support for TDD which is prescribed by the treating physician

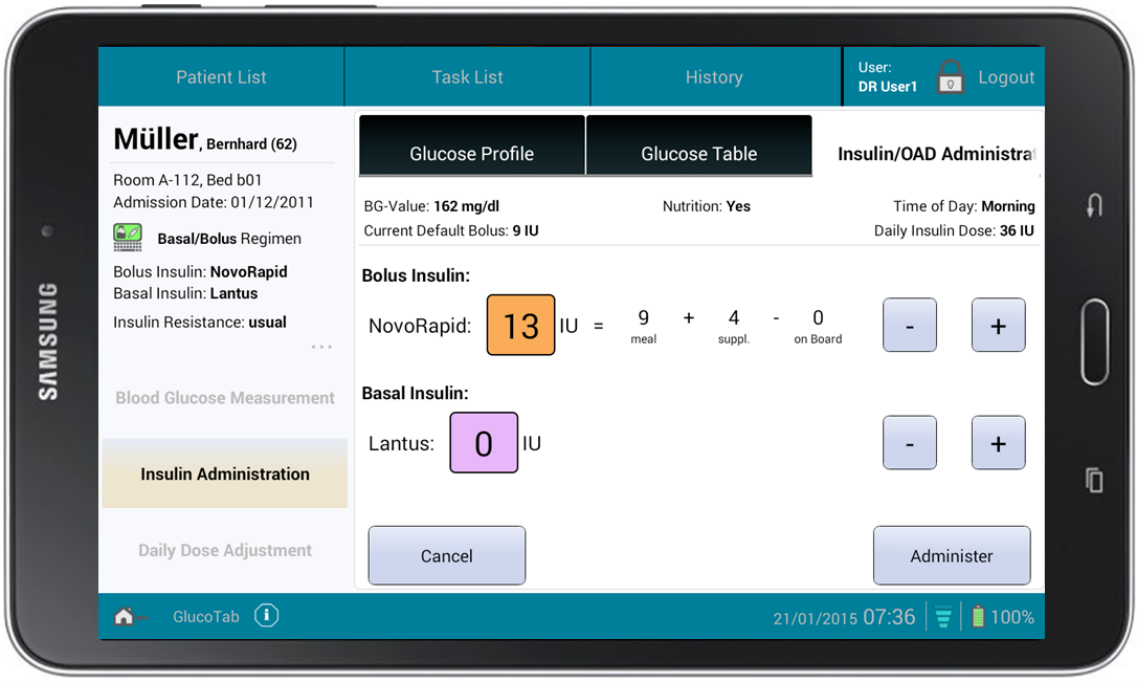

Figure 14 Decision support for individual insulin administration

Statistical analysis

Study 3 is a feasibility study without group comparison. In order to evaluate safety, usability and efficacy of the GlucoTab system, the total number of patients was set to 15 per study part.

An exploratory descriptive analysis was performed. For numerical parameters, means ± standard deviations or medians ± interquartile ranges were used to describe the outcome data. For categorical data, proportions were used to describe the outcome data. The statistical analysis was performed using R version 2.13.1 software [34].

RESULTS: FIRST-TIME GLUCOTAB IN CLINICAL PRACTICE

In total, 98.1% of the BG documentation, 97.4% of basal insulin administrations and 93.5% of bolus insulin administrations were successfully performed with the GlucoTab system. Non-performance of BG documentation and insulin administrations with the GlucoTab system were related to technical errors which have been fixed during the clinical study. Related user errors have been considered in a more detailed training of health care professionals.

Efficacy and safety of glycaemic control

The mean BG was 166 ± 34 mg/dl (algorithm part 1) vs. 144 ± 27 mg/dl (modified algorithm in part 2). 30.1% and 21.5% of BG values were in the hyperglycaemic range (>180 mg/dl), in part 1 and modified algorithm in part 2 respectively. 1.7% (8/459) and 1.5% (7/462) of BG values were in the hypoglycaemic range (<70 mg/dl), in part 1 and modified algorithm in part 2 respectively. In both groups no BG value was below 40 mg/dl.

CGM data confirmed that the modified algorithm improved efficacy and safety of glycaemic management in hospitalised patients. By using the modified bolus insulin distribution in part 2 a distinctively flattened curve with a reduced BG peak value at noon and a lower number of hypoglycaemic events in the afternoon was achieved compared to the CGM curve when using the algorithm in part 1 (Figure 15).

The mean TDD was 47 ± 29 units (basal: 20 ± 13 units and bolus: 27 ± 16 units) for the algorithm in part 1 and 47 ± 27 units (basal: 22 ± 12 units and bolus: 25 ± 15 units) for the modified algorithm in part 2 [29].

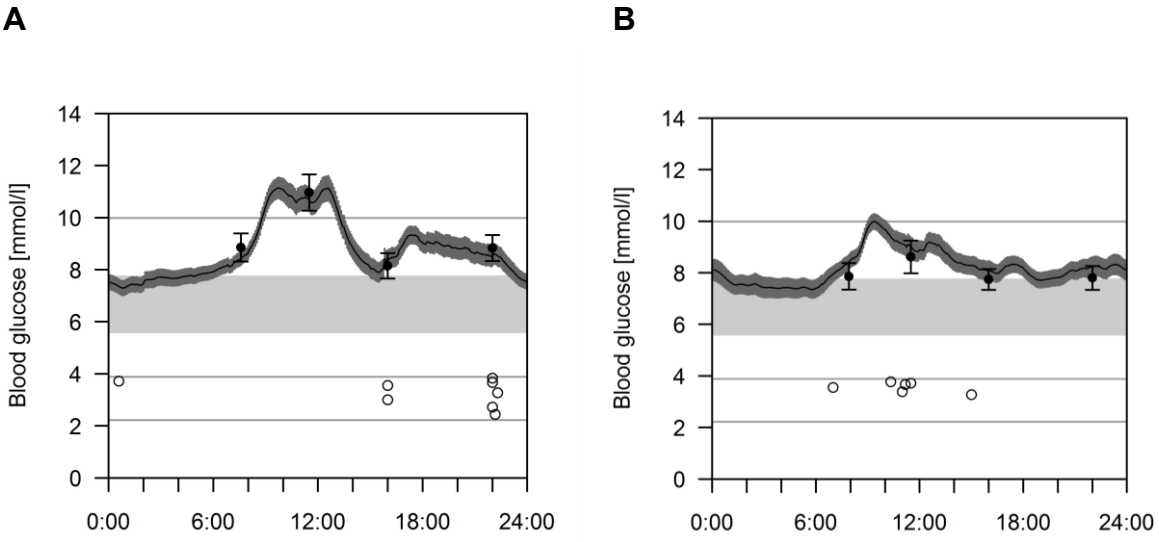

Figure 15 CGM data and hypoglycaemic events (circles) of (A) patients treated with algorithm in part 1 and (B) in patients treated with modified algorithm in part 2

Questionnaire about the usability of the GlucoTab system

Twelve nurses and six physicians (16 female, mean age 32 ± 11 years, work experience 0.1-32 years) filled out the questionnaire at the end of the study. 17 health care professionals felt safe using the GlucoTab system. 98% of suggested TDD were accepted by the physicians. The nurses accepted the suggested basal- and bolus-insulin dose to 98% and 95% respectively. 17 health care professionals stated that the GlucoTab system supported achieving BG in the recommended glycaemic target range. All health care professionals reported that the GlucoTab system prevents insulin dosing errors and that glycaemic management is efficient. The GlucoTab system supports the daily glycaemic workflow processes at a general hospital ward (n=16) as well as the independent clinical decisions made by nurses (n=17). The work effort by using the GlucoTab system was stated as follows: decreased (n=3), increased (n=10), unchanged (n=5) [30].

Table 8 Efficacy and safety of the GlucoTab in the feasibility study

Patients (n)	**Patients of part 1 (n=15)**	**Patients of part 2 (n=15)**
Length of hospital stay (days)	8.4 ± 3.9	8.3 ± 5.2
Length of study (days)	8.4 ± 3.9	8.3 ± 5.2
Pre-enrolled BG (mg/dl)	206 ± 76	178 ± 81
Efficacy and safety		
Mean daily BG (mg/dl)	166 ± 34	144 ± 27
Mean pre-breakfast BG (mg/dl)	159 ± 38	142 ± 36
Mean pre-lunch BG (mg/dl)	198 ± 49	155 ± 44
Mean pre-dinner BG (mg/dl)	147 ± 34	139 ± 29
Mean bedtime BG (mg/dl)	159 ± 35	141 ± 32
BG in different ranges (%)		
<40 mg/dl	0	0
40-<70 mg/dl	1.7	1.5
70-<100 mg/ dl	10.0	12.8
100-140 mg/dl	31.4	41.3
>140-<180 mg/dl	26.8	22.9
180-<300 mg/dl	27.0	19.5
>=300 mg/dl	3.1	2.0
Antidiabetic therapy		
First calculated TDD (units)	40 ± 20	48 ± 33
First TDD/kg of body weight (units)	0.47 ± 0.21	0.50 ± 0.34
Mean daily insulin dose during study (units)		
Injected bolus insulin dose*	27 ± 16	25 ± 15
Injected basal insulin dose	20 ± 13	22 ± 12
Concomitant drugs (n)		
Patients with steroids	0	2

*The first and last study day is excluded for each patient, mean ± SD

SUMMARY OF FIRST-TIME GLUCOTAB IN CLINICAL PRACTICE

Guidelines recommend the development and evaluation of evidence-based clinical decision support systems for health care professionals in the hospital. Within Study 3, the GlucoTab system was used in clinical practice for the first time.
Therefore, the aim of the feasibility study was to evaluate the performance (safety), efficacy and usability of two versions of the computerised algorithm for basal-bolus insulin therapy for glycaemic management in hospitalised patients with type 2 diabetes.

The feasibility study was conducted in two parts with 30 patients. First, the implemented algorithm of the GlucoTab system was the same as in the paper-based Study 2. In the second part of the study, the algorithm with a modified distribution of daily bolus insulin doses was implemented in the GlucoTab system.

The mean BG was lower in patients treated with the algorithm in part 1 than in patients treated with algorithm in part 2. 1.7% and 1.5% BG values were in the hypoglycaemic range below 70 mg/dl, part 1 and 2 respectively. The feasibility implementation of the GlucoTab system was well accepted by health care professionals and supported the workflow processes of an effective inpatient glycaemic management.

Therefore, the modified algorithm improved glycaemic control without increased risk of hypoglycaemia in hospitalised patients with type 2 diabetes. The feasibility findings supported the implementation of the GlucoTab system at other general wards in the hospital.

STUDY 4 – GLUCOTAB AT GENERAL WARDS

Main results were published in a scientific peer-reviewed journal.

Standardised glycaemic management with a computerised workflow and decision support system for hospitalised patients with type 2 diabetes on different wards

Neubauer KM, Mader JK, Höll B, Aberer F, Donsa K, Augustin T, Schaupp L, Spat S, Beck P, Fruhwald FM, Schnedl C, Rosenkranz AR, Lumenta DB, Kamolz LP, Plank J, Pieber TR

Published in: Diabetes Technol Ther 2015, 17:685–692

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GLUCOTAB AT GENERAL WARDS

International guidelines suggest the development and evaluation of evidence-based computerised decision support systems, including computerised insulin and BG data display that will not only improve glycaemic control but also workflow and communication among health care professionals. Integrated decision support strategies and systems should guide health care professionals in the glycaemic management process [12]. Based on the efficacious, safe and user-friendly glycaemic management at the Endocrinology ward in Study 3, the GlucoTab system was implemented and evaluated at different general wards in the hospital [29, 30].

AIM OF STUDY 4: GLUCOTAB AT GENERAL WARDS

The aim of the study was to investigate the efficacy, safety and usability of the standardised glycaemic management with the GlucoTab system for non-critically ill patients with type 2 diabetes. The mobile version of the GlucoTab system was used for the first time to guide the glycaemic management process at four different general wards in divisions of internal medicine and surgery [3].

This study was the basis for CE marking of the GlucoTab system as a medical device.

METHODICAL APPROACH OF GLUCOTAB AT GENERAL WARDS

This study was an open, non-controlled interventional study in hospitalised patients with type 2 diabetes. The study was conducted at four general wards of the Medical University of Graz. The participating wards were Endocrinology, Cardiology, Nephrology and Plastic Surgery, which are each independently managed by the respective division. All patients gave written informed consent prior to any study activity and the study was approved by the ethical board of the Medical University of Graz (NCT01932775, EK-No. 25-344 ex 12/13). This study was conducted in full accordance with the principles of the “Declaration of Helsinki” [3].

Patient characteristics

The GlucoTab system was subsequently implemented at the four participating general wards. In total, 99 hospitalised patients with type 2 diabetes were competitively recruited from May 2013 to December 2013. Hospitalised patients who met the inclusion criteria were included in the study after they consented to participate. The demographic and clinical characteristics of the study participants are presented in Table 9. Inclusion criteria were: age ≥18 years and type 2 diabetes (treated with diet, OADs, non-insulin injected antidiabetic drugs, insulin or any combination of the four therapies) or newly diagnosed hyperglycaemia requiring subcutaneous insulin therapy [3].

