# Summary of results

**PROPRIETARY DRUG NAME® / GENERIC DRUG NAME:** Insulin Glargine (Lantus®, Solostar®) and Insulin Aspart (Novorapid®, Flexpen®)

**PROTOCOL TITLE:**

English title: An open, single-centre, controlled trial to investigate the efficacy and usability of published best practice to control glycemia in hospitalised patients with type 2 diabetes

German title: Offene, monozentrische, kontrollierte Studie zur Untersuchung der Effizienz und Anwendbarkeit von publizierter, bester therapeutischer Praxis um den Blutzucker in hospitalisierten Patienten mit Typ 2 Diabetes einzustellen.

**Research Article title:**

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

**Sponsor Details:**

Organisation Details

Principal investigator and Sponsor: Univ. Prof. Dr. Thomas Pieber, Medical University of Graz, email: thomas.pieber@medunigraz.at

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**Study Centers:**

Medical University of Graz (Division of Endocrinology and Metabolism, Division of Cardiology)

**Study Initiation and Final Completion Dates:**

| | |
|---|---|
| FPFV | 08-Jul-2011 |
| LPLV | 23-Apr-2012 |

**Study Objectives:**

The primary objective was to compare the efficacy of enhanced published best practice paper-based insulin titration protocol for glycemic control in hospitalised patients with type 2 diabetes for the length of hospital stay, with a maximum of 21 days.

The secondary study objectives were to evaluate safety, efficacy and usability of the enhanced published best practice paper-based insulin titration protocol for glycemic control in hospitalised patients with type 2 diabetes, with a maximum of 21 days.

**METHODS:**

Table – Baseline characteristics of study population

| | Algorithm Group | Standard Group |
|---|---|---|
| n | 37 | 37 |
| Gender, f (%) | 11 (30%) | 13 (35%) |
| Age (years) | 70 ± 12 | 67 ± 9 |
| BMI (kg/m$^2$) | 29.7 ± 6.8 | 30.5 ± 6.6 |
| Weight (kg) | 84.0 ± 19.1 | 88.3 ± 21.1 |
| Race (caucasian/other) | 35/2 | 37 |
| Serum creatinine (mg/dl) | 1.5 ± 0.5 | 1.2 ± 0.4 |
| HbA1c (%) | 9.1 ± 2.8 | 8.3 ± 1.8 |
| Diabetes duration (years) | 14 ± 12 | 12 ± 7 |

**Number of Subjects:** n=37 in algorithm group, n=37 in standard group

**Diagnosis and Main Criteria for Inclusion:**

Inclusion Criteria:

- Informed consent obtained after being advised of the nature of the study
- Male or female aged 18 - 90 years (both inclusive)
- Type 2 diabetes (diagnosed at least 3 months prior to study start) treated with diet, oral agents, non-insulin injected anti-diabetic medicine, insulin therapy or any combination of the four
- Blood glucose in the range between 7.8-22.2 mmol/l
- Expected stay ≥ 48 hours

Main Exclusion criteria

- Hyperglycemia without known history of type 2 diabetes mellitus
- Impaired renal function (serum creatinine ≥3.0mg/dL)
- Clinically relevant hepatic disease
- Presence or history of diabetic ketoacidosis
- Pregnancy
- Any mental condition rendering the patient incapable of giving his consent
- Terminally ill patients
- Participation in a trail within 3 months prior to this trail
- Known or suspected allergy to insulin

**Safety assessments:**

Subcutaneous insulin therapy is an established method in hospital practice and recommended to control glycaemia in the hospital setting. In previous investigations glycaemic control could be established safely following the advice of the paper-based protocol and was superior as compared to routine care (Umpierrez et al 2007, 2009, 2011). A recent audit of local glycaemic management revealed levels above the recommended target range. Thus, the patients may directly benefit from the implementation of enhanced published best practice paper-based insulin titration protocol by means of improved blood glucose control.

The nursing staff could at any time decide to take an additional blood glucose measurement and/or neglect the decision as suggested by the enhanced published best practice paper-based insulin titration protocol in case an advice generated is implausible and could possibly endanger the

patient's health. For glucose measurement, routine standard devices were being used (Accuchek Inform®). For subcutaneous insulin injection standard insulin (Insulin Lantus®, insulin Novorapid®) as it was also used under routine conditions in the hospital is being used during this study.

