Blood glucose control and monitoring in the critically ill
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Chapter 13

Summary and General Discussion

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Summary

The aims of this thesis

This thesis deals with blood glucose control and blood glucose monitoring in intensive care unit (ICU) patients: two important aspects of care for and monitoring of critically ill patients. While the precise targets of blood glucose control in ICU patients remain a matter of debate, currently many, if not all, critically ill patients are treated with insulin at some point during their stay in the ICU. Although many patients are currently treated with insulin, it could be that certain patient groups benefit more from blood glucose control than other patient groups. Several quality and safety metrics for blood glucose control are proposed to be used, among others the mean blood glucose level, the proportion of patients developing or samples showing dysglycemia, and glycemic variability. However, these metrics of quality and safety for blood glucose control are only partly, and frequently inconsistently used. Blood glucose levels are still monitored manually using point–of–care devices with significant inaccuracies. Manual blood glucose monitoring is not only time– and blood–consuming, but also bears the risk of incorrect adjustments of the insulin infusion rate.

The three key aims of this thesis are:

- To discuss practical aspects of and metrics for blood glucose control in critically ill patients (Part I of this thesis);
- To investigate factors that could affect quality and safety of blood glucose control (Part II of this thesis);
- To study blood glucose monitoring, in particular new devices for automatic and continuous blood glucose monitoring (Part III of this thesis).

Summary of Part I

Part I contains reports of studies that investigated practical aspects of blood glucose control and frequently used metrics for quality and safety of blood glucose control in critically ill patients. Chapter 2 gives an overview of how blood glucose could be controlled, discussing the use and practicalities of insulin and oral anti–hyperglycemic agents in the ICU setting [1]. Next to prevention of hyperglycemia and hypoglycemia, one goal of blood glucose control in critically ill patients could include minimization of glycemic variability. Frequent or continuous monitoring of blood glucose levels could improve efficacy and safety of blood glucose control in ICU patients. Chapter 3 focuses on how continuous blood glucose monitoring systems could reduce blood glucose variability [2]. Chapter 4 is a comment on a previously published study [3] that concluded that the 'mean of the highest and lowest blood glucose level within the first 24 hours of ICU admission’ adequately reflects the quality of blood glucose control over the entire ICU admission. We hypothesized this to be untrue, and therefore compared their metric with one calculated from blood glucose levels obtained over the entire ICU stay [4]. We tested this by looking into blood glucose datasets from a multicenter cohort of patients in The Netherlands that compared blood glucose control before and after an important change in the local guideline [5]. While the metric of the original study did not change, our metric clearly did, from before to after the change. In other words, it does matter which metric is chosen when reporting on quality of blood glucose control in critically ill patients.
Chapter 5 describes the results of a national survey and retrospective analysis of prospectively collected blood glucose levels in ICUs that provided robust blood glucose datasets between 2008 and 2014 to the National Intensive Care Evaluation (NICE) registry. We hypothesized that blood glucose control in ICUs in the Netherlands did change after publication of the NICE–SUGAR trial in 2009 [6] and the latest version of the Surviving Sepsis Campaign–guidelines in 2012 [7]. The NICE–SUGAR trial, a large multi-center randomized controlled trial, showed a lack of benefit of blood glucose control targeting normoglycemia and even suggested harm from this strategy [6]. Based on the results from the NICE–SUGAR trial and on results from several observational studies suggesting harm from hypoglycemia in critically ill patients [8, 9], the latest version of the Surviving Sepsis Campaign–guidelines recommends against targeting normoglycemia and to accept higher blood glucose levels [7]. To test our hypothesis, we performed a national survey focusing on (timing of) changes in targets in local guidelines for blood glucose control in ICUs in The Netherlands and calculated several quality and safety metrics for blood glucose control in those ICUs from which we obtained the blood glucose datasets. In more than half of the responding ICUs the local guideline for blood glucose did change. Furthermore, changes in metrics for blood glucose were noticeable in all ICUs, however changes differed between ICUs. Overall, the mean blood glucose level increased, although only slightly, with less hypoglycemic and more hyperglycemic measurements. Thus, blood glucose control did change in ICUs in the Netherlands and needs to be taken into account when planning future studies of blood glucose control.

Summary of Part II
Part II contains reports on studies that investigated associations between a history of diabetes, transitions from hypoglycemia to hyperglycemia, bolus infusion of hydrocortisone and outcome, and their association with safety and quality metrics for blood glucose control.

Chapter 6 describes the results of a large retrospective international study [10]. Here we hypothesized that a history of diabetes would attenuate the associations between dysglycemia and mortality. The mean blood glucose level, the minimum blood glucose level and the coefficient of variation were used as metrics for hyperglycemia, hypoglycemia and glycemic variability, respectively. Blood glucose levels and demographic data were collected for 44,964 patients in 23 ICUs in 9 countries, of whom 14 to 39% had a history of diabetes. The most important finding was that in non–diabetic patients having a mean blood glucose level between 80 and 140 mg/dL, was independently associated with decreased mortality, while in diabetic patients having a mean blood glucose level between 80 and 110 mg/dL was independently associated with increased mortality. Furthermore, the association between hypoglycemia and mortality was not affected by the diabetic status, but increased glycemic variability was only associated with increased mortality in non–diabetic patients. Finally, in patients without a history of diabetes, derangements of more than one domain of blood glucose control had a cumulative association with mortality. This association was not found in patients with a history of diabetes. The findings of this retrospective study suggest that clinicians may want to consider other targets in blood glucose control in diabetic patients and non–diabetic patients.
However, evidence from randomized controlled trials is needed before we should change daily practice.

