A comparison of two insulin infusion protocols in the medical intensive care unit by continuous glucose monitoring

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Abstract

Background: Achieving good glycemic control in intensive care units (ICU) requires a safe and efficient insulin infusion protocol (IIP). We aimed to compare the clinical performance of two IIPs (Leuven versus modified Yale protocol) in patients admitted to medical ICU, by using continuous glucose monitoring (CGM). This is a pooled data analysis of two published prospective randomized controlled trials. CGM monitoring was performed in 57 MICU patients (age 64 ± 12 years, APACHE-II score 28 ± 7, non-diabetic/diabetic: 36/21). The main outcome measures were percentage of time in normoglycemia (80–110 mg/dl) and in hypoglycemia (<60 mg/dl), and glycemic variability (standard deviation, coefficient of variation, mean amplitude of glucose excursions, mean of daily differences).

Results: Twenty-two subjects were treated using the Leuven protocol and 35 by the Yale protocol; >63,000 CGM measurements were available. The percentage of time in normoglycemia (80–110 mg/dl) was higher (37 ± 15 vs. 26 ± 11%, p = 0.001) and percentage of time spent in hypoglycemia was lower (0[0–2] vs. 5[1–8]%; p = 0.001) in the Yale group. Median glycemia did not differ between groups (118[108–128] vs. 128[106–154] mg/dl). Glycemic variability was less pronounced in the Yale group (median SD 28[21–37] vs. 47[31–71] mg/dl, p = 0.001; CV 23[19–31] vs. 36[26–50]%, p = 0.001; MODD 35[26–41] vs. 60[33–94] mg/dl, p = 0.001). However, logistic regression could not identify type of IIP, diabetes status, age, BMI, or APACHE-II score as independent parameters for strict glucose control.

Conclusions: The Yale protocol provided better average glycemia, more time spent in normoglycemia, less time in hypoglycemia, and less glycemic variability than the Leuven protocol, but was not independently associated with strict glycemic control.

Keywords: Intensive care unit, Continuous glucose monitoring, Insulin infusion protocol, Hypoglycemia

Background

Consensus exists that overt hyperglycemia (>150 mg/dl) in patients admitted to the intensive care unit (ICU) should be treated to improve morbidity and survival [1]. However, there is little agreement on the ideal target range of glycemia [2]. Strict glycemic control (80–110 mg/dl) is no longer recommended for most ICUs, but in highly standardized ICUs a strict target may be feasible without increasing hypoglycemia. Achieving strict glycemic control is a complex task since during ICU stay severity of illness and degree of insulin resistance may fluctuate, nutritional delivery may change, and interventions (e.g., administration of corticosteroids) may produce frequent changes in insulin needs [2]. Therefore, multiple insulin infusion protocols (IIPs) were created, all meant to balance efficacy with safety (avoid hypoglycemia), and attainability (nursing workload).

So far, no single IIP has been established as the most effective for obtaining tight glycemic control. Earlier observational studies and randomized controlled trials...
(RCTs) in medical ICU (MICU) or mixed ICU settings, and targeting a glycemia between 80 and 110 mg/dl, reported that 22–60% of all blood glucose values were in target for paper-based IIPs [3–14], compared to 42–69% for computerized decision-supported algorithms [4, 10, 11, 14, 15]. The efficacy and safety of different IIPs on glycemic control have recently been investigated using computer simulation models [16, 17] and in RCTs in cardiac surgery patients [18, 19]. However, to the best of our knowledge, comparing the effect of different IIPs in patients admitted to MICU, by means of continuous glucose monitoring (CGM), allowing a complete picture of glucometrics.

Methods
This is a pooled data analysis of two published prospective RCTs [5, 6], we assessed the clinical performance of two IIPs (Leuven versus modified Yale protocol) in patients admitted to MICU, comparing the effect of different IIPs on glycemic control has never been investigated in MICU patients. With this pooled data analysis of two published prospective RCTs [5, 6], we assessed the clinical performance of two IIPs (Leuven versus modified Yale protocol) in patients admitted to MICU, by means of continuous glucose monitoring (CGM), allowing a complete picture of glucometrics.

Glucose monitoring
Forty-eight-hour CGM was initiated within the first 48 h after admission using a microdialysis-based device that is not equipped with alarms (GlucoDay® in the first study and GlucoDay®S in the second study, A. Menarini Diagnostics, Florence, Italy). The methodology has been described before [5, 6]. Briefly, a microdialysis fiber (Medica, Medolla, Italy) was inserted subcutaneously into the periumbilical region using an 18-gauge Teflon® (DuPont, Wilmington, DE) catheter as a guide. The device does not use any coagulant. The device uses a glucose oxidase-based amperometric biosensor to measure glucose concentrations in the interstitial dialysate every 3 min over a 48 h period.

Data analysis for accuracy and glucometrics was performed by applying, in silico to the CGM signal, a two-point calibration according to the manufacturer’s requirements (one calibration every 24 h). This was performed in order to avoid an overestimation of the system’s accuracy if one uses a higher number of calibration points. In the RT-CGM group, however, to be as safe as possible and to account for possible changes in subcutaneous glucose recovery due to hemodynamic alterations (e.g., hypotension, shock, vasoactive drugs), for each sensor, a six-point calibration was performed (after 2, 6, 12, 18, 24, and 36 h) using arterial BG values, but these data were not used for statistical analysis [6]. This was done to assure that the glucose readings and trends shown by RT-CGM would be clinically reliable. At present, RT-CGM is becoming more common practice, but at the time of the study, a real-time CGM device was not approved to make clinical adjustments of insulin therapy, and our ethical committee would not approve clinical decisions to be made solely on the basis of RT-CGM at that time. In order to avoid clinical decisions being made on potentially inaccurate CGM data, nurses had to take an additional arterial blood glucose sample. Thus, direct corroboration of the data was explicitly needed. The RT-CGM system was thus used only as a prompt to take an extra blood glucose sample if the rate of change in glucose exceeded 25 mg/dl per 30 min. Since no differences in glucometrics were observed in the REGIMEN trial between in patients randomized to RT-CGM versus blinded CGM, we pooled the data. For all patients, adjustments of insulin therapy were made on the basis of arterial blood glucose values [6].

