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Abstract *Background:* Glucose control (GC) with insulin decreases morbidity and mortality of critically ill patients. In this study we investigated GC performance over time during implementation of GC strategies within three intensive care units (ICUs) and in routine clinical practice. *Methods:* All adult critically ill patients who stayed for >24 h between 1999 and 2007 were included. Effects of implementing local GC guidelines and guideline revisions on effectiveness/efficiency-related indicators, safety-related indicators, and protocol-related indicators were measured. *Results:* Data of 17,111 patient admissions were evaluated, with 714,141 available blood glucose levels (BGL) measurements. Mean BGL, time to reach target, hyperglycemia index, sampling frequency, percentage of hyperglycemia events, and in-range measurements statistically changed after introducing GC in all ICUs. The introduction of simple rules on GC had the largest effect. Subsequent changes in the protocol had a smaller effect than the introduction of the protocol itself. As soon as the protocol was introduced, in all ICUs the percentage of hypoglycemia events increased. Various revisions were implemented to reduce hypoglycemia events, but levels never returned to those from pre-implementation. More intensive implementation strategies including the use of a decision support system resulted in better control of the process. *Conclusion:* There are various strategies to achieve GC in routine clinical practice but with variable success. All of them were associated with an increase in hypoglycemia events, but GC was never stopped. Instead, these events have been accepted and managed. Statistical process control is a useful tool for monitoring phenomena over time and captures within-institution changes.

Keywords Glucose control · Glucose regulation · Critical care · Clinical guideline · Statistical process control · Decision support system

Introduction

Hyperglycemia is frequently encountered in critically ill patients [1, 2]. The underlying physiology of hyperglycemia that drives mortality, independently of glucose control (GC), has been described [3, 4]. GC aiming at normoglycemia [i.e., blood glucose level (BGL) of 80–110 mg/dl, frequently referred to as "tight glycemic control"] decreased morbidity and mortality of critically ill patients in two randomized controlled trials [5, 6]. Recent published meta-analysis [7, 8] could not confirm the benefits of GC, but there are some important methodological concerns about this study [9, 10] and many intensive care units (ICUs) still use GC in their routine clinical practice. Although some studies showed that the implementation of GC with insulin came with the risk of hypoglycemia [5, 6, 11–13], others did not [14–18]. Some studies therefore advise maintaining a BGL <150 mg/dl [19–21]. Another recent randomized controlled trial showed that maintaining BGL <180 mg/dl is superior to adhering to the tight glycemic control in terms of mortality and morbidity [22]. However, this result should be interpreted in the context of the specific implemented guideline and the level of compliance with it. This context is important because the quality of GC and outcome are directly linked [1, 23, 24].

Determining how and for whom GC is safe and effective remains quite elusive [25–27]. Implementing GC as well as the performance of the GC process itself is of great importance in intensive care medicine. To measure GC performance one has to determine and define adequate performance indicators and analyze these indicators over time. This implies monitoring the implementation process and determining whether GC is truly applied and functioning at a consistent and acceptable level. Statistical process control (SPC) is a powerful tool for quality measurement of phenomena over time and the improvement of processes [28].

Our objective was to study GC performance over time during implementation of this strategy in three different ICUs. First, we described and analyzed the performance of GC in the early stage of GC but before implementation of local guidelines, and after the implementation of a written guideline in each center. Second, we analyzed differences between simple and complex guidelines, and between non-computerized and computerized GC. In addition, we described the influence of concerns of clinicians and nurses regarding the safety of GC.

Methods

Study locations

Collection of data was performed in three closed-format mixed medical-surgical ICUs in the Netherlands. ICU-A is a 30-bed ICU of an academic hospital. ICU-B is a 10-bed ICU of a nonacademic teaching hospital. ICU-C is an 18-bed ICU of a nonacademic teaching hospital. In ICU-A and ICU-C, physicians are constantly present.

ICU-A (March 2002) and ICU-C (April 2001) were equipped with a patient data management system (PDMS). The PDMS can display and process all BGLs directly after their measurement with a maximum delay of 1 min.

Local glucose control guidelines

Tables 1 and 2 show the guideline characteristics and changes in them over time. Note that for severe hypoglycemia events, the guidelines recommend stopping insulin infusion as well as injecting glucose.

Patients

All adult critically ill patients who stayed for >24 h between 1999 and 2007 were included. The hospital information system and PDMS were searched for all records on BGL for these patients. The first BGLs directly after ICU admittance were excluded from the final analysis because we considered them not to be influenced by any ICU regimen.

