Intensive Care Med (2021) 47:1271–1283
https://doi.org/10.1007/s00134-021-06526-8

ORIGINAL

Individualised versus conventional glucose control in critically-ill patients: the CONTROLING study—a randomized clinical trial

Julien Bohé[1*], Hassane Abidi[1], Vincent Brunot[2], Amna Klich[3,4,5,6], Kada Klouche[2,7], Nicholas Sedillot[8], Xavier Tchenio[8], Jean-Pierre Quenot[9,10,11], Jean-Baptiste Roudaut[9], Nicolas Mottard[1], Fabrice Thiollière[1], Jean Dellamonica[12,13], Florent Wallet[1], Bertrand Souweine[14,15], Alexandre Lautrette[14,15], Jean-Charles Preiser[16], Jean-François Timsit[17], Charles-Hervé Vacheron[1], Ali Ait Hssain[14] and Delphine Maucort-Boulch[3,4,5,6]on behalf of the CONTROLe INdividualisé de la Glycémie (CONTROLING) Study Group

© 2021 The Author(s)

Abstract

Purpose: Hyperglycaemia is an adaptive response to stress commonly observed in critical illness. Its management remains debated in the intensive care unit (ICU). Individualising hyperglycaemia management, by targeting the patient's pre-admission usual glycaemia, could improve outcome.

Methods: In a multicentre, randomized, double-blind, parallel-group study, critically-ill adults were considered for inclusion. Patients underwent until ICU discharge either individualised glucose control by targeting the pre-admission usual glycaemia using the glycated haemoglobin A1c level at ICU admission (IC group), or conventional glucose control by maintaining glycaemia below 180 mg/dL (CC group). A non-commercial web application of a dynamic sliding-scale insulin protocol gave to nurses all instructions for glucose control in both groups. The primary outcome was death within 90 days.

Results: Owing to a low likelihood of benefit and evidence of the possibility of harm related to hypoglycaemia, the study was stopped early. 2075 patients were randomized; 1917 received the intervention, 942 in the IC group and 975 in the CC group. Although both groups showed significant differences in terms of glycaemic control, survival probability at 90-day was not significantly different (IC group: 67.2%, 95% CI [64.2%; 70.3%]; CC group: 69.6%, 95% CI [66.7%; 72.5%]). Severe hypoglycaemia (below 40 mg/dL) occurred in 3.9% of patients in the IC group and in 2.5% of patients in the CC group ($p = 0.09$). A post hoc analysis showed for non-diabetic patients a higher risk of 90-day mortality in the IC group compared to the CC group (HR 1.3, 95% CI [1.05; 1.59], $p = 0.018$).

*Correspondence: julien.bohe@chu-lyon.fr
[1] Service d'Anesthésie-Réanimation-Médecine intensive, Groupement hospitalier sud, Hospices Civils de Lyon, 165 Chemin du grand Revoyet, 69310 Pierre Bénite, France
Full author information is available at the end of the article

Julien Bohé and Hassane Abidi contributed equally to this article.

The members of The CONTROLe INdividualisé de la Glycémie (CONTROLING) Study Group are listed in Acknowledgements.

Springer

Conclusion: Targeting an ICU patient's pre-admission usual glycaemia using a dynamic sliding-scale insulin protocol did not demonstrate a survival benefit compared to maintaining glycaemia below 180 mg/dL.

Keywords: Glucose control, Hyperglycaemia, Individualised glucose control, Glycated haemoglobin A1c, Insulin

Introduction

Acute hyperglycaemia can be an adaptive response to stress [1]. It is commonly observed in critically ill adults [1] and is associated with poor clinical outcome [2–5]. Although glycaemic control has been studied in many clinical trials over the past two decades, the optimal glycaemic target for critically ill adults is still debated [6]. The first two single-centre trials conducted by Van den Berghe et al. found a benefit of maintaining glycaemia within normal range, i.e. between 80 and 110 mg/dL, rather than observing a liberal strategy, i.e. infusion of insulin only if the glycaemia exceeded 215 mg/dL and maintenance of glycaemia between 180 and 200 mg/dL [7, 8]. However, these results were not confirmed in multi-centre studies [9–13]. The NICE-SUGAR study, which included the largest number of patients, found almost opposite results, showing a benefit of maintaining glycaemia below 180 mg/dL rather than within a range of 81 to 108 mg/dL [12]. Since then, a glycaemia maintained below 180 mg/dL has been considered as the conventional glycaemic target for adults in intensive care unit (ICU) [14, 15]. However, some observational studies suggested various relationships between glycaemia in ICU and the occurrence of hypoglycaemia or mortality, depending on the patient pre-admission glycaemia, the mean glycaemia during ICU stay associated with the lowest mortality rate being higher in diabetic patients compared to non-diabetic patients [16–25]. These observations are consistent with the results of the randomized controlled trials conducted by Van den Berghe et al. that did not show a benefit of normalizing hyperglycaemia in diabetic patients [26]. Hence, it seems important to evaluate the potential benefit of using an individualised glycaemic target in the ICU context.

The hypothesis made herein was that the optimal glycaemic target for critically ill patients could be individualised by targeting the usual glycaemia, i.e. the glycaemia prior to critical illness and ICU admission. A multi-centre study was thus performed to determine whether using an individualised glycaemic target decreased mortality and morbidity among critically ill patients, compared to the conventional strategy of maintaining glycaemia below 180 mg/dL.

Methods

The CONTROLING (CONTROLe INdividualisé de la Glycémie) study is a multi-centre, randomized, double-blind, parallel-group clinical trial conducted in medical, surgical, and mixed adult ICUs.

Take-home message

Targeting an ICU patient's pre-admission usual glycaemia using a dynamic sliding-scale insulin protocol did not demonstrate a survival benefit compared to maintaining glycaemia below 180 mg/dL.

The complete study protocol, available in the ESM Appendix, p. 27, was approved by the regional ethics committee (Sud-Est II Lyon, France). The study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Consent from patients or the closest family member was obtained after adequate written and oral information provided by the local investigator according to French legislation in place at the time of the study. A Data and Safety Monitoring Board (DSMB) reviewed safety data and results of the planned interim analyses (ESM Appendix, p. 5).

There was no commercial support. All authors vouch for the accuracy of the data and analysis and the fidelity of the study to the protocol.

Participants

Patients were recruited from May 2015 to July 2016. As part of routine care, all adult patients (≥ 18 years) admitted to the participating ICUs for whom oral feeding was impossible and who were not expected to be discharged from the ICU within 2 days were considered for inclusion. A blood sample was drawn for the measurement of glycated haemoglobin A1c (A1C) level. Their glycaemia was controlled by the bedside nurse to remain below a conventional glycaemic target of 180 mg/dL [14, 15] following instructions provided by CPG (https://cpg.chu-lyon.fr), a non-commercial web application developed by two of the authors (Julien Bohé and Hassane Abidi; ESM Appendix, p. 6).

Briefly, CPG is an algorithm based on multiple insulin infusion rate sliding scales and rules to move within a scale and from one scale to another. CPG gave the nurse (without physician intervention) all the instructions for the pre-scheduled time of glycaemia sampling, administration of the intravenous insulin, and correction of hypoglycaemia. The interval of time between glycaemia measurements ranged from 1 to 6 h, depending on the

level and stability of the previous glycaemia measurements. Briefly, insulin therapy was administered as a continuous intravenous infusion via an automated syringe and was initiated when glycaemia was measured above a glycaemic target of 180 mg/dL. Insulin infusion was then eventually gradually increased to keep glycaemia below the glycaemic target. It remained unchanged when glycaemia was between the glycaemic target-29 mg/dL and the glycaemic target. It was gradually reduced before being eventually discontinued when glycaemia dropped between 63 mg/dL and glycaemic target-29 mg/dL or, in case of ongoing infusion, when glycaemia was less than 63 mg/dL. In that case, 20–40 mL of 30% dextrose solution were administered.

Exclusion criteria were pregnancy, legal guardianship, previous enrolment in the study, admission to ICU for severe hypoglycaemia, therapeutic limitation (which included the decision not to resuscitate, not to reintubate, not to increase vasopressor infusion rate, and not to initiate renal replacement therapy), and refusal to participate in the study. For safety reasons, patients with known history of diabetes who underwent transfusion of more than 3 red blood cell units over the past 3 months prior to ICU admission were also not included, as this may artificially reduce A1C levels.