Insulin infusion protocols
Twenty-two patients received continuous IV insulin (regular insulin Actrapid; Novo Nordisk, Bagsvaerd, Denmark) according to the Leuven protocol, targeting a blood glucose between 80 and 110 mg/dl [5, 13]. Thirty-five subjects were treated with IV insulin (insulin aspart, Novo Nordisk, Bagsvaerd, Denmark) according to a modified Yale protocol, targeting a blood glucose level between 80 and 120 mg/dl [6].

In both groups, arterial blood glucose levels were measured using an on-site blood gas analyzer (Rapidlab® 1265, Siemens, München, Germany) and they were used to adjust the insulin infusion rate. Insulin in a concentration of 50 units in 50 cc 0.9% NaCl was infused using...
Diabetic subjects differed between groups (13/22 Leuven vs. 8/35 Yale; \(p = 0.0016\)). Patients in the Yale group tended to be older. Reasons for admission were comparable between groups with exception of neurologic disease/coma. Feeding habits were different in the two groups \((p = 0.003)\) with enteral feeding being less frequently used in the Leuven group (3/22 vs. 20/35). The APACHE-II score was similar, whereas the SOFA score tended to be higher in the Yale group.

Patients in the Leuven group required much more IV insulin compared to those treated by the Yale protocol (Table 1). Despite a similar number of arterial blood glucose measurements, patients in the Yale protocol had better glucometrics with a higher percentage of time in target glycemia \((80–110 \text{ mg/dl})\) \((37 \pm 15 \text{ vs. } 26 \pm 11, p = 0.001)\) and a lower percentage of time spent in hypoglycemia \((0[0–2] \text{ vs. } 5[1–8]\%\), \(p = 0.001)\). Also percentage of time spent between 60 and 150 \text{ mg/dl} \((81 \pm 7 \text{ vs. } 66 \pm 24\%, \ p < 0.0001)\), 80–125 \text{ mg/dl} \((57 \pm 18 \text{ vs. } 36 \pm 21\%, \ p < 0.0001)\), between 80 and 145 \text{ mg/dl} \((74 \pm 17 \text{ vs. } 48 \pm 23\%, \ p < 0.0001)\), and between 70 and 180 \text{ mg/dl} \((91 \pm 10 \text{ vs. } 69 \pm 19\%, \ p < 0.0001)\) was higher in the Yale group. Figure 1 shows the time-in-band for the different ranges of targets for both groups.

Median glycemia, however, did not differ between groups \((118[108–128] \text{ (log: } 122[99–136]) \text{ mg/dl})\) (Table 1). Glycemic variability was less pronounced with the use of the Yale protocol \((\text{median}[\text{IQR}] \text{ SD } 28[21–37] \text{ vs. } 47[31–71] \text{ mg/dl}, \ p = 0.001; \text{median CV } 23[19–31] \text{ vs. } 36[26–50]\%\), \(p = 0.001; \text{median MODD } 35[26–41] \text{ vs. } 60[33–94] \text{ mg/dl, } \ p = 0.001)\). Significant better LBGI and HBGI were observed in the Yale group (Table 1). Eight insulin/glucose plots comparing non-diabetic and diabetic patients treated according to the Leuven protocol versus according to the modified Yale protocol are shown in Fig. 2, providing the reader with a good visual image.

Characteristics of subjects achieving strict versus above-target glycemic control