Performance indicators and definitions

The most common performance indicators [29] were selected to show the quality of glucose regulation in the three ICUs. The indicators, described in Table S1 in the electronic supplementary material (ESM), were categorized in three groups: effectiveness/efficiency-related indicators (mean BGL, BGL within predefined targets, and time to reach target), safety-related indicators (severe hypoglycemia, hyperglycemia, and hyperglycemia index), and protocol-related indicators (sampling frequency).

Statistical analysis

We used the SPC technique, described in the ESM, and the XMR control chart [30] to construct and analyze the processes. Due to big subgroup size and the increasing chance of a false-positive result, we used the XMR chart in place of attribute charts [31, 32]. The quality indicators that we chose were calculated per quarter and plotted as points on the XMR chart. The mean of the points before GC implementation was calculated along with the ±3 sigma limits. To determine whether a change in the process occurs further along the time axis, the mean and process control limits were extrapolated over the entire

Table 1 Short description of changes in glucose control protocol over time

ICU	ICU-A			ICU-B			ICU-C		
Change in glucose control	I	II	III	I	II	III	I	II	III
Glucose control protocol characteristics									
Type of protocol	Simple set of rules	Sliding scales	Sliding scales	Simple set of rules	Sliding scales	Simple set of rules	Sliding scales	Sliding scales	Sliding scales
Present in what form(s)	Written	Written	Written	Written	Written	Written	Written	Written	Written
Decision support present	No	No	No	No	No	No	No	No	Yes
Who is responsible for glucose control									
Start of insulin: ICU nurse or physician	Physician	Nurse	Nurse	Nurse	Nurse	Nurse	Nurse	Nurse	Nurse
Dosing of insulin: ICU nurse or physician	Nurse + physician	Nurse	Nurse	Nurse + physician	Nurse + physician	Nurse	Nurse	Nurse	Nurse
Correction of hypoglycemia: ICU nurse or physician	Nurse + physician	Nurse	Nurse	Nurse + physician	Nurse + physician	Nurse + physician	Nurse	Nurse	Nurse
Protocol thresholds and targets									
Start of insulin (mg/dl)	>144	>144	>144	>144	>144	>110	>126	>126	>126
BGL targets (mg/dl)	80–144	80–144	90–144	90–144	80–144	80–110	72–126	72–126	72–126
Timing of BGL measurements described in or mandated by the protocol	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes
Rules on stopping insulin									
Threshold to stop insulin infusion	<80	<63 or 63–80 with >50% reduction in BGL	<63 or 63–144 with >50% reduction in BGL	< 90	<54 or 54–80 with >50% reduction in BGL	<54	<80	<80	<80
Other reason for stopping insulin	–	Feeding stopped	Feeding stopped	–	Feeding stopped	Feeding stopped	–	–	–
Action in case of hypoglycemia									
BGL < 40 mg/dl	–	50 ml 20% glucose	50 ml 20% glucose	–	50 ml 50% glucose	20 ml 50% glucose	20 ml 30% glucose	20 ml 30% glucose	20 ml 30% glucose

In all three centers, change *I* indicates the initiation of glucose control (directly or shortly after the publication of the first randomized control trial showing beneficial effects of tight glycemic control); major changes *II* and *III* in ICU-A were in August 2004 and May 2005, respectively; major changes *II* and *III* in ICU-B were in September 2004 and May 2005, respectively; major change *II* and *III* in ICU-C were in January 2003 and May 2003; see text for details on changes. Timing of major changes corresponds with dashed lines in the figures. Mainly arterial (and only occasionally venous) blood samples were used for BGL measurements. In ICU-A, for almost all BGL measurements blood gas analyzers (Rapidlab 865, Bayer, Germany) were used. In ICU-B two types of glucose analyzers were used (Hitachi 917, Roche Diagnostics, and Accutrend Sensor, Roche Diagnostics). In ICU-C, all BGL measurements were performed with the Accu-check (Roche Diagnostics). The term "sliding scale" here refers to a dynamic protocol for intravenous insulin infusion

ICU Intensive care unit, *BGL* blood glucose level, – no advice given in the protocol