Patients were switched to insulin therapy in case of hyperglycaemia judged by the treating physician according to evidence-based recommendations to use insulin therapy as the preferred method for glycaemic control in hospitalised patients [20, 21]. Glycaemic management with the GlucoTab system was not performed in patients with the following exclusion criteria: type 1 diabetes, gestational diabetes, any condition which the investigator or treating physician felt would interfere with the study or the safety of the patient, pregnancy, any mental condition rendering the patient incapable of giving consent, known or suspected allergy to insulin glargine or insulin aspart, continuous parenteral nutrition or participation in another study which could interfere with this study [3].

Table 9 Clinical characteristics of the study population at different wards (adapted from Neubauer et al. 2015 [3])

Patients	Total (n=99)	Nephro (n=15)	Cardio (n=30)	Endo (n=42)	Plast Surg (n=12)	*P*
Gender, female (n/%)	41/41	3/20	12/40	20/48	6/50	0.28
Ethnicity (Caucasian/African) (n)	98/1	15/0	30/0	42/0	11/1	0.13
Age (years)	67 ± 11	64 ± 8	70 ± 12	67 ± 11	65 ± 10	0.31
Body Mass Index (kg/m²)	30.4 ± 6.5	31.0 ± 5.4	29.4 ± 6.8	31.1 ± 6.8	29.4 ± 6.3	0.57
Weight (kg)	88 ± 21	92 ± 17	84 ± 24	89 ± 20	86 ± 17	0.22
Serum creatinine (mg/dl)	1.8 ± 1.5	3.8 ± 2.1	1.4 ± 0.9	1.6 ± 1.3	1.0 ± 0.2	<0.05†
Renal dialysis (n)	9	6	1	2	0	-
HbA1c						
mmol/mol	65 ± 21	57 ± 10	65 ± 21	70 ± 24	55 ± 13	0.13
%	8.1 ± 4.1	7.4 ± 3.1	8.1 ± 4.1	8.6 ± 4.4	7.2 ± 3.3	
Diabetes duration (years)	14 ± 9	13 ± 8	11 ± 8	15 ± 10	14 ± 10	0.51
Pre-admission diabetes therapy (n/%)						
Diet only	3/3	0/0	1/3	2/5	0/0	
OAD only	16/16	0/0	6/20	8/19	2/17	
Insulin only	55/56	12/80	13/44	24/58	6/50	0.60
OAD, GLP1 analogues	1/1	0/0	0/0	1/2	0/0	
Insulin, OAD	22/22	3/20	9/30	6/14	4/33	
Insulin, GLP1 analogues	2/2	0/0	1/3	1/2	0/0	
Discharge diabetes therapy (n/%)						
Diet only	3/3	0/0	1/3	1/2	1/8	
OAD only	17/17	0/0	8/27	7/17	2/17	-
Insulin only	57/58	14/93	16/53	22/52	5/42	
Insulin, OAD	22/22	1/7	5/17	12/29	4/33	
Admission type (n/%)						
Planned	38/38	6/40	17/57	8/19	7/58	<0.05‡
Acute	61/62	9/60	13/43	34/81	5/42	
Admission diagnosis (n/%)						
Hematological disease	1/1	1/7	0/0	0/0	0/0	
Gastrointestinal disease	1 /1	1/7	0/0	0/0	0/0	
Endocrine	11/11	0/0	1/3	10/24	0/0	
Cardiovascular disease	44/44	4/27	29/97	11/26	0/0	-
Neurological disease	1/1	1/7	0/0	0/0	0/0	
Infectious disease	23/23	1/7	0/0	19/45	3/25	
Renal disease	8/8	7/47	0/0	1/2	0/0	
Musculoskeletal disease	9/9	0/0	0/0	1/2	8/58	
Other	1/1	0/0	0/0	0/0	1/8	
Discharge to (n)						
Home	78	14	26	28	10	-
Nursing home	2	0	0	2	0	
Transfer to other hospital	19	1	4	12	2	

† Significant difference between Cardiology and Nephrology, Cardiology and Plastic Surgery, Endocrinology and Nephrology, Endocrinology and Plastic Surgery, Nephrology and Plastic Surgery, ‡ significant differences between Cardiology and Endocrinology, and Endocrinology and Plastic Surgery, mean ± SD

Standardised glycaemic management with GlucoTab

Glycaemic management was performed according to Figure 10. BG measurements were performed four times daily (pre-breakfast, pre-lunch, pre-dinner, and at bedtime). Insulin adjustments and administration were performed according to the suggestions of the GlucoTab system which is presented in detail in Study 3. The computerised suggestion of the TDD was divided to 50% basal insulin (insulin glargine, Sanofi-Aventis, Frankfurt am Main, Germany) and 50% pre-meal bolus insulin with additional corrective dose if necessary (insulin aspart, NovoNordisk, Bagsværd, Denmark). Bolus insulin was administered three times a day according to part 2 of Study 3 (45% of the total dose for breakfast bolus, 25% for lunch bolus and 30% for dinner bolus).
The following safety innovative features were implemented into the GlucoTab system: The GlucoTab system took into account the amount of bolus insulin that was still active in the patient's body from a previous dose ("insulin on board"), by reducing bolus insulin by 25% per hour [35]. Another safety feature was to reduce the dose of basal insulin if the current basal dose injection was delayed.

At the beginning of the standardised glycaemic management, patient's pre-existing antidiabetic therapy with glinides, sulfonylureas and glitazones was stopped and patients were assigned to receive standardised glycaemic management according to the GlucoTab system. Metformin and/or incretin-based therapies were maintained if there was no contraindication. At discharge, patients returned to their previous antidiabetic treatment, unless the treating physician decided to continue the insulin therapy performed during the study or to change to another insulin therapy [3].

All health care professionals were instructed on the study protocol, study specific procedures, handling of the GlucoTab system and Good Clinical Practice before study start. Health care professionals were invited to participate in a workshop about diabetes before study start and to fill out an usability questionnaire at the end of the study [3].

Capillary BG values were measured by using a point of care testing device (Roche Accu Check® Inform System, Roche Diagnostics, Rotkreuz, Switzerland) which is integrated into the laboratory quality management system of the hospital. Capillary

BG measurements and insulin dosing were performed and documented by the nurse on duty [3].

CGM data (iPro^{TM}2, Medtronic, Northridge, CA) were available in a subset of 35 patients from totally 42 patients at the Endocrinology ward, because one patient lost the sensor, three patients had too few data for analysis and for another three patients no sensor transmitter was available. As CGM data were analysed retrospectively the treatment was not influenced by these data [3].

Statistical analysis

A sample size calculation was performed in order to test the study hypothesis by using a one-tailed one-sample t-test weighted by the total number of BG measurements per subject, with a 5% level of significance and a power of 95%.
In order to test whether the mean percentage of BG values in the target range 70-140 mg/dl (primary outcome) was greater than the recent best-practice study with the criterion-value of 42% [27], an one-tailed one-sample t-test was applied, weighted by the total number of BG values per subject. The level of significance was set to 5%.
The wards were compared by using non-parametric Kruskal-Wallis rank sum test (metric variables) for analyses of secondary outcomes, since patients were unequally distributed among the wards with some table cells being unacceptably small for an analysis of variance ANOVA. In case of a significant Kruskal-Wallis test, pairwise comparisons by using (non-parametric) Mann-Whitney U test were performed. Fisher's exact test was used for nominal scales. No corrections for multiple testing were used and the level of significance was set to 5% for all tests [3].
Finally, a multiple regression model to predict the mean daily BG value over all study days (except study day 1) was fitted to the data. Study day 1 was excluded due to incomplete data sets. Variables were sex, age, serum creatinine, HbA1c, Body Mass Index, first TDD per kg bodyweight, diabetes duration, pre-existing insulin therapy at admission (yes, no), OADs at admission (yes, no), clinical ward, admission type (planned, acute) and the interaction between admission type and clinical ward. Model simplification was performed by using the Akaike's information criterion. Statistical analysis was performed using R 2.13.1 [3, 34].

RESULTS OF EVALUATION OF GLUCOTAB AT GENERAL WARDS

Implementation of standardised glycaemic management

The standardised workflow support with the GlucoTab system was highly accepted by health care professionals at all participating clinical wards as indicated by the performance of the expected BG measurements and the adherence to insulin dose suggestions (Table 10) [3].

In total, physicians adhered to the suggested TDD in 97.5% (Table 10), and nurses' adherence rates with suggested bolus insulin doses and basal insulin doses were 96.5% and 96.7%, respectively. If corrections were performed by health care professionals, the changes were relatively small: 0.7 ± 1.6 units for bolus insulin and 0.9 ± 2.8 units for basal insulin [3].

Efficacy of standardised glycaemic management

By using the GlucoTab system, the percentage of BG values in the target range increased over time in all participating clinical wards (Figure 16). Overall, the mean percentage of BG values in the target range 70-140 mg/dl was 50.2 ± 22.2%, which was significantly higher than the criterion-value of 42% deriving from a recent best-practice study (*P*=0.001) [3]. 72.2% of the patients had a reduction of the mean BG during hospital stay compared to the estimated BG based on HbA1c at admission [16]. In all patients with an estimated average BG >200 mg/dl based on the HbA1c the mean BG during the study was improved (Figure 16C). The overall mean of 2,466 BG values was 154 ± 35 mg/dl. Details of glycaemic management across the clinical wards are shown in Table 10 [3].

The percentage of BG in the target range 70-140 mg/dl was highest at the Plastic Surgery ward (64.9 ± 24.6%). The lowest value was found at the Nephrology ward (39.3 ± 13.7%). Analysis of the 24 hours CGM data of patients at the Endocrinology indicated that more than half of the study time (54.0%) subcutaneous BG values were in the target range of 70-140 mg/dl (Figure 17A) and confirmed that reference BG values were representative (52.3% in the target range, Table 10) [3]. Figure 17B and C show an improvement from 42% on the first day to 62% on the last day in target range 70-140 mg/dl.

Although observations suggest variations concerning glycaemic management between the clinical wards, a regression analysis to predict the mean daily BG value showed that the BG value was not affected by a specific clinical ward. Patients with pre-existing insulin therapy at admission had, on average, higher (+ 26 mg/dl) mean daily BG values during GlucoTab treatment than patients without pre-existing insulin therapy. Particularly at the Cardiology ward the type of admission had a strong impact on the mean daily BG value. Acutely admitted patients at the Cardiology ward had on average higher (+ 30 mg/dl) mean daily BG values than patients with acute admissions at the other wards (+ 4 mg/dl). The correlation of acutely admitted patients at Cardiology and higher mean BG values is interpreted in Neubauer et al. 2015 [3]. Furthermore, the regression analysis showed that a higher first insulin dose per kg bodyweight by 0.1 units or a lower HbA1c value at admission by 10 mmol/mol were associated with a lower mean BG by 5 mg/dl and 4 mg/dl, respectively [3].

Safety of standardised glycaemic management

The number of hypoglycaemic events at the different wards using the GlucoTab system was comparable (Table 10). No severe hypoglycaemic event below 40 mg/dl was observed. 0.5% of all measurements in the range 40-<60 mg/dl occurred in nine different patients. 1.4% of the measurements in the range of 60-<70 mg/dl occurred in 24 different patients. In patients at the Endocrinology ward, the analysis of the CGM data confirmed a low risk for developing hypoglycaemia, 0% and 1.2% for measurements in the range <40 mg/dl and 40-<60 mg/dl, respectively (Figure 17) [3].

28 mild and moderate adverse events and one serious adverse event (stent thrombosis) occurred. None of these events were recognised as related to the GlucoTab system [3].

Table 10 Efficacy, safety and usability of the GlucoTab system at different general wards (adapted from Neubauer et al. 2015 [3])

Patients	Total (n=99)	Nephro (n=15)	Cardio (n=30)	Endo (n=42)	Plast Surg (n=12)
Length of hospital stay (days)	12.0 ± 7.6	11.9 ± 8.9	10.9 ± 7.4	11.7 ± 5.6	15.4 ± 10.5
Length of study (days)	7.8 ± 4.5	8.5 ± 5.4	6.8 ± 4.1	8.8 ± 4.4	5.9 ± 3.7
Time to inclusion (days)	4.1 ± 6.0	2.9 ± 4.1	4.3 ± 7.0	3.3 ± 4.2	7.8 ± 8.4
Implementation					
Performance of expected (%)					
BG measurement	95.2	92.4	97.2	94.8	98.4
Bolus insulin injections	94.2	96.8	97.4	93.2	86.5
Basal insulin injections	99.4	100	100	98.7	100
Adherence to (%)					
TDD	97.5	98.5	97.5	98.0	92.9
Bolus dose suggestion	96.5	94.3	97.2	96.3	95.1
Basal insulin suggestion	96.7	91.1	96.3	96.8	91.0
Efficacy and safety					
Pre-enrollment BG (mg/dl)	188 ± 73	185 ± 43	173 ± 58	204 ± 88	158 ± 55
Mean daily BG (mg/dl)	154 ± 35	162 ± 34	163 ± 33	150 ± 35	134 ± 31
Mean pre-breakfast BG (mg/dl)	147 ± 43	151 ± 38	156 ± 47	147 ± 44	119 ± 28
Mean pre-lunch BG (mg/dl)	170 ± 54	197 ± 59	179 ± 58	163 ± 50	137 ± 36
Mean pre-dinner BG (mg/dl)	153 ± 41	141 ± 51	164 ± 40	146 ± 36	164 ± 42
Mean bedtime BG (mg/dl)	153 ± 39	165 ± 41	164 ± 31	146 ± 39	136 ± 42
BG in target 70-140 mg/dl (%)*	50.2 ± 22.2	39.3 ± 13.7	40.7 ± 18.9	52.3 ± 20.7	64.9 ±24.6
BG in different ranges (%)					
<40 mg/dl	0.0	0.0	0.0	0.0	0.0
40-<60 mg/dl	0.5	0.2	0.0	0.8	0.4
60-<70 mg/dl	1.4	0.8	0.3	2.2	1.3
70-<180 mg/dl	72.5	64.6	70.6	74.4	83.7
180-<300 mg/dl	22.9	29.4	27.2	20.0	14.2
>=300 mg/dl	2.7	5.0	1.9	2.6	0.4
Antidiabetic therapy					
First calculated TDD† (units)	38.9 ± 21.7	33.6 ± 11.3	33.5 ±16.6	44.8 ± 27.5	38.3 ± 15.1
First TDD/kg bodyweight (units)	0.43 ± 0.19	0.36 ± 0.10	0.39 ± 0.11	0.49 ± 0.24	0.44 ± 0.14
Mean daily injected insulin dose during study (units)					
Injected bolus insulin dose	28.5 ± 19.2	27.3 ± 14.9	25.8 ± 12.3	32.5 ± 25.1	21.0 ± 6.7
Injected basal insulin dose	22.9 ± 18.2	21.0 ± 7.6	17.8 ± 8.6	28.7 ± 25.0	17.1 ± 7.4
Concomitant drugs (n)					
Patients with OADs	36	2	13	14	7
Patients with GLP1 analogues	6	0	2	4	0
Patients with steroids	4	1	1	1	1