Randomization, interventions

For randomization to occur, the investigator had to indicate in the CPG application within the first 96 h of ICU stay that the patient was eligible, as did the biologist by entering the A1C assay result. Study participants were randomly allocated by CPG into either of the two glycaemic target groups (1:1). Randomization was stratified by centre. In each centre, if by chance the proportion of patients already included in each group differed by more than 4%, the next included patient was automatically allocated to the group with the lowest number of patients. In the individualised glucose control group (IC group), A1C at ICU admission was used to assess the usual glycaemia of each patient: usual glycaemia = 28.7 × A1C-46.7 (in mg/dL, with A1C in %) [27]. The glycaemic target was set to usual glycaemia + 15 mg/dL or less. In the conventional glucose control group (CC group), the glycaemic target of 180 mg/dL or less used prior to randomization was maintained. Apart from the glycaemic target-related differences between the two groups, CPG operated in a similar manner in both groups, as previously described. It should be noted that for A1C = 7.4%, the glycaemic target was the same for both groups (180 mg/dL). In the IC group and for safety reasons, the limits of the glycaemic target were arbitrarily set to a minimum of 111 mg/dL (corresponding to an A1C level of 4.96%) leading to a reduction of insulin flow when glycaemia dropped below 111−29 = 82 mg/dL, and to a maximum of 217 mg/dL (corresponding to an A1C level of 8.67%). Usual glycaemia and glycaemic target values according to A1C levels are provided in ESM Appendix (p. 16). The intervention began when the first glycaemia result was entered into CPG after randomization.

All clinicians were blinded to the A1C result, randomization process and time, and group allocation. After randomization, access to glycaemia and insulin infusion rate history was disabled in order to maintain double-blinding. For safety reasons, the CPG application enabled the nurse in charge to view only the last glycaemia value entered and the current insulin infusion rate and, if any, the history of all hypoglycaemia below 63 mg/dL. Neither the A1C result nor the glycaemia or insulin infusion rate were documented in the patient's medical file after randomization.

The intervention was maintained until patient discharge from ICU. The intervention could be stopped earlier if the care delivered became non-relevant to critical care procedures, i.e. pending transfer to general ward, decision for end-of-life care.

Glycaemic control and glycated haemoglobin A1C

In each centre, glycaemia was determined using point-of-care glucose meters from arterial blood sample ideally; if this was not possible, from a capillary blood sample. All point-of-care glucose meters were regularly maintained, checked, and calibrated according to the manufacturer's recommendations (ESM Appendix, p. 11).

The CPG application had been implemented in all participating units for several months or years prior to the start of the study. All nurses of the participating units were trained in the use of CPG during a one to two-hour session.

A1C assays were performed in the central laboratories of each hospital centre using high-performance liquid chromatography or automated immunometric techniques (ESM Appendix, p. 11).

Other treatments

Other than glycaemia management, patient care was left to the discretion of the attending physician. Regarding nutrition, procedures in each unit followed the latest recommendations from the French learned societies (ESM Appendix, p. 12) [28].

Data collection

At baseline, data regarding the demographic and clinical characteristics of the patients were collected, including medical history of diabetes, main type and reason for ICU admission, and the Simplified Acute Physiology Score II (SAPS II) that can range from 0 to 164—higher

scores indicating a more severe illness [29]. Patients were considered as diabetic if they had a medical history of diabetes and/or an A1C level ≥ 6.5%. From the moment of randomization to that of ICU discharge, data concerning all glycaemia measurements, insulin administration, type and volume of all enteral and parenteral nutrition, body weight (measured daily), use of vasopressor support, non-prophylactic antimicrobial treatment, mechanical ventilation, and renal-replacement therapy were collected. For 90-day mortality, hospital medical records were examined and direct contact with participants or surrogates was used for patients discharged alive from the hospital. All data were recorded through CPG either during routine care or by the investigator for the purpose of the study.

Outcomes

The primary outcome measure was death from any cause within 90 days after randomization.

The secondary outcome measures were 28-day mortality, ICU length of stay, and duration (in days) of vasoactive support, non-prophylactic antimicrobial treatment, mechanical ventilation, and renal-replacement therapy, all of them after randomization.

Adverse events

Severe hypoglycaemia, defined by a glycaemia below 40 mg/dL, and death in ICU were considered as serious adverse events. A detailed report of each serious adverse event was transmitted by the investigator to the DSMB. Moderate hypoglycaemia (glycaemia between 40 and 71 mg/dL) were also recorded. Hypoglycaemia was considered as insulin-related if insulin was being infused during the 3 hours prior to its occurrence [30].

Statistical analysis

Assuming a 90-day mortality rate slightly lower than that observed in the NICE-SUGAR study [12], the enrolment of 2100 patients per group would achieve power of 90% to detect a 4%-decrease of absolute 90-day mortality from a baseline of 22% in the CC group using the Chi-squared test with a two-sided significance level of 5%.

Patient characteristics at inclusion were described according to each study group. All quantitative data were expressed as median [interquartile range, IQR]. All qualitative data were summarized by the absolute and relative frequency in each category of the variable (missing data were not included).

The 90-day survival curves for the two groups were estimated using the Kaplan–Meier method and compared using the Log-rank test [31]. Patients who were either lost to follow-up or who withdrew consent before 90 days were censored as of the last date of contact. The hazard ratios (HR) with their 95% CI were estimated using a Cox proportional hazards model adjusted on the age, sex, body mass index, Charlson score, diabetes status, ICU admission type, SAPS II score and invasive ventilation. The same analysis was performed to compare the mortality at 28 days between the two treatment groups. Different subgroups of patients were studied in a post-hoc analysis. In each subgroup, the 90-day-mortality HR with their 95% CI were estimated using the previous adjusted Cox proportional hazards model (if the subgroup was defined from one of the adjusted variables, this variable was removed from the model). Additionally, interactions were tested introducing interaction term between randomisation arm and subgroup variable.

To minimize the influence of variations in sampling intervals, the time-weighted average glycaemia and insulin infusion rate were calculated for each patient using the trapezoidal rule from the area under the curve of the time course of glycaemia and insulin infusion rate, respectively, divided by the time of measurement [32]. These time-weighted average glycaemia and insulin infusion rate were described in the two glycaemic target groups according to various strata of A1C (≤ 5%, > 5 and ≤ 6%, > 6 and ≤ 7%, > 7 and ≤ 8%, and > 8%). Then, they were compared between the two glycaemic target groups stratifying on A1C using the stratified Wilcoxon–Mann–Whitney test. Glycaemic variability was evaluated using the standard deviation SD and coefficient of variability CV calculated for each patient [33].

The time spent in different glycaemic ranges was studied: below 40 mg/dL (severe hypoglycaemia), below 72 mg/dL (any hypoglycaemia), between 72 mg/dL (lowest value for normal glycaemia) and glycaemic target, and between glycaemic target-36 mg/dL and glycaemic target (i.e. between 144 and 180 mg/dL for the CC group). The proportion of patients who had at least one episode of hypoglycaemia or severe hypoglycaemia was estimated in each group and compared using the Chi-squared test. The proportion of time spent in the various glycaemic ranges, days in ICU, and days of use of intensive care resources and treatments were expressed as median [IQR], and compared between groups using the Wilcoxon–Mann–Whitney test. In a post hoc analysis, we estimated the 90-day survival probability with regard to the occurrence of a hypoglycaemic event.

The Data Safety and Monitoring Board (DSMB) was composed of two physicians and one biostatistician. The DSMB requested up to four interim analyses that were pre-planned, the first of which was scheduled after 1400 inclusions. The DSMB had access to unblinded results on serious adverse events. According to French laws on studies of standard care, the protocol pre-specified that enrolment would continue during the interim analyses. The

interim analysis results were not disclosed to the investigators, who were told only whether the study would be stopped or continued. All analyses were conducted on a modified intention-to-treat basis (the analysis was performed only on the patients who received the intervention). The statistical analyses were performed using R software, version 3.3.1 (Free Software Foundation, http://www.r-project.org). The significance level was set at 5%.