Table 2 Description of guidelines revisions in three studied ICUs

ICU	Date of change	Description
A	Before November 2001	For a long time, hyperglycemia was considered an adaptive response to critical illness. Therefore before publication of the first randomized controlled trial showing benefit of tight glycemic control, only BGL >200 mg/dl was a reason to start insulin infusion.
	November 2001 (major change I)	A simple guideline on glucose control was implemented involving all ICU patients. The BGL target in this first written protocol was 80–144 mg/dl. Glucose control was considered a combined ICU physician and ICU nurse activity; initiation of insulin infusion was by the attending ICU physician (and never the ICU nurse), changes in insulin infusion were by ICU physician and/or ICU nurse. The protocol did not make recommendations on timing of BGL measurements.
	August 2004 (major change II)	A more strict guideline was implemented. The recommendations on infusion pump speeds were far more complex, using sliding scales. This protocol was completely nurse-driven; initiation of and all changes in insulin infusion were done only by the attending ICU nurse (and never the ICU physician). The new guideline made recommendations on timing of BGL measurements. In addition, there were now also recommendations for treatment of hypoglycemia and for the frequency of BGL measurements after hypoglycemia.
	May 2005 (major change III)	The guideline was slightly revised to decrease the risk for severe hypoglycemia. From then on the guideline recommendations strived for BGL of 90–144 instead of 80–144 mg/dl.
B	November 2001 (major change I)	A written guideline on glucose control was introduced. The guideline was similar to the one used in ICU-A, with the exception that this guideline aimed at BGL of 90–144 instead of 80–144 mg/dl.
	September 2004 (major change II)	A more strict glucose control guideline was implemented, aiming at BGL between 80 and 144 mg/dl. Similar to the first version, in this guideline glucose control was also a combined ICU physician and ICU nurse activity. The new guideline made recommendations on timing of BGL measurements. The protocol provided recommendations for infusion pump speeds, using sliding scales. In addition, there were recommendations for treatment of hypoglycemia and for the frequency of BGL measurements after hypoglycemia.
	May 2005 (major change III)	The ICU team concluded that the guideline was too strict and rigid; in particular it was considered to cause too many hypoglycemic events. It was decided to no longer use the guideline and a simple order was added to the chart by the attending ICU physician stating that the BGL should be between 80 and 110 mg/dl. It was left to the ICU nurses to decide whether or not to use the previous guideline and to start and adapt insulin infusion whenever necessary. The same held for the BGL measurements, i.e., they were taken whenever ICU nurses considered that to be necessary. Only in case of difficulties in making decisions pertaining to glucose control the attending ICU physician was consulted. Thus from then on the guideline was considered to be merely ICU nurse based.
C	Before November 2001	BGLs were considered acceptable between 180 and 216 mg/dl.
	November 2001 (major change I)	It was simply recommended that BGL should be more strictly controlled.
	April 2002	A simple written guideline aiming at glucose control with BGL targets of 72–126 mg/dl was introduced. This guideline was completely nurse-driven.
	January 2003 (major change II)	The guideline was evaluated and found insufficient. This led to the development of a new written guideline, introduced at the bedside. The guideline provided recommendations for infusion pump speeds, using a diagram. Compared to the 1-page sliding scale used in ICU-A and ICU-B, this 4-page diagram was far more complex. It had many extra steps and more detailed rules, with recommendations on timing of BGL measurements. There were also recommendations for treatment of hypoglycemia and for the frequency of BGL measurements after hypoglycemia.
	May 2003 (major change III)	This elaborate guideline was transformed into a computerized decision support system (CDSS), a custom-made Visual Basic application integrated within the PDMS [37]. This CDSS was introduced at 50% of the beds (as part of a study). The application displayed glucose and insulin data and suggested adjustments in insulin dose and the interval to the next BGL measurement.
	September 2003	The CDSS is used for all ICU patients.

study period. Because the time of intervention is known and because the process is stable (i.e., not "out of control" according to the SPC rules) before and after the intervention, the mean and process control limits were recalculated in the intervention period. The Kruskal-Wallis *H*, Mann-Whitney *U*, and chi-squared tests were used to assess the statistical significance of differences among pre- and post-intervention periods and to compare these results with those of the SPC analysis. All analysis was performed with Systat 12.

Results

Patients

In total 9,392, 2,968, and 4,751 admissions from ICU-A and ICU-B (from 1 January 1999 to 31 September 2007) and ICU-C (from 1 January 2001 to 31 September 2007), respectively, were extracted and analyzed. Table S2 in the ESM shows the patient baseline characteristics including age, gender, APACHE III score, admission type, ICU mortality, and length of stay in each year of study. SPC

showed that they were stable and did not change significantly during the study period.