*Primary endpoint: significant differences between Endocrinology and Cardiology (P=0.02), Plastic Surgery and Nephrology (P=0.01), Plastic Surgery and Cardiology (P=0.02), Nephrology and Endocrinology (P=0.01), † TDD total daily insulin dose might deviate from the injected TDD of day 1 depending on time of day when a patient was started on GlucoTab therapy, mean ± SD

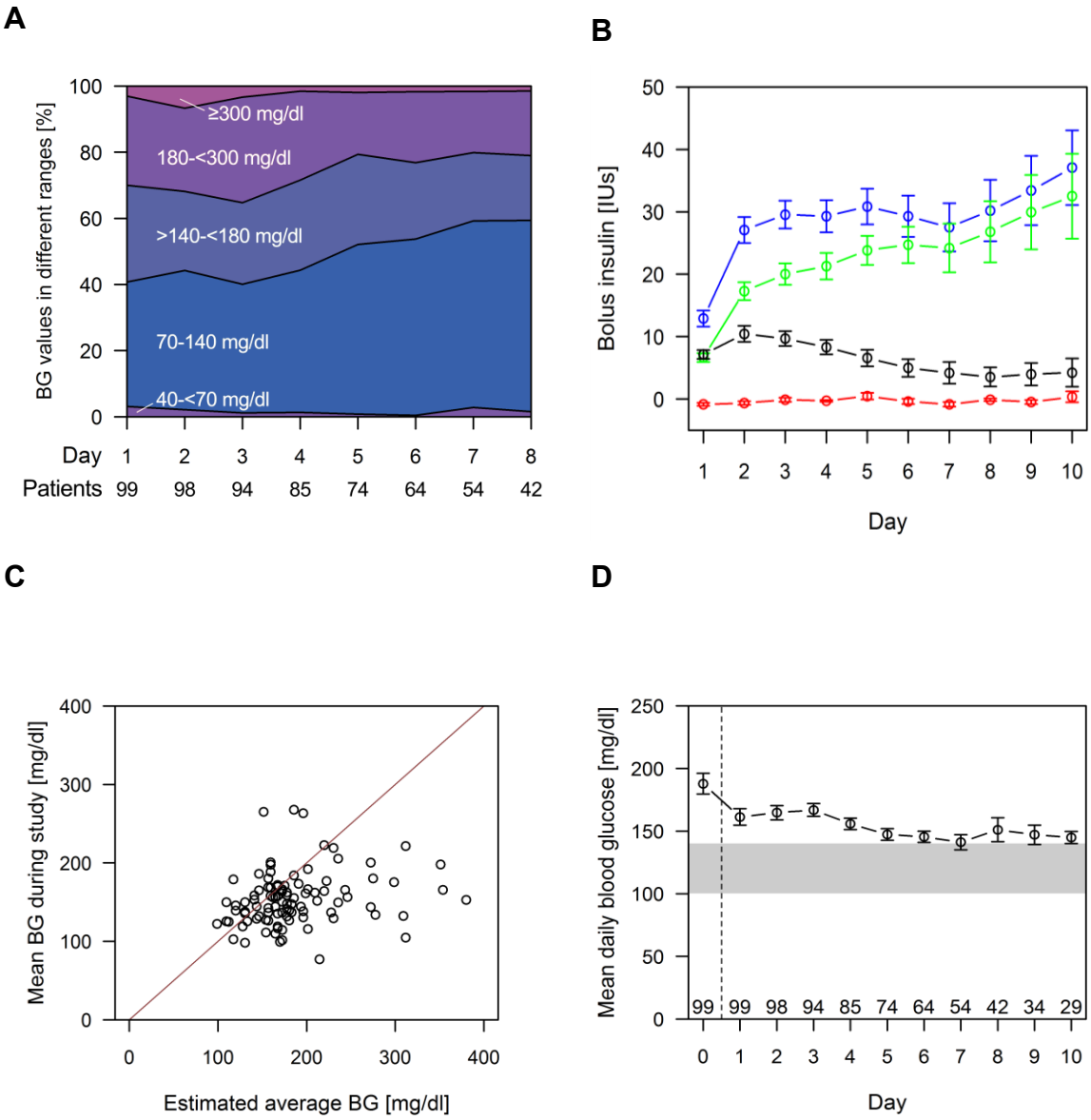

Figure 16 (A) Mean percentage of pre-meal and bedtime BG values in different ranges. (B) Injected bolus insulin (blue), suggested bolus insulin (green), bolus insulin correction by the algorithm (black), Bolus correction by the nurse (red) (mean ± standard error, insulin dose on day 1 was lower depending on time of day when a patient was started on GlucoTab therapy). (C) Comparison of estimated BG based on HbA1c at admission with mean BG during hospital stay. (D) Mean daily BG values during 10 days of hospital stay (adapted from Neubauer et al. 2015 [3])

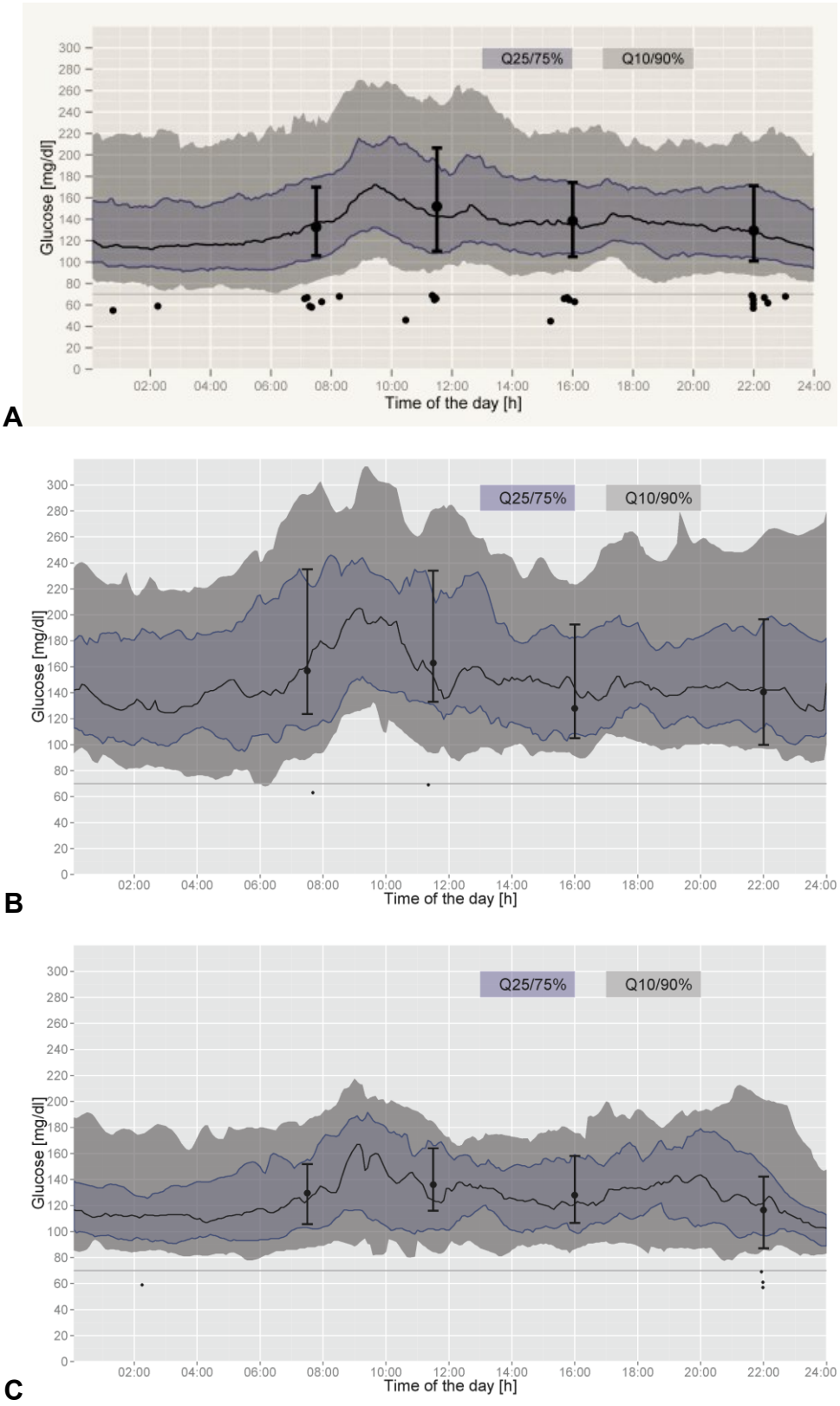

Figure 17 (A) Daily CGM profiles and reference BG values in 35 patients at Endocrinology ward. CGM data of (B) first and (C) last day with standardised glycaemic management (back circles=reference BG values (adapted from Neubauer et al. 2015 [3])

Usability of standardised glycaemic management

At the end of the study, 65 health care professionals completed a questionnaire (54 female/11 male, mean age 36 ± 11 years, 51 nurses, and 14 physicians). 42 health care professionals already had experience with the use of mobile devices. 59 health care professionals (91%) felt confident in performing glycaemic management with the GlucoTab system. 58 health care professionals (89%) believed that the system was practical to use in daily clinical routine. 52 participants (80%) stated that using the GlucoTab system could prevent medical errors associated with drug prescriptions. 56 health care professionals (86%) answered that when using the system, physicians had to be consulted less often about glycaemic management. 55 health care professionals (85%) stated that glycaemic control was more efficient when using the GlucoTab system. Different perceptions of workload were assessed. 13 health care professionals indicated a workload increase, 33 a workload decrease and twelve indicated no change in the workload, when using the GlucoTab system. Seven health care professionals did not answer this question (Figure 18) [3].

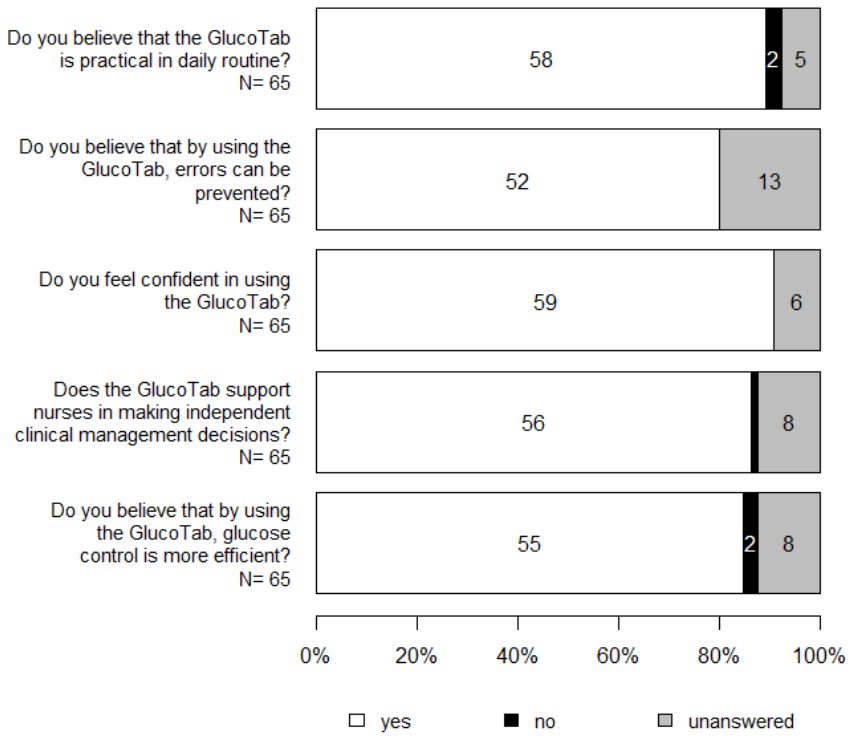

Figure 18 Usability questionnaire of standardised glycaemic management

SUMMARY OF GLUCOTAB AT GENERAL WARDS

In Study 4 the final version of the GlucoTab system was used for the first time to guide the glycaemic management process at four different general wards. This study was the basis for CE marking of the GlucoTab system as a medical device. Therefore, the aim of the study was to investigate the efficacy, safety and usability of the standardised glycaemic management with the GlucoTab system.