This study is registered on ClinicalTrials.gov, number NCT02244073.

Results

The first interim analysis was performed by the DSMB on the first 1860 randomized patients. Owing to a low likelihood of benefit and evidence of the possibility of harm related to hypoglycaemia, the DSMB recommended to stop the trial (ESM Appendix, p. 13). When the trial was stopped, 2075 patients of the 4200 scheduled (49%) had been included.

During the study period (from May 19th, 2015 to July 6th, 2016), 5326 patients were admitted to 12 participating ICUs in France (ESM Appendix, p. 17). Among them, 2075 patients (39%) underwent randomization; 1917 patients (36%) had at least one glycaemia measurement after randomization and therefore received the intervention (942 in the IC group and 975 in the CC group; Fig. 1). A total of 636/1917 patients (33%) were considered as diabetic (Table 1).

Primary outcome (90-day mortality) data were available for 938 patients in the IC group and 968 in the CC group: 90 days after randomization, 308 patients (32.8%) in the IC group and 295 patients (30.5%) in the CC group had died. Survival at 90 days was not significantly different between the two groups (67.2%, 95% CI [64.2%; 70.3%] for the IC group, and 69.6%, 95% CI [66.7%; 72.5%] for the CC group, $p = 0.23$; Fig. 2a).

After adjustment on age, sex, body mass index, Charlson score, diabetes status, ICU admission type, SAPS II score, and use of invasive ventilation, there was no significant difference in mortality risk at 90 days between groups (HR 1.1, 95% CI [0.97; 1.36], $p = 0.1$).

Secondary outcomes related to glucose control are detailed in Table 2, Fig. 3, and ESM Appendix (pp. 18 and 24). During the intervention, by stratifying on A1C level, the median time-weighted average glycaemia was significantly different between the two groups ($p < 0.0001$). In the IC group, the median time-weighted average glycaemia increased linearly with A1C values as expected based on the predictive equation used. In the CC group, the median time-weighted average glycaemia progressively increased with A1C to reach the constant glycaemic target of 180 mg/dL. When A1C was in the range of 7 to 8% (131/1917 patients, 7%), the glycaemic target was similar in both groups (equal to 180 mg/dL for A1C = 7.4%) as was the median time-weighted average glycaemia. When A1C was out of this range (1786/1917 patients, 93%), the median time-weighted average glycaemia was significantly different between the two groups, being lower in the IC group than in the CC group when A1C was less than 7%, and higher in the IC group than in the CC group when A1C was above 8%. As most patients from the CC group had a spontaneous glycaemia well below the glycaemic target, they spent little time with a glycaemia within the interval glycaemic target-36 mg/dL and glycaemic target, compared to patients from the IC group. Patients from the IC group required more glycaemia measurements each day and displayed a higher glycaemia variability assessed with CV, but not with SD, compared to patients from the CC group.

As for the median time-weighted average glycaemia, the median time-weighted average insulin infusion rates, stratified on A1C levels, were significantly different between the two groups ($p < 0.0001$). For the IC patients with A1C ranging from 4.96% to 8.67%, although glycaemic target increased with A1C level, the time-weighted average insulin infusion rate did not change in a significant manner. In the CC group, for which the glycaemic target was constant, the time-weighted average insulin infusion rate increased progressively with the A1C.

Survival at 28 days in the IC group (74.3%, 95% CI [71.6%; 77.2%]) was not significantly different than that of the CC group (78%, 95% CI [75.4%; 80.6%], $p = 0.07$). There was also no significant difference between groups in terms of ICU length of stay post randomization (4.10 days [1.80–9.99] in the IC group and 4.32 [1.85–10.02] in the CC group; $p = 0.23$) and in use of intensive care resources (ESM Appendix, p. 21).

Nutrition was not significantly different between the two groups (Table 2, ESM Appendix, p. 25). Non-continuously administered nutrition was not comprehensively recorded by all centres and is not reported.

Regarding the occurrence of adverse events, no significant difference was found in the frequency of severe hypoglycaemia between the two groups (3.9% for IC group vs. 2.5% for CC group, $p = 0.09$). However, hypoglycaemia below 72 mg/dL was significantly more frequent in the IC group (31.2%) than in the CC group (15.8%, $p < 0.0001$; Table 2).

Post-hoc analysis: we explored different subgroups of patients. Among them, after adjustment on various confounders, there was a significantly higher risk of mortality at 90 days in the IC group for non-diabetic patients (HR 1.3, 95% CI [1.05; 1.59], $p = 0.018$; interaction p-value = 0.08), for surgical patients (HR 1.83, 95% CI [1.12; 3.02], $p = 0.017$; interaction p-value = 0.04) and for patients with an A1C level between 5 and 6% (HR

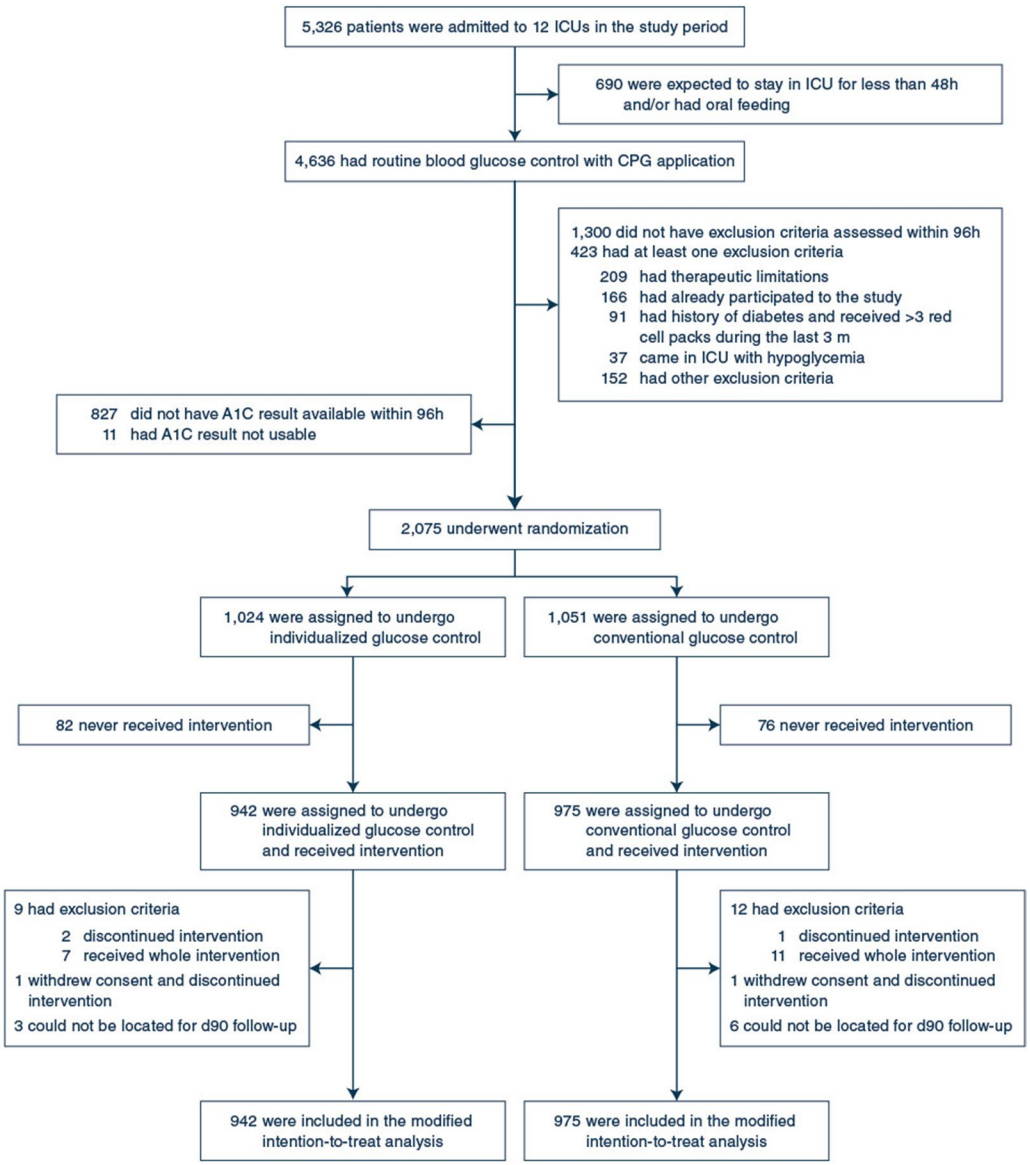


Fig. 1 Assessment, randomization, and follow-up of the study patients. During the stay in the intensive care unit (ICU), a family member of one patient from both groups withdrew consent to continue the study intervention. At this time, the intervention and the recalling of the data were stopped for these two patients

