Intensive Care Med (2014) 40:171–181
DOI 10.1007/s00134-013-3189-0

SEVEN-DAY PROFILE PUBLICATION

Tight computerized versus conventional glucose control in the ICU: a randomized controlled trial

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Received: 29 October 2013
Accepted: 4 December 2013
Published online: 14 January 2014

We dedicate this article to the memory of our distinguished colleague Xavier Leverve, MD, PhD, who sadly did not live to see the result of the trial.

Take-home message: Despite the increase in the incidence of severe hypoglycemia in our experimental group, based on the absence of difference in mortality between patients on tight computerized glucose control and those on less stringent glucose control without CDSS, this study could pave the way for future randomized controlled trials assessing new generation CDSSs allowing the safe implementation of blood glucose control in the ICU that take into account the complexity of glucose control throughout the ICU stay and the variability of individualized insulin needs.

Trial registration: Clinicaltrials.gov Identifier NCT01002482.

Electronic supplementary material
The online version of this article (doi:10.1007/s00134-013-3189-0) contains supplementary material, which is available to authorized users.

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Abstract *Purpose:* The blood glucose target range and optimal method to reach this range remain a matter of debate in the intensive care unit (ICU). A computer decision support system (CDSS) might improve the outcome of ICU patients through facilitation of a tighter blood glucose control. *Methods:* We conducted a multi-center randomized trial in 34 French ICU. Adult patients expected to require treatment in the ICU for at least 3 days were randomly assigned without blinding to undergo tight computerized glucose control with the CDSS (TGC) or conventional glucose control (CGC), with blood glucose targets of 4.4–6.1 and <10.0 mmol/L, respectively. The primary outcome was all-cause death

within 90 days after ICU admission. *Results:* Of the 2,684 patients who underwent randomization to the TGC and CGC treatment groups, primary outcome was available for 1,335 and 1,311 patients, respectively. The baseline characteristics of these treatment groups were similar in terms of age (61 ± 16 years), SAPS II (51 ± 19), percentage of surgical admissions (40.0 %) and proportion of diabetic patients (20.3 %). A total of 431 (32.3 %) patients in the TGC group and 447 (34.1 %) in the CGC group had died by day 90 (odds ratio for death in the TGC 0.92; 95 % confidence interval 0.78–1.78; $p = 0.32$). Severe hypoglycemia (<2.2 mmol/L) occurred in 174 of 1,317 patients (13.2 %) in the TGC group and 79 of 1,284 patients (6.2 %) in the CGC group ($p < 0.001$). *Conclusions:* Tight computerized glucose control with the CDSS did not significantly change 90-day mortality and was associated with more frequent severe hypoglycemia episodes in comparison with conventional glucose control.

Keywords Critical care · Glucose control · Computerized decision-support systems · ICU · Mortality · Randomized controlled trials

Introduction

Stress hyperglycemia and insulin resistance are common in critically ill patients, regardless of their diabetic status before intensive care unit (ICU) admission and are associated with poor outcome [1–3]. Van den Berghe et al. [4] reported a one-third reduction in hospital mortality in critically ill surgical patients when using an intensive insulin therapy that targeted a tight low range for blood glucose (BG) levels (between 4.4 and 6.1 mmol/L) as compared to insulin-based glucose control aimed at maintaining BG levels between 10.0 and 11.1 mmol/L. Subsequently, recommendations to implement more stringent glucose control in ICUs have been incorporated in guidelines [5], even though such tight glucose control is associated with an increased risk for severe hypoglycemia [6, 7] and higher nurse workload [8]. Repeating the same study design in medical ICU patients (commonly named the second Leuven study), Van den Berghe et al. failed to reproduce this improvement in survival, demonstrating only a reduction in morbidity in the patients randomized to tight glucose control and a reduction in mortality in the subset of patients with an ICU stay of ≥3 days [9]. Further large randomized controlled trials (RCTs) have failed to replicate any mortality benefit [10–13] or have even shown an increased mortality [14], thereby highlighting both the high rate of severe hypoglycemia in the experimental arms and the difficulties in reaching the targeted range. A recent meta-analysis suggested that the difference in outcome between the two Leuven studies [4, 9] and subsequent RCTs [10–13] could be related to the excessive calories provided parenterally in the Leuven studies [15]. Based on these results several professional organizations have published updated recommendations advocating a less stringent glucose control in the ICU, i.e. to avoid high BG levels with an upper limit of 10.0 mmol/L [16–18] or even 11.1 mmol/L [19]. In parallel, because of difficulties in implementing glucose control in the ICU, clinical computerized decision-support systems (CDSSs) have been developed, most often without prior preclinical validation [20], to reduce the rate of hypoglycemia and to improve the time spent in lower target ranges, the user's facility and nurse compliance with recommendations [21–23]. Thus, whether the method used to achieve tight glucose control in the ICU could impact the outcome remains still a matter of debate. In addition, the multiplicity of CDSSs contrasts with the lack of large-scale RCTs with the aim to assess the impact of these systems on the outcome of critically ill patients [24].

We designed a randomized study to test the hypothesis that tight glucose control with a CDSS (target range 4.4–6.1 mmol/L) reduces the mortality in adult ICU patients at 90 days as compared to conventional glucose control protocols following most actual recommendations, i.e. targeting BG levels to <10.0 mmol/L [16–18].