In this open, non-controlled intervention study, glycaemic management of 99 patients with type 2 diabetes was guided by the mobile GlucoTab system providing automated workflow support and suggestions for insulin dosing to health care professionals.

The primary outcome measure, percentage of BG values target range from 70-140 mg/dl, occurred in 50.2 $\pm$ 22.2% of all measurements. BG measurements from 60-70 mg/dl, 40-60 mg/dl and <40 mg/dl occurred in 1.4%, 0.5% and 0.0% of all values, respectively. The adherence to insulin dosing suggestions was high (96.5% bolus, 96.7% basal). 91% of the health care professionals felt confident with the GlucoTab system, 89% believed in its practicability and 80% in its ability to prevent medication errors.

An efficacious, safe and user-accepted implementation of the GlucoTab system at four different wards was demonstrated, which resulted in a CE marking. This successful milestone provided the opportunity to implement and use the GlucoTab system in patients with type 2 diabetes in hospital routine care.

STUDY 5 – GLUCOTAB IN ROUTINE CARE

Parts of the study results were submitted to a scientific conference for presentation and publication.

Efficacy, safety and usability of a clinical decision support system for basal-bolus insulin therapy in hospital routine care

Neubauer KM, Mader JK, Aberer F, Tuca A, Donsa K, Augustin T, Höll B, Schaupp L, Beck P, Plank J, Pieber TR

Abstract accepted for oral presentation at 76th Scientific Session, American Diabetes Association, June 10-14, 2016, New Orleans, USA

GLUCOTAB IN ROUTINE CARE

The GlucoTab system supports an efficacious, safe and health care professional accepted glycaemic management in patients with type 2 diabetes at different hospital wards at the Medical University of Graz. The GlucoTab system potentially can simplify glycaemic management in hospitalised patients with type 2 diabetes [3, 36].

After the successful CE marking of the GlucoTab, the system was implemented in routine care at three different wards at the hospital of the Medical University of Graz (Endocrinology, Cardiology and Plastic Surgery) to support health care professionals in optimising standardised glycaemic management processes.

AIM OF STUDY 5: GLUCOTAB IN ROUTINE CARE

The aim of the study was to investigate risks of the routine use of the GlucoTab system, assessed by the percentage of BG values <70 mg/dl and ≥300 mg/dl, for glycaemic management in non-critically ill patients with type 2 diabetes at general wards. To further evaluate the GlucoTab in hospital routine care efficacy, safety and usability parameters were analysed. The GlucoTab system was used for the first time in routine care at three general wards.

METHODICAL APPROACH - GLUCOTAB IN ROUTINE CARE

This study was an open, single-centre, non-controlled clinical study according to MPG §40(5) (Austrian medical device law) in hospitalised patients with type 2 diabetes. According to MPG §40(5) the use of the medical devices in a clinical study has to correspond to the defined intended use and cannot include any additional diagnostic and therapeutic interventions. An approval of the ethical board is also necessary for this type of clinical trial.
The study was conducted at three general wards of the Medical University of Graz. The participating wards were Endocrinology, Cardiology and Plastic Surgery. All patients gave written informed consent prior to any study activity and the study was approved by the ethical board of the Medical University of Graz (NCT02053077, EK-No. 26-072 ex 13/14). This study was conducted in full accordance with the principles of the “Declaration of Helsinki”.

Patient characteristics

The GlucoTab system was implemented in routine care at the three participating general wards. In total, 92 hospitalised patients treated with GlucoTab in routine care were recruited from February 2014 to May 2015. The demographic and clinical characteristics of the study participants are presented in Table 11.
Hospitalised patients who were treated with the GlucoTab system and met the inclusion criteria were included in the study after they had consented to participate. Inclusion criteria were: age ≥18 years and type 2 diabetes or new-onset hyperglycaemia which required s.c. insulin therapy during hospital stay. Exclusion criteria were the following: type 1 diabetes, gestational diabetes, pregnancy, any mental condition rendering the patient incapable of giving consent, known or suspected allergy to insulin glargine or insulin aspart, continuous parenteral nutrition and hyperglycaemic episodes (ketoacidosis, hyperosmolar state) if they required intravenous insulin therapy.

Statistical analysis

The primary and secondary parameters were analysed by means of descriptive statistical methods. Means/standard deviations or medians/interquartile ranges were used to describe the outcome variables. Results in this chapter are based on an interim analysis. The statistical analysis was performed using R version 2.13.1 software [34].

Table 11 Clinical characteristics of patients treated with GlucoTab in routine care

Patients	Total (n=92)
Gender, female (n/%)	40/44
Ethnicity (Caucasian/African) (n)	91/1
Age (years)	70 ± 11
Body Mass Index (kg/m²)	29.3 ± 5.7
Weight (kg)	83 ± 17
Serum creatinine (mg/dl)	1.3 ± 0.6
HbA1c	
mmol/mol	74 ± 24
%	8.9 ± 4.3
Diabetes duration (years)	15 ± 11
Pre-admission diabetes therapy (n/%)	
Diet only	13/14.1
OAD only	18/19.6
Insulin only	33/35.8
Insulin, OAD	26/28.3
GLP1 analogues, insulin	1/1.1
OAD, GLP1 analogues, insulin	1/1.1
Discharge diabetes therapy (n/%)	
Diet only	13/14
OAD only	18/20
Insulin only	33/36
Insulin, OAD	26/28
GLP1 analogues, insulin	1/1
OAD, GLP1 analogues, insulin	1/1
Admission type (n/%)	
Planned	18/20
Acute	74/ 80
Admission diagnosis (n/%)	
Endocrine	35/38
Cardiovascular disease	39/42
Infectious disease	8/9
Renal disease	3/3
Other	7/8
Discharge to (n)	
Home	81
Nursing home	1
Transfer to other hospital	8
Other (rehabilitation, death)	2

Mean ± SD

RESULTS OF GLUCOTAB IN ROUTINE CARE

Safety and efficacy of GlucoTab in routine care

Overall, the risk of hypoglycaemia was low. None of the BG values was below 40 mg/dl. By using the GlucoTab system in routine care, the percentage of BG values <70 or ≥300 mg/dl was 4.2% (2.3% and 1.9% of all BG values were <70 mg/dl and ≥300 mg/dl, respectively, Table 12, Figure 19A). There were 18 hypoglycaemic events (0.64%) in the range from 40-<60 mg/dl which occurred in twelve different patients and 46 episodes (1.64%) in the range from 60-70 mg/dl which occurred in 21 different patients. In total, the 64 episodes (2.28%) in the range from 40-70 mg/dl occurred in 33 different patients. Detected hypoglycaemic events occurred in all different day times. Most (31.2%) of the hypoglycaemic events were recorded between 14:00 and 17:59 (Table 12).

The occurrence of BG values <70 mg/dl in patients with OAD and/or GLP1 analogue therapy vs. in patients without add-on therapy is comparable (2.41% vs. 2.23%). In addition, the occurrence of BG values in the hyperglycaemic range (≥300 mg/dl) is comparable in patients with OAD and/or GLP1 analogues therapy vs. patients without add-on therapy (1.27% vs. 2.08%).

Results of Study 5 show that patients with hypoglycaemic events (BG <70 mg/dl) had on average lower HbA1c values (65 ± 19 vs. 79 ± 25 mmol/mol), longer length of hospital stays (12.0 ± 7.6 vs. 6.9 ± 3.2 days) and longer diabetes durations (20 ± 12 vs. 13 ± 10 years) than patients without hypoglycaemic events. Age, serum creatinine value and Body Mass Index were comparable in both groups (Table 13).

The overall patients' daily BG value was 159 ± 28 mg/dl. The overall pre-lunch BG value during treatment with the GlucoTab system was 186 ± 45 mg/dl, the overall pre-breakfast BG value was 144 ± 35 mg/dl (Table 12). In total, 68.8% of the BG values were in the accepted range 70-<180 mg/dl. 28.9% of the BG measurements were 180 mg/dl or higher (Figure 19, Table 12).

Table 12 Efficacy, safety and antidiabetic therapy of the GlucoTab system in routine care

Variable	Total (n=99)
Length of hospital stay (days)	13.3 ± 8.8
Length of study (days)	8.7 ± 5.7
Time to inclusion (days)	3.5 ± 3.8
Efficacy and safety	
Pre-enrollment BG (mg/dl)	228 ± 88
Mean daily BG (mg/dl)	159 ± 28
Mean pre-breakfast BG (mg/dl)	144 ± 35
Mean pre-lunch BG (mg/dl)	186 ± 45
Mean pre-dinner BG (mg/dl)	160 ± 34
Mean bedtime BG (mg/dl)	151 ± 34
BG in different ranges (%)	
<40 mg/dl	0.0
40-<70 mg/dl	2.3
70-<100 mg/dl	13.7
100-<140 mg/dl	31.7
140-<180 mg/dl	23.4
180-<300 mg/dl	27.0
>=300 mg/dl	1.9
Day time of hypoglycaemic events (n/%)	
06:00-09:59	13/20.3
10:00-13:59	8/12.5
14:00-17:59	20/31.2
18:00-21:59	9/14.1
22:00-05:59	14/21.9
Antidiabetic therapy	
First calculated TDD[†] (units)	35.5 ± 22.3
First TDD/kg bodyweight (units)	0.42 ± 0.21
Mean daily injected insulin dose during study (units)	
Injected bolus insulin dose	27.8 ± 13.9
Injected basal insulin dose	20.4 ± 12.6
Concomitant drugs (n)	
Patients with OADs	25
Patients with GLP1 analogues	1
Patients with steroids	1

[†] TDD total daily insulin dose might deviate from the injected TDD of day 1 depending on time of day when a patient was started on GlucoTab therapy; mean ± SD

Usability of GlucoTab system in routine care

96.3% of all suggested BG measurements, 92.7% of all suggested bolus insulin injections and 98.9% of all suggested basal insulin injections were performed by nurses as recommended by the GlucoTab system (Table 14).

In general, health care professionals' adherence to the suggested insulin doses was very high after day 1. In total, physicians adhered to the suggested total daily insulin dose in 93.0% of cases after day 1. Nurses' adherence rate to suggested bolus and basal insulin doses were 95.0% and 97.6%, respectively (Table 14, Figure 19B).

The mean number of stops of the decision support was 2.1 ± 2.5 (n=92) per patient. Main reasons for stops were missed TDD adjustment (50%) and modification of data entry (the reason for 31.6% of all stops of the decision support were retrospective modifications of data entries (BG values or insulin injections), Table 14).

There were 17 (18.5%) patients for whom GlucoTab was used for the complete hospital stay. The mean use of the GlucoTab during hospital stay was 72.5 ± 22.2% (15.6% of days were not covered by GlucoTab treatment at the beginning of hospital stay; GlucoTab was not used in 11.9% of days at the end of hospital stay).

Table 13 Characteristics of patients with and without hypoglycaemic events

Patient	**Patients with hypoglycaemic events (n=33)**	**Patients without hypoglycaemic events (n=59)**
Age (years)	70 ± 10	69 ± 11
Body Mass Index (kg/m²)	29.7 ± 5.5	29.0 ± 5.9
Weight (kg)	87 ± 17	81 ± 17
Serum creatinine (mg/dl)	1.3 ± 0.5	1.3 ± 0.7
HbA1c		
mmol/mol	65 ± 19	79 ± 25
%	8.1 ± 3.9	9.4 ± 4.4
Diabetes duration (years)	20 ± 12	13 ± 10
Length of study (days)	12.0 ± 7.6	6.9 ± 3.2

Mean ± SD

Table 14 Usability of the GlucoTab system in routine care

Patients	**Total (n=99)**
Performance of expected (%)	
BG measurement	96.3
Bolus insulin injections	92.7
Basal insulin injections	98.9
Adherence to (%)	
TDD	93.0
Bolus dose suggestion	95.0
Basal insulin suggestion	97.6
Decision support stops per patient (n)	2.1 ± 2.5
Decision support stops per day (n)	0.2 ± 0.2
Reasons for decision support stop (n/%)	
Missed TDD adjustment	95/50
Missing BG value	35/18
Modification of data entry	60/32