Subjects achieving strict glycemic control \((n = 19)\), defined as having an average glycemia \(\leq 110 \text{ mg/dl}\), did not differ with regard to gender, diabetic status, age, BMI, reason for admission, severity of illness, and interventions used as compared to the ones not obtaining an average glycemia \(\leq 110 \text{ mg/dl}\), with the exception of the use of glucocorticoids \((p = 0.001)\) (Table 2). The distribution according to insulin infusion protocol used (Leuven vs. Yale) also did not differ between groups. Insulin doses infused and a number of arterial blood glucose measurements were similar as well. Most glucometrics \((% \text{ of time within target})\) including glycemic variability \((\text{SD, MODD, LBGI and HBGI})\) were better in the group achieving...
| Table 1 Baseline characteristics, interventions used and glucometrics of patients treated by the Leuven versus Yale protocol |
|-------------------------------------------------|
| **Total cohort** | **Leuven** | **Yale** | **Statistics** |
| Number of patients | 57 | 22 | 35 | p value |
| Patient demographics | | | | NS |
| Men/women | 30/27 | 13/9 | 17/18 | |
| Diabetic status (no/type1/type2) | 36/6/15 | 9/4/9 | 27/2/6 | 0.0016 |
| Age (years) | 64 ± 12 | 60 ± 13 | 66 ± 10 | 0.055 |
| BMI (kg/m²) | 26.8 ± 5.4 | 27.5 ± 7.1 | 26.3 ± 4.0 | NS |
| Admission reason | | | | NS |
| Septic shock | 22 | 13 | 9 | |
| Neurologic disease/coma | 9 | 0 | 9 | 0.004 |
| Cardiopulmonary resuscitation | 9 | 1 | 8 | NS |
| Respiratory failure | 6 | 1 | 5 | NS |
| Cardiogenic shock | 7 | 3 | 4 | NS |
| Other | 4 | 4 | 0 | NS |
| Severity of illness | | | | |
| APACHE-II score | 28 ± 7 | 27 ± 7 | 28 ± 7 | NS |
| SOFA score | 10 ± 4 | 9 ± 4 | 11 ± 3 | 0.072 |
| Clinical interventions | | | | NS |
| Mechanical ventilation | 44 | 16 | 28 | |
| Vasopressor therapy | 35 | 14 | 21 | NS |
| Inotropic therapy | 20 | 6 | 14 | NS |
| Hemodialysis | 14 | 9 | 5 | NS |
| No/total parenteral/enteral feeding | 17/17/23 | 9/10/3 | 8/7/20 | 0.003 |
| Glucocorticoids | 27 | 12 | 15 | NS |
| Blood transfusion | 15 | 4 | 11 | NS |
| Antibiotics | 46 | 19 | 27 | NS |
| Outcome parameters | | | | |
| LOS in ICU (days) | 15 ± 9 | 11 ± 6 | 17 ± 10 | 0.019 |
| In hospital mortality | 20 | 7 | 11 | NS |
| Insulin dose | | | | |
| Day 1 (units) | 138 (48–190) | 50 (27–80) | 0.001 |
| Day 2 (units) | 116 (54–116) | 56 (28–81) | 0.006 |
| Glucose parameters | | | | |
| HbA1c (%) | 6.3 (5.8–7.0) | 6.0 (5.7–6.6) | NS |
| HbA1c (mmol/mol) | 45 (40–53) | 42 (39–49) | NS |
| Median glycemia (mg/dl) | 128 (106–154) | 118 (108–128) | NS |
| % of time at glycemia | | | | |
| <60 mg/dl | 5 (1–8) | 0 (0–2) | 0.001 |
| 80–110 mg/dl | 26 ± 11 | 37 ± 15 | 0.001 |
| >150 mg/dl | 29 ± 23 | 17 ± 13 | <0.0001 |
| >200 mg/dl | 13 ± 19 | 3 ± 5 | <0.0001 |
| 60–150 mg/dl | 66 ± 24 | 81 ± 7 | <0.0001 |
| 70–180 mg/dl | 69 ± 19 | 91 ± 10 | <0.0001 |
| Nr of art blood glc measurements/day | 10 ± 2 | 10 ± 4 | NS |
| Glucose variability parameters | | | | |
| SD (mg/dl) | 47 (31–71) | 28 (21–37) | 0.001 |
| Coefficient of variation (%) | 36 (26–50) | 23 (19–31) | 0.001 |
| IQR | 66 (47–82) | 37 (27–43) | <0.0001 |
| MAGE (mg/dl) | 73 (47–128) | 52 (37–83) | 0.061 (NS) |
strict glycemic control. Logistic regression analysis could not identify type of IIP, diabetes status, age, BMI, or APACHE-II score as independent parameters for strict glucose control. The only parameter which showed an independent association with strict glucose control was the administration of glucocorticoids ($p = 0.001$).

Characteristics of diabetic versus non-diabetic subjects

No differences in patient demographics except for BMI ($p = 0.02$), in reason for admission, severity of illness, and clinical interventions used, were present between diabetic ($n = 21$) and non-diabetic critically ill patients (Table 3). There were more diabetic patients in the Leuven protocol ($p = 0.009$). Diabetic subjects required more insulin, had a worse median glycemia (131[110–166] vs. 116[107–128] mg/dl, $p = 0.034$), spent less time in target glycemia (25 ± 12 vs. 36 ± 15%, $p = 0.006$), more time in hypoglycemia (4[1–10] vs. 0[0–1]%, $p = 0.001$) than non-diabetic subjects. All other glucometrics, including glycemic variability parameters, were worse as well in diabetic patients (see Table 3).

In the non-diabetic group, patients in the Yale protocol spent more time in target glycemia (40 ± 15 vs. 25 ± 10%, $p = 0.009$), less time in hypoglycemia (0[0–0] vs. 1[0–6]%, $p = 0.013$), and glycemic variability tended to be smaller (SD $p = 0.076$, CV $p = 0.057$, MODD $p = 0.021$) than those treated by the Leuven protocol. Median glycemia was similar (117[108–127] vs. 115[101–140]) in both groups (Additional file: Table S1). In the diabetic subjects, insulin needs were lower ($p = 0.044$) and patients spent less time at a glycemia >150 mg/dl (26 ± 21 vs. 35 ± 25%, $p = 0.003$) in the Yale compared to the Leuven group. However, median glycemia (120[108–140] vs. 136[111–169] mg/dl), time spent in hypoglycemia or at target range, and parameters of glycemic variability were similar between groups (Additional file 1: Table S1).

Discussion

Achieving strict glycemic control without risk of hypoglycemia in the ICU is difficult. It requires a comprehensive and safe insulin infusion protocol (IIP) that is both detailed enough and practical enough to be easily implemented by ICU nurses [2, 28]. Multiple IIPs have been developed, but to the best of our knowledge this is the first study comparing the clinical efficacy (% time in target glycemia) and safety (hypoglycemia, glycemic variability) of two IIPs in MICU patients by means of CGM. Overall, compared to existing data (see Table 4, [3–15, 29–38]), both our IIPs were able to obtain reasonably strict glucose control without excessive risk of hypoglycemia. The percentage of time in normoglycemia was higher (37 vs. 26%), and percentage of time in hypoglycemia lower (0 vs. 5%) and glycemic variability was less pronounced in patients treated with the Yale IIP. Diabetes status can, however, be a confounding factor [34].