Patients and methods

The Computerized Glucose Control in Critically Ill Patients (CGAO–REA) study is a non-blinded parallel-group RCT trial involving adult patients admitted to medical, surgical or mixed medical–surgical ICUs. The study was approved by the Institutional Review Board of Tours, France and is reported according to the extension of the Consolidated Standards Of Reporting Trials (CONSORT) statement to randomized trials of non-pharmacological treatment [25].

Patients

Adult patients assumed to require ≥3 days in the ICU were eligible for inclusion. We excluded moribund patients or those for whom there were do-not-resuscitate orders or the attending physicians were not committed to full supportive care, patients admitted for treatment of diabetic ketoacidosis or hyperosmolar state, patients

expected to be eating before the end of the day following the day of admission in the ICU, patients who had previously suffered hypoglycemia without documented full neurological recovery and patients considered to be at high risk of suffering hypoglycemia. Written informed consent, obtained before randomization, or delayed consent was obtained from each patient or a legal surrogate, which prevented inclusion of consecutively admitted patients.

Study design

Within 24 h after admission, patients were randomly assigned without blinding to undergo tight computerized glucose control (TGC, experimental arm) or conventional non-computerized glucose control (CGC, control arm). It was not mandatory that the patient should experience an episode of hyperglycemia within 24 h after admission to be included in the study. Randomization was stratified according to type of admission (scheduled surgical, emergency surgical, medical), diabetic status prior to admission and conventional glucose control management in the ICU before the beginning of the study. All possible glucose control methods used in the control arm were classified into five types defined according the calculation of the insulin rate after each glucose measure: (1) protocols based on static scales, i.e. insulin rates depending only on the last glucose measure and not on the previous insulin rate; (2) protocols based on dynamic scales, i.e. insulin rates depending on at least the last glucose measure and the previous insulin rate; (3) new individualized orders written each day by the attending physician based on static scales; (4) new individualized orders written each day by the attending physician based on dynamic scales; (5) nurse-driven protocols determined only by a target glucose order. In each participating center, the same method for glucose control was used for patients in the control arm and for patients necessitating continuous intravenous insulin and not included in the study.

Patients were randomized electronically (absence of center stratification allowed concealment of allocation before randomization) using permuted blocks of four.

Common aspects in both arms

Blood samples for glucose measurement were obtained by means of arterial catheters whenever possible; the use of capillary samples was discouraged. BG were measured with bedside glucose readers or preferentially with arterial blood gas analyzer devices when available. At least one BG value per day was measured by the hospital central laboratory on a morning sample (morning laboratory BG). Only the BG values measured at the bedside (e.g. either with point-of-care glucose readers or with blood gas analyzers located in the ICU) were used uncorrected for the adaptation of insulin infusion rate. Each ICU used regular human insulin in saline with the same concentration (50 IU in 50 ml of 0.9 % sodium chloride) with the use of a pump. A dedicated line for intravenous insulin infusion was encouraged to avoid occult administration of insulin or delay for effective application of a new insulin rate [17]. The main reason for discontinuation of continuous intravenous insulin before ICU discharge, at the discretion of the treating physician regardless of the group assignment, was reported as due to a severe adverse event, switch to palliative care or other reasons (for example, if the patient was eating again or because the patient no longer required insulin or required a very low daily insulin dose, thus permitting replacement by subcutaneous insulin). Enteral feeding was attempted as early as possible according international guidelines [26]. The usual nurse–patient ratio in France (1/2.5) was respected and not modified during the study period. All other aspects of patient care, including nutritional management, were carried out at the discretion of the treating physicians, and were the same in both arms.

Experimental arm

Tight computerized glucose control was performed with the assistance of the CGAO (Contrôle Glycémique Assisté par Ordinateur) software (LK2, Saint-Avertin, France) set for targeting a low BG range of 4.4–6.1 mmol/L (80–110 mg/dL). This software is an open-loop CDSS for glucose control management producing at bedside explicit recommendations regarding not only insulin titration with an algorithm based on a proportional integral controller [27], but also time for the next BG measurement and the quantity of intravenous glucose needed for correction of eventual hypoglycemia. The algorithm features of the software are described in Electronic Supplementary Material (ESM) 2. The attending nurse could choose to accept or decline the recommendations after each BG measure, and if necessary, to ask the attending physician for assistance. If the recommendations were not followed, it was not mandatory to indicate the reason in the CDSS; only the recommended insulin infusion rate and the actually applied insulin infusion rate after each BG reading were recorded. Once the patient was included in this experimental arm of the study, the software was intended to be used as long as the patient required continuous intravenous insulin, for example, during the entire stay in the ICU, unless a reason to discontinue intensive insulin therapy occurred (see above). To ensure adequate training of the staff, the software was used in each ICU for a training period of 1–3 months before the first patient was included in the study, with technical and educational support provided by the software manufacturer.

Control arm

Glucose control was based on current practice already used in the participating ICU before the beginning of the study, and the target BG was ≤10.0 mmol/L (180 mg/dL).

Assessment and data collection for both arms are presented in ESM3.