1.33, 95% CI [1.04; 1.72], $p = 0.026$) (Fig. 2b and ESM Appendix, p. 22). Glycaemic metric for the subgroups of patients based on A1C range and diabetes status are presented in ESM Appendix, p. 18. By stratifying on A1C level, the median time-weighted average glycaemia and insulin infusion rates were significantly different between the two groups of non-diabetic patients ($p < 0.0001$), while only the median time-weighted average glycaemia ($p = 0.029$) was significantly different for diabetic patients. Hypoglycaemic events were significantly more frequent in the IC group for non-diabetic patients, but not for diabetic patients. Despite the fact that no adverse event such as loss of consciousness, seizure, or death, thought to be directly induced by hypoglycaemia was reported by the investigator, survival probability at 90 days was lower in patients from both groups who had hypoglycaemia compared to patients whose glycaemia never dropped below 72 mg/dL (ESM Appendix, p. 23).

Discussion

In this large, multi-centre, randomized trial, targeting the estimated usual glycaemia for each patient by using

Table 1 Characteristics of the patients at baseline

Variable	Individualised glucose control *N* = 942	Conventional glucose control *N* = 975
Age—years	68 [56–77]	69 [58–79]
Female sex—number of patients (%)	364 (38.6)	378 (38.8)
Weight—kg[a]	75 [64–89]	75 [64–88]
Body-mass index[a,b]	26.3 [22.9–31]	26.2 [22.6–30.4]
ICU admission type—number of patients (%)		
Medical	771 (81.8)	796 (81.6)
Emergency surgery	91 (9.7)	94 (9.6)
Scheduled surgery	40 (4.2)	53 (5.4)
Trauma with emergency surgery	13 (1.4)	16 (1.6)
Trauma without emergency surgery	27 (2.9)	16 (1.6)
Reason for ICU admission—number of patients (%)		
Respiratory	351 (37.3)	348 (35.7)
Neurological (including stroke and toxicology)	154 (16.3)	156 (16)
Cardiac	132 (14)	158 (16.2)
Gastroenterological / hepatic	131 (13.9)	137 (14.1)
Urology / nephrology	68 (7.2)	71 (7.3)
Hematological / cancer	23 (2.4)	35 (3.6)
Endocrinology / metabolism	19 (2)	24 (2.5)
Bone / joint / muscle	24 (2.5)	23 (2.4)
Ears, nose and throat / stomatology / ophthalmology	19 (2)	12 (1.2)
Dermatology	15 (1.6)	8 (0.8)
Obstetrics / gynecology	6 (0.6)	3 (0.3)
Charlson score—number of patients (%)[c]		
0	192 (20.4)	174 (17.8)
1–2	334 (35.4)	349 (35.8)
> = 3	416 (44.2)	452 (46.4)
Mc Cabe score—number of patients (%)[d]		
A	604 (64.1)	585 (60)
B	264 (28)	306 (31.4)
C	74 (7.9)	84 (8.6)
SAPS II score[e]	46 (35–62)	48 (37–62)
Diabetic patients—number of patients (%)[f]	321 (34.1)	315 (32.3)
History of diabetes	236 (25.1)	232 (23.8)
Insulin-dependent	75 (8)	79 (8.1)
Non-insulin dependent treated with oral antidiabetic agent	128 (13.6)	122 (12.5)
Non-insulin dependent treated with diet only	33 (3.5)	31 (3.2)
No history of diabetes and A1C ≥ 6.5%	85 (9)	83 (8.5)
Glycated haemoglobin level—%	5.8 [5.4–6.4]	5.8 [5.4–6.4]
In non-diabetic patients	5.6 [5.2–5.9]	5.6 [5.3–5.9]
In diabetic patients	6.9 [6.4–8.2]	6.9 [6.4–7.8]
Glycaemic level at randomization—mg/dL[g]	139 [113–171]	140 [114–175]
Insulin dose at randomization—IU/h	0 [0–0.1]	0 [0–0.18]
Receiving insulin at randomization—no. of patients (%)	241 (25.6)	250 (25.7)
Other interventions at randomization day—no. of patients (%)[h]		
Vasopressors[i]	274 (31.1)	286 (31.2)
Invasive ventilation	473 (53.6)	484 (52.8)
Non-invasive ventilation	184 (20.9)	186 (20.3)

Table 1 (continued)

Variable	Individualised glucose control *N* = 942	Conventional glucose control *N* = 975
Renal-replacement therapy	84 (9.5)	92 (10)
Non- prophylactic anti-infective agents	656 (74.4)	665 (72.6)
Interval from ICU admission to randomization—days	1.2 [0.9–2.1]	1.3 [0.9–2.1]

Values are expressed as median [interquartile range] or number (%)

[a] *N* = 919 in the Individualised Glucose Control group and *N* = 946 in the conventional glucose control group

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

[c] The Deyo–Charlson score ranges from 0 to 33, higher scores are indicative of a higher burden of chronic illness [41]

[d] A McCabe score of A indicates no underlying disease that compromises life expectancy, B an estimated life expectancy with the chronic disease of less than 5 years, and C an estimated life expectancy with the chronic disease of less than 1 year [42]

[e] The simplified acute physiology score (SAPS) II ranges from 0 to 164, with higher scores indicating greater severity of symptoms [29]. The score was assessed during the first 24 h in ICU

[f] Diabetic patients are patients with a history of diabetes or patients with no history of diabetes and glycated haemoglobin level ≥ 6.5%; non-diabetic patients are the others

[g] *N* = 931 in the Individualised Glucose Control group and *N* = 963 in the Conventional Glucose Control Group (for the remaining included patients, the post-randomization trigger for initiating the intervention was a change in nutrition infusion rate, and glycaemic level was not measured). To convert glycaemic level to mmol/L, multiply values by 0.0556

[h] Interventions were recorded for patients who did not leave the ICU the day of randomization, 882 in the IC group and 916 in the CC group

[i] Epinephrine or norepinephrine infusion rate above 1 mg/h

the A1C did not improve 90-day survival compared to maintaining glycaemia below a fixed level of 180 mg/dL. All clinical trials conducted on glycaemic control in ICU have previously compared two fixed glycaemic targets: a target close to a supposed normal glycaemia, defined for non-diabetic patients without any acute illness, and a target allowing a certain level of hyperglycaemia related to stress [7–12]. In this study, an individualised glycaemic target was used for the first time on a large-scale.

The present study was also the first on glycaemic control in ICU to be performed in a double-blinded manner. Moreover, the exclusion criteria were not numerous allowing the participation to the study of nearly 40% of the patients admitted to ICUs during the study period, thus giving an optimal representation of patients admitted to non-specialized ICUs. Glycaemic control was also managed similarly in both groups via a web application protocol used in routine practice by the nurses without any medical intervention. Finally, almost no protocol deviation for glycaemic control (less than 1%, data not shown) was observed herein, which is potentially related to the routine use of the web application for a long time prior to the study initiation as well as, presumably, the user confidence in its use.

