Real-Time Continuous Glucose Monitoring in Critically Ill Patients

A prospective randomized trial

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OBJECTIVE — To evaluate the impact of real-time continuous glucose monitoring (CGM) on glycemic control and risk of hypoglycemia in critically ill patients.

RESEARCH DESIGN AND METHODS — A total 124 patients receiving mechanical ventilation were randomly assigned to the real-time CGM group ($n = 63$; glucose values given every 5 min) or to the control group ($n = 61$; selective arterial glucose measurements according to an algorithm; simultaneously blinded CGM) for 72 h. Insulin infusion rates were guided according to the same algorithm in both groups. The primary end point was percentage of time at a glucose level <110 mg/dl. Secondary end points were mean glucose levels and rate of severe hypoglycemia (<40 mg/dl).

RESULTS — Percentage of time at a glucose level <110 mg/dl (59.0 ± 20 vs. 55.0 ± 18% in the control group, $P = 0.245$) and the mean glucose level (106 ± 18 vs. 111 ± 10 mg/dl in the control group, $P = 0.076$) could not be improved using real-time CGM. The rate of severe hypoglycemia was lower in the real-time CGM group (1.6 vs. 11.5% in the control group, $P = 0.031$). CGM reduced the absolute risk of severe hypoglycemia by 9.9% (95% CI 1.2–18.6) with a number needed to treat of 10.1 (95% CI 5.4–83.3).

CONCLUSIONS — In critically ill patients, real-time CGM reduces hypoglycemic events but does not improve glycemic control compared with intensive insulin therapy guided by an algorithm.

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Hyperglycemia, a frequent finding in up to 90% of all critically ill patients, is associated with increased morbidity and mortality (1,2). In three monocentric studies, intensive insulin therapy to achieve and maintain normoglycemia resulted in decreased morbidity and mortality (3–5). However, in two subsequent multicenter studies, normoglycemia was not adequately reached, and the studies were stopped prematurely because of safety reasons with increased rates of severe hypoglycemia (6,7). However, in a recent trial, intensive insulin therapy resulted in improved short-term outcome in pediatric intensive care; another recent trial demonstrated increased mortality among adults under intensive glucose control (5,8). An updated meta-analysis of 26 randomized trials including 13,567 patients reported that intensive insulin therapy had no effect on the overall risk of death but simultaneously resulted in a sixfold increased risk of severe hypoglycemia. Currently, there is still an intense and conflicting discussion on the difficulty of obtaining near-normoglycemia and thereby avoiding the risk of severe hypoglycemia (9). In critically ill patients, accurate real-time continuous glucose monitoring (CGM) might be the best way to minimize a consistently reported increased rate of severe hypoglycemia associated with intensive insulin therapy and to increase effectiveness and safety of tight glucose control.

Numerous studies in diabetic patients tested CGM devices and demonstrated high accuracy of the CGM-derived glucose values compared with blood glucose measurements (10–12). In particular, these devices were highly sensitive in detecting rapid glucose excursions (12). Recently, these CGM techniques have also been evaluated in critically ill patients and have yielded similar positive results (13–17). Mainly, subcutaneous CGM devices have been intensely investigated (13–17). Accuracy and reliability of a subcutaneous CGM device could be demonstrated both in critically ill patients with and without circulatory shock (16). Subcutaneous CGM worked equally in patients without and with norepinephrine therapy. Validity of the subcutaneous CGM under norepinephrine therapy was furthermore independent of levels of blood glucose values, severity of illness, and patients' BMI (16). With use of this subcutaneous CGM device, ~99% of all measured sensor glucose values were within the acceptable treatment zone according to an insulin titration grid analysis (16). Based on these underlying data, we hypothesized that subcutaneous real-time CGM improves glucose control, simultaneously reducing the risk of hypoglycemia.

RESEARCH DESIGN AND METHODS

— The study was performed in the intensive care unit (ICU) of the Department of Medicine III at the Medical University Hospital of Vienna, Vienna, Austria. Patients were recruited between June 2006 and August 2008.