![Fig. 1 Average percentage time in range and SD over the groups (Yale vs. Leuven) for the different glycemia target ranges. $P < 0.0001$ for all three ranges](image)
observed an imbalance in the number of diabetic subjects with more diabetic patients in the Leuven group. Diabetic as compared to non-diabetic subjects required more insulin, had worse glycemic control, and larger glycemic variability, thereby possibly blunting the effect of the IIP. However, logistic regression could not identify type of IIP, diabetes status, or severity of illness as independent parameters associated with strict glucose control. When comparing Yale versus Leuven protocol in non-diabetic subjects, patients in the Yale protocol had better glycometrics. This was evident, despite the low number of patients. In the diabetic subgroup, however, the advantages of the Yale protocol were less pronounced.

Up till now no single IIP has been established as the most effective for obtaining tight glycemic control [28, 39, 40]. The IIP should be tailored to the subset of patients being treated and to local resources, because an excellent validated IIP is no guarantee for optimal glucose control unless it is carefully implemented. Most IIPs show significant similarities, but differences relate to target glucose levels (80–110 mg/dl versus ranges varying between 90 and 180 mg/dl), initial glycemic threshold (>150–200 mg/dl), infusion rates, use of boluses, and frequency of monitoring. Changes in insulin infusion rate may relate to actual glycemia, direction and/or velocity of change in glycemia, degree of insulin resistance, and insulin dose. The population treated (surgical vs. medical ICU, diabetes status) may also affect the performance of the IIP [2, 28, 39, 40]. The competence of the nurses and clarity of instructions also influence outcome.
Table 2 Baseline characteristics, interventions used and glucometrics of patients reaching an average glycemia ≤110 mg/dl versus those with an average glycemia >110 mg/dl

| Patient demographics          | Avg glyc ≤ 110 mg/dl | Avg glyc >110 mg/dl | Statistics |
|-------------------------------|----------------------|---------------------|------------|
| Number of patients            | 19                   | 38                  |            |
| Men/women                     | 8/11                 | 22/16               | NS         |
| Diabetic status (no/type1/type2) | 14/1/4              | 23/4/11             | NS         |
| Age (years)                   | 65 ± 11              | 63 ± 12             | NS         |
| BMI (kg/m²)                   | 26.3 ± 3.8           | 27.1 ± 6.1          | NS         |
| Severity of illness           |                      |                     |            |
| APACHE-II score               | 27 ± 6               | 28 ± 7              | NS         |
| SOFA score                    | 10 ± 4               | 10 ± 3              | NS         |
| Clinical interventions        |                      |                     |            |
| Mechanical ventilation        | 14                   | 31                  | NS         |
| Vasopressor therapy           | 12                   | 23                  | NS         |
| Hemodialysis                  | 5                    | 9                   | NS         |
| No/total parenteral/enteral feeding | 4/6/9            | 13/11/14            | NS         |
| Glucocorticoids               | 15                   | 12                  | 0.01       |
| Antibiotics                   | 17                   | 29                  | NS         |
| Protocol (Leuven/ Yale)       | 7/12                 | 15/23               | NS         |
| Insulin dose                  |                      |                     |            |
| Day 1 (units)                 | 62 (33–133)          | 63 (39–128)         | NS         |
| Day 2 (units)                 | 67 (23–101)          | 70 (42–120)         | NS         |
| Glucose parameters            |                      |                     |            |
| HbA1c (%)                     | 6.1 (5.6–6.7)        | 6.0 (5.8–6.9)       | NS         |
| HbA1c (mmol/mol)              | 43 (38–50)           | 70 (42–120)         | NS         |
| Median glycemia (mg/dl)       | 104 (100–108)        | 128 (119–141)       | <0.0001    |
| % of time at glycemia         |                      |                     |            |
| <60 mg/dl                     | 5 (0–8)              | 0 (0–4)             | 0.067      |
| 60–110 mg/dl                  | 41 ± 14              | 27 ± 13             | 0.001      |
| >150 mg/dl                    | 6 ± 6                | 28 ± 18             | <0.0001    |
| >200 mg/dl                    | 1 ± 2                | 10 ± 16             | 0.017      |
| 60–150 mg/dl                  | 89 ± 11              | 69 ± 19             | <0.0001    |
| 70–180 mg/dl                  | 86 ± 14              | 80 ± 19             | NS         |
| Nr of art blood glc measurements/day | 10 ± 3            | 10 ± 4              | NS         |
| Glucose variability parameters|                      |                     |            |
| SD (mg/dl)                    | 25 (20–36)           | 38 (29–63)          | 0.003      |
| Coefficient of variation (%)  | 25 (20–33)           | 29 (23–44)          | NS         |
| IQR                           | 33 (27–55)           | 45 (35–76)          | 0.031      |
| MAGE (mg/dl)                  | 50 (34–72)           | 60 (43–100)         | 0.085      |
| MODD (mg/dl)                  | 29 (22–45)           | 42 (32–76)          | 0.005      |
| M-100                         | 2 (1–4)              | 6 (4–14)            | 0.001      |
| CONGA1 (mg/dl)                | 15 (12–19)           | 21 (15–35)          | 0.008      |
| CONGA2 (mg/dl)                | 22 (17–28)           | 32 (20–48)          | 0.010      |
| CONGA4 (mg/dl)                | 29 (18–43)           | 42 (27–69)          | 0.011      |
| LBG1                           | 2.7 (0.9–3.8)        | 0.7 (0.2–1.9)       | 0.001      |
| HBGI                           | 0.3 (0.2–1.1)        | 2.0 (1.4–4.5)       | <0.0001    |
| Glucose variability           | 21 (17–28)           | 36 (29–53)          | <0.0001    |