Beside this, all patients were treated according to the standard clinical practice of the hospital. After discharge the study had no consequences for the patients. The patients, who were treated with insulin during the hospital stay, received after discharge their usual anti-diabetic medication unless a further insulin therapy is indicated by the treating physician.

Adverse Events (AEs) were defined as any undesirable experience occurring to a patient during the trial, whether or not considered related to the method under investigation. All AEs reported spontaneously by the patient or observed by the investigator or the nurses were recorded.

**Statistical analysis:**

The primary endpoint was defined as the mean daily blood glucose (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 [Diabetes Care 2011;34:256–261] and on a pretest chart review, which was conducted at the two wards [Neubauer et al. 2012, Diabetes 2012;61:A628]. For sample size determination, we anticipated that with algorithm treatment, the mean daily BG per treatment day can be reduced from 9.4 ± 2.2 mmol/l (baseline) to an outcome of 8.0 ± 1.9 mmol/l. A one-tailed matched pairs t-test with 2.5% level of significance, power of 80% and a correlation between paired measurements (corresponding to the beginning and the end of treatment) of 0.15 would require a total of 33 patients. To also correct for a drop-out rate of ~10% [Umpierrez et al. 2011], the number of patients was increased to 37. Analysis was based on the intention to treat population. For the remaining analyses Pearson's chi-squared tests were used to analyze nominal data. Fisher's exact test was computed when a table had a cell with an expected frequency <5. Prior to data analysis, all metric outcome variables were checked for normality by means of a Shapiro-Wilk's test. Normally distributed metric variables were tested with Student's t-test. In case of not normally distributed metric variables, nonparametric tests were applied. We used Wilcoxon's signed rank test for matched samples, and the Mann-Whitney U test for independent observations. The level of significance was set to 5% for all tests. The statistical analysis was performed using R.2.13.1 software.

**Results:**

**Glycemic control**

Mean daily BG (primary endpoint) in the algorithm group decreased significantly from baseline to the last 24 hours of hospital stay (from 11.3 ± 3.6 mmol/l to 8.2 ± 1.8 mmol/l, $p<0.001$). In the algorithm group, nine BG values in a total of five patients (14%) were <3.3 mmol/l (0.9% of all measurements), including one event <2.2 mmol/l. None of the events was associated with unconsciousness or required intravenous glucose infusion. In the standard care group no BG value was <3.3 mmol/l. For the entire study population no hypoglycemia related adverse outcomes were reported.

The percentage of bolus BG values in the target range (5.6-7.8 mmol/l) was significantly higher in the algorithm group (34%) compared with the standard care group (23%, $p<0.001$). Similarly, a significantly higher percentage of patients in the algorithm group had BG levels between 3.9 - 10.0 mmol/l (73% vs. 53%, $p<0.001$).

**Glycemic management**

In the algorithm group the mean TDD was 41 ± 30 IU. The mean daily bolus insulin dose (23 ± 16 IU) was significantly higher than the mean daily basal insulin dose (19 ± 14 IU, $p<0.001$). In the standard care group 24 patients were on oral agents during the hospital stay. The mean daily insulin dose was

20 ± 16 IU in 28 patients receiving any insulin therapy during the hospital stay. In the standard care group no basal insulin was given to patients without pre-existing insulin therapy at any time.

There was a 95% physicians' adherence to the algorithm-calculated TDD and a 98% nurses' adherence to the algorithm-calculated basal dose and 93% adherence to the algorithm-calculated bolus dose. 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 ($p>0.05$).

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

**Conclusion:**

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

In the algorithm group, the mean achieved BG levels were significantly more often within target range and well comparable to BG levels established in previous trials using basal-bolus algorithms [Umpierrez et al. 2011]. The integration of the algorithm in the daily workflow of a general ward was assessed by thorough documentation. Such a detailed workflow analysis will enable us to support future development of a decision support system for in-hospital glucose management.

This study, which applies a paper-based algorithm, is an intermediate step in the design of a computerized decision support system. Across a variety of clinical settings the implementation of such systems has been shown to improve performance by an increased adherence to guidelines, reduced prescription errors, and enhanced monitoring of patients. Although the use of electronic prescriptions has been cited in diabetes care guidelines as key strategy to provide an efficient inpatient management.

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

In summary, we successfully demonstrated the implementation of a paper-based workflow-integrated algorithm for basal-bolus insulin therapy in hospitalized patients with type 2 diabetes by means of adequate glycemic control and high user acceptance rate. Overall, our findings support the implementation of the algorithm in an electronic decision support system.