

