Data are presented as numbers, as mean ± SD or median (25–75th percentile)

*LOS in ICU* length of stay in ICU, *IQR* interquartile range, *MAGE* mean amplitude of glycemic excursions, *MODD* mean of daily differences, *LBGI* low blood glucose index, *HBGI* high BGI.
Computerized decision-supported algorithms might provide superior glucose control compared to paper-based IIPs because of reduced errors by enabling the use of complex mathematical calculations and better protocol consistency. In MICUs and mixed ICUs where a glycemic control between 80 and 110 mg/dl was targeted, 22–60% of all blood glucose values were reported to be in target for paper-based IIPs [3–14], compared to a higher percentage (42–69%) for computerized IIPs [4, 10, 11, 14, 15] (Additional file 1: Digital Content—Table S1). In contrast, in a before–after study in 192 surgical ICU patients, Barletta et al. [29] could not observe significant glucometric differences between the computer-assisted versus paper-based IIP. It is probably not the paper or computer that makes the largest difference; but the IIP algorithm itself and the competence of the staff.

A head-to-head comparison of different IIPs on glycemic control has only been performed in RCTs in cardiac surgery. Blaha et al. [18] compared two paper protocols with a computerized IIP in 120 patients, showing that the computerized IIP provided better average glucose control, but with a longer time in hypoglycemia risk range than the paper protocols. Dumont and Bourguignon [19] compared the effect of a computerized (EndoTool) versus a paper IIP (modified Portland protocol) in 300 ICU patients, showing better glucose control and nurses’ satisfaction with the EndoTool IIP. In both studies, however, it was not only the protocol that differed but also the way it was implemented (paper vs. computerized), making it difficult to assess the true value of the protocol itself.

Measurement frequency is an inherent part of an IIP and will affect glucometrics. Recently, the effect of the IIP (Yale vs. University of Washington), frequency of glucose measurements (hourly vs. every 5 min), and measurement imprecision on glycemic control efficacy was studied using a simulation model [16]. In both IIPs, the rates of hypo- and hyperglycemia and of glycemic variability increased with increasing measurement imprecision. Others investigated the performance of the IIP versus methodology of glucose measurements (blood glucose meter vs. CGM) at different levels of measurement accuracy [17]. The protocol itself proved to have a greater effect on glycemic control efficacy than the glucose measurement method, with the Yale protocol showing the best performance. However, hypoglycemia risk was lower in CGM-informed IIPs [17]. Thus, efficacy of the IIP together with performance and accuracy of the CGM device used both contribute to the success of tight glucose control. In the future, validated computerized IIPs can be guided by real-time CGM in a semi-closed loop, thereby improving efficacy, safety and reducing nursing workload.

Comparison of glucometrics between studies using different IIPs is difficult due to differences in population,

Table 3 Baseline characteristics, interventions used and glucometrics of non-diabetic versus diabetic patients

|                       | Non-DM | DM      | Statistics |
|-----------------------|--------|---------|------------|
| Number of patients    | 36     | 21      |            |
| Patient demographics  |        |         |            |
| Men/women             | 19/17  | 11/10   | NS         |
| Age (years)           | 65 ± 11| 62 ± 12 | NS         |
| BMI (kg/m²)           | 26 ± 4 | 29 ± 7  | 0.02       |
| Severity of illness   |        |         |            |
| APACHE-II score       | 29 ± 6 | 26 ± 7  | NS         |
| SOFA score            | 11 ± 4 | 9 ± 3   | NS (0.064) |
| Clinical interventions |        |         |            |
| Mechanical ventilation| 27     | 17      | NS         |
| Vasopressor therapy   | 23     | 12      | NS         |
| Hemodialysis          | 12     | 2       | NS (0.06)  |
| No/total parenteral/enteral feeding | 7/13/16 | 10/4/7 | NS (0.075) |
| Glucocorticoids       | 20     | 7       | NS         |
| Antibiotics           | 30     | 16      | NS         |
| Protocol (Leuven/Yale) | 9/27   | 13/8    | 0.009      |
| Insulin dose          |        |         |            |
| Day 1 (units)         | 48 (26–82) | 127 (51–175) | 0.001      |
| Day 2 (units)         | 46 (25–85) | 113 (67–168) | 0.009      |
| Glucose parameters    |        |         |            |
| HbA1c (%)             | 5.9 (5.6–6.3) | 6.9 (6.1–7.3) | <0.0001    |
| HbA1c (mmol/mol)      | 41 (38–45) | 52 (43–56) | <0.0001    |
| Median glycemia (mg/dl)| 116 (107–128) | 131 (110–166) | 0.034      |
| % of time at glycemia |        |         |            |
| <60 mg/dl             | 0 (0–1) | 4 (1–10) | 0.001      |
| 80–110 mg/dl          | 36 ± 15 | 25 ± 12 | 0.006      |
| >150 mg/dl            | 32 ± 15 | 24 ± 11 | 0.001      |
| >200 mg/dl            | 3 ± 15  | 15 ± 20 | 0.001      |
| 60–150 mg/dl          | 83 ± 12 | 63 ± 23 | <0.0001    |
| 70–180 mg/dl          | 90 ± 11 | 69 ± 19 | <0.0001    |
| Nr of art blood glc measurements/day | 10 ± 4 | 10 ± 3 | NS         |
| Glucose variability parameters |        |         |            |
| SD (mg/dl)            | 28 (21–35) | 53 (40–75) | <0.0001    |
| Coefficient of variation (%) | 23 (19–30) | 38 (29–51) | <0.0001    |
| IQR                   | 38 (28–45) | 66 (41–108) | <0.0001    |
| MAGE (mg/dl)          | 49 (35–66) | 87 (56–127) | 0.002      |
| MODD (mg/dl)          | 35 (26–42) | 59 (35–116) | <0.0001    |
| M-100                 | 4 (2–5)  | 12 (6–29) | <0.0001    |
| CONGA1 (mg/dl)        | 15 (13–20) | 30 (19–41) | <0.0001    |
| CONGA2 (mg/dl)        | 22 (17–30) | 44 (26–59) | <0.0001    |
| CONGA4 (mg/dl)        | 30 (21–43) | 60 (37–86) | <0.0001    |
| LBGI                  | 0.7 (0.3–1.8) | 2.3 (0.9–3.7) | 0.013      |
| HBG1                  | 1.2 (0.4–1.8) | 3.0 (1.4–10.3) | 0.002      |
| Glucose variability   | 28 (20–34) | 44 (34–79) | <0.0001    |