Effectiveness and efficiency of glucose control

Figure 1 shows the quality process control charts for the effectiveness/efficiency-related indicators of GC in the three ICUs. Mean BGL decreased and became "out of process control" (i.e., a change was detected) after implementing the GC guideline in all three ICUs. The introduction of simple rules on GC had the largest effect in ICU-A, since GC became more stable with less variation. Subsequent changes in the guidelines did not have effects as large as the introduction of the guideline itself. Mean BGL in ICU-B was reduced by the introduction of the guideline but the mean BGL still remained higher and less stable from quarter to quarter than in the other two ICUs. Similar to ICU-A, in ICU-C the implementation of the GC guideline had a large effect on BGL, but with the introduction of the computerized decision support system (CDSS) the mean BGL decreased further and GC stabilized.

The percentage of BGLs within locally defined targets increased after introducing GC guidelines in all three ICUs. In ICU-A, the subsequent revisions in the protocol did not change this percentage. As with mean BGLs, the percentage of BGLs within target in ICU-B changed significantly with the two changes in the protocol. In ICU-C, both the introduction of GC as well as the introduction of the CDSS increased the percentage of BGLs within targets.

Time to reach targets decreased after introducing the first GC guideline in ICU-A and ICU-C. The means of this indicator in ICU-A were better than in ICU-C before introducing the protocol. But in ICU-C after protocol introduction, and especially with CDSS implementation, the mean of this indicator rapidly decreased and eventually it was half of that in ICU-A. After protocol implementation in ICU-B, the mean time to reach target ranges decreased stepwise with changes in the protocol, but was comparable to the other two ICUs with less stability and higher mean.

Safety of glucose control

Process control charts of safety-related quality indicators are shown in Figs. 2 and 3. As soon as the guidelines were introduced, in all three ICUs the percentage of BGL measurements $\leq$40 mg/dl increased. In ICU-A, the first revision of the guideline decreased both severe and non-severe hypoglycemia events. In ICU-B, with all changes in the protocol, the incidence of hypoglycemia increased. In ICU-C, these indicators increased after introducing GC and further increased after CDSS implementation. Compared to the other two ICUs, the percentage of BGL measurements $\leq$40 mg/dl in ICU-B was less stable with more variation from quarter to quarter before the third revision in the GC guideline.

Protocol-related indicator

Mean interval between BGL measurements decreased after introducing the GC guidelines in ICU-A and ICU-C (Fig. 4). In ICU-A this interval was smaller than in ICU-C before introducing the protocol. But after introduction of the guideline in ICU-C, especially with the CDSS implementation, this mean rapidly decreased and was even half of that in ICU-A. With the introduction and subsequent changes of the guideline in ICU-B, the mean interval between BGL measurements decreased, but compared to the other two ICUs, with less stability and with higher means especially before the third revision. Both reductions were statistically significant.

The results of nonparametric and chi-squared tests on the effect of introducing GC and related changes on these indicators were concordant with the SPC results (data not shown).

We used all data from 31 September 2005 till 31 September 2007 because all ICUs declared there were no other interventions that could have affected GC in this period. The SPC charts also showed the processes were stable for all indicators in all three ICUs in this period. Median BGL in ICU-C and ICU-B was significantly lower than ICU-A. The percentage of patients with at least one hypoglycemia event and overall percentage of hypoglycemia and severe hypoglycemia events were significantly higher in ICU-C and ICU-B. Other statistically (and seemingly clinically) significant differences were in BGL measurement interval, and time to reach target, which were lower in ICU-C (Table S3 in the ESM).

Discussion

The effect of introducing GC guidelines and the various implementations on the quality of GC, especially for an extended period of time, is unknown. The implementation strategies of GC ranged from raising awareness to employing a computerized decision support system. In all three ICUs, regardless of strategy, there was a continuous and significant improvement in the effectiveness and efficiency indicators, an increase in hypoglycemic-related indicators, and an increase in BGL measurements. However, the speed of change and the final outcomes differed significantly among the three ICUs.

With SPC, data are plotted and interpreted in a time series rather than merely comparing before and after measures. With this method special causes of variation were easily distinguished from common causes. Process