Outcome measures

The primary outcome measure was death from any cause within 90 days after ICU admission. Secondary predefined outcome measures were death in the ICU, in-hospital death, death within 28 days after ICU admission, the Sequential Organ Failure Assessment score (SOFA) scores at days 3, 7 and 14 [28], 28-day-ICU-free days, 28-day-hospital-free days, 28-day-ventilator-free days, 28-day-free-of-catecholamines days, and 28-day-life-support-free days [either mechanical or non-invasive ventilation, use of catecholamines (defined either as use of epinephrine or norepinephrine whatever the dose or use of dobutamine or dopamine with a dose >8 μg kg^{-1} min^{-1}), or renal replacement therapy]. These 28-day free-of-treatment days were calculated by subtracting the actual treatment duration in days from 28, with patients who died at day 28 or before being assigned 0 free-days. Other secondary measures were days with antibiotics in the ICU, presence of bacteremia (defined as the presence of any positive blood culture whatever the microorganism except for coagulase-negative staphylococci for which two positive blood cultures for the same microorganism were required), presence of tracheostomy performed during the ICU stay, necessity for red blood cell transfusions and volume of the transfusion. A BG level of ≤2.2 mmol/L accompanied with observed or suspected neurological symptoms was considered a priori as a serious adverse event.

Statistical analysis

All comparisons were performed using an intention-to-treat analysis. Our primary hypothesis was that mortality at day 90 would be reduced from 25 to 22 %. We planned three interim analyses using the O'Brien and Flemming rule [29]. Considering a two-sided 5 % level and a power of 80 %, we planned to recruit 6,422 patients. Data analysis was performed on patients for whom we had no consent withdrawal. Because the study was prematurely stopped, analyses were not adjusted for interim analyses. The primary outcome and other binary outcomes were analyzed using a χ^2 test. An adjusted logistic regression (taking into account stratification variables) was also performed. Outcomes with respect to 28-day free-of-treatment days were analyzed using Wilcoxon tests, as well as BG parameters. Finally, a mixed model was fitted to compare BG level and SOFA score over time, thus taking into account the correlation within patients. Subgroup analyses were conducted as post hoc analyses considering interaction terms within logistic regression models. Analyses were performed using SAS version 9.2 (SAS Institute Inc., Chicago, IL) and R 2.15.1. software.[1]

Results

Study participants

Following the first interim analysis performed after 1,517 patients were included, the data safety monitoring board recommended continuing the study but to increase the total number of patients to 10,606. The steering committee had at first attempted to increase the resources required for continuation but finally decided to stop the study because of the contrast between the expected duration of the study of about 10 years and the possibility of only a marginal effect of the intervention.

The study, carried out between October 2009 and June 2011, involved 34 ICUs (19 in academic tertiary care hospitals and 15 in community hospitals). Among the 2,684 randomized patients, 36 patients were discarded from any analysis: 35 because they withdrew consent and one because he/she was included twice. In the end, The TGC and CGC arms of the study included 1,336 and 1,312 patients, respectively (Fig. 1).

The baseline characteristics of the treatment groups were similar (Table 1). The mean age was 61 ± 16 years; the percentage of male patients, 64.4 %; the body mass index, 26.9 ± 6.4; the mean Simplified Acute Physiology Score (SAPS) II, 51 ± 19; the percentage of surgical admissions, 40.0 %, and the percentage of diabetic patients, 20.3 %. The SOFA score and its components as well as the main treatment characteristics implemented during the first day in ICU were similar (ESM 4).

The percentages of patients who stayed in the ICU for ≥3 days were not significantly different between the two groups: 1,250 of 1,336 patients (93.6 %) in the TGC group and 1,218 of 1,312 patients (92.8 %) in the CGC control group.

Insulin administration, and treatment effects on glucose control

Data were available for 1,317 (98.6 %) patients in the TGC group and for 1,284 (97.9 %) patients in the CGC

[1]Available at: http://cran.r-project.org/. Last date accessed November 2013.