Mean ± SD, * modification of BG values or insulin injections

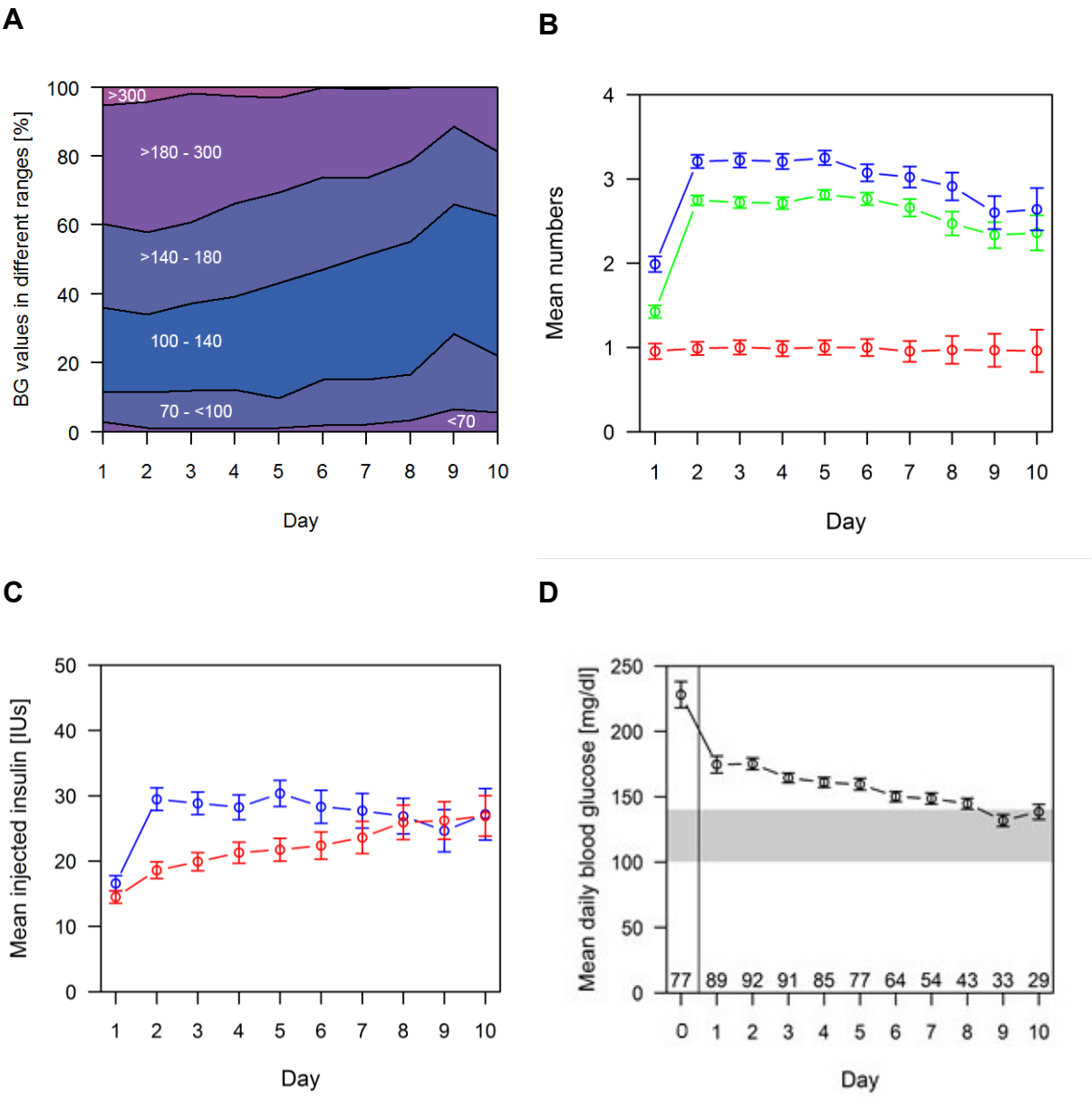

Figure 19 (A) Mean percentage of BG values in different ranges. (B) Mean number of pre-meal bolus insulin injections (green), mean number of bolus insulin injections (blue), mean number of basal insulin injections (red). (C) Mean injected bolus insulin dose (blue), mean injected basal insulin dose (red), (D) Mean daily BG values during 10 days of hospital routine care

SUMMARY OF GLUCOTAB IN ROUTINE CARE

The aim of this study was to investigate efficacy, safety and usability of the GlucoTab system in hospital routine care of non-critically ill patients with type 2 diabetes. 92 patients with type 2 diabetes were treated with basal-bolus insulin therapy by using the GlucoTab system in routine care.

By using the GlucoTab system in routine care, the overall mean BG value was 159 ± 28 mg/dl. Percentage of BG measurements in the range 70–180 mg/dl occurred in 68.8%. BG measurements in the ranges <40mg/dl, <70mg/dl, >180 - <300 and ≥300 mg/dl were observed in 0%, 2.3%, 27.0% and 1.9% of all measurements, respectively. Healthcare professionals' adherence to the suggested workflow tasks and insulin doses was >92% and >93%, respectively. The mean use of GlucoTab during hospital stay was 72.5 ± 22.2%. In 17 patients GlucoTab was used during the complete hospital stay.

The GlucoTab system supported an efficacious and safe glycaemic control in hospital routine care. The use of GlucoTab treatment during patient's hospital stay demonstrated that decision and documentation support systems for alternative therapy types (e.g. basal only, prandial insulin therapy) as well as variable glycaemic targets and discharge management are needed. When the GlucoTab system was not used for documentation of glycaemic management, health care professionals used a paper-based diabetes curve. This occurred primarily at the beginning and at the end of hospital stays based on the reasons mentioned above.

STUDY 6 – GLUCOTAB IN DIFFERENT AGE GROUPS

Parts of the study results were published and presented at a scientific conference.

Efficacy and safety of standardised glycaemic control in adult and geriatric hospitalised patients with type 2 diabetes mellitus

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Published in: Diabetologia 2015, 58(Suppl 1):S445-S445

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Presented at 51st Annual Meeting of the European Association for the Study of Diabetes, September 14-18, 2015, Stockholm, Sweden

GLUCOTAB IN DIFFERENT AGE GROUPS

International guidelines suggest glycaemic target ranges depending on patient's age and health status. In addition, recommendations highlight that hypoglycaemia should be avoided and that glycaemic goals might be reasonably relaxed in older patients with diabetes. However, hyperglycaemia and symptoms or risks of hyperglycaemic complications should be avoided in all patients with diabetes [22]. Until now, the evaluation of the efficacy and safety of well-established basal-bolus insulin algorithms in patients with diabetes in different age groups is not yet evaluated.

AIM OF STUDY 6: GLUCOTAB IN DIFFERENT AGE GROUPS

The aim of this analysis was to investigate efficacy and safety of the standardised glycaemic management supported by the computerised algorithm of the GlucoTab system in adult (<70 years) and geriatric (≥70 years) patients with diabetes in the hospital [4].

METHODICAL APPROACH - GLUCOTAB IN DIFFERENT AGE GROUPS

This study was a post-hoc analysis based on pooled patient data of Study 3, 4 and 5. The study was conducted at general wards (Endocrinology, Cardiology, Nephrology, Plastic Surgery) of the Medical University of Graz. Main in- and exclusion criteria were based on Study 3, 4 and 5. All patients gave written informed consent prior to any study activity and the study was approved by the ethical board of the Medical University of Graz (NCT01766752, NCT01932775 and NCT02053077). In addition, this study was conducted in full accordance with the principles of the “Declaration of Helsinki”.

Patient characteristics

The GlucoTab system provided automated dosing for basal-bolus insulin therapy for health care professionals in 191 non-critically ill hospitalised patients with type 2 diabetes for 8.3 days. Insulin therapy was started with a TDD of 0.5 units per kg bodyweight in adult patients (<70 years) and 0.3 units per kg bodyweight in geriatric patients (≥70 years) or in patients with a serum creatinine value ≥2 mg/dl (n=16) [4].

The demographic and clinical characteristics of 97 adult patients and 94 geriatric patients treated with the standardised insulin therapy using the GlucoTab system are presented in Table 15 [4].

Statistical analysis

An exploratory descriptive analysis was performed. Means/standard deviations or medians/interquartile ranges were used to describe the outcome data. For categorical data, proportions were used to describe the outcome data.
Results of this chapter are based on a post-hoc analysis of pooled patient data. The statistical analysis was performed using R version 2.13.1 software [34].

Table 15 Clinical characteristics of patients treated with GlucoTab in different age groups

Patients	Adult patients (n=97)	Geriatric patients (n=94)
Gender, female (n/%)	30/30.9	48/51.1
Ethnicity (Caucasian/African) (n)	96/1	93/1
Age (years)	60 ± 7	77 ± 5
Body Mass Index (kg/m²)	31.0 ± 6.8	28.6 ± 5.5
Weight (kg)	92 ± 21	88 ± 16
Serum creatinine (mg/dl)	1.7 ± 1.4	1.5 ± 0.9
HbA1c		
mmol/mol	72 ± 26	64 ± 19
%	8.7 ± 4.5	8.1 ± 3.9
Diabetes duration (years)	13 ± 8	17 ± 12
Pre-admission diabetes therapy (n/%)		
Diet only	4/4.1	8/8.5
OAD only	21/21.7	22/23.4
Insulin only	44/45.4	40/42.6
OAD, GLP1 analogues	1/1.0	0/0.0
Insulin, OAD	24/24.7	23/24.4
GLP1 analogues, insulin	3/3.1	1/1.1
Discharge diabetes therapy (n/%)		
Diet only	2/2.1	4/4.3
OAD only	12/12.4	16/17.0
Insulin only	51/52.5	53/56.4
OAD, GLP1 analogues	1/1.0	0/0.0
Insulin, OAD	25/25.8	21/22.3
GLP1 analogues, insulin	3/3.1	0/0.0
OAD, GLP1 analogues, insulin	3/3.1	0/0.0
Admission type (n/%)		
Planned	32/33	18/19
Acute	65/67	76/81
Admission diagnosis (n/%)		
Endocrine	22/22.7	19/20.2
Cardiovascular disease	37/38.1	48/51.1
Infectious disease	22/22.7	14/14.8
Renal disease	5/5.2	5/5.3
Musculoskeletal disease	3/3.0	1/1.1
Other	8/8.3	7/7.5
Discharge to (n)		
Home	79	75
Nursing home	0	3
Transfer to other hospital	18	12
Unknown	0	4

Mean ± SD

RESULTS OF GLUCOTAB IN DIFFERENT AGE GROUPS

First provided TDD was 0.49 ± 0.16 vs. 0.37 ± 0.24 units per kg bodyweight in adult and geriatric patients, respectively (Figure 20). The overall mean daily BG value was 155 ± 33 mg/dl (adult patients) and 157 ± 31 mg/dl (geriatric patients). 69.6% vs. 71.7% of BG values were in the range 70-<180 mg/dl for adult and geriatric patients, respectively. 2.5% vs. 1.5% of BG values occurred in adult and geriatric patients in the range <70 mg/dl. In both groups no BG value <40 mg/dl was detected. 25.1% vs. 25.0% and 2.8% vs. 1.8% of BG values were in the hyperglycaemic ranges of 180-<300 mg/dl and ≥300 mg/dl in adult and geriatric patients, respectively (Table 16, Figure 20) [4]. Mean daily injected insulin dose during the study was lower in geriatric than in adult patients. After day six, geriatric patients received a higher proportion of bolus insulin than adult patients.

Table 16 Efficacy, safety of the GlucoTab system (adapted from Neubauer et al. 2015 [4])

Patients	Adult patients (n=97)	Geriatric patients (n=94)
Length of study (days)	8.6 ± 5.7	8.1 ± 4.7
Efficacy and safety		
Pre-enrollment BG (mg/dl)	199 ± 80	206 ± 87
Mean daily BG (mg/dl)	155 ± 33	157 ± 31
Mean pre-breakfast BG (mg/dl)	145 ± 42	146 ± 37
Mean pre-lunch BG (mg/dl)	175 ± 54	179 ±46
Mean pre-dinner BG (mg/dl)	151 ± 39	158 ± 36
Mean bedtime BG (mg/dl)	153 ± 38	150 ± 35
BG in different ranges (%)		
<40 mg/dl	0.0	0.0
40-<70 mg/dl	2.5	1.5
70-<100 mg/dl	15.5	12.2
100-140 mg/dl	31.7	33.8
>140-<180 mg/dl	22.4	25.7
180-<300 mg/dl	25.1	25.0
>=300 mg/dl	2.8	1.8
Antidiabetic therapy		
First calculated TDD† (units)	46 ± 18	28 ± 16
First TDD/kg bodyweight (units)	0.49 ± 0.16	0.37 ± 0.24
Mean daily injected insulin dose during study (units)		
Injected bolus insulin dose	31.5 ± 18.3	24.3 ± 14.6
Injected basal insulin dose	25.7 ± 17.0	16.6 ± 13.0