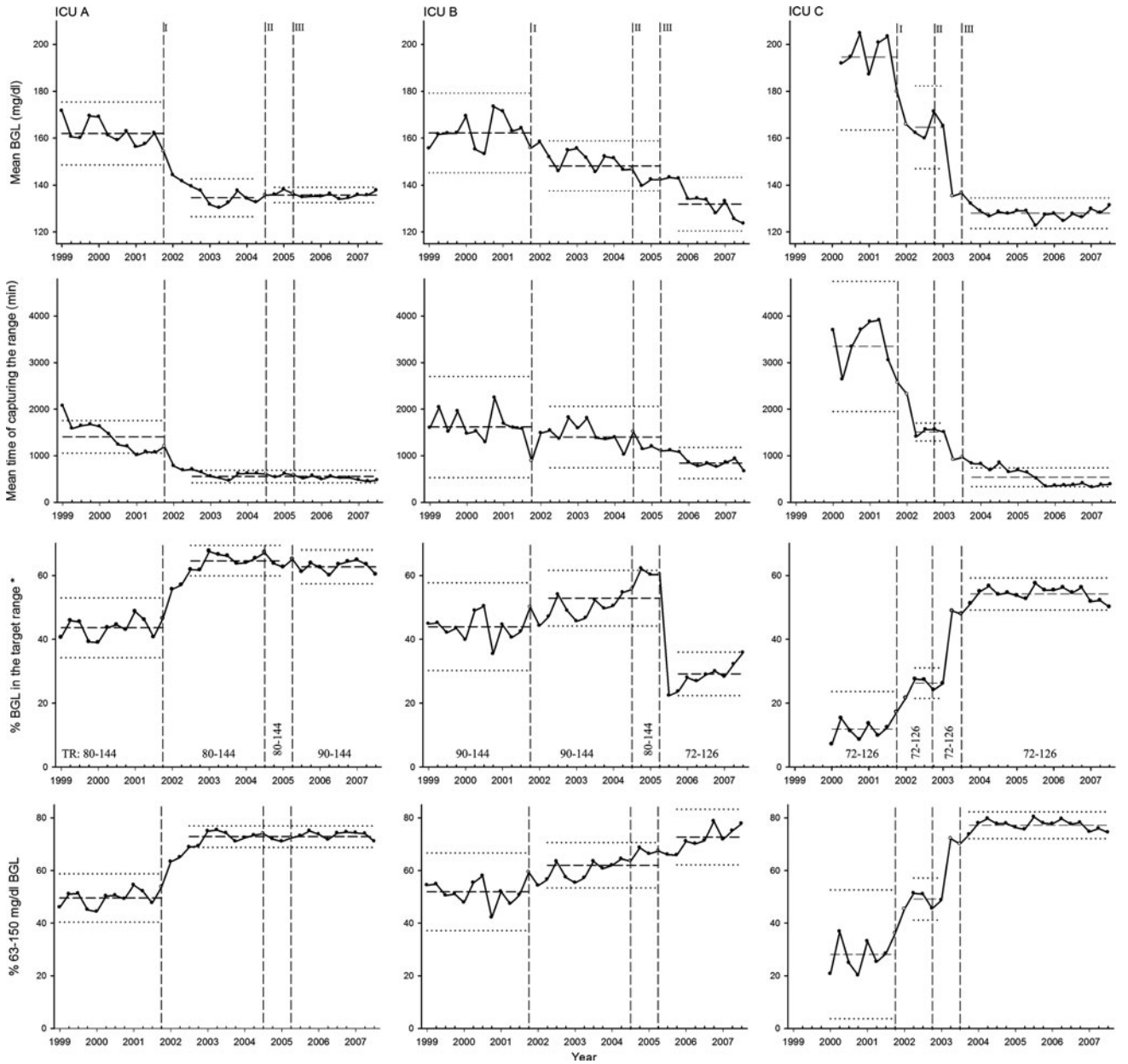

Fig. 1 Control charts of mean BGL, time to reach target range, percentage of BGLs in range predefined in the protocols, and percentage of BGLs between 63 and 150 mg/dl (efficiency-related indicators). An *asterisk* means that the indicator was not only influenced by performance but also by definition of targets, and that because of the latter sharp changes over time could be recognized. When the data points are, without any special-cause variation, within the process control limits then the process is said to be "in control" and stable. Common rules for distinguishing a special-cause variation (i.e., a structural change): one or more points above or below the process control limit, a run of eight (or seven) or more points on one side of the center line, two out of three consecutive points appearing beyond 2 sigmas on the same side of the center line, a run of eight (or seven) or more points all trending up or down. Because the time of intervention (major changes) is known and because the process was stable (i.e., not "out of control" according to the SPC rules) before and after the intervention, the mean and process control limits are recalculated in the intervention period

control charts showed which parts of the processes were more stable and also showed the duration of change after each intervention. SPC charts in Figs. 1, 2, 3 and 4 showed the diversity in results for implementing similar protocols in three different centers and reflected a range of "error", all else being equal, in implementing a protocol with differing interpretations and implementation details. Those wishing to use SPC as a tool for