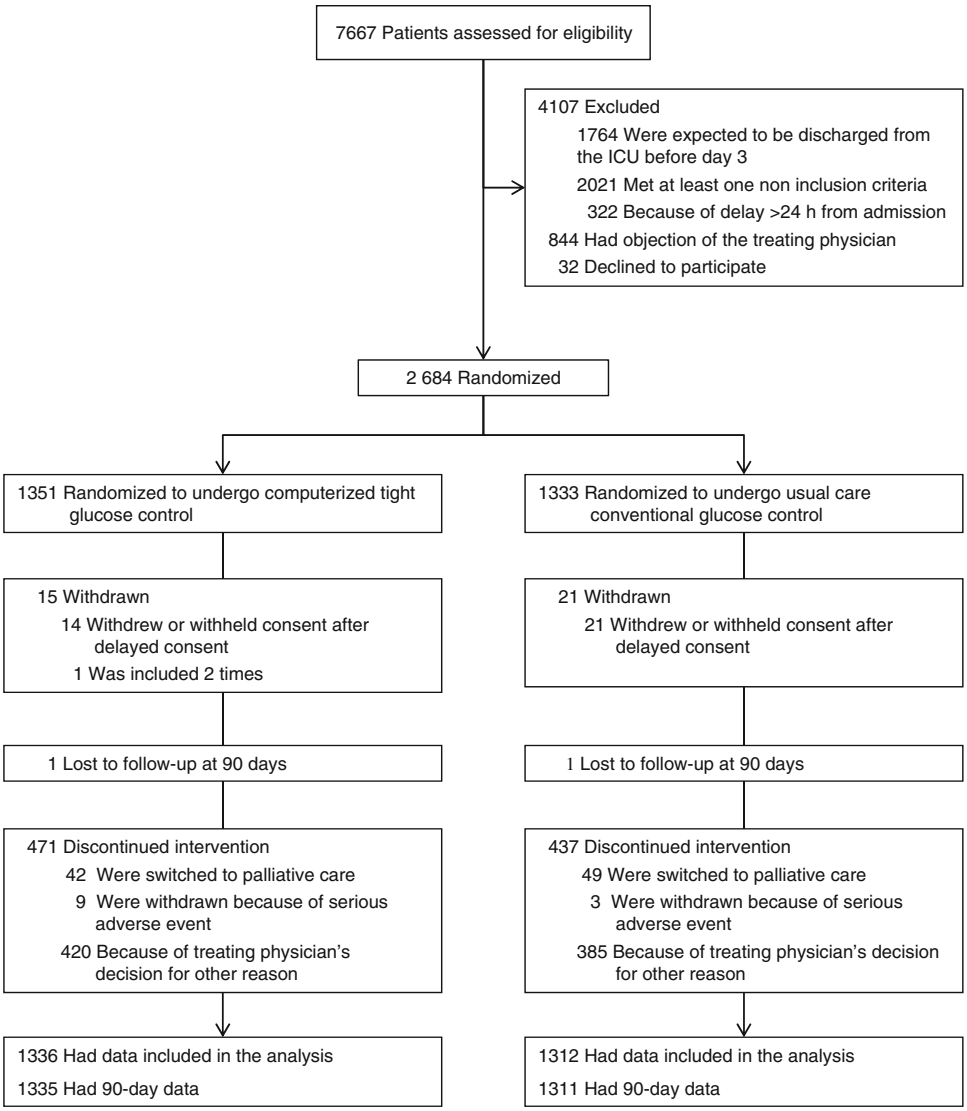

Fig. 1 Consolidated Standards Of Reporting Trials (CONSORT)-style flow diagram of patients screening, eligibility and enrollment in the trial. *ICU* Intensive care unit

group (Table 2; Fig. 2). Patients undergoing TGC were more likely than those undergoing CGC to have received continuous intravenous insulin. The mean BG was significantly lower in the TGC group than in the CGC group. There was no significant difference in BG standard deviation between the two groups. The minimal BG was significantly lower in the TGC group than in the CGC group. Severe hypoglycemia was recorded in 174 of the 1,317 (13.2 %) patients with available glucose control data undergoing TGC, as compared to 79 of the 1,284 CGC patients (6.2 %) ($p < 0.001$). No unexpected neurological symptom attributable to hypoglycemia was reported.

Patients in the TGC group were significantly more frequently monitored with bedside BG measurements than those in the CGC group. The difference between actual and recommended time for the next BG measurement was 9 (interquartile range −4 to 39) min with 66 % of BG measurements performed after the recommended time; 85 % of recommended insulin rates after each BG measurement were followed-up by the nursing staff.

Outcomes

The 90-day mortality was not significantly different between the two groups: 431 of 1,336 patients (32.3 %) in the TGC control group died, as compared to 447 of 1,312 patients (34.1 %) in the CGC group ($p = 0.32$). Adjustment on stratification variables did not change the result (data not shown). With respect to 90-day mortality, post hoc subgroup analyses (including the analysis applied only to patients staying in the ICU for ≥3 days) suggested