Mean ± SD

Patients <70 years **Patients ≥70 years**

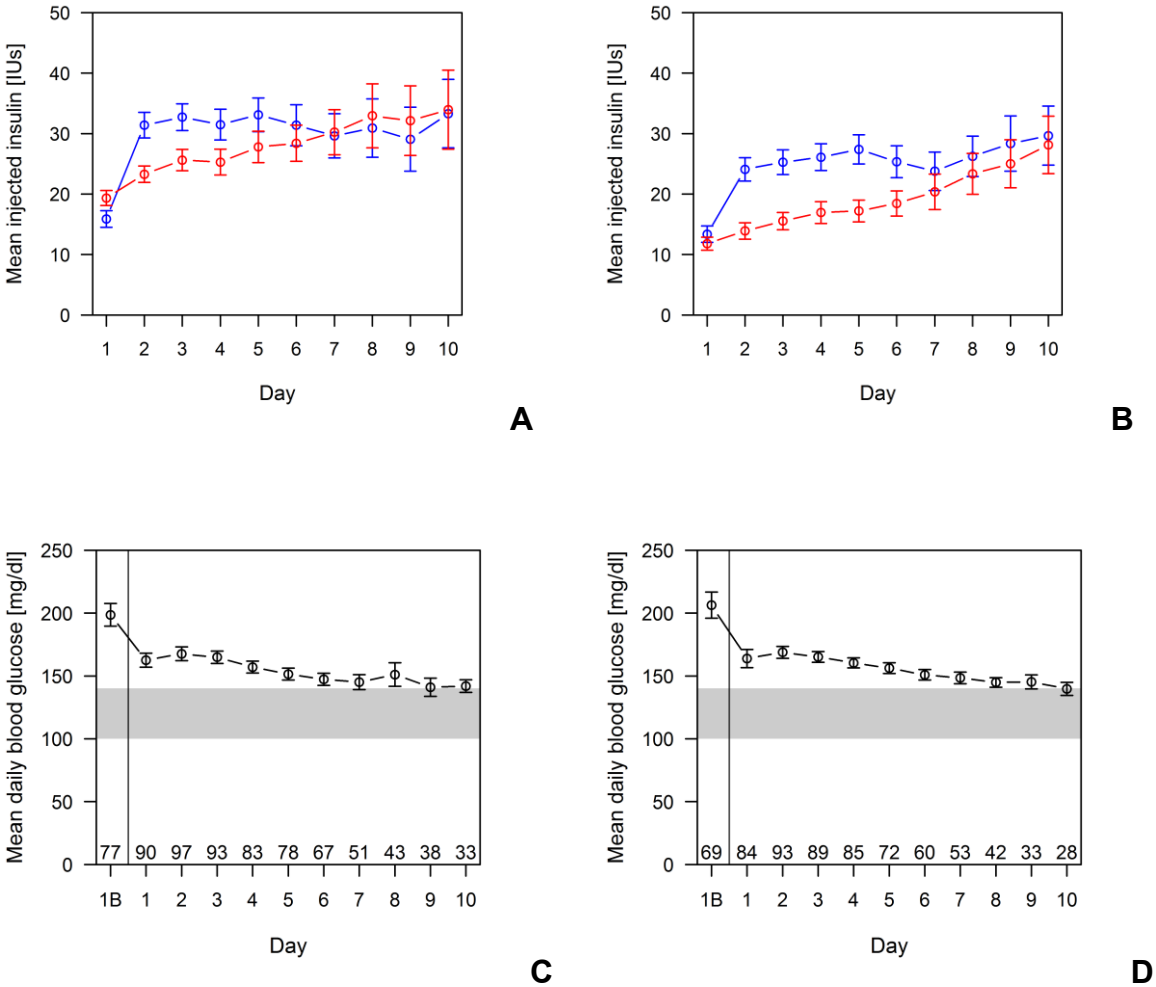

Figure 20 (A/B) Injected basal (red) and bolus (blue) insulin dose (mean ± SD) of patients <70 years and patients ≥70 years. (C/D) Mean daily BG of patients <70 years and patients ≥70 years (adapted from Neubauer et al. 2015 [4])

SUMMARY OF GLUCOTAB IN DIFFERENT AGE GROUPS

The aim of this analysis was to investigate the efficacy and safety of the standardised glycaemic management supported by the computerised algorithm of the GlucoTab system in adult (<70 years) and geriatric (≥70 years) patients with diabetes in the hospital.

This study was a post-hoc analysis based on pooled patient data of three different Studies (Study 3, 4 and 5) conducted at general wards of the Medical University of Graz. Insulin therapy by using the GlucoTab system was started with a TDD of 0.5 units per kg bodyweight in 97 adult patients (<70 years) and 0.3 units per kg bodyweight in 94 geriatric patients (≥70 years) or in patients with a serum creatinine value ≥2 mg/dl.

By using the GlucoTab system in different age groups, the overall mean BG value was 155 ± 33 mg/dl in adult patients and 157 ± 31 mg/dl in geriatric patients, respectively. BG values in the target range 70-<180 mg/dl were comparable in both groups. No BG value was detected below 40 mg/dl.

The standardised insulin starting dose suggested by the GlucoTab system with 0.5 and 0.3 units per kg bodyweight supported an efficacious and safe glycaemic control for adult and geriatric patients during hospital stay.

STUDY 7 – INSULIN THERAPY ADJUSTMENT BY NURSES

Parts of the presented concept were submitted for publication in an Austrian journal.

Decision Support für Diabetes

Neubauer KM, Tax C, Pieber TR

Article accepted for publication in Das österreichische Gesundheitswesen ÖKZ 2016, ÖKZ EXTRA: IT & Prozesse: 57. Jg.

INSULIN THERAPY ADJUSTMENT BY NURSES

Results of Study 2 to 6 showed that the GlucoTab system supports an efficacious, safe and user-friendly standardised glycaemic management in the hospital. Based on the highly accepted standardised workflow and decision support it is considered that nurses (legal term in Austria: *gehobener Dienst für Gesundheits- und Krankenpflege)* perform insulin therapy adjustments supported by the GlucoTab system. Thus, the aim of Study 7 was to develop a comprehensive concept for insulin therapy adjustments by nurses including workflow simplifications and how to react in critical situations concerning glycaemic management in the hospital.

This innovative feature is a milestone in the history of nursing in Austria increasing the competence for the nursing profession and the possibility to extend their independent work process. This feature simplifies the workflow of glycaemic management, minimises interruption in the workflow and decision support due to missed insulin adjustments by physicians, reduces the time required for tasks and aims to reduce workflow and medication errors by minimising interfaces among health care professionals.

However, within the current Austrian legal regulations insulin therapy adjustment by nurses is only permitted under certain conditions. A joint field of responsibility for the activity of nurses (*"mitverantwortliche Tätigkeitsbereich")* has to be considered for insulin dosing: nurses are responsible for the implementation of diagnostic and therapeutic procedures after ordered by a physician (according to §15 Abs. 1 Gesundheits- und Krankenpflegegesetz (GuKG), BGBI. I Nr. 108/1997) [37].
According to Abs. 2 and 3 leg.cit. the ordering physicians carry the responsibility for ordering and the performing nurses carry the responsibility for the implementation. Furthermore, each order must be made in written form by the physicians before the order is implemented by nurses.

According to Abs. 5 Z 1 and 2 leg.cit. the joint field of responsibility includes among other things

(1) the administration of drugs

(2) the preparation and administration of subcutaneous, intramuscular and intravenous injections [37], which includes insulin administration.

Based on these present regulations, a dialog with the Austrian Federal Ministry of Health was started. A letter of inquiry was sent to the Federal Ministry of Health in April 2014 regarding the question if the nurses are permitted to perform insulin adjustment when using technical support (Figure 21).

The reply of the Federal Ministry describes that the insulin adjustment by nurses is permitted under certain conditions (Bescheid BMG[2]).The conditions defined by the Federal Ministry were analysed in detail, discussed with a multidisciplinary team and implemented in the GlucoTab feature *insulin adjustment by nurses*.

The conditions of the Federal Ministry are implemented as follows:

Condition 1

„Der/Die anordnende Arzt/Ärztin hat sich im Rahmen seiner Anordnungsverantwortung von der Eignung des technischen Hilfsmittels zu überzeugen.“ (Bescheid BMG)

The physician is still ordering the start of GlucoTab therapy for the individual patient during hospital stay. At the beginning of GlucoTab therapy health care professionals in each hospital will define conditions for the implementation for insulin adjustment by nurses. In addition, the GlucoTab system is a CE marked medical device and was developed with a strong focus on quality and risk management. The efficacy and safety of the GlucoTab system was evaluated in clinical studies which are described in Study 3 to 6.

[2] Unpublished data which are described in following letter: „Stationäres Blutzuckermanagement: GlucoTab System“ (Hausreither M, 04.12.2014, Bundesministerium für Gesundheit, Allgemeine Gesundheitsrechtsangelegenheiten und Gesundheitsberufe)

Condition 2

„Der/Die anordnende Arzt/Ärztin hat im Rahmen seiner Anordnung nachweislich ein Werte-Intervall festzulegen, innerhalb dessen die medikamentösen Therapieanpassungen von Angehörigen des gehobenen Dienstes für Gesundheits- und Krankenpflege durchgeführt werden dürfen.“ (Bescheid BMG)

GlucoTab therapy has to be ordered in a written form at therapy start. In this order the physician defines the types of insulin, insulin starting dose, glycaemic target range, insulin sensitivity and the frequency of BG measurements (Figure 22). After the performance of this workflow task (therapy start) the decision support for insulin dosing and therapy adjustment is activated for nurses. Thus, an independent work process for nurses in well-defined limits is possible. With this feature nurses are now legally allowed to adjust the insulin therapy every day during hospital stay (Figure 21, Figure 23).

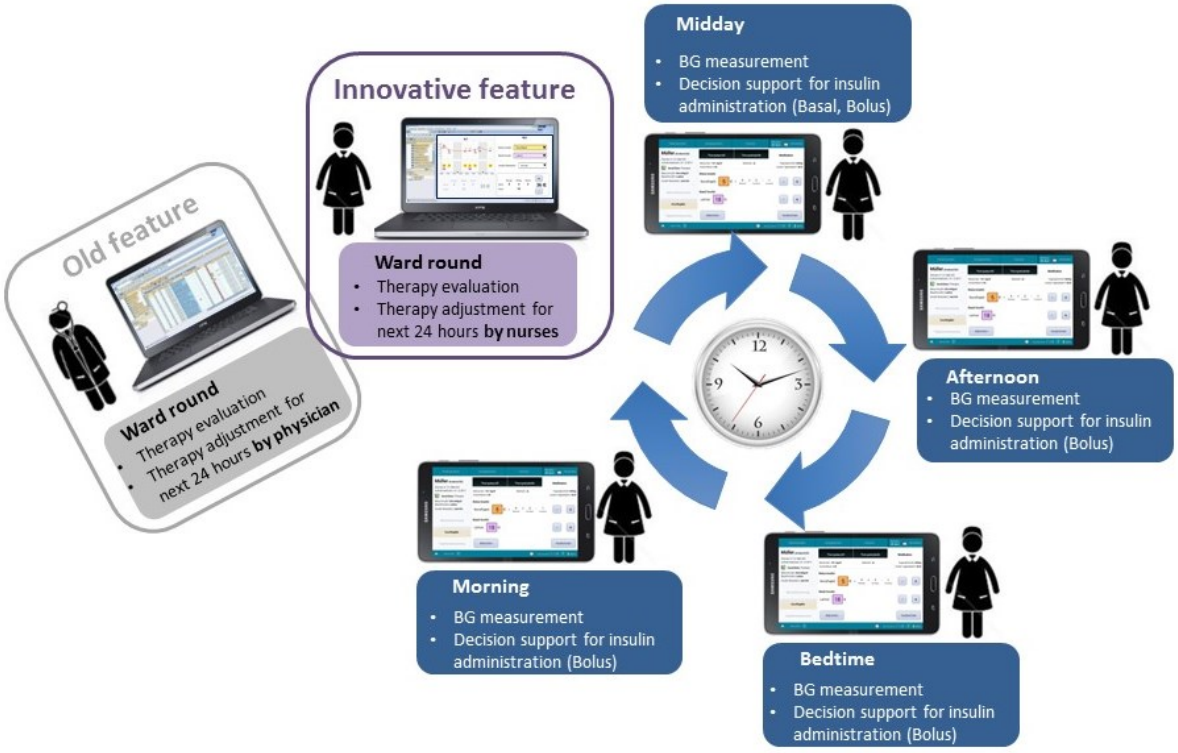

Figure 21 Glycaemic management process with insulin therapy adjustment by nurses

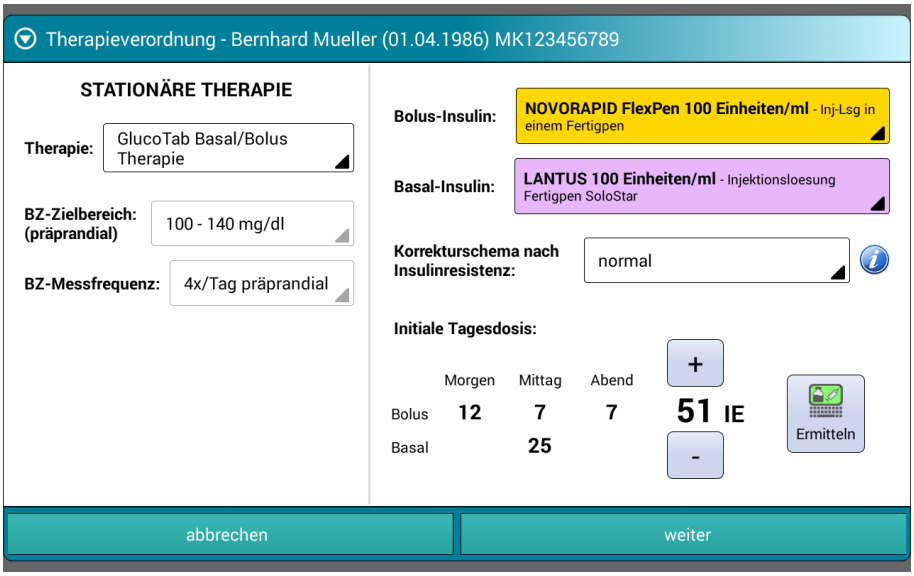

Figure 22 Physician's order at therapy start of GlucoTab decision support for basal-bolus insulin algorithm