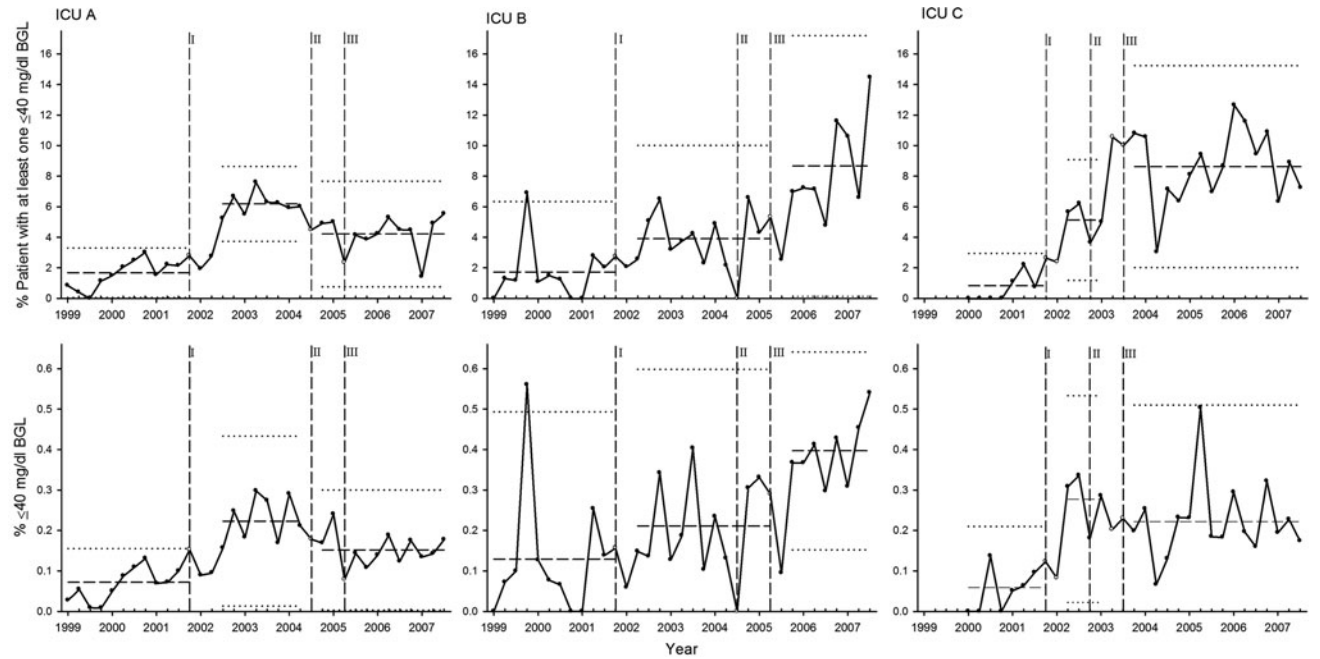

Fig. 2 Control charts of percentage of patients with at least one BGL ≤ 40 mg/dl and percentage of BGL ≤40 mg/dl (safety-related indicators)