Data are presented as numbers, as mean ± SD or median (25–75th percentile).

LOS in ICU length of stay in ICU, IQR interquartile range, MAGE mean amplitude of glycemic excursions, MODD mean of daily differences, LBGI low blood glucose index, HBG1 high BGI.

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| Authors                  | ICU type               | Study               | n   | % Diabetic patients | Protocol | Target glycemia (mg/dl) | Method of glucose measurements                                      |
|-------------------------|------------------------|---------------------|-----|---------------------|----------|-------------------------|---------------------------------------------------------------------|
| Goldberg et al. (2004)  | MICU                   | Observational       | 52  | 56                  | Yale     | 100–139                 | Hospital glucose meter: near hourly measurements                     |
| Van den Berghe et al. (2006) | MICU               | RCT                 | 1200| 17                  | Paper: Leuven | 80–110               | ABG: q1-4 h                                                          |
| Kulnik et al. (2008)    | MICU                   | Observational       | 10  | 20                  | eMPC (computer) | 80–110               | Variable sampling rate: q20 min-4 h                                 |
| Shetty et al. (2012)    | MICU                   | Observational       | 90  | 66                  | Yale     | 120–160                 | POC meter: hourly measurements                                      |
| Holzinger et al. (2010) | MICU                   | RCT                 | 124 | 19                  | Leuven   | 80–110                 |                                                                      |
| De Block et al. (2015)  | MICU                   | RCT                 | 35  | 23                  | Yale     | 80–110                 | CGM                                                                  |
| Finney et al. (2003)    | Mixed                  | Observational       | 523 | 16                  | Paper    | 90–145                 |                                                                      |
| Juneja et al. (2007)    | Mixed                  | Observational       | 2398| NR                  | Clarian Gluco Stabilizer | 80–110 | POC: q1-2 h |
| Chase et al. (2008)     | Mixed                  | Observational       | 371 | 17                  | SPRINT   | 80–110                 | Sampling rate: q1-2 h                                                |
| Morris et al. (2008)    | Mixed                  | Before–after        | 755 | NR                  | eProtocol-insulin versus paper | 80–110 | POC: q1-4 h |
| Preiser et al. GLU-CONTROL (2009) | Mixed       | RCT                 | 1078| 21                  | Paper: glucontrol | 80–110 | POC: q1-4 h |
| NICE SUGAR (2009)       | Mixed                  | RCT                 | 6104| 20                  | Paper: Leuven | 81–108 | ABG |
| Marvin et al. (2013)    | Mixed                  | Retrospective       | 1657| NR                  | Computerized Yale | 100–140 | POC: variable time interval |
| Van Herpe et al. (2013) | Mixed                  | RCT                 | 300 | 21                  | LOGIC-insulin computerized | 80–110 | ABG: variable time interval: q1-4 h |
| Krinsley et al. (2015)  | Mixed                  | Retrospective       | 3297| 23                  | Paper: Stamford | 70–140 | POC: q3 h |
| Vogelzang et al. (2005) | SICU                   | Observational       | 179 | 15                  | GRIP     | 72–135                 | POC blood gas analyzer: variable                                    |
| Plank et al. (2006)     | SICU: cardiothoracic surgery | RCT             | 60  | 23                  | eMPC versus paper | 80–110 | POC: variable sampling rate: q1 h-4 h |
| Hovorka et al. (2007)   | SICU: cardiac surgery  | RCT                 | 60  | 45                  | eMPC     | 80–110                 | Variable sampling rate: q1 h-4 h                                    |
| Saager et al. (2008)    | SICU: cardiothoracic ICU | RCT               | 40  | 100                 | EndoTool (computer) versus paper | 90–150 | POC: hourly |
| Dortch et al. (2008)    | SICU: trauma ICU       | RCT                 | 552 |                    | Computer versus paper | 80–110 | POC q1-4 h |
| Blaha et al. (2009)     | SICU: cardiac surgery  | RCT                 | 120 | 14                  | eMPC versus paper (Matias versus Bath) | 80–110 | ABG: protocol dependent: q1-4 h |
| Barletta et al. (2011)  | SICU                   | Before–after        | 192 | 28                  | Computer versus paper | 80–110 | POC: variable sampling rate: q20 min-2 h versus q2 h |
| Dumont et al. (2012)    | SICU: cardiovascular ICU | RCT               | 300 | 43                  | Computer (EndoTool) versus paper (modified Portland) | 80–150 | NA |
### Table 4 continued