Regarding glucose control, glycaemic levels in the present study were in line with the results from published trials. Indeed, at randomization, and taking into account that 25.6% of patients were receiving insulin, the median [IQR] glycaemia of 140 mg/dL [113–173] found herein is comparable to the mean ± SD glycaemia of 145 ± 50 mg/dL prior to insulin administration reported in the NICE-SUGAR study [12]. After randomisation, the median [IQR] glycaemic target of 135 mg/dL [123–152] in the IC group was consistent with the recommendations available at the time of designing the study [15, 34], but higher than in the previous trials where the upper limit of the intensive control group was set at 108–110 mg/dL [7–12]. Nevertheless, the time-weighted average glycaemia was very close to the targeted preadmission usual glycaemia (ESM Appendix, p. 18). In the CC group, the time-weighted average glycaemia of 139 mg/dL [122–165] was well below the fixed glycaemic target of 180 mg/dL, which was probably a consequence of an unexpected low level of resistance to insulin. However, the glycaemic level found herein in the CC group was similar to the mean ± SD time-weighted average glycaemia of the NICE-SUGAR study (144 ± 23 mg/dL) [12] and, not surprisingly, a bit lower than the mean ± SD morning glycaemia of the first study by Van den Berghe et al. in which insulin was initiated at a higher glycaemic threshold, the glycaemic target was higher, and patients received higher rates of carbohydrates during the first days of ICU stay (153 ± 33 mg/dL) [7]. For patients whose A1C level was close to 7.4%, the glycaemic targets and subsequently the glycaemia were comparable in the two groups. All these points made the glycaemia difference between the two groups quantitatively small, and smaller compared to other trials. [7, 8, 12] Nevertheless, this difference was highly significant, but perhaps quantitatively insufficient to allow to merge clinical outcome differences other than

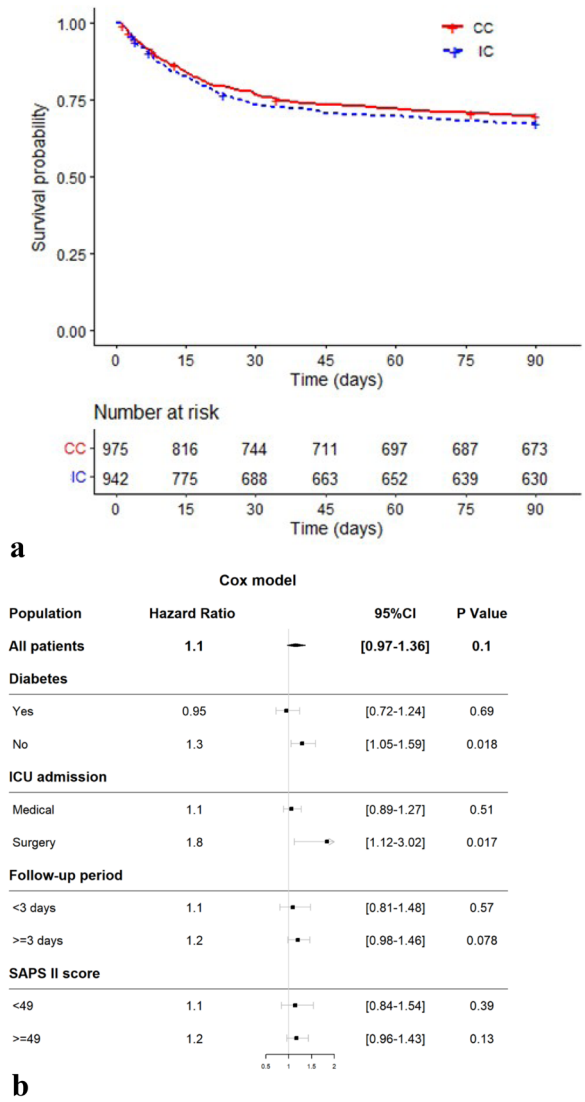


Fig. 2 Probability of survival and hazard ratios for death, according to treatment group. Panel **a** shows Kaplan–Meier estimates for the probability of survival, which at 90 days was similar in both the conventional glucose control (CC) group and the individualised glucose control (IC) group (log rank test, $p = 0.23$). Each "+" represents a censoring. Panel **b** shows the hazard ratios (and 95% confidence intervals) for death from any cause in the individualised glucose control group compared to the conventional glucose control group, among all patients and in different subgroups (post hoc analysis). The hazard ratios were estimated from the Cox model adjusted on the age, sex, body mass index, Charlson score, diabetes status, ICU admission type, SAPS II score, and invasive ventilation. If the subgroup was defined from one of the adjusted variables, this variable was removed from the model. Surgery includes emergency and scheduled surgeries

hypoglycaemia events, as reported in other trials [7, 8, 12].

In post hoc analysis, it was found that patients without diabetes from the IC group (for whom the glycaemic target was 129 mg/dL [118–138]) had a significantly lower survival rate than patients in the CC group. This result is consistent with the NICE-SUGAR study that has found that an intensive glycaemic control was harmful for the whole population [12]. The lowering of potentially beneficial stress-related hyperglycaemia and/or the high rate of moderate hypoglycaemia could explain the higher mortality rate observed in these two studies. However, such a difference was not observed for patients with diabetes. This absence of difference might be explained by the design of the controlling study. Indeed, in diabetic patients, the median [IQR] A1C level was 6.9% [6.4–8%], which is close to 7.4%, a level for which the glycaemic target was the same in both groups. By aggregating these data, it could be suggested that the glycaemic target might be individualised but, rather than targeting the usual glycaemia, it could target a glycaemia systematically higher than the usual glycaemia, a level that would match the stress-induced hyperglycaemia. Targeting a glycaemia above the usual glycaemia would also more effectively prevent the occurrence of hypoglycaemia, as already observed for diabetic patients. [35] Future trials should be designed to test this hypothesis. Finally, after adjustments on diabetes status and other confounders, the numerically small subgroup of surgical patients seemed harmed by individualized glucose control, as already reported in the NICE SUGAR study for postoperative patients under intensive glycaemic control [12].

Regarding hypoglycaemia, the rate of moderate hypoglycaemia (glycaemia between 40 and 71 mg/dL) was much lower in the IC group than in the group targeting the normal glycaemia range in the NICE-SUGAR study (27.3% vs. 74.2%) [36]. Regarding severe hypoglycaemia, the frequency was not significantly different between the two groups, but lower compared to groups targeting normal glycaemia from published studies (3.9% vs. from 5.1 to 18.7%) [7–12]. Nevertheless, the principle of precaution was applied in view of the adverse outcomes that some authors have reported to be associated with moderate hypoglycaemia [36–38] especially in the absence of signal of a potential benefit in the present study, which was prematurely terminated.

Our trial has some limitations. The eligibility of 1300 patients (24% of ICU admissions) was not assessed during the 96 h following admission. These patients stayed for a short time in ICU (median stay of 1.6 days [0.8–3.8]). As randomization needed the input of A1C in CPG within 96 h, 827 patients (16% of ICU admissions) lacked the imputation of this result on time, and for included patients the intervention was delayed (median delay of 1.2 days after admission). Some patients in the IC group were then exposed for a longer period to the pre-randomization conventional target < 180 mg/dL than to the randomization personalized target. Nevertheless,

Table 2 Glycaemic level management, hypoglycaemia, and calorie administration according to treatment group

Variable	Individualised glucose control $N = 942$	Conventional glucose control $N = 975$	p value [a]
Days on treatment algorithm	3.9 [1.5–9.5]	4 [1.5–9.8]	0.37
Number of glycaemic controls			
Per patient	30 [9–78]	25 [9–63]	0.03
Per patient and per day	7 [5–9]	5 [3–8]	< 0.0001
Type of glycaemic sampling—no. of patients (%)			0.47
Exclusively arterial	620 (66)	644 (66)	
Exclusively capillary	240 (25)	260 (27)	
Arterial or capillary	82 (9)	71 (7)	
% of time spent with glycaemia between 72 mg/dL and the glycaemic target[b,c]	72 [57-87]	94 [70-100]	< 0.0001
% of time spent with glycaemia between glycaemic target—36 mg/dL and the glycaemic target[b,c,d]	51 [35-69]	25 [7-42]	< 0.0001
Glycaemia standard deviation—mg/dL[b]	27.6 [18.5–38.9]	27.3 [19.1–39]	0.64
Treated with insulin—no. of patients (%)	702 (74.5)	486 (49.8)	< 0.0001
Hypoglycaemia[e]			
Severe hypoglycaemia			
Among all patients—number of patients (%)	37 (3.9)	24 (2.5)	0.09
No. of episodes	50	26	
% of time spent in severe hypoglycaemia	0.4 [0.1–1.4]	1.1 [0.5–8.1]	
With episode(s) related to insulin administration—number of patients (%)	24/37 (65)	5/24 (21)	
Time elapsed with the glycaemic measurement following hypoglycaemia—min	75 [51–118]	74 [59–109]	
Time elapsed with the glycaemic measurement before hypoglycaemia—min	131 [98–224]	170 [109–214]	
Among non-diabetic patients—no. of patients (%)	26 (4.2)	12 (1.8)	0.02
Among diabetic patients—number of patients (%)	11 (3.4)	12 (3.8)	0.96
Any hypoglycaemia			
Among all patients—number of patients (%)	294 (31.2)	154 (15.8)	< 0.0001
% of time spent in any hypoglycaemia	1.4 [0.5–3.5]	1.4 [0.3–6]	
Among non-diabetic patients—number of patients (%)	224 (36.1)	92 (13.9)	< 0.0001
Among diabetic patients—number of patients (%)	70 (21.8)	62 (19.7)	0.57
Nutrition[f]			
Patients receiving only enteral nutrition			
Calories administered—kcal/day	762 [373–1296]	819 [453–1149]	0.94
No. of patients (%)	148 (16)	129 (13)	
Patients receiving only parenteral nutrition			
Calories administered—kcal/day	615 [0–1078]	640 [0–1083]	0.77
Number of patients (%)	169 (18)	195 (20)	
Patients receiving both enteral and parenteral nutrition			
Calories administered—kcal/day	1268 [983–1606]	1242 [985–1611]	0.79
Number of patients (%)	255 (27)	256 (26)	
Patients receiving no artificial nutrition			
Number of patients (%)	370 (39)	395 (41)	