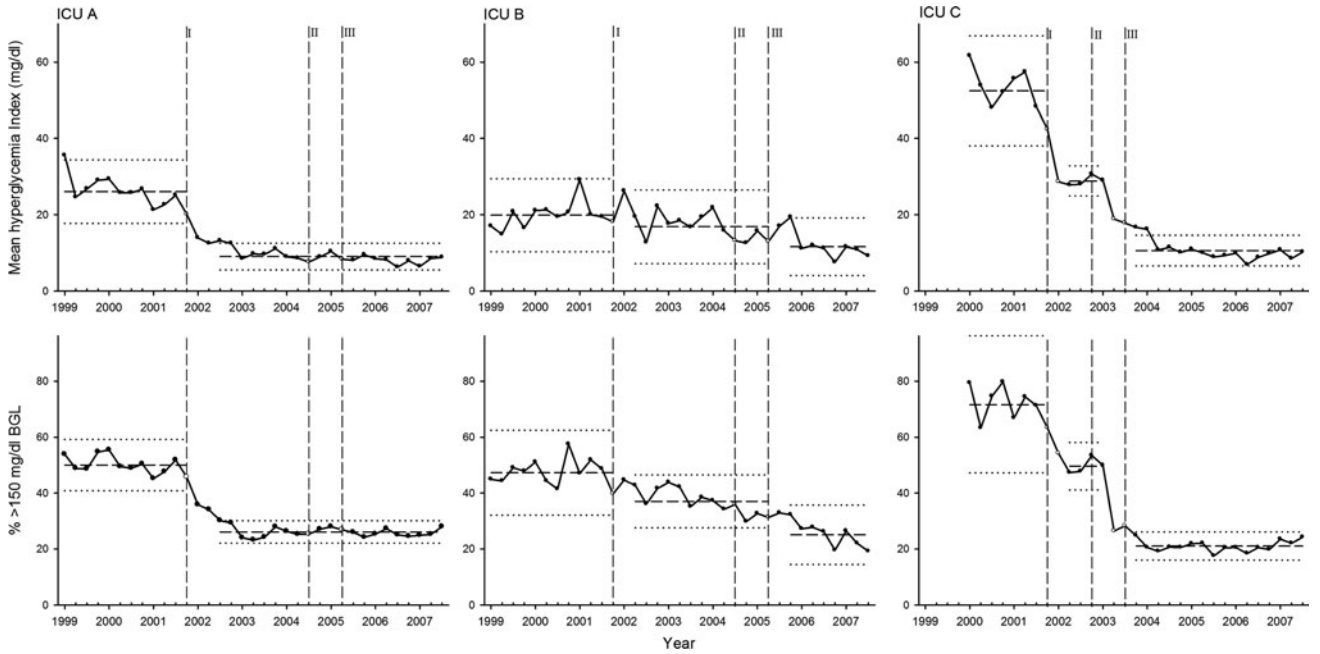

Fig. 3 Control charts of mean hyperglycemia index and percentage of BGL > 150 mg/dl (safety-related indicators)

longitudinal self-examination of performance are referred to [31].

This study has three main strengths. First, to our knowledge this is the first report on effects of GC in routine daily clinical practice over an extended period of time. Second, to visualize and make inferences on the longitudinal development of quality indicators, we used the powerful instrument of process control charts from the field of SPC. Third, we studied three different ICUs employing different GC strategies. There are however

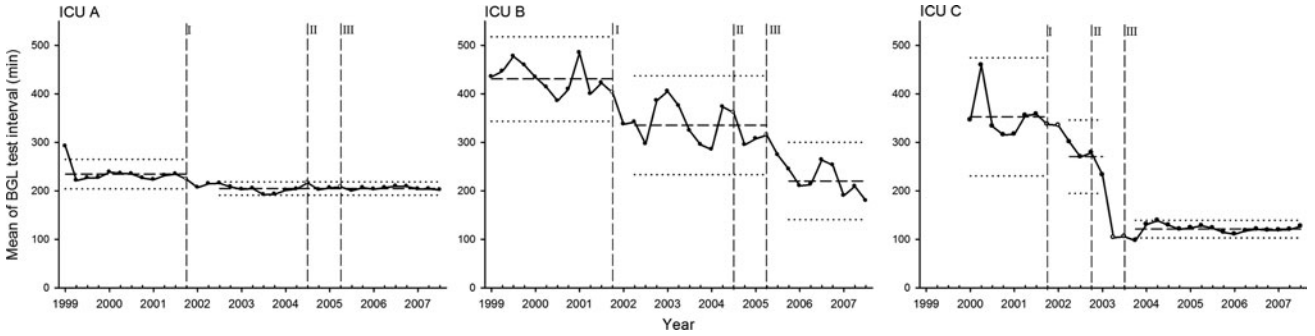

Fig. 4 Control chart of mean BGL sampling intervals (protocol-related indicator)

also limitations to our study. First, we did not perform subgroup analysis (such as surgical vs. medical patients). Second, we did not investigate the influence of GC on clinically relevant endpoints such as survival. However, as GC has been shown to be an evidence-based strategy that decreases morbidity and mortality [5, 6], adherence to this strategy is commonly advocated. Third, the actual adherence to the protocols is unknown. However, the fact that the quality indicators were significantly influenced implies that the protocols are being increasingly followed. Finally, because nutrition data were not available for the whole study period, we could not investigate the possible effect of nutrition on the quality of GC. However, nutrition input is not likely to have changed over the study period within each hospital. In addition, the protocol should be robust to reasonable fluctuations in the given nutritional carbohydrate levels.

Usually routine clinical practice characteristics and limitations are not considered in randomized control trial (RCTs) and guidelines. This is one explanation for the underuse of treatments in routine practice that were beneficial in trials and that are recommended in guidelines. Among tight glycemic control (TGC) studies, some have explicitly considered routine practice issues in their design, e.g., [14, 15, 17]. However, we in addition monitored performance during actual use of the protocol over time with SPC.