Patients were eligible for inclusion in the study within 24 h after ICU admission if they were aged ≥18 years, intubated,

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receiving mechanical ventilation, and expected to stay >48 h in the ICU after initiation of intensive insulin therapy. Patients were not enrolled in the study if any of the following criteria were present: ICU stay expected to be <48 h, mechanical ventilation not expected for >48 h, arterial glucose values within the normal range (80–110 mg/dl) before enrollment, enrollment in another study, and no availability of a CGM device during the screening phase. The study protocol was approved by the research ethics committee of the Medical University of Vienna. According to the Austrian law and the guidelines of the research ethics committee, written informed consent was obtained from patients after they regained consciousness.

Intensive insulin therapy to maintain normoglycemia (80–110 mg/dl) was performed by the nurses in all patients included in the study. In the control group, intensive insulin therapy was performed strictly according to a previously described insulin titration algorithm (18). In short, this algorithm is a slightly modified version of the algorithm used in the Leuven studies (3,4). It prescribes both insulin infusion rate, time of next glucose measurement, and, in case of hypoglycemia, dextrose administration depending on glucose levels and glucose trends. Consequently, it defines nine different states requiring different actions, although leaving space for interpretation (for the responsible nurse) because it includes dynamic variables such as glucose trends. In the control group, selective arterial blood glucose measurements were done according to the algorithm (18). On the basis of these arterial blood glucose values, nurses guided intensive insulin therapy. A continuous intravenous insulin regimen was used in all patients (insulin aspart, Novo Nordisk). Nutritional support was standardized in all patients according to a nutritional protocol. Energy requirements were calculated with 25 kcal · kg body wt^{-1} · day^{-1}. For every patient included, the following data were documented: age, sex, ICU admission reasons, height, weight, BMI, cumulative fluid balance and insulin use during the study period, norepinephrine therapy, comedication including dextrose infusion, length of ICU stay, and ICU and hospital mortality. Severity of illness was assessed by the Simplified Acute Physiology Score (SAPS II) and the Sepsis-related Organ Failure Assessment (SOFA) (19,20).

CGM

Within 24 h after ICU admission, eligible patients were randomly assigned, in a 1:1 ratio, to the real-time CGM group or to the control group. Responsible ICU staff was informed about inclusion of patients. In addition, a user manual for the CGM device was placed at the bedside. In the real-time CGM group, glucose values were given every 5 min by the subcutaneous real-time CGM system for 72 h (Guardian; Medtronic MiniMed, Northridge, CA). On the basis of these displayed subcutaneous glucose values, nurses guided insulin therapy according to the recommended insulin dose of the insulin titration algorithm in the real-time CGM group also (18). However, in the intervention group, nurses were requested to take real-time glucose readings in close intervals according to clinical necessity at their personal discretion, but at least every 2 h in contrast with the control group. In the control group, simultaneously blinded subcutaneous continuous glucose reading by the CGM System Gold (Medtronic MiniMed) was performed for 72 h. These subcutaneous glucose values were blinded to ICU staff and were retrospectively downloaded to a computer using the MiniMed Com-Station and a special program (MiniMed Solutions Software CGMS Sensor MMT-7310; Medtronic MiniMed). Stored glucose data from the real-time CGM system (Guardian) were also downloaded (Guardian Solutions Software, MMT-7315 version 2.16D; Medtronic MiniMed). The CGM system used in both groups included the same technology and comprised a Holter-style sensor system, a pager-size glucose monitor, and a disposable subcutaneous needle-type enzymatic glucose electrode connected to the monitor. In all patients, the sensor was placed subcutaneously in the lateral abdominal region using a SenSerter device (Medtronic MiniMed). The actual glucose level was displayed on the monitor screen only in the real-time CGM group using the Guardian. No alarm levels were set. The first pair of arterial blood glucose/sensor glucose values, which was used for initial calibration of the CGM system, was not used for statistical analysis. According to the manufacturer's instruction manual, both CGM systems were calibrated against arterial blood glucose measurements four times per day (every 5–6 h). Arterial blood glucose measurements were obtained using an automated blood gas analyzer (ABL 700; Radiometer Medical, Copenhagen, Denmark). Subcutaneous sensors were planned to stay in place for 72 h. The place of insertion was inspected daily for local irritations, bleeding, and infection.

Statistical analysis

Sample size was calculated using the GraphPad StatMate software program (GraphPad Software, San Diego, CA). Anticipated proportions were compared with a χ^2 test. The anticipated proportion was 0.57 for the control group and 0.80 for the real-time CGM group. α was 0.05 (two-tailed). A sample size of 120 was calculated for a power of 80%; 10 dropouts were calculated. A dropout was defined as removal of the CGM sensor within 12 h after insertion.