Values are expressed as median [interquartile range] or number (%). To convert glycaemic level to mmol/L, multiply values by 0.0556

[a] Wilcoxon–Mann–Whitney test for quantitative variables, Chi^2 test for qualitative variables

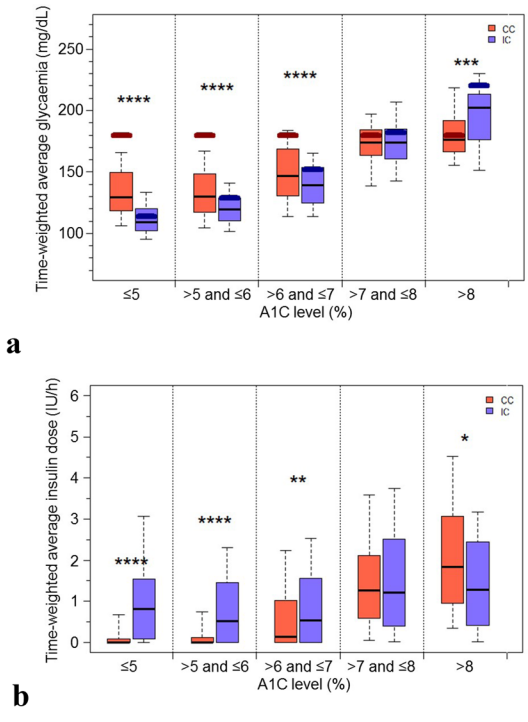
[b] Calculated only for the patients who had at least two glycaemic level measurements. (897 patients in the individualised glucose control group and 931 in the conventional glucose control group)

[c] Glycaemic target was 28.7 × A1C-31.7 (in mg/dL, with A1C in %) in the individualised glucose control group and 180 mg/dL in the conventional glucose control group

[d] Between 144 and 180 mg/dL for the conventional glucose control group

[e] Severe hypoglycaemia was defined as a glycaemic level below 40 mg/dL and any hypoglycaemia as a glycaemic level below 72 mg/dL

[f] Calories from propofol and 2.5% or 5% dextrose solutions were not recorded



A1C subgroups	≤5%	>5 and ≤ 6%	>6 and ≤7%	>7 and ≤8%	>8%
CC group — no. of patients	91	492	215	68	65
IC group — no. of patients	100	440	215	63	79

Fig. 3 Glycaemic level and insulin administration during intervention according to treatment group and A1C level. Patients are separated into five subgroups according to A1C levels (≤ 5%, > 5 and ≤ 6%, > 6 and ≤ 7%, > 7 and ≤ 8% and > 8%). Panel **a** shows the relationship between time-weighted average glycaemic level and A1C level. Panel **b** shows the relationship between time-weighted average insulin infusion rate and A1C level. Conventional glucose control group and individualised glucose control group are displayed in red and blue, respectively. Horizontal line indicates the median value. Box height indicates IQR with the lower and upper edges of the box representing the 25th and 75th percentiles, respectively. The lower whisker represents the 10th percentile and the upper whisker the 90th percentile. If no horizontal line is present within the box, the median value is the same as the 25th percentile. The coloured horizontal lines indicate the glycaemic target for each group. Only the patients who had at least two glycaemia measurements are represented (897 patients in the individualised glucose control group and 931 in the conventional glucose control group). The number of patients in each group and in each A1C level subgroup is provided below the figure. P values for the comparison between groups in each A1C level subgroup were calculated using the Wilcoxon–Mann–Whitney test: *< 0.05, **< 0.01, ***< 0.001, ****< 0.0001. To convert glycaemic level to mmol/L, multiply values by 0.0556

patients from the IC group, spent a median [IQR] of 74% [55%-89%] of their time in ICU with the individualised glycaemic target. All these points might have underpowered the study. The present trial also used the CPG algorithm—an assessment of which has been performed, but not published—to control glycaemia and, therefore, it cannot be excluded that different results would have been obtained using another algorithm. As no gas analyser was available in any of the participating units, glycaemia was measured with point of care glucose meters and this might impair the precision of some measurements [14]. To maintain blinding during the study, the nurse did not have access to the history of glycaemia or to changes in the flow of insulin therapy. It is possible that this could have limited the possibilities for the nurse to override a recommendation given by CPG on the flow of insulin therapy. However, outside the study, while the nurse had access to the entire history of glycaemia and insulin flow rates, override of CPG instructions remained also exceptional, below 1%. Finally, herein, the individualised glycaemic target was maintained constant during the entire ICU stay, which might not match the changes in insulin resistance that can occur during the course of critical illness [39]. Indeed, insulin resistance that is linked to illness severity is expected to change during ICU stay, being higher during the first days, and then decreasing as the patient improves [40]. However, the characterization of the illness-severity phases occurring during the course of critical illness is still debated and could not be taken into account in the present study. More precise tools aiming at determining the severity phase and thus insulin resistance level could help test this hypothesis in future studies.

In conclusion, targeting a patient's usual glycaemia by using pre-admission A1C level with a dynamic sliding-scale insulin protocol did not show any survival benefit in critically ill adults compared to maintaining glycaemia below 180 mg/dL.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1007/s00134-021-06526-8.

Author details

[1] Service d'Anesthésie-Réanimation-Médecine intensive, Groupement hospitalier sud, Hospices Civils de Lyon, 165 Chemin du grand Revoyet, 69310 Pierre Bénite, France. [2] Service de Médecine Intensive Réanimation, Centre Hospitalier Universitaire, Montpellier, France. [3] Service de Biostatistique-Bioinformatique, Pôle Santé Publique, Hospices Civils de Lyon, Lyon, France. [4] Université de Lyon, Villeurbanne, France. [5] Université Lyon 1, Villeurbanne, France. [6] CNRS, UMR5558, Laboratoire de Biométrie et Biologie Évolutive, Équipe Biostatistique-Santé, Villeurbanne, France. [7] PhyMedExp, INSERM, CNRS, Université de Montpellier, Montpellier, France. [8] Service de réanimation, Hôpital Fleyriat, Bourg en Bresse, France. [9] Service de Médecine Intensive Réanimation, CHU Dijon Bourgogne, Dijon, France. [10] INSERM, U1231, Equipe Lipness and 4 LipSTIC LabEx, Fondation de coopération scientifique Bourgogne-Franche-Comté, Dijon, France. [11] NSERM, CIC 1432, Module Epidémiologie Clinique, Dijon, France. [12] Service de Médecine Intensive Réanimation, CHU Hôpital de l'Archet, Nice, France. [13] UR2CA Unité de Recherche Clinique Côte d'Azur, Université Côte d'Azur, Nice, France. [14] Service de Médecine Intensive Réanimation, CHU Hôpital Gabriel-Montpied, Clermont-Ferrand, France. [15] CNRS, Laboratoire Microorganismes: Génome et Environnement, Université Clermont

Auvergne, Clermont-Ferrand, France. [16] Department of Intensive Care, Erasme University Hospital, Université libre de Bruxelles, Brussels, Belgium. [17] Réanimation Médicale et des Maladies infectieuses, Université Paris Diderot/Hôpital Bichat, Assistance Publique Hôpitaux de Paris, Paris, France.