Table 1 Baseline characteristics of the study patients

Characteristics	TGC (n = 1,336)	GGC (n = 1,312)
Age, year; mean (SD)	61 (16)	62 (16)
Male sex, *n* (%)	862 (64.5)	844 (64.3)
Weight, kg; mean (SD), [*n*]	80 (20) [1,278]	78 (20) [1,271]
Body mass index[a], mean (SD), [*n*]	26.9 (6.8) [1,251]	26.8 (6.0) [1,243]
<18.5, *n* (%)	48/1,251 (3.8)	34/1,243 (2.7)
18.5–30, *n* (%)	930/1,251 (74.3)	928/1,243 (74.7)
>30, *n* (%)	273/1,251 (21.8)	281/1,243 (22.6)
SAPS II score[b], mean (SD), [*n*]	51 (19) [1,334]	51 (19) [1,309]
SAPS II >50, *n* (%)	633/1,334 (47.5)	617/1,209 (47.1)
McCabe score, mean (SD)	1.4 (0.6)	1.5 (0.6)
Reason for ICU admission		
Surgical (emergency), *n* (%)	417 (31.2)	380 (29.0)
Surgical (scheduled), *n* (%)	121 (9.1)	141 (10.7)
Nonsurgical, *n* (%)	798 (59.7)	791 (60.3)
Polytrauma patients, *n* (%)	91 (6.8)	85 (6.5)
Location before admission		
Emergency department, *n* (%)	589 (44.1)	539 (41.1)
Hospital floor (or ward), *n* (%)	370 (27.7)	398 (30.3)
Another ICU, *n* (%)	153 (11.5)	135 (10.3)
Intermediate care unit, *n* (%)	189 (14.2)	212 (16.2)
Extended care facility center, *n* (%)	35 (2.6)	28 (2.1)
History of diabetes mellitus, *n* (%)	262/1,335 (19.6)	274 (20.9)
Type 1 diabetes, *n* (%)	42/1,335 (3.1)	43 (3.3)
Type 2 diabetes, *n* (%)	220/1,335 (16.5)	231 (17.6)
Previous treatment with insulin[c], *n* (%)	71/262 (27.1)	64/274 (23.4)
Previous treatment with antidiabetic drugs[d], *n* (%)	71/220 (32.3)	69/231 (29.9)
Category of main diagnosis[e]		
Respiratory, *n* (%)	346 (25.9)	310 (23.6)
Cardiovascular, *n* (%)	170 (12.7)	201 (15.3)
Gastrointestinal or liver, *n* (%)	41 (3.1)	59 (4.5)
Renal, *n* (%)	28 (2.1)	20 (1.5)
Neurologic, *n* (%)	188 (14.1)	198 (15.1)
Hematologic or oncologic, *n* (%)	9 (0.7)	7 (0.5)
Metabolic, *n* (%)	10 (0.7)	7 (0.5)
Other medical category, *n* (%)	44 (3.3)	43 (3.3)
Gastrointestinal or urological surgery, *n* (%)	182 (13.6)	187 (14.3)
Cardiac surgery, *n* (%)	111 (8.3)	91 (6.9)
Vascular surgery, *n* (%)	41 (3.1)	35 (2.7)
Neurosurgery, *n* (%)	76 (5.7)	76 (5.8)
Orthopedic surgery, *n* (%)	29 (2.2)	28 (2.1)
Thoracic surgery, *n* (%)	36 (2.7)	34 (2.6)
Other surgical category, *n* (%)	25 (1.9)	15 (1.1)
Blood glucose level, mmol/L; mean (SD), [*n*]	9.4 (4.6) [1,292]	9.1 (4.2) [1,271]
Blood glucose level >10.0 mmol/L, *n* (%)	400/1,292 (31.0)	386/1,271 (30.4)
Plasma creatinine, μmol/L; mean (SD), [*n*]	142 (138) [1,333]	142 (140) [1,308]
Plasma urea, mmol/L; mean (SD), [*n*]	11.2 (9.7) [1,330]	10.9 (8.9) [1,307]

Data are presented as the number, with the percentage in parenthesis unless other specified. Each statistic was computed on the non-missing value, i.e., the whole sample unless specifically indicated. International System of Units (SI) conversion factors: to convert blood glucose levels from mmol/L to mg/dL, multiply by 18.01

TGC Tight computerized glucose control, *CGC* conventional non-computerized glucose control, *SAPS* simplified acute physiology score, *ICU* intensive care unit

[a] The body mass index is the weight in kilograms divided by the square of the height in meters

[b] Simplified Acute Physiology Score (SAPS II) scores can range from 0 to 156. with higher scores indicating more severe illness [30]

[c] Percentages of patients with previous treatment with insulin were calculated only for patients with an history of diabetes mellitus

[d] Percentages of patients with previous treatment with antidiabetic drugs were calculated only for patients with type 2 diabetes

[e] Category of main diagnosis is known in 1,311 of the 1,312 patients of the CGC group

no difference between the TGC group and the CGC group (Fig. 3). The ICU mortality, 28-day mortality, and in-hospital mortality were not significantly different in both groups. There was no difference between the two groups in the numbers of any 28-day-free-of-treatment days, in the numbers of days with antibiotics, in the rates of positive blood cultures, red blood cell transfusions, or tracheostomy (Table 3).

Table 2 Blood glucose management, according to treatment group

Management strategy	TGC (n = 1,336)	CGC (n = 1,312)	p
Patients with BG data, n (%)	1,317 (98.6)	1,284 (97.9)	
Morning laboratory BG, mmol/L; median (IQR)	6.5 (5.9; 7.3)	6.9 (6.2; 7.9)	<0.001
Mean bedside BG, mmol/L; median (IQR)	6.4 (6.0; 7.1)	7.0 (6.3; 7.9)	<0.001
Standard deviation of bedside BG, mmol/L; median (IQR)	1.6 (1.2; 2.3)	1.6 (1.2; 2.2)	0.17
Minimal BG, mmol/L; median (IQR)	3.2 (2.6; 3.9)	3.9 (3.2; 4.8)	<0.001
Interval between 2 measures, min; median (IQR)	139 (120; 161)	175 (141; 210)	<0.001
Severe hypoglycemia, n (%)[a]	174/1,317 (13.2)	79/1,284 (6.2)	<0.001
Moderate hypoglycemia, n (%)[a]	743/1,317 (56.4)	384/1,284 (29.9)	<0.001
Treated with insulin, n (%)[b]	1,239/1,314 (94.3)	1,052/1,290 (81.6)	<0.001
Daily insulin dose, IU[c]; median (IQR)	43.1 (24.5; 70.0)	34.1 (17.9; 58.3)	<0.001

Each statistic was computed on the non-missing value, i.e., the whole sample unless specifically indicated. SI conversion factors: to convert blood glucose levels from mmol/L to mg/dL: multiply by 18.01

BG Blood glucose measured at bedside, *IQR* interquartile range

[a] Incidences of severe and moderate hypoglycemia were calculated in the patient population for whom data with respect to blood glucose levels were available as the percentages of patients who experienced at least one episode of severe and moderate hypoglycemia (defined as BG $\leq$2.2 and $\leq$3.3 mmol/L, respectively)