Relaxing the GC range to a wider, locally workable target can perhaps be explained by an associated "fear" of hypoglycemia. Brunkhorst et al. showed that the rate of patients with at least one episode of severe hypoglycemia ($\leq$40 mg/dl) was higher in the study group than in the control group (17.0 vs. 4.1%, $P<0.001$) [11]. Although they reported that no serious adverse events were found, the trial was nonetheless stopped due to the hypoglycemic episodes. Interestingly our results showed that in routine practice, and in contrast to the clinical trials, GC was not stopped although the rate of patients with at least one hypoglycemia event were relatively high even with less tight target ranges (9% in the ICU-B and ICU-C after the last guideline revision). Although concern about increasing the percentage of hypoglycemic patients resulted in terminating the use of the more detailed protocol in ICU-B, thereafter an even tighter target range was used in this ICU, and the percentage of hypoglycemic patients increased even after these revisions. Protocol failure and/or lack of compliance could partly explain this result, but we do not have data to test these hypotheses. Vriesendorp et al. and Chase et al. showed that TGC-induced hypoglycemia was not associated with worse outcome [17, 33], although recent studies have reported such an association [22, 34]. Association of hypoglycemia with worse outcome may be related to the protocols in use. Fear of hypoglycemia and its reputation as being more dangerous than hyperglycemia in the critically ill may well be based on deeply rooted emotional beliefs rather than on evidence [35]. Our study demonstrates that as long as continuous measurement tools are not available, hypoglycemia events are considered acceptable and can be consequently managed.

Our results also showed that any decrease in mean BGL resulted in an increase in the percentage of hypoglycemia events. ICU-C, which eventually had the lowest mean BGL, also had the highest percentage of hypoglycemia events. The complex guidelines and the use of the CDSS, resulting in a mean measurement interval in ICU-C of 120 min, may have led to more early (and possibly more frequent) detection of the hypoglycemia. Also minimum BGL in ICU-A and ICU-B was associated with maximum percentage of hypoglycemia events. Revising the protocol in ICU-A decreased the hypoglycemia events but could not return the level to what it was before implementing GC.

Shortly after the first presentation on TGC in November 2001 [6], there were either no written guidelines in the participating ICUs or the guidelines were very simple and in a development phase. SPC charts showed that awareness of TGC, regardless of the guidelines in place, brought about the maximum changes in the related indicators. However, thereafter there remained little room for improvement. After this stage, stronger interventions, such as more complex protocols and the use of a CDSS,

were called upon to bring about change, but the level of change was smaller.

Different strategies were developed to achieve GC in the three ICUs studied. All have managed to reach an acceptable control but with different speeds of change and different variability over time. Both ICUs with detailed written protocols (ICU-A and ICU-C) had better results and more stable processes with lower variability from quarter to quarter than ICU-B. Using a detailed written protocol with clearly defined steps compared to simple rules (ICU-B) seems to help the nurses to make better decisions to control blood glucose.

Our results show that a complex protocol with more steps and detail in ICU-C had improved effects but only after including the CDSS as an intervention. In ICU-C the mean BGL measurement interval also became smaller than in ICU-A after the CDSS. We can conclude that the CDSS influenced the nurses' behavior by reminding them about the time of the next BGL test. Probably the shorter time between measurements is based on differences between protocols, not the effect of CDSS. However it is unclear whether the beneficial effects of the CDSS are mainly due to the more frequent measurements or due to the complex protocol rules. With the current data we cannot answer this question. In addition, to achieve such a low mean BGL, higher costs (CDSS and more nursing and laboratory utilization) were incurred and patients experienced more hypoglycemia events. Cost-benefit analysis merits more research when aiming at lower mean BGL.

Frequent BGL measurement is a key element in TGC, in order to steer the process in a timely manner [14, 17, 36]. In the three studied ICUs, better results were associated with more frequent measurements. In ICU-A, there were many BGL measurements before introducing GC, since BGL measurements were included with blood gas analysis, even when there was no intention to measure it. This might explain some of the fast improvement in glucose regulation in ICU-A after introducing the guideline and the very small variation in sample interval.

Conclusions

There are different successful strategies to realize GC in routine clinical practice but they have various speeds and implementations. All of the strategies studied here were associated with an increase in hypoglycemia events. More intensive implementation strategies resulted in better control of the process but at the cost of more ICU resources, including the use of a decision support system. SPC is a useful tool for monitoring phenomena over time and allows for capturing within-institution changes. Within quality measurement and/or improvement efforts, SPC can show where the special variations are and where opportunities lie for improving (adherence to) protocols.

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