| Authors                  | Duration of glucose monitoring | Glucometric to measure target | % of time at target glycaemia: intervention versus control group | Mean glycaemia (mg/dl): intervention versus control group | Hypoglycaemia: intervention versus control group | Glycemic variability | References |
|--------------------------|--------------------------------|-------------------------------|------------------------------------------------------------------|-----------------------------------------------------------|--------------------------------------------------|---------------------|------------|
| Goldberg et al. (2004)   | 61 h                           | Percent of hourly BG values in target range | 52%                                                              | 124 ± 15                                                  | % of data at glc <60 mg/dl: 0.3%                    | NA                  | [8]        |
| Van den Berghe et al. (2006) | NR                             | Mean morning BG               | NA                                                              | 111 ± 29 versus 153 ± 31                                  | % of patients: glc <40 mg/dl: 18.7 versus 3.1%       | NA                  | [13]       |
| Kulnik et al. (2008)     | 72 h                           | Percent of BG values in target range | 47 ± 13%                                                         | 109 ± 13                                                  | % data at glc <40 mg/dl: 0%                         | NA                  | [15]       |
| Shetty et al. (2012)     | 59 h                           | Percent of BG values in target range | 42%                                                             | 156 ± 23                                                  | % of data <70 mg/dl: 0.3%                           | NA                  | [37]       |
| Holzinger et al. (2010)  | 72 h                           | CGM data: percent of data in target range | 59 ± 20 versus 55 ± 18                                         | 106 ± 18 versus 111 ± 10                                  | Rate: 1.9% versus 11.5%                            | NA                  | [9]        |
| De Block et al. (2015)   | 96 h                           | CGM data: percent of data in target range | 37 ± 12 versus 34 ± 10                                         | 119 ± 17 versus 122 ± 11                                  | % of time at glc <60 mg/dl: 0.6 ± 1.6 versus 2.4 ± 4.9% | No differences between groups in SD, MAGE, MODD, CV | [6]        |
| Finney et al. (2003)     | 22–89 h                        | Time spent in glucose band 80–110 mg/dl | 4 (0–20)%                                                       | 0 ± 1%                                                    | % data at glc <50 mg/dl: 0.4 versus 0.5%             | NA                  | [31]       |
| Juneja et al. (2007)     | NR                             | Percent of data in target range | 52 versus 32%                                                    | 107 ± 39                                                  | % data at glc <72 mg/dl: 3.8%                       | SD: 27 mg/dl        | [4]        |
| Chase et al. (2008)      | 53 h                           | Percent of BG values in target range | 54%                                                             | 108 ± 27                                                  | % of data at glc <70 mg/dl: 11.1 versus 5.1%        | NA                  | [11]       |
| Morris et al. (2008)     | 4–22 days                      | Percent of BG values in target range | 42 versus 28%                                                   | 116 versus 134                                             | % data at glc <40 mg/dl: 6.8 versus 0.5%             | NA                  | [11]       |
| Preiser et al. GLUCONTROL (2009) | 48–216 h (=2–9 days) | Proportion of time of BG values in range | 43%                                                              | 117 (IQR: 108–130) mg/dl                                 | Proportion of time at glc <40 mg/dl: 5.9 ± 27%       | SD: 36 mg/dl        | [12]       |
| NICE SUGAR (2009)        | 4.2 days                       | Time-weighted mean BG         | NR                                                              | 115 ± 18 versus 144 ± 23                                  | % of patients: glc <40 mg/dl: 6.8 versus 0.5%        | NA                  | [7]        |
| Marvin et al. (2013)     | NR                             | Percent of hourly BG values in target range | 92%                                                             | 124                                                      | % of data 40–70 mg/dl: 1.1% and in 17.6% of patients | NA                  | [34]       |
| Van Herpe et al. (2013)  | 26–113 h                       | Percent of BG values in target range | 69 ± 17 versus 60 ± 19                                         | 106 ± 9 versus 107 ± 11                                   | % data at glc <60 mg/dl: 0.6 versus 1.2%             | Max change in glc/24 h: 31 versus 37 mg/dl           | [14]       |
| Krinsley et al. (2015)   | 36–120 h                       | Percent of time of BG values in target range | Non-DM versus DM: 81 (61–94) versus 55 (35–71)%                 | Non-DM versus DM: 121 (112–133) versus 140 (128–155) mg/dl | % of patients: glc <70 mg/dl: non-DM versus DM: 18 versus 31% | CV: non-DM versus DM: 18 versus 27%                  | [33]       |
| Vogelzang et al. (2005)  | 1.6 (0.8–4.7) days             | Percent of time of BG values in target | 78 (66–88)%                                                      | 121 (108–135)                                             | % of patients: glc <40 0.6%; glc <63: 11.2%         | NA                  | [38]       |
target glycaemia, and frequency of glucose monitoring. In addition, many different glucometrics are reported in different studies, including metrics of central tendency (mean or median glycaemia, time-averaged glucose, admission glycaemia, proportion of glucose values in target), metrics of extremes (percentages or episodes of hypo- or hyperglycaemia), and metrics of dispersion (SD, coefficient of variation, MAGE). The robustness of glucometrics depends largely on the number of measurements per time unit used for its calculation. Accurate assessment of time in target glycaemia, or in hypo- or hyperglycaemia, and of glucose variability can only be done by using validated CGM methodology.