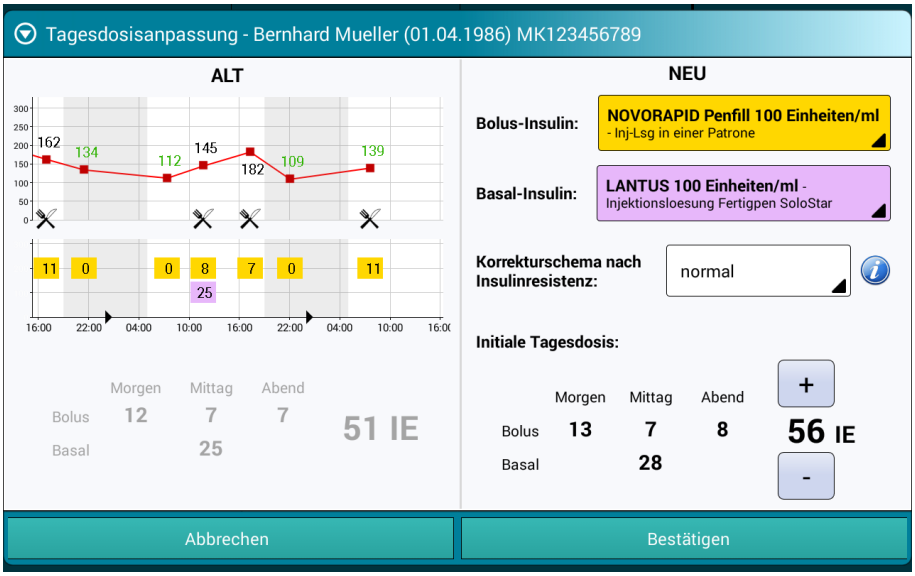

Figure 23 Concept of insulin therapy adjustment by nurses with the GlucoTab system

Condition 3

„Angehörige des gehobenen Dienstes für Gesundheits- und Krankenpflege haben unverzüglich den/die anordnende/n Arzt/Ärztin zu verständigen, wenn Werte (z.B. Blutzucker) ermittelt wurden, die außerhalb des festgelegten Intervalls liegen.“ (Bescheid BMG)

Under the following conditions the nurse must inform the physician when performing the therapy adjustment for the next 24 hours:

(1) adjustment of insulin sensitivity,
(2) adjustment of insulin types,
(3) increasing/reducing the suggested insulin dose by more than a specified percentage,
(4) very high TDD (e.g. >200% of initial TDD) and
(5) occurrence of a critical BG value within the last 24 hours (Figure 24).

In addition, nurses are obliged to inform the attending physician when the individual suggested insulin dose is changed by more than a certain percentage. The obligation to inform after a critical hypo- and hyperglycaemic BG value (e.g. <50 mg/dl, >400 mg/dl) is also recommended.

The physician confirms verbal orders on the GlucoTab screen *Mündlichen Anordnung* (Figure 25). Health care professionals in each hospital can adapt the conditions under which the nurse must inform the physician.

Condition 4

„Angehörige des gehobenen Dienstes für Gesundheits- und Krankenpflege sind nachweislich auf das entsprechende technische Hilfsmittel einzuschulen.“ (Bescheid BMG)

A training course for nurses and physicians is obligatory based on the Ordinance on Medicinal Products (Medizinproduktebetreiberverordnung). Therefore, nurses and physicians are demonstrably trained by using a protocol. The clinical ward is responsible for performing the training course. The manufacturer of the GlucoTab system supports the clinical ward by delivering a training concept and materials.

Figure 24 Concept of nurses' information obligation of therapy adjustment with a high BG value within the last 24 hours

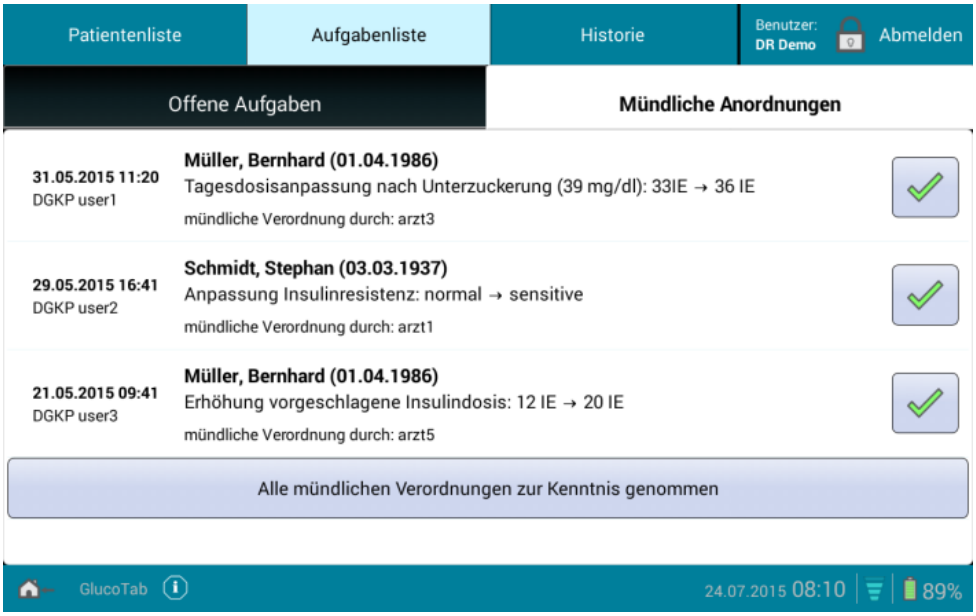

Figure 25 Concept of physician's task list of verbal orders

Condition 5

„Die Kontinuität in der Verwendung des technischen Hilfsmittels auf der betreffenden Abteilung wäre sicherzustellen.“ (Bescheid BMG)

The continuous use of GlucoTab at clinical wards and the continuous application of GlucoTab for individual patients are essential and should be ensured. The soon-to-be use of the GlucoTab system for all patients with different antidiabetic therapy types helps to ensure this goal. This condition is fulfilled, due to the fact that the GlucoTab system will be used for all patients with different antidiabetic therapy types. Furthermore, the decision support of the GlucoTab stops when the defined conditions are not fulfilled. Additionally, the GlucoTab system needs to be serviced regularly to guarantee its functionality.

Based on a confirmation of the nursing head of the LKH-Univ.Klinikum Graz this concept will be implemented into the GlucoTab software. Then, this innovative feature will be evaluated in a feasibility study in clinical practice at the LKH-Univ.Klinikum Graz.

SUMMARY OF INSULIN THERAPY ADJUSTMENT BY NURSES

The aim of Study 7 was to develop a concept that will allow insulin therapy adjustments by nurses including workflow simplifications and how to react in critical situations of glycaemic management in the hospital.

The Austrian Federal Ministry of Health now permits insulin dose adjustment by nurses under certain conditions. These conditions are fulfilled within an innovative feature of the GlucoTab system. Therefore, for the first time it is legally allowed in Austria that nurses adjust insulin therapy when supported by technology for standardised glycaemic management (e.g. GlucoTab system). The innovative feature of the GlucoTab system will be evaluated in cooperation with the nursing head at the LKH-Univ.Klinikum Graz.

CHAPTER 4

GENERAL DISCUSSION

GENERAL DISCUSSION

The following chapter summarises and discusses the main results of the doctoral thesis. A methodological reflection of the conducted studies and an outlook of ongoing GlucoTab research are provided.

The overall aims of this thesis were (A) to determine the quality of state of the art of glycaemic management in the hospital, (B) to develop and evaluate a paper-based algorithm for basal-bolus insulin therapy and (C) to develop and evaluate the workflow and decision support system GlucoTab in hospitalised patients with type 2 diabetes.

STATE OF THE ART ANALYSIS

In Study 1 the effects of a physician-based standard glycaemic management at two general hospital wards were assessed retrospectively. Glycaemic management effort in relation to standard glycaemic care parameters was analysed. In both wards approximately two-thirds of patients' BG values remained >140 mg/dl, indicating a failure to control hyperglycaemia regarding recent international recommendations for glycaemic control in non-critically ill patients with diabetes [1, 20, 21].

Very few hypoglycaemic events <70 mg/dl occurred, whereas a substantial proportion of hyperglycaemic events >300 mg/dl was documented. These results are just presenting the quality of glycaemic management of two hospital wards. However, the results are similar to other retrospective studies of glycaemic control reporting that hyperglycaemia was common in a clinical setting, but hypoglycaemic events were rare. Retrospective and prospective studies outlined the same difficulties even when a higher BG level of 180 mg/dl had been set as the target [1, 6, 38–40].

Study 1 assessed, whether persistent hyperglycaemia might have been caused by insufficient glycaemic management effort or heavy workload. No ward reported a significant change from first to second half, neither in the number of BG measurements or the number of insulin injections per day nor in the insulin dose adjustments. Basal-bolus insulin therapy, which is considered as a key intervention by international guidelines, was not routinely used and although insulin dosing was individually adjusted, it did not result in a significant improvement of glycaemic control [1].

Although many studies reported similar values of hyperglycaemia in a hospital setting independent of the glycaemic management protocols, it is difficult to find a common explanation. The failure to adhere to BG target values and avoid hyperglycaemia is caused by a number of factors, such as lack of training, health care professionals' fear 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 [12, 23, 24]. Often, physicians are aware of diabetes and stress hyperglycaemia at admission, but during hospitalisation this diagnosis is often considered secondary [38]. Skepticism about the benefit of tighter glycaemic control also contributes to this problem [1, 41].

Although it was not possible in Study 1 to identify a single underlying reason for the lack of improvement from the first to the second half of patients' stays, the findings provide a starting-point on how to assess and improve glycaemic management in non-critically ill patients in the hospital [1]. Periodical quality assessment and standardised audits comparable to the National Diabetes Inpatient Audit in England are an important tool to further improve glycaemic management in the hospital. As a starting point, the project *DiabCurve* was initiated, which aims to assess the quality of glycaemic management at the LKH-Univ.Klinikum Graz and to develop and implement a standardised diabetes patient record. Such projects should be rolled out nationally.

In addition, educational training or algorithms could lead to adequate insulin adjustments to improve glycaemic management [1, 21, 24, 42, 43]. Based on Study 1 and international findings two important components, ***workflow support***

and ***decision support*** were identified to improve standardised glycaemic management in the hospital: These two components are discussed below.

WORKFLOW SUPPORT

Based on Study 1 and international findings a paper-based algorithm was modified and applied as an intermediate step in the design of a computerised workflow and decision support system. In Study 2 the paper-based workflow-integrated algorithm for basal-bolus insulin therapy was evaluated. Results of Study 2 demonstrated that the use of the workflow-integrated algorithm was efficacious in establishing glycaemic control in hospitalised patients with type 2 diabetes. Additionally, the evaluation indicated that health care professionals had a high adherence rate to the provided paper-based workflow process [2].

The workflow-integrated algorithm included the following essential components: First, a standardised protocol for initialisation of insulin therapy at admission was provided for physician considering individual patient's characteristics. The second component of the standardised workflow support affected nurses and included four times daily BG measurements and four times daily insulin injections taking into account the nutritional intake and a correctional insulin dose. Third, the workflow-integrated algorithm suggested a daily standardised insulin adjustment during ward round.

In Study 2 the provided workflow support was paper-based and health care professionals calculated each insulin dose manually according to the protocol. Despite this paper-based glycaemic management effort, health care professionals highly adhered to the paper-based algorithm and felt confident using the standardised workflow support.

Furthermore, in the algorithm group, the mean BG values were more often within target range and well comparable to BG values established in previous randomised studies using basal-bolus algorithms [2, 25–27]. In Study 2 the treatment allocation was not randomised but ward-controlled to avoid a carry-over effect caused by biased treatment of algorithm-trained health care professionals.

However, in the algorithm group the integration of the algorithm in the daily workflow of a general hospital ward was assessed additionally by thorough documentation: For the first time, a CGM system was used to closely monitor BG values and retrospectively assess efficacy of the algorithm. Such a detailed workflow analysis supported the development and improvement of a decision support system for in-hospital glycaemic management [2]: 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 [44]. Elevated lunch BG values required higher bolus insulin doses at lunch and could have caused hypoglycaemic events in the afternoon that were also indicated by CGM. In the feasibility Study 3, strategies, such as shifting more units of the daily bolus insulin to the morning dose were evaluated to minimise the BG peak value at noon and the risk of hypoglycaemia in the afternoon [2]. Based on the successful results using the modified bolus insulin dosing (45% breakfast bolus, 25% lunch bolus, and 30% dinner bolus) this distribution was maintained. Therefore, CGM data provided BG patterns that would not have been recognised by using point of care measurements only [45, 46].

The rigorous evaluation and the highly user-accepted paper-based workflow-integrated algorithm in Study 2 pushed the design of an innovative system. The next step of the development and evaluation was to provide a user-friendly computerised workflow and decision support system helping to simplify glycaemic management for health care professionals compared to the paper-based algorithm.

DECISION SUPPORT

Across a variety of clinical settings the implementation of a decision support system has improved performance by an increased adherence to guidelines, reduced prescription errors, and enhanced monitoring of patients [47–51]. Although the use of electronic prescriptions has been recommended in diabetes care guidelines as a key strategy to provide an efficient inpatient management [20], a recent review of clinical decision support systems found only two cluster-randomised studies applying such systems in inpatient diabetes care [52]. 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 values relative to standard insulin treatment [20]. However, glycaemic control was moderate (algorithm group: 195 ± 66 mg/dl vs. standard group: 224 ± 57 mg/dl) compared to Study 3. Additionally, 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 values >180 mg/dl for the algorithm vs. the standard group (76% vs. 63%) [53].

Additionally, providing a computerised order set in daily routine care does not guarantee an efficient implementation of the electronic tool [54] as not all advices seem to be adhered to [55]. In order to increase the use by health care professionals, it is important to consider organisational and contextual characteristics when designing a computerised decision support system [52].