Acknowledgements
The CONTROLING study was supported by the Hospices Civils de Lyon and funded by the Programme Hospitalier de Recherche Clinique interregional 2012 of the French Ministry of Health (#PHRC interregional- 12-005).

We thank all the collaborators of the CONTROLING study group which are listed below. Among these collaborators, Hervé Hyvernat, M.D., Pierre Eric Danin, M.D., Julio Badie, M.D., Richard Jospe, M.D., Jérôme Morel, M.D., Ph.D., Ali Mofredj, M.D., Abdelhamid Fatah, M.D., Jocelyne Drai, PharmD, Anne Mialon, PharmD, and Eric Fontaine, M.D., Ph.D. full filled the four criteria of the ICMJ to be co-authors. The maximum number of authors authorized to appear in the byline required that they appear among the collaborators We thank the staff of the 12 participating ICUs and the clinical research assistants for data entry. We are indebted to Véréna Landel and Hélène Boyer (Direction de la Recherche Clinique et Innovation, Hospices Civils de Lyon) for proofreading the manuscript.

The CONTROLe INdividualisé de la Glycémie (CONTROLING) Study Group: Aurèle Buzancais, M.D. (Service de Médecine Intensive Réanimation, CHU de Montpellier, Hôpital Lapeyronie, Montpellier); Anne Marie Dupuy, M.D., Ph.D. (Laboratoire de Biochimie et Hormonologie, CHU de Montpellier, Hôpital Lapeyronie, Montpellier); Rémi Bruyère, M.D. (Service de Réanimation, Hôpital Fleyriat, Bourg en Bresse); Henri de Montclos, PharmD (Laboratoire de Biologie Médicale, Hôpital Fleyriat, Bourg en Bresse); Marion Provent (Service d'Anesthésie-Réanimation-Médecine Intensive, Groupement Hospitalier Sud, Hospices Civils de Lyon, Pierre Bénite); Jocelyne Drai, PharmD (Laboratoire de biochimie, Groupement Hospitalier Sud, Hospices Civils de Lyon, Pierre Bénite); Joëlle Goudable, PharmD, Ph.D. (Laboratoire de biochimie, Groupement Hospitalier Sud, Hospices Civils de Lyon, Pierre Bénite); Anne Mialon, PharmD (Laboratoire de biochimie, Groupement Hospitalier Sud, Hospices Civils de Lyon, Pierre Bénite); Bernard Allaouchiche, M.D., Ph.D. (Service d'Anesthésie-Réanimation-Médecine Intensive, Groupement Hospitalier Sud, Hospices Civils de Lyon, Pierre Bénite); Arnaud Friggeri, M.D., Ph.D. (Service d'Anesthésie-Réanimation-Médecine Intensive, Groupement Hospitalier Sud, Hospices Civils de Lyon, Pierre Bénite); Véréna Landel (Direction de la Recherche Clinique et de l'Innovation, Hospices Civils de Lyon, Lyon); Hélène Boyer (Direction de la Recherche Clinique et de l'Innovation, Hospices Civils de Lyon, Lyon); Hervé Hyvernat, M.D. (Service de Médecine Intensive Réanimation, CHU de Nice, Hôpital de l'Archet, Nice); Céline Caruba-Bafghi, PharmD (Laboratoire de Biochimie, CHU de Nice, Hôpital Pasteur, Nice); Edouard Soum, M.D. (Service de Médecine Intensive Réanimation, CHU de Clermont Ferrand, Hôpital Gabriel-Montpied, Clermont Ferrand); Christophe Leroy, M.D. (Service de Médecine Intensive Réanimation, CHU de Clermont Ferrand, Hôpital Gabriel-Montpied, Clermont Ferrand); Laurence Roszyk, PharmD (Service de Biochimie, CHU de Clermont Ferrand, Hôpital Estaing, Clermont Ferrand); Pierre Eric Danin, M.D. (Service de Réanimation médico-Chirurgicale, CHU de Nice, Hôpital de l'Archet, Nice); Julio Badie, M.D. (Service de Réanimation, Hôpital Nord Franche Comté, Trévenans); Stefan Georgiev, M.D. (Service de Réanimation, Hôpital Nord Franche Comté, Trévenans); Martine Laplace, PharmD (Laboratoire de Biologie, Hôpital Nord Franche Comté, Trévenans); Richard Jospe, M.D. (Département d'Anesthésie et Réanimation, CHU de Saint Etienne, Hôpital Nord, Saint Etienne); Jérôme Morel, M.D., Ph.D. (Département d'Anesthésie et Réanimation, CHU de Saint Etienne, Hôpital Nord, Saint Etienne); Ali Mofredj, M.D. (Service de Réanimation, Hôpital du Pays Salonais, Salon de Provence); Abdelbaki Azaouzi, M.D. (Service de Réanimation, Hôpital du Pays Salonais, Salon de Provence); Jean-Paul Aubry, PharmD (Laboratoire de Biologie, Hôpital du Pays Salonais, Salon de Provence); Abdelhamid Fatah, M.D. (Service de Réanimation, Hôpital Pierre Oudot, Bourgoin Jallieu); Stanislas Ledochowski, M.D. (Service de Réanimation, Hôpital Pierre Oudot, Bourgoin Jallieu); Sabine Zaepfel, PharmD (Laboratoire de Biologie, Hôpital Pierre Oudot, Bourgoin Jallieu); Eric Fontaine, M.D., Ph.D. (INSERM U1055 – LBFA, Université Joseph Fourier, Grenoble).

Author contributions
JB and HA designed the study. JB, AK, and DMB had access to all data and take full responsibility for their integrity and the accuracy of the analyses. DMB and AK did the statistical analysis. JB, VB, KK, NS, XT, JPQ, JBR, NM, FT, JD, FW, BS, AL, approved the design of the study, coordinated individual sites, participated in the inclusion of study participants, and collected the data. JB wrote the first draft of the report with input from AAH, DMB, AK, CHV, JCP, and JFT. JB, HA, AK, CHV and DMB verified the underlying data. All authors revised the report, and read and approved the final version before submission. The corresponding author had final responsibility for the decision to submit for publication.

Funding
The study was funded by the French ministry of health. The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Availability of data and material
Research data and statistical analysis plan will be made available to the scientific community, immediately on publication. All requests should be submitted to the corresponding author who will review with the other investigators for consideration. A data use agreement will be required before the release of participant data and institutional review board approval as appropriate.

Declarations

Conflicts of interest
We declare no competing interests.

Open Access
This article is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License, which permits any non-commercial use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by-nc/4.0/.

Publisher's Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 31 January 2021 Accepted: 2 September 2021
Published online: 29 September 2021

References
1. Lheureux O, Prevedello D, Preiser J-C (2018) Update on glucose in critical care. Nutrition 59:14–20. https://doi.org/10.1016/j.nut.2018.06.027
2. Falciglia M, Freyberg RW, Almenoff PL et al (2009) Hyperglycemia-related mortality in critically ill patients varies with admission diagnosis. Crit Care Med 37:3001–3009. https://doi.org/10.1097/CCM.0b013e3181b083f7
3. Badawi O, Waite MD, Fuhrman SA, Zuckerman IH (2012) Association between intensive care unit-acquired dysglycemia and in-hospital mortality. Crit Care Med 40:3180–3188. https://doi.org/10.1097/CCM.0b013e3182656ae5
4. Roberts GW, Quinn SJ, Valentine N et al (2015) Relative hyperglycemia, a marker of critical illness: introducing the stress hyperglycemia ratio. J Clin Endocrinol Metab 100:4490–4497. https://doi.org/10.1210/jc.2015-2660
5. Liao W-I, Wang J-C, Chang W-C et al (2015) Usefulness of glycemic gap to predict ICU mortality in critically ill patients with diabetes. Medicine (Baltimore) 94:e1525. https://doi.org/10.1097/MD.0000000000001525
6. Krinsley JS, Preiser J-C (2019) Is it time to abandon glucose control in critically ill adult patients? Curr Opin Crit Care 25:299–306. https://doi.org/10.1097/MCC.0000000000000621
7. Van den Berghe G, Wouters P, Weekers F et al (2001) Intensive insulin therapy in critically ill patients. N Engl J Med 345:1359–1367. https://doi.org/10.1056/NEJMoa011300
8. Van den Berghe G, Wilmer A, Hermans G et al (2006) Intensive insulin therapy in the medical ICU. N Engl J Med 354:449–461. https://doi.org/10.1056/NEJMoa052521