Data are presented as means ± SD or as absolute and relative frequency as adequate. Baseline data were compared qualitatively to assess successful randomization and quantitatively by *t* tests or Fisher's exact tests as appropriate. The primary end point was percentage of time at a glucose level <110 mg/dl. This variable was normally distributed; therefore, a *t* test was used to test the null hypothesis of no difference. Secondary end points were mean glucose level, median time from start of intensive insulin therapy to achievement of normoglycemia, incidence of hypoglycemia (defined as glucose level <40 mg/dl), and percentage of time at a glucose level <150 mg/dl. The effect of the intervention versus standard therapy was estimated as risk ratio with 95% CI. The Fisher exact test was used to test the null hypothesis of no effect.

For subgroup analyses, stratum-specific effects of the intervention versus control on the primary end point were calculated. To assess differences between subgroups, *P* values for interaction by using linear regression models including interaction terms of the group allocation subgroup variable were calculated.

For data management and analysis, MS Excel for Windows and STATA (release 9.0 for Mac; StataCorp., College Station, TX) were used. Two-sided $P < 0.05$ was generally considered statistically significant.

RESULTS — Figure 1 shows the trial profile. Baseline demographics, patients' characteristics at ICU admission, and reason for ICU admission did not differ significantly between both groups (Table 1). Groups were well matched with respect to comedication that could potentially influence blood glucose (hydrocortisone 25 vs. 30 patients, $P = 0.4754$; propofol 34

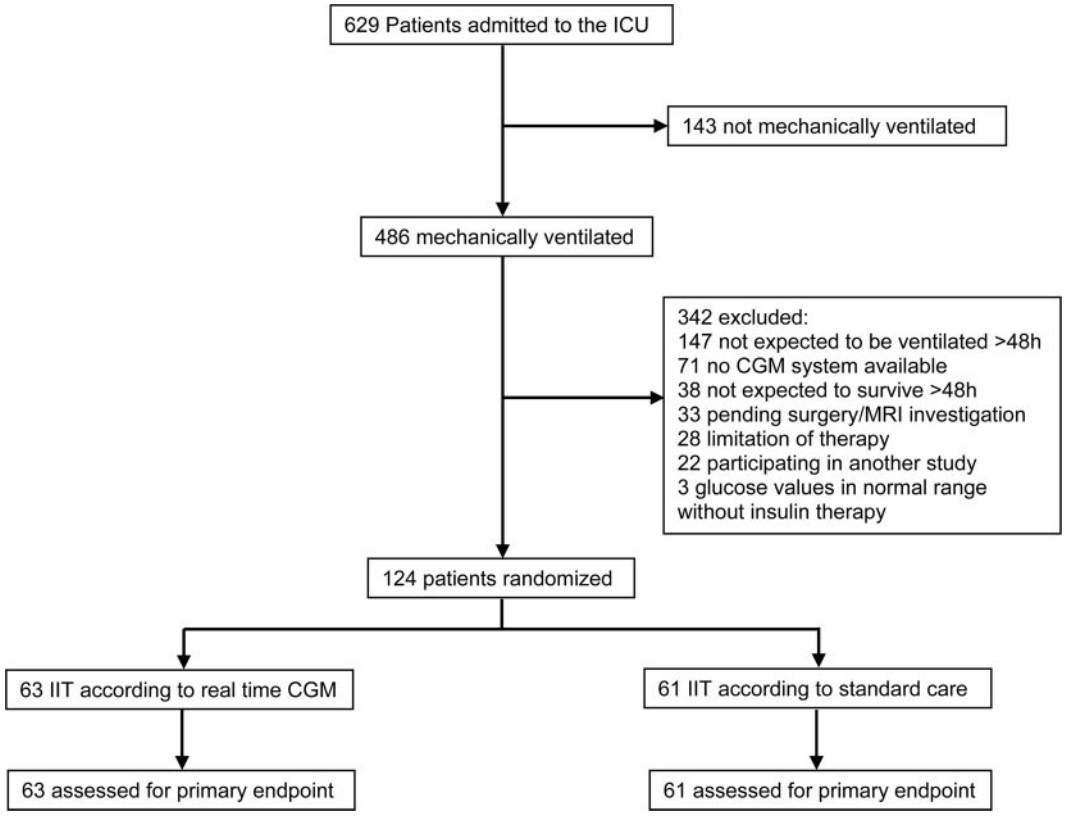

Figure 1—*Trial profile. IIT, intensive insulin therapy; MRI, magnetic resonance imaging.*