**Chapter 7** describes a study on dynamics of the blood glucose level after hypoglycemia in critically ill patients. Our hypothesis was that a transition from hypoglycemia to hyperglycemia would show an independent association with ICU mortality. In a pooled cohort of 19,505 patients over a six–year period from seven ICUs in The Netherlands, 4,512 patients developed hypoglycemia. We found a U–shaped association between changes in blood glucose levels following hypoglycemia and ICU mortality. However, our hypothesis was rejected since a transition from hypoglycemia to hyperglycemia was not independently associated with outcome. These results are in contrast with preclinical studies in animals and clinical studies in other patient populations. However, we should be careful with translating these results into guidelines for blood glucose control. The analysis was retrospective and data regarding how hypoglycemia was corrected when it appeared could not be collected.

The hypothesis of the study described in **Chapter 8** was that bolus infusion of hydrocortisone would independently be associated with increased glycemic variability and insulin infusion rate variability in ICU patients under glycemic control aiming at blood glucose levels between 90–144 mg/dL. We tested this hypothesis in a retrospective study in a mixed medical–surgical ICU in a university hospital and compared 962 patients who had been treated with bolus infusion of hydrocortisone to 5,447 patients who did not receive hydrocortisone during their stay in the ICU. The frequency of blood glucose measurements was higher in patients who received hydrocortisone; these patients had higher glycemic variability and also higher insulin infusion rate variability. The association between hydrocortisone treatment and glycemic variability was independent of disease severity. Nevertheless, the effect of hydrocortisone treatment on blood glucose variability was weaker in the more severely ill patients. Hydrocortisone infusion was as well associated with increased insulin infusion rate variability, and was independent of disease severity and also of glycemic variability. These findings suggest that continuous infusion of hydrocortisone may be preferred over bolus infusion of hydrocortisone.

**Summary of Part III**

**Part III** contains reports of studies on practical aspects of blood glucose monitoring, in particular new devices for blood glucose monitoring. **Chapter 9** provides an overview of diverse continuous glucose monitoring techniques and devices intended for use in the ICU setting [11]. This chapter also deals with the issue of point and trend accuracy of continuous glucose monitoring systems.

**Chapter 10** and 11 describe two observational trials of two new glucose monitoring systems for use in the ICU [12, 13]. We hypothesized both systems to be point accurate and reliable in a cohort of mixed medical–surgical ICU patients. In **chapter 10**, the results of a trial in which we tested the OptiScanner® (OptiScan Biomedical Corporation, Hayward, CA, USA) in 71 critically ill patients are presented [12]. The OptiScanner® automatically draws blood every 15 minutes via central venous catheters and creates plasma through automatic centrifugation. Subsequently the OptiScanner® measures the plasma glucose level through mid–infrared spectroscopy at the bedside. We collected 463 comparative samples for
the accuracy analysis. After calibrations for previously unrecognized interferences the accuracy of the OptiScanner® improved remarkably, resulting in a high point accuracy.

Chapter 11 presents the results of a trial in which we tested the Sentrino® (Medtronic MiniMed, Northridge, CA, USA) in 50 critically ill patients [13]. The Sentrino® is an interstitial continuous glucose monitoring device especially designed for use in critically ill patients. The disposable sensors of this device are inserted into the subcutaneous tissue to measure the glucose levels. Individual measurements from the glucose oxidase–based probes of the sensor are combined and displayed on the monitor every minute. We collected 929 comparative samples for the accuracy analysis. The point accuracy of this device was low, therefore we conclude that this device cannot replace manual blood glucose measurements.

Finally, Chapter 12 describes the results of a health economic evaluation of implementation of a guideline for blood glucose control targeting normoglycemia with point–of–care testing in three ICUs in the Netherlands. We hypothesized that costs would increase after implementation of a guideline targeting normoglycemia, as it would increase the number of blood glucose measurements. Both costs of blood glucose measurements as well as the downstream costs were included and related to effectiveness of the treatment defined as the number of patients in target glucose levels. Effectiveness was estimated in 3,195 patients 12 months before and 24 months after implementation of a new guideline. As expected, the number of blood glucose measurements increased significantly, from 4.8 to 8.0 per patients per day, accruing 58% higher costs for point–of–care testing of blood glucose levels in the new guideline compared to before its implementation. When taking total hospital costs and clinical effects into account, implementation of SGC increased hospitals costs with 1.8%, while the number of patients in target glucose levels increased. Although results could be generalizable to the Dutch context, transferring the results to other countries or settings requires adaptation of the model inputs to reflect local costs and practice variations.