Our study has some limitations and strengths. This is a pooled data analysis of two prospective RCTs conducted at the medical ICUs, using relatively old data. Indeed, patients were recruited between 04/2004 and 03/2005 for the first study and between 07/2007 and 09/2009 for the second study. However, pooling the CGM data is justifiable in our opinion because the same CGM sensor was used in both studies and the study population and standards of care in both services were comparable. However, our results might not be applicable to a mixed or surgical ICU setting. Despite more than 63,000 CGM glucose measurements being available for analysis, due to the small number of patients and heterogeneity of groups, statistical superiority of the Yale protocol could not be proven.

A major strength, in our opinion, when comparing IIPs, is the use of CGM data which provides a complete picture of glucometrics. We did not make use of study IIPs, is the use of CGM data which provides a complete picture of glucometrics. We did not make use of study IIPs, is the use of CGM data which provides a complete picture of glucometrics. We did not make use of study IIPs, is the use of CGM data which provides a complete picture of glucometrics. We did not make use of study.

In summary, the use of a safe and efficient IIP is a prerequisite to correctly implement strict glycaemic targets. Both IIPs have proven to balance efficacy with safety (avoid hypoglycaemia and glycaemic variability) and attainability (nursing workload). Overall, the modified Yale protocol provided better glucose control with more time spent in normoglycaemia, less time spent in hypoglycaemia, and less glycaemic variability as compared to the Leuven protocol.

Table 4 continued

| Authors         | Duration of glucose monitoring | Glucometric to measure target | % of time at target glycaemia: intervention versus control group | Mean glycaemia (mg/dl): intervention versus control group | Hypoglycaemia: intervention versus control group | Glycaemic variability | References |
|-----------------|--------------------------------|------------------------------|---------------------------------------------------------------|-----------------------------------------------------------|---------------------------------------------------|-----------------------|------------|
| Plank et al. (2006) | 48 h                           | Percent of time in target range | 52 (17–92) versus 19 (0–71)%                                  | 117 (102–144) versus 131 (97–237)                          | Number of hypo episodes (<54 mg/dl): over 48 h: 0 versus 2 | NA [35]                 |
| Hovorka et al. (2007) | 24 h                           | Percent of time in target range | 60 ± 23 versus 28 ± 16                                          | 112 ± 20 versus 130 ± 20                                    | % of data at glc <52 mg/dl: 0% versus 0%            | NA [32]                 |
| Saager et al. (2008) | 9 h                            | Percent of BG values in target | 84 versus 60%                                                   | 126 ± 18 versus 147 ± 27                                    | Episodes of hypo (<60 mg/dl) during ICU: 4 versus 1 | NA [36]                 |
| Dortch et al. (2008) | NR                             | Percent of BG values in target | 42 versus 34%                                                   | 116 ± 37 versus 120 ± 37                                    | % data at glc <40 mg/dl: 0.2 versus 0.5%            | NA [30]                 |
| Blaha et al. (2009) | 45–48 h                        | Time in target range           | 46 ± 3 versus 38 ± 3 versus 40 ± 3%                            | 106 ± 4 versus 121 ± 4 versus 117 ± 4                       | Time in hypo (<52 mg/dl): 0 ± 0 versus 0.4 ± 0.2 versus 0.4 ± 0.3% | NA [18]                 |
| Barletta et al. (2011) | 67 versus 98 h                 | Percent of BG values in target | 49 ± 14 versus 40 ± 12                                          | 113 ± 11 versus 116 ± 11                                    | % data at glc <40 mg/dl: 2.1 versus 4.1%            | SD: 25 ± 9 versus 31 ± 11 mg/dl [29] |
| Dumont et al. (2012) | NA                             | Percent of BG values in target range | 70 ± 15 versus 62 ± 18                                          | 138 ± 16 versus 141 ± 20                                    | Number of hypo events <60 mg/dl: 7 (5%) versus 18 (11%) | SD:36 ± 18 versus 42 ± 21 [19] |

MICU medical intensive care unit, SICU surgical ICU, RCT randomized controlled trial, NR not reported, NA not assessed, ABG arterial blood glucose, POC point of care, SD standard deviation

References
Additional file

Additional file 1: Table S1. Baseline characteristics and glucometics of patients treated by the Leuven versus Yale protocol, analysed according to diabetes status.

Abbreviations
BMI: body mass index; CGM: continuous glucose monitoring; CONGA: continuous overlapping net glycemic; HBGI: high blood glucose index; ICU: intensive care unit; IIP: insulin infusion protocol; IV: intravenous; LBGI: low blood glucose index; MAGE: mean amplitude of glucose excursions; MICU: medical intensive care unit; MODD: mean of daily differences; RCT: randomized controlled trial(s); SD: standard deviation; UZA: Universitair Ziekenhuis Antwerpen (Antwerp University Hospital).

Authors' contributions
All authors made important intellectual contributions to the conception and analysis of the study. Every author reviewed and provided comments on manuscript drafts and gave final approval of this version to be published. CEMDB was responsible for the final design of the study. CEMDB, PR, and PG recruited patients, implemented the study protocol, and acquired data. CS, who was masked for clinical data and treatment arm, analyzed the CGM profiles with patients being coded. CEMDB and TS performed the statistical analysis. CEMDB drafted the manuscript. All authors read and approved the final manuscript.

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Competing interests
The authors declare that they have no competing interests.

Availability of data and materials
The datasets supporting the conclusions of this article will be available in a repository upon publication of the manuscript.

Ethics approval
The studies were approved by the ethics committees of both hospitals (Middelheim approval no. 2345 and UZA 6/43/211) and conducted in accordance with the amended Declaration of Helsinki.

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