[b] The numbers of patients for whom data with respect to insulin treatment were available are slightly different from the numbers of patients for whom data with respect to blood glucose levels were available

[c] Daily insulin dose was calculated only for patients treated with insulin

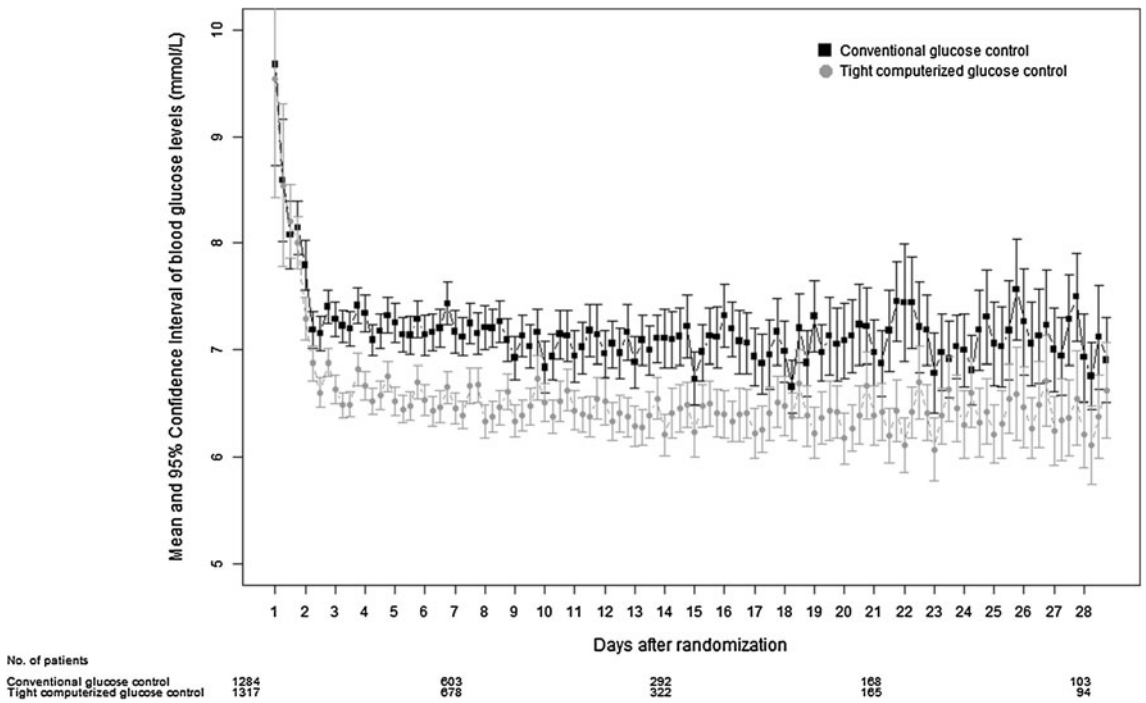

Fig. 2 Bedside blood glucose levels in the tight computerized glucose control (TGC) and conventional non-computerized glucose (CGC) groups

Discussion

In this large randomized multi-center study involving medical and surgical critically ill adults treated in university and non-university hospitals, tight computerized glucose control (TGC) performed with CDSS did not significantly reduce the risk of death at 90 days. The use of CDSS was not associated with other clinically important outcomes, but was associated with an increase in the rate of severe hypoglycemia in comparison with conventional glucose control (CGC).

In our study, patients who were assigned to TGC had lower BG levels and received more insulin than those assigned to CGC. Our findings are consistent with the