In Study 2, the integration of the algorithm in the workflow of daily routine care met these requirements. The high adherence of health care professionals to the paper-based algorithm-calculated dose and the positive response in the questionnaire indicated a successful integration into daily routine care. These findings supported the implementation of the algorithm in a computerised decision support system [2] and the idea to develop a modern, flexible and an intelligent system was born. The GlucoTab system aims to support clinical decision making, to balance missing, reduced or forgotten expertise and knowledge and to implement evidence-based guideline recommendations regarding glycaemic management in the hospital. By using a mobile device, glycaemic management is more flexible and easier to

handle. It allows decision support and documentation at point of care and thereby reduces medication errors and increases quality of glycaemic management [56]. Algorithm components of the decision support such as considering renal function, patient's age, weight, current BG values, nutritional intake, insulin on board etc. contribute to improved glycaemic control in hospitalised patients with diabetes. A future feature should enable automated documentation of measured BG values in the GlucoTab patient record by using automated data transfer between the Glucometer and the GlucoTab. This feature should minimise transcription errors and reduce nurses' workload.

In Study 3 and 4 the adherence to the workflow and decision support for the TDD and each individual insulin dose was high. The great number of BG measurements and insulin injections according to suggested standardised care showed that the GlucoTab system was highly accepted and continuously used by health care professionals and that it was able to successfully guide glycaemic management processes. This was also confirmed by the user questionnaires and by the tight adherence of health care professionals to the suggested insulin doses. Adherence of health care professionals was considerably higher than in previous studies [53, 57]. Schnipper et al. performed a study on computerised order sets and reported that 67% of the patients received an adequate initial dose of nutritional insulin and that in only 37% of the patients insulin orders were changed [3, 53]. This computerised order set only supported physicians in initialising insulin therapy. The GlucoTab system also supports nurses in decision making for each individual insulin dose. Such a workflow and decision support for nurses has not yet been developed and evaluated.

Based on the high adherence rate to the decision support of the GlucoTab system it was considered that it should be permitted for nurses to perform daily insulin adjustments when supported by IT technology. Therefore, the innovative feature *insulin adjustment by nurses* was conceptualised. Based on a dialog with the Austrian Federal Ministry of Health, for the first time it is legally allowed that nurses adjust insulin therapy. This is a successful milestone in the nursing profession in Austria and has a political impact. The concept *insulin therapy adjustment by nurses* was approved by the nursing head of the LKH-Univ.Klinikum Graz. After the implementation, this innovative feature will be evaluated in clinical practice.

Special endpoints have to be defined to evaluate the impact of the modified glycaemic management processes. Additionally, this new feature of the GlucoTab system could also be relevant for other settings (e.g. nursing home, home care) and other countries. An investigation of the legal regulations in other countries has to be carried out.

GLUCOTAB AT GENERAL WARDS – THE APPROVAL STUDY

The development and evaluation of the GlucoTab system was the main focus of this doctoral thesis. Therefore the GlucoTab system was developed with a strong focus on quality and risk management and an approval study at different hospital wards was performed to evaluate the efficacy and safety of the GlucoTab system for CE marking. Nevertheless, a randomised controlled trial with the GlucoTab system, which should investigate endpoints such as economic impact and patient outcomes (infection rate, length of hospital stay, re-admission rate, mortality, etc.), is still missing. However, in Study 1 the retrospective assessment of glycaemic control at two wards achieved 57% (Endocrinology) and 51% (Cardiology) in range 70-180 mg/dl in routine care, respectively. Compared to that, the results of Study 2 showed that patients in the paper-based basal-bolus algorithm group had a significantly higher percentage of BG values in the range 70-180 mg/dl than patients in the routine care group (73% vs. 53%). These data and results of Study 4 indicate that glycaemic control was improved by the use of the GlucoTab system compared to the routine care [3].

Furthermore, data of Study 4 showed that standardised glycaemic management guided by the GlucoTab system for workflow and decision support was implemented efficiently and safely at different wards in the hospital. 50.2 $\pm$ 22.2% of BG measurements were in the target range (70-140 mg/dl) when using GlucoTab. Moreover, the system was implemented without any occurrence of severe hypoglycaemia (<40 mg/dl) [3] and a low risk of hypoglycaemia. Hypoglycaemic events were evenly distributed among patients. The percentage of BG measurements in the different hypoglycaemic ranges and in the target range were similar to those found in comparable studies, although diabetes duration was longer and the level of patients previously treated with insulin were higher in

GlucoTab Studies. In the study by Umpierrez & Gianchandani et al. (2013), the number of hypoglycaemic events was lower. However, the sample size was relatively small and only patients with low-dose insulin therapy were included in the study (Table 17) [25–27, 58]. A lot of reasons may have contributed to the low rate of hypoglycaemic events in GlucoTab Studies (e.g. the insulin on board calculator, insulin sensitivity, daily insulin dose adjustment, reduced calculation and prescription errors by using a computerised system) [36, 56]. However, retrospective CGM data of Study 3 and 4 showed an additional proportion of low glucose values overnight. It might be interesting, if undetected low glucose values overnight would have any influence on decision making of health care professionals or even on clinical patient outcomes [46].

Table 17 Hypoglycaemic events with GlucoTab compared to best practice studies

Study	Study 2	Study 3	Study 4	Study 5	Umpierrez, Smiley et al. 2013	Umpierrez, Gianchandani et al. 2013	Umpierrez et al. 2011	Umpierrez et al. 2007
Patients (n)	37	15+15	99	92	144	26	104	65
Insulin therapy (admission, %)	54	87	80	66	20	38*	20	0
Diabetes duration (years)	14	14/17	14	15	10	8	6	-
BG values <70 mg/dl (%)	3.0	1.7/1.5	1.9	2.3	1.7	0.9	2.0	-
BG values <60 mg/dl (%)	0.9	0.4/0.2	0.5	0.6	0.7	0.0	0.8	0.4
BG values <40 mg/dl (%)	0.1	0.0	0.0	0.0	0.1	0.0	0.2	0.0

*low insulin dose: ≤0,4 IU/kg/day

In conclusion, data of Study 4 demonstrated that the GlucoTab system allowed an efficacious and safe implementation of standardised glycaemic management in different general wards in the hospital setting. This was also confirmed in a Commentary of Guillermo Umpierrez, a high-ranking international scientist and the author of the comparable randomised best-practice studies. Gianchandani & Umpierrez (2015) stated that based on results of Study 4 the GlucoTab system potentially can simplify glycaemic management in hospitalised patients. Such

systems are welcome, especially when diabetes experts or teams are not available to guide insulin therapy adjustment [36].
Consequently, the system can support health care professionals in improving glycaemic management relying on evidence based guidelines for non-critically ill hospitalised patients [3] which was demonstrated in Study 5. The GlucoTab system was implemented at three general hospital wards to evaluate the safety and efficacy of the GlucoTab system in routine care. Overall the GlucoTab supported a safe glycaemic management in routine care and the risk of hypo- and hyperglycaemia was low and comparable with Study 4. Due to the effective and safe results of Study 5 the GlucoTab system is currently used in routine care and evaluation is ongoing to investigate future versions of the GlucoTab system.

Based on the successful studies with the GlucoTab system, the patent *insulin dosage proposal system* (PCT/EP2015/059880) was applied.

BASAL BOLUS INSULIN ALGORITHM

The successful decision support of the GlucoTab system is based on a basal-bolus insulin algorithm which was further developed and evaluated within the Studies 2, 3 and 4. Previous findings and recent guideline recommendations have demonstrated that fine-tuning of the algorithm is required. Additionally, decision support for other innovative features which are illustrated below is recommended.

According to the regression analysis of Study 4, further fine-tuning of the basal-bolus insulin algorithm may be required for a more personalised care. The pre-existing home insulin therapy, the HbA1c value in addition to the type of hospital admission, acute cardiac events (most resistant patient group) and the first TDD might be essential factors that influence the mean BG values during hospitalisation. Thus, these factors should be considered for a more personalised algorithm [3].

Furthermore, patients with impaired renal function in Study 4 were initiated with a lower TDD of 0.3 units per bodyweight. Fewer patients at Nephrology ward reached the glycaemic target range. A personalised algorithm may suggest

several different insulin starting doses. Criteria for a personalised algorithm have to be defined for an ongoing development of the GlucoTab.

Another concept for fine-tuning of the algorithm affects strategies, such as administration of basal insulin at other day times. The administration of basal insulin at other day times should be evaluated to further minimise the risk of hypoglycaemia and elevated pre-lunch BG values. In Study 5, the mean BG values in different day times were comparable with mean BG values of Study 4. However, the highest difference was observed between the pre-lunch BG values (186 ± 45 vs. 170 ± 54 mg/dl).
Despite the modified distribution of bolus insulin since Study 3, mean pre-lunch BG values were still higher than mean BG values at other day times and higher CGM postprandial glucose excursions were observed compared to other meals during the day. Reasons for the higher insulin requirements may be due to the large carbohydrate load at breakfast, the dawn phenomenon, or a late breakfast with delayed insulin administration [36].
It should be noted that the GlucoTab suggests basal insulin administration before lunch allowing physicians to evaluate the insulin dose response of the last 24 hours before modifying it and also reducing the basal insulin dose if the administration is delayed.
Furthermore, Gianchandani & Umpierrez (2015) stated in their Commentary that patients in the hospital, especially those with impaired renal function, have a high insulin sensitivity overnight and less hypoglycaemic events when administering basal insulin at daytime [36].
Basal insulin dose administration at other day times (morning, afternoon) will be evaluated in a pilot study. The use of CGM systems for detailed analysis is recommended.

Another concept for fine-tuning of the algorithm affects individualised glycaemic target ranges. By using the GlucoTab system in different age groups in Study 6, the overall mean BG values were comparable in adult and geriatric patients. The standardised insulin starting dose suggested by the GlucoTab system with 0.5 and 0.3 units per kg bodyweight supported an efficacious and safe glycaemic control for adult and geriatric patients during hospital stay.

However, glycaemic goals might reasonably be relaxed in some older patients with diabetes in the hospital. The avoidance of hyperglycaemia and symptoms or risks of hyperglycaemic complications should be taken into account [22].
A more personalised approach needs to be developed and evaluated [3] because the American Diabetes Association recently recommended modified glycaemic target ranges for non-critically ill patients with diabetes. This guideline recommends a target range of 140-180 mg/dl for the majority of non-critically ill patients. A basal plus a correctional bolus insulin therapy should be the preferred method in patients with poor nutritional intake. For patients with good oral intake an insulin therapy with basal, nutritional and correctional insulin should be considered [22]. Therefore, it should be focused on modifying the basal-bolus algorithm for several individualised target ranges based on patients nutritional intake or health status [59].

Basal-bolus insulin therapy is the preferred method for the majority of hospitalised patients due to the flexible treatment regime considering individual influencing factors of patient's health status (nutritional intake, current BG value etc.). However, patients stay only few days in the hospitals and it is essential to prepare glycaemic management and the best therapy for the individual patient after discharge. Because of the complexity of a basal-bolus insulin therapy, this might not be the preferred method for the majority of patients after hospital discharge. Therefore, international guidelines recommend the implementation of structured discharge plans tailored on the individual patient [63]. A decision support feature of the GlucoTab may guide health care professionals in standardised discharge management for the individual patient.

Further, it should be considered, that a basal-bolus insulin therapy might not be the preferred method for all hospitalised patients with diabetes. In Study 5, there were only 17 (18.5%) patients for whom GlucoTab was used during the complete hospital stay. The use of the GlucoTab treatment during hospital stay was 72.5 ± 22.2%. The use of GlucoTab treatment demonstrates that decision and documentation support systems for alternative therapy types (e.g. basal only, prandial insulin therapy) are urgently needed. The future feature *documentation of other therapy types* will consider individual frequency of BG measurements and freely selectable BG target ranges. In addition, short acting insulin and correctional

schemes with automated insulin dose calculation will be supported by the GlucoTab system. After implementation of the feature *documentation of other therapy types*, the GlucoTab system should be implemented and evaluated in other hospitals. It also should be borne in mind that the decision support system might be more powerful if it is integrated into an in-hospital electronic medical record [36].

Additionally, decision support for other insulin algorithms should be developed to support nurses and physicians in routine care. For example, an algorithm for basal insulin is needed for geriatric patients or patients with less insulin resistance. The concept of such an algorithm considering patient's health status has already been developed and will be evaluated in an acute geriatric care hospital. After evaluation of this concept, this algorithm might be implemented and further adapted for other settings. Furthermore, the need of a mixed insulin algorithm should be reconsidered.
After the evaluation of the basal-insulin algorithm the GlucoTab system will be expanded for other health care settings (long-term care, home care). As a first step a workflow analysis and a quality assessment of glycaemic management in other institutions (acute geriatric care and long-term care facilities) have been performed. Based on this analysis further research is ongoing.

Last but not least, another focus lies on tele monitoring supported by the GlucoTab system. The GlucoTab system could be integrated in a disease management program for diabetes including a tele monitoring system. Health care professionals, patients and relatives could be supported in simplifying and handling glycaemic management.

Within this doctoral thesis, the development and evaluation of the GlucoTab system was a starting point to improve glycaemic management in the hospital. Ongoing projects show that there are a lot of possibilities to further improve glycaemic management and patient outcomes. Health care professionals and patients in the hospital and other health care settings need to be further supported.

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LIST OF FIGURES

LIST OF TABLES