9. Brunkhorst FM, Engel C, Bloos F et al (2008) Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med 358:125–139. https://doi.org/10.1056/NEJMoa070716
10. Preiser J-C, Devos P, Ruiz-Santana S et al (2009) A prospective randomised multi-centre controlled trial on tight glucose control by intensive insulin therapy in adult intensive care units: the Glucontrol study. Intensive Care Med 35:1738–1748. https://doi.org/10.1007/s00134-009-1585-2
11. Kalfon P, Giraudeau B, Ichai C et al (2014) Tight computerized versus conventional glucose control in the ICU: a randomized controlled trial. Intensive Care Med 40:171–181. https://doi.org/10.1007/s00134-013-3189-0
12. NICE-SUGAR Study Investigators (2009) Intensive versus conventional glucose control in critically ill patients. N Engl J Med 360:1283–1297. https://doi.org/10.1056/NEJMoa0810625
13. Yamada T, Shojima N, Noma H et al (2017) Glycemic control, mortality, and hypoglycemia in critically ill patients: a systematic review and network meta-analysis of randomized controlled trials. Intensive Care Med 43:1–15. https://doi.org/10.1007/s00134-016-4523-0
14. American Diabetes Association (2019) 15. Diabetes care in the hospital: standards of medical care in diabetes-2019. Diabetes Care 42:S173–S181. https://doi.org/10.2337/dc19-S015
15. Ichai C, Preiser J-C, Société Française d'Anesthésie-Réanimation et al (2010) International recommendations for glucose control in adult non diabetic critically ill patients. Crit Care 14:R166. https://doi.org/10.1186/cc9258
16. Plummer MP, Bellomo R, Cousins CE et al (2014) Dysglycaemia in the critically ill and the interaction of chronic and acute glycaemia with mortality. Intensive Care Med 40:973–980. https://doi.org/10.1007/s00134-014-3287-7
17. Kar P, Plummer MP, Bellomo R et al (2016) Liberal glycemic control in critically ill patients with type 2 diabetes: an exploratory study. Crit Care Med 44:1695–1703. https://doi.org/10.1097/CCM.0000000000001815
18. Di Muzio F, Presello B, Glassford NJ et al (2016) Liberal versus conventional glucose targets in critically ill diabetic patients: an exploratory safety cohort assessment. Crit Care Med 44:1683–1691. https://doi.org/10.1097/CCM.0000000000001742
19. Egi M, Bellomo R, Stachowski E et al (2008) Blood glucose concentration and outcome of critical illness: the impact of diabetes. Crit Care Med 36:2249–2255. https://doi.org/10.1097/CCM.0b013e318181039a
20. Sechterberger MK, Bosman RJ, Oudemans-van Straaten HM et al (2013) The effect of diabetes mellitus on the association between measures of glycaemic control and ICU mortality: a retrospective cohort study. Crit Care 17:R52. https://doi.org/10.1186/cc12572
21. Krinsley JS, Egi M, Kiss A et al (2013) Diabetic status and the relation of the three domains of glycemic control to mortality in critically ill patients: an international multicenter cohort study. Crit Care 17:R37. https://doi.org/10.1186/cc12547
22. van Vught LA, Holman R, de Jonge E et al (2017) Diabetes is not associated with increased 90-day mortality risk in critically ill patients with sepsis. Crit Care Med 45:e1026–e1035. https://doi.org/10.1097/CCM.0000000000002590
23. Krinsley JS, Preiser J-C, Hirsch IB (2017) Safety and efficacy of personalized glycemic control in critically ill patients: a 2-year before and after interventional trial. Endocr Pract 23:318–330. https://doi.org/10.4158/EP161532.OR
24. Kwan TN, Zwakman-Hessels L, Marhoon N et al (2020) Relative hypoglycemia in diabetic patients with critical illness. Crit Care Med 48:e233. https://doi.org/10.1097/CCM.0000000000004213
25. Krinsley JS, Rule P, Pappy L et al (2020) The interaction of acute and chronic glycemia on the relationship of hyperglycemia, hypoglycemia, and glucose variability to mortality in the critically ill*. Crit Care Med 48:1744–1751. https://doi.org/10.1097/CCM.0000000000004599
26. Van den Berghe G, Wilmer A, Milants I et al (2006) Intensive insulin therapy in mixed medical/surgical intensive care units: benefit versus harm. Diabetes 55:3151–3159. https://doi.org/10.2337/db06-0855
27. Nathan DM, Kuenen J, Borg R et al (2008) Translating the A1C assay into estimated average glucose values. Diabetes Care 31:1473–1478. https://doi.org/10.2337/dc08-0545
28. Lefrant J-Y, Hurel D, Cano NJ et al (2014) Guidelines for nutrition support in critically ill patient. Ann Fr Anesth Reanim 33:202–218. https://doi.org/10.1016/j.annfar.2014.01.008
29. Le Gall JR, Lemeshow S, Saulnier F (1993) A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA 270:2957–2963
30. Agus MS, Hirshberg E, Srinivasan V et al (2017) Design and rationale of Heart and Lung Failure-Pediatric INsulin Titration Trial (HALF-PINT): a randomized clinical trial of tight glycemic control in hyperglycemic critically ill children. Contemp Clin Trials 53:178–187. https://doi.org/10.1016/j.cct.2016.12.023
31. Kaplan EL, Meier P (1958) Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457–481. https://doi.org/10.1080/01621459.1958.10501452
32. Badawi O, Yeung SY, Rosenfeld BA (2009) Evaluation of glycemic control metrics for intensive care unit populations. Am J Med Qual 24:310–320. https://doi.org/10.1177/1062860609336366
33. Egi M, Bellomo R, Stachowski E et al (2006) Variability of blood glucose concentration and short-term mortality in critically ill patients. Anesthesiology 105:244–252. https://doi.org/10.1097/00000542-200608000-00006
34. Dellinger RP, Levy MM, Carlet JM et al (2008) Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Intensive Care Med 34:17–60. https://doi.org/10.1007/s00134-007-0934-2
35. Luethi N, Cioccari L, Biesenbach P et al (2018) Liberal glucose control in ICU patients with diabetes: a before-and-after study. Crit Care Med 46:935–942. https://doi.org/10.1097/CCM.0000000000003087
36. NICE-SUGAR Study Investigators, Finfer S, Liu B et al (2012) Hypoglycemia and risk of death in critically ill patients. N Engl J Med 367:1108–1118. https://doi.org/10.1056/NEJMoa1204942
37. Hermanides J, Bosman RJ, Vriesendorp TM et al (2010) Hypoglycemia is associated with intensive care unit mortality. Crit Care Med 38:1430–1434. https://doi.org/10.1097/CCM.0b013e3181de562c
38. Krinsley JS, Schultz MJ, Spronk PE et al (2011) Mild hypoglycemia is independently associated with increased mortality in the critically ill. Crit Care 15:R173. https://doi.org/10.1186/cc10322
39. Preiser J-C, Ichai C, Orban J-C, Groeneveld ABJ (2014) Metabolic response to the stress of critical illness. Br J Anaesth 113:945–954. https://doi.org/10.1093/bja/aeu187
40. Pretty CG, Le Compte AJ, Chase JG et al (2012) Variability of insulin sensitivity during the first 4 days of critical illness: implications for tight glycemic control. Ann Intensive Care 2:17. https://doi.org/10.1186/2110-5820-2-17
41. Charlson ME, Pompei P, Ales KL, MacKenzie CR (1987) A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 40:373–383
42. McCabe WR, Treadwell TL, De Maria A (1983) Pathophysiology of bacteremia. Am J Med 75:7–18