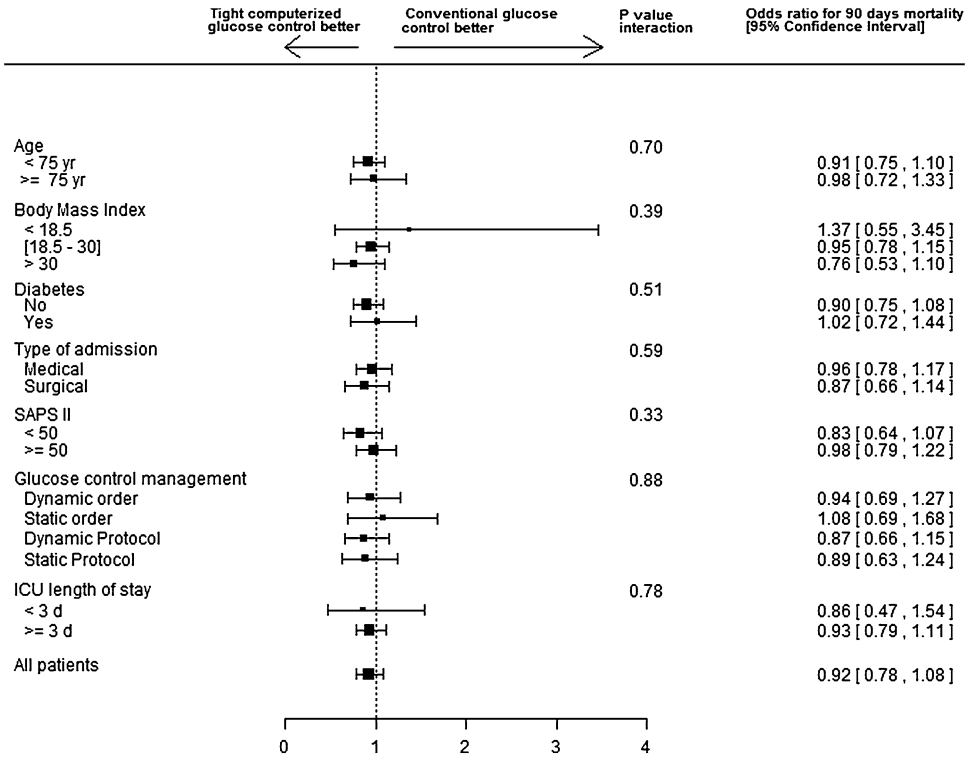

Fig. 3 Subgroup analysis with respect to 90-day mortality

Table 3 Outcomes

Variable	TGC (n = 1,336)	CGC (n = 1,312)	p value
Death: no. of patients/total no. (%)			
At day 90	431/1,336 (32.3 %)	447/1,312 (34.1 %)	0.32
At day 28	326/1,336 (24.4 %)	328/1,312 (25.0 %)	0.72
In ICU	302/1,336 (22.6 %)	310/1,312 (23.6 %)	0.53
In hospital	376/1,336 (28.1 %)	393/1,312 (30.0 %)	0.30
SOFA[a]			0.048
Day 1: median (IQR)	8 (5–11) (n = 1,287)	8 (5–11) (n = 1,264)	
Day 3: median (IQR)	7 (3–10) (n = 1,210)	6 (3–10) (n = 1,164)	
Day 7: median (IQR)	5 (3–8) (n = 826)	5 (2–9) (n = 751)	
Day 14: median (IQR)	4 (2–7) (n = 448)	4 (2–7) (n = 420)	
28-day-ICU-free days: median (IQR)	14 (0–22)	13 (0–23)	0.98
28-day-hospital-free days: median (IQR)	0 (0–11.5)	0 (0–11)	0.41
28-day-ventilator-free days: median (IQR)	18 (0–25)	18 (0–25)	0.82
28-day-free-of-catecholamines days: median (IQR)	24 (0–28)	24 (0–28)	0.48
28-day life-support-free-days: median (IQR)	16 (0–24)	17 (0–24)	0.86
Days with antibiotics in ICU: median (IQR)	3 (3–11)	6 (2–11)	0.22
Bacteremia: no. of patients/total no. (%)	183/1,335 (13.7 %)	172/1,311 (13.1 %)	0.66
Tracheotomy: no. of patients/total no. (%)	144/1,335 (10.8 %)	135/1,311 (10.3 %)	0.68
Transfusion of red cells: no. of patients/total no. (%)	440/1,272 (34.6 %)	452/1,234 (36.6 %)	0.29
Units of packed red cells: median (IQR)	4 (2–6)	4 (2–8)	0.19

TGC Tight computerized glucose control, *CGC* conventional non-computerized glucose control, *ICU* intensive care unit, *SOFA* sequential organ failure assessment, *IQR* interquartile range

[a] For the SOFA (Sequential Organ Failure Assessment) score, the p value is associated to the group–time interaction term

most recent meta-analysis showing that intensive glucose control did not significantly alter mortality but did increase the risk of severe hypoglycemia [6]. However, our findings contrast with those recently reported in the largest study involving unselected adults in the ICU, the NICE–SUGAR study, which showed that tight glucose control resulted in higher mortality than conventional glucose control [14]. In our study there was no significant difference between the two groups concerning outcome, although episodes of severe and moderate hypoglycemia,

whose association with an increase risk of death has been suggested [31], were twofold higher in the experimental group than in the control group. These conflicting results between the two studies could be explained by higher severity scores at admission in our study, by a lower difference in BG levels between the two groups than expected and by differences in the algorithms used to reach the same BG targets but leading to different glucose control properties, in relation to central tendency, dispersion of BG reflecting glycemic variability [32–34] and minimal BG. Indeed, according Mackenzie et al. [35], glucose control could be associated with the outcome on the basis of these new metrics.

The limitations of our study are similar to those of previous RCTs, including the same subjective criterion (expected requirement of $\geq$3 days in the ICU), the inability to use the assigned treatment to control BG levels on admission because of the necessity to obtain informed consent (however, all the patients were included within 24 h after admission), the inability to make treating staff unaware of the treatment group assignments and the lack of standardization of bedside BG measurements [36]. Another limitation of our study is the absence of data regarding nutritional intakes and intravenous glucose in non-nutritional solutions and in parenteral solutions. In comparison with previous large randomized studies, our study is the only one allowing a precise assessment of nurse compliance with recommendations in the experimental arm. Whether this non-optimal compliance rate with the recommended insulin rate [37] and the delay for BG measurement could explain the lack of benefit on the outcome of the tested intervention is unclear. The experimental arm was defined by the use of a specific CDSS, the CGAO software, the performance of which is clearly upgradable, especially with respect to prevention of severe hypoglycemia. Indeed, the CDSS used in our study could be improved by taking into account all of the glucose intake rates in order to estimate current insulin resistance and consequently calculate the optimized insulin rate after each BG measurement. Another improvement might be an automatic recognition of any situation at risk for severe hypoglycemia leading to a reduction in the recommended insulin rate and a more sophisticated calculation of the time for the next BG measurement. Whether the use of a different controller embedded in another CDSS would have achieved the objective of improving the outcome would require further studies.