vs. 41 patients, $P = 0.3588$; norepinephrine 39 vs. 34 patients, $P = 0.278$; enteral nutrition 57 vs. 59 patients, $P = 1.0$; parenteral nutrition 4 vs. 4 patients, $P = 1.0$; control group vs. real-time CGM group, respectively). Dropouts (sensor time <12 h) did not occur. In nine patients, sensors were accidentally removed after 12–48 h. Data for these nine patients were analyzed until accidental removal of sensors. Table 2 shows blood glucose control in both treatment groups. The primary end point, percentage of time at <110 mg/dl, and the secondary end points, mean sensor and blood glucose levels, as well as percentage of time at <150 mg/dl, were not different in either groups. Baseline glucose values, time to reach the target glucose value of 110 mg/dl, and insulin dose during the study period also were not different. Rate of hypoglycemia was significantly lower in the real-time CGM group than in the control group (1.6 vs. 11.5%, $P = 0.0312$). Relative risk reduction for severe hypoglycemia is 86% (95% CI 21–98%) using real-time CGM. This denotes an absolute risk difference of 9.9% (1.2–18.6) and a number needed to treat of 10.1 (5.4–83.3). All patients with hypoglycemic events just experienced one episode of hypoglycemia except one patient in the control group, who experienced two episodes (on days 2 and 3 of the study period). Glucose measurements were performed 1,228 times in the control group. Glucose readings of the real-time CGM system were taken 1,772 times. According to the insulin therapy algorithm, the glucose measurements in the control group and glucose readings in the real-time CGM group were distributed (in the algorithm-defined states) in the following way: glucose >140 mg/dl: 118 glucose measurements vs. 221 glucose readings, $P = 0.017$; glucose range 110–140 mg/dl: 32 glucose measurements vs. 98 glucose readings, $P = 0.0002$; approaching target range number 1: 117 glucose measurements vs. 155 glucose readings, $P = 0.5049$; approaching target range number 2: 226 glucose measurements vs. 367 glucose readings, $P = 0.1274$; steady in the target range: 585 glucose measurements vs. 780 glucose readings, $P = 0.0574$; decreasing steeply: 22 glucose measurements vs. 57 glucose readings, $P = 0.0223$; glucose range 60–80 mg/dl: 90 glucose measurements vs. 57 glucose readings, $P < 0.0001$; glucose range 40–60 mg/dl: 32 glucose measurements vs. 36 glucose readings, $P = 0.3618$; and glucose <40 mg/dl: 6 glucose measurements vs. 1 glucose reading, $P = 0.0428$. Glucose measurements/readings are given as control group versus real-time CGM group, respectively.

Dextrose 33% was administered one time in the real-time CGM group and six times in the control group. In two patients in the control group, hypoglycemic events remained unrecognized and were only recorded by the blinded CGM. In these two patients, blinded CGM recorded a short hypoglycemic event after an antihypoglycemic action of the nurse (stopping of the intravenous insulin, assurance of glucose intake), whereas the next blood glucose measurement (after 1 h) already showed an increased blood glucose value.

Subgroup analysis revealed a significant benefit concerning the primary end point (percentage of time at <110 mg/dl) from real-time CGM for patients with a SOFA score >11 (64.4 vs. 54.7%, $P = 0.025$) and for patients with a positive fluid balance >6,000 ml during the study period (62.7 vs. 51.9%, $P = 0.031$). Differences for all subgroups are given in supplementary Figure A (available in an online appendix at http://care.diabetesjournals.org/cgi/content/full/dc09-1352/DC1). Local complica-