General discussion
The results of the studies presented in this thesis show the importance of how blood glucose control is reported. Several metrics for blood glucose control are suggested to be helpful in reporting on blood glucose control, but the metrics are used inconsistently and authors frequently report selectively on sets of metrics that provide insight in quality (e.g., the mean blood glucose level), safety (e.g. the proportion of patients developing hypoglycemia, or the proportion of measurements showing hypoglycemia), or variability. Inconsistent and incomplete use of metrics for blood glucose control could not only lead to incorrect conclusions, but also limits comparison between studies. Several studies presented in this thesis also suffer from this shortcoming, due to the fact that journals request authors to focus on the hypothesis to be tested and to keep reports short. Consequently, valuable information is lacking at times. Recently, consensus recommendations on reporting of blood glucose control in critically ill patients were published [14]. It was recommended to report on all three domains of blood glucose control in a standardized manner, using 1) at least one metric for central tendency (i.e., the mean blood glucose level), 2) at least one metric for hypoglycemia, and 3) at least one metric for dispersion of the
blood glucose levels (i.e., glycemic variability), next to details on frequency of blood glucose measurements, blood glucose measurement technique, and sampling source [14]. Applying these recommendations could prevent incomplete reporting of blood glucose control and enables comparison between studies and practices of blood glucose control worldwide. Unfortunately, the consensus recommendations did not suggest which metric should be used and, as clearly shown in Chapter 4 of this thesis, not all metrics measure the same [4]. In addition, the consensus recommendations only concern reports on studies of blood glucose control using manual blood glucose measurements, which could be very different from that using continuous blood glucose measurement devices (see below).

Furthermore, the results of the studies presented in this thesis show that certain patient groups may benefit more from blood glucose control than other patient groups in the ICU and that blood glucose control evolves with the years. Indeed, the effects of blood glucose control could be different in patients with a history of diabetes, as shown in Chapter 6 of this thesis [10]. And, probably alike elsewhere, targets of blood glucose control in critically ill patients has changed in recent years, likely as a response to the publication of the NICE–SUGAR trial [6] and the latest version of the Surviving Sepsis Campaign guidelines [7]. This means two things. First, we need to perform randomized controlled trials of blood glucose control in different patient groups. Second, when planning such trials we need to know how patients, and certain patient groups, are presently being treated with insulin, as this should be the strategy to be followed in the control arm of such a trial. There could be differences between countries and even between ICUs within a single country. Certainly, our findings in the Netherlands suggest changes in blood glucose control in seven ICUs in the Netherlands. However, we remain uncertain on how this is managed in other ICUs in the Netherlands, and beyond. Ideally, we would like to see trials to report similar metrics for blood glucose control, so that trial results can be compared, and eventually metaanalyzed. It would be even better if complete blood glucose datasets were shared so that (new) metrics of interests can be calculated across a large population of patients. Uniform databases or registries, collecting blood glucose datasets, patient information, and information on ICU outcome are welcomed.

We need to invest in studies that allow us to conclude whether certain associations, as those found in Chapters 6, 7 and 8, reflect causal relationships. These studies were observational or retrospective, like many studies that suggest causal relationships between certain factors and the effects of blood glucose control. Although characteristics of associations could be investigated to support causality [15], it still could be very difficult to accept whether a certain association reflects causation. Thus, if possible, we should perform randomized controlled trials when observational studies suggest causation.

Moreover, there is hope that continuous blood glucose monitoring improves blood glucose control in critically ill patients. Continuous blood glucose monitoring could not only improve the quality of blood glucose control (by lowering the mean blood glucose level, and preventing hyperglycemia), but also its safety (by preventing hypoglycemia). It could also be that continuous blood glucose monitoring reduces the variability of the blood glucose level. In addition, continuous blood glucose monitoring devices may use less blood and use up less time of nurses
practicing blood glucose control. This all needs to be addressed in future studies, after extensive testing of the several continuous blood glucose monitoring devices that are now entering the market. Testing should address both point accuracy and trend accuracy [11, 16]. One other aspect which should be taken in mind, is the cost associated with the use of continuous blood glucose monitoring devices. Important to realize is that metrics for blood glucose control using continuous blood glucose monitoring could be different from those used for blood glucose control using manual blood glucose measurements [2].

Future Perspectives

As pointed out in Chapter 2 blood glucose control with insulin is common care in most ICUs. We moved away from blood glucose control targeting normoglycemia, to safe blood glucose control accepting slightly higher blood glucose levels. The targets of blood glucose control could be different between certain patient groups and should depend on local possibilities: can nurses perform frequent blood glucose measurements, than we could possibly target lower blood glucose levels – and if blood glucose control could use continuous blood glucose measurement devices we could even aim at lower levels, maybe completely preventing hypoglycemia, and lowering blood glucose variability. These hypotheses need to be tested in future trials, which should also contain cost–effectiveness analyses.

In conclusion, focus on the development of new techniques is important to make blood glucose control and monitoring in critically ill patients more safe and efficient.

References