A striking feature in our study is that BG levels were lower than expected in the control group, leading to a lower difference in BG levels between the two groups in comparison with previous studies. Thus, patients in the control group received more insulin than required for targeting BG levels of <10.0 mmol/L, leading to an increased rate in severe hypoglycemia episodes in comparison with previous studies. Whether the treating nurses did not systematically follow the insulin protocols for patients in the control group because of a spill-over effect on the nurses' behavior induced by using CDSS in the experimental group is unclear.

Our experimental group differs from the control group by the BG target range and the method used to achieve it. We did not design our study to test separately the impact on the outcome of each intervention. Indeed, we considered first that clinicians would have declined to implement tight glucose control without CDSS for safety reasons after the NICE–SUGAR study; secondly, we considered that the need for CDSS was less critical when the BG target is only defined by an upper limit of 10.0 mmol/L.

The strengths of our study, which is the second largest RCT in the field of glucose control in the ICU after the NICE–SUGAR study, were the following: (1) the severity at admission of included patients ensures the adequate representativeness of critically ill patients; (2) in our study, the very high percentage of patients still hospitalized in the ICU on the third day in accordance with our only inclusion criterion contrasts favorably with the percentage obtained in the second Leuven study [9]; (3) the comparison of our intervention was performed with usual care in France with respect to glucose control and not with a specific non-computerized algorithm for intravenous insulin titration, allowing generalization of our findings.

Our study failed to show an improvement in the outcome of ICU patients associated with a CDSS facilitating tight glucose control. Meanwhile, new therapeutic goals for glucose control in the ICU have emerged, realizing a paradigm shift from a unique BG target range to a more sophisticated individualized glucose control that takes into account glycemic variability, prevention of hypoglycemic episodes and diabetic status [38–40]. Therefore, CDSSs are likely to be more proposed to assist physicians and nurses for implementing advanced glucose control in the ICU. Based on the absence of a difference in mortality between tight computerized glucose control and less stringent glucose control without CDSS, despite the increase in the incidence of severe hypoglycemia in our experimental group this study could pave the way for future RCTs assessing new generation CDSSs.

In conclusion, the results of our RCT showed that tight computerized glucose control performed with CDSS (slightly reducing BG central tendency, without decreasing glycemic variability, and increasing the rate of severe hypoglycemia) did not significantly reduce the risk of death at 90 days in adult unselected medical and surgical critically ill patients, in comparison with conventional glucose control.

Acknowledgments The CGAO–REA study was supported, in part, by the Société Francaise d'Anesthésie et de Réanimation (SFAR) and Baxter Healthcare Corporation. The study sponsor was Centre

Hospitalier de Chartres, France. Dr. Kalfon is honored to have received the "Grand prix pour la Recherche 2008" from the Société Francaise d'Anesthésie et de Réanimation (SFAR) supporting the CGAO–REA study. We gratefully thank all members of the nursing staff of each participating ICU for their strong involvement and motivation in the study. We gratefully thank Amélie Le Gouge, and Mathieu Lemaire (INSERM Centre d'investigation clinique 202, Centre Hospitalier Universitaire de Tours), for participating in the statistical analysis; Gaëtan Roudillon and Gilles Rafalli (LK2, Saint-Avertin, France) for their major and invaluable role during the deployment of the software CGAO in 34 centers and for participating under the supervision of the lead investigator in training of clinical staffs and providing technical and educational support; Bérangère Bonnel, Cécile Jourdain, Dr Caroline Touboul, Patrick Piesvaux, Sylvie Aprelon, Emilie Breton, Isabelle Tessier and Leslie Leshayes (Hôpital Louis Pasteur, Centre Hospitalier de Chartres, Chartres) for their invaluable help in collecting data; Dr David Baker, DM, FRCA, (Department of Anesthesiology and Critical Care, Hôpital Necker-Enfants Malades, Paris) for reviewing the manuscript. Dr. Kalfon, and Mr. Giraudeau had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs. Kalfon, Ichai, Riou and Mr. Giraudeau participated in the study concept and design. Drs. Kalfon, Ichai, Brechot, Cinotti, Dequin, Riu-Poulenc, Montravers, Annane and Dupont participated in the acquisition of data. Drs. Kalfon, Riou, Ichai, Chastre (see ESM), Dequin, Montravers, Annane, Dupont, Mr. Giraudeau, Mr. Guerrini and Mr. Sorine participated in the analysis and interpretation of data. Drs. Kalfon, Ichai, Riou, Chastre (see ESM) and Mr. Giraudeau participated in the drafting of the manuscript and the critical revision of the manuscript for important intellectual content. Mr. Giraudeau performed the statistical analysis. Dr. Kalfon obtained funding. Drs. Kalfon, Ichai, Dequin, Montravers, Annane, Dupont, Riou, Mr. Giraudeau, Mr. Guerrini, and Mr. Sorine participated in the administrative, technical, or material support. The study supervision was performed by Dr. Kalfon.

Conflicts of interest Dr. Kalfon is a board member of LK2 (Saint-Avertin, France) and has shares in LK2. On behalf of all remaining authors, the corresponding author states that the remaining authors have no conflict of interest.

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