Table 1—*Baseline characteristics*

	Real-time CGM	Control	*P*
n	63	61	
Admission reason (patients in category)			
Respiratory failure	15 (24)	13 (21)	—
Cardiopulmonary resuscitation	12 (19)	15 (25)	—
Sepsis/septic shock	13 (20)	12 (20)	—
Heart failure	8 (13)	11 (18)	—
Neurological disease/coma	9 (14)	4 (7)	—
Pulmonary embolism	3 (5)	3 (5)	—
Gastrointestinal bleeding/acute liver failure	3 (5)	2 (4)	—
History of diabetes	12 (19)	12 (20)	1
Age (years)	58 ± 15	62 ± 16	0.168
Sex (female/male)	(20/43)	(26/35)	0.265
BMI (kg/m²)	27.1 ± 5.1	26.6 ± 3.8	0.501
SAPS II	59 ± 16	58 ± 17	0.891
SOFA score	11.4 ± 3.8	10.82 ± 3.9	0.400
Baseline glucose value (mg/dl)	138.0 ± 21.4	140.8 ± 23.1	0.465
Baseline blood pH	7.39 ± 0.08	7.37 ± 0.11	0.280
Baseline lactate	1.32 ± 0.49	1.49 ± 1.07	0.260
Fluid balance (ml, study period)	6,475 (2,585–8,943)	5,356 (1,183–9,440)	0.567
Baseline systolic blood pressure (mmHg)	124 ± 24	123 ± 22	0.881
Baseline diastolic blood pressure (mmHg)	62 ± 12	60 ± 11	0.272
Baseline norepinephrine dose ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	0.12 ± 0.08	0.15 ± 0.16	0.956

Data are *n* (%), means ± SD, or median (interquartile range), unless otherwise stated.

tions at the sensor insertion site did not occur.

CONCLUSIONS — Management of hyperglycemia in critically ill patients has been one of the most controversial topics in intensive care medicine for the past few years (9). Although it is generally accepted that stress hyperglycemia is associated with increased morbidity and mortality, it is still uncertain whether tight glycemic control is beneficial or even harmful for critically ill patients (1,2,6–8). Irrespective of the selected blood glucose target range, in all randomized clinical studies, the predefined target range was not reached in the majority of patients, which resulted in an increased rate of severe hypoglycemia (6–8). Thus, real-time CGM seems to be the optimal approach to increase the effectiveness and safety of intensive insulin therapy in critically ill patients. However, in our prospective randomized study, glucose control could not be significantly improved using real-time CGM. Compared with that in previous studies, glucose control in our control group was well maintained, possibly offering little space for improvement (13). This fact may be due to the long-term clinical experience with tight glycemic control in our ICU (16,18). Nevertheless, sample size calculation was based on the assumption that real-time CGM would lead to a 23% improvement in glucose control. This goal was definitely not met. One obstacle may be imperfect adherence to the order to check online glucose values at least every 2 h. We attached great importance to this order; however, a nurse-to-patient ratio of 1:2 in our ICU and the pressure of work, especially during for night shift, may have weakened adherence to the order. Although more glucose readings in the real-time CGM group led to a remarkable insulin infusion increase (more readings of >140 mg/dl and between 110 and 140 mg/dl) in the hyperglycemic range than in the control group, more glucose readings also required a remarkable reduction in the insulin infusion rate (more readings regarded as decreasing steeply), resulting in a lack of benefit concerning glucose control.

Another reason may be the omnipresent fear of hypoglycemic events. This fear seems to be justified because the rate of hypoglycemia was 11.5% in the control group, and even blinded CGM revealed unrecognized hypoglycemic events, which were not detected by selective arterial blood glucose measurements according to the insulin titration algorithm.

Real-time CGM, however, reduced severe hypoglycemic events significantly. In the real-time CGM group, more glucose readings were regarded as decreasing steeply according to the algorithm. According to our algorithm, this requires a large reduction (by half) in the insulin infusion rate and an early (1-h) next glucose measurement/reading. In the control group, however, more glucose values between 60 and 80 mg/dl occurred. According to the algorithm, glucose values between 60 and 80 mg/dl only required a reduction of the insulin infusion rate by 0.5 IU/h (no 1-h glucose measurement order). These two facts may have contributed to the prevention of hypoglycemic events in the real-time CGM group and led to hypoglycemic events in the control group. Glucose trends are recognized easily with the real-time CGM system because glucose values (mean of every 5

Table 2—*Primary and secondary end points*

	Real-time CGM	Control	*P*
n	63	61	
Mean sensor glucose (mg/dl)	105.8 ± 18.1	110.6 ± 10.4	0.076
Mean blood glucose (mg/dl)	113.2 ± 14.3	114.0 ± 11.0	0.731
Time of glucose <110 mg/dl (%)	59.0 ± 20.4	55.0 ± 18.0	0.245
Time of glucose <150 mg/dl (%)	94.2 ± 7.9	92.9 ± 8.4	0.395
Time to reach 110 mg/dl (min)	150 (48–275)	118 (45–240)	0.557
Rate of hypoglycemia (% of patients)	1.6	11.5	0.031
Insulin (IU/72 h, study period)	104 ± 78	110 ± 52	0.320
Length of stay	17.4 ± 14.4	16.8 ± 12.2	0.785
ICU mortality (%)	22	26	0.677
Hospital mortality (%)	33	31	0.849

Data are means ± SD, median (interquartile range), or %.

min) for the last 2 h can be viewed on the monitor. The reduction of severe hypoglycemic events was significant with a number needed to treat of 10 using the real-time CGM system. Real-time CGM is therefore a suitable system to improve patients' safety while practicing intensive insulin therapy. This point is of major importance because high rates of (recognized) severe hypoglycemia have been criticized in all studies concerning tight glycemic control (3–8). The most recent multicentric clinical trial indicated that tight glycemic control may even have harmful effects, possibly mediated by an increased rate of hypoglycemia (8). The results of our study suggest that the negative effects of intensive insulin therapy might also be caused by up-to-now unrecognized hypoglycemic events. Real-time CGM offers the possibility of performing clinical trials using intensive insulin therapy without increased rates of severe hypoglycemia because it is able not only to detect them but also to prevent them.

The use of real-time CGM was not able to shorten the time to reach blood glucose values <110 mg/dl in our study. However, the time to reach target blood glucose levels in our study, which was 118 and 150 min, respectively, is regarded as adequate from our point of view. An even more rapid achievement of the target range increases the risk of overshooting, resulting in both more hypoglycemic and consequently more hyperglycemic events. Because high glucose variability has also been shown to be associated with higher mortality in critically ill patients, overshooting insulin therapies and too rapid glucose changes might be avoided (21).

Subgroup analysis showed a significant beneficial effect on the primary end point in the most severely ill patients. In addition, although not statistically significant, patients in the real-time CGM group with SAPS II >59 had a higher percentage of time with a glucose level <110 mg/dl. In one of our previous studies, we could demonstrate that tight glycemic control was less successfully reached in more severely ill patients (16). In this special group of patients in the ICU, blood glucose levels may be more fluctuant and delicate. Therefore, we assume that the sickest patients in the ICU in particular may benefit from the real-time CGM.

Validation studies of subcutaneous CGM have shown accuracy and reliability not only in patients with diabetes but also in patients with cystic fibrosis and critically ill patients (10–13,16,17,22,23). Several outcome studies using real-time CGM in patients with type 1 diabetes and pregnant women with diabetes indicated promising results concerning improved glucose control and also increased safety for patients by reducing hypoglycemic events (24,25). Therefore, more research into CGM to improve ease of use and safety of intensive insulin therapy for critically ill patients is needed.

A limitation of this study is the relatively small number of patients included. The number was adequately calculated for our primary end point; however, many more patients are required to assess possible benefits of CGM on morbidity and mortality. Another aspect may be the short duration of our intervention, which was limited to one sensor lifetime of 72 h.

The monocentric design of the study may also be a limitation because of the long-term experience of all groups of health professionals in our ICU, who have been performing intensive insulin therapy for years in a cooperative and successful way (18). In other settings with personnel less experienced and less successful in intensive insulin therapy, the benefits from the application of real-time CGM may be even greater.

A further limitation may be the use of the same insulin titration algorithm with respect to the insulin infusion rate in both the control group and the real-time CGM group. Future studies may benefit from the development of a new algorithm, including guidelines for insulin adjustment and readjustment, guidelines for the next use of CGM data, and guidelines for offsetting trends versus reacting to measured results when using real-time CGM.

The results of our study indicate that real-time CGM increases the safety of tight glycemic control in critically ill patients by significantly reducing severe hypoglycemic events. However, real-time CGM could not improve glucose control defined as percentage of time at <110 mg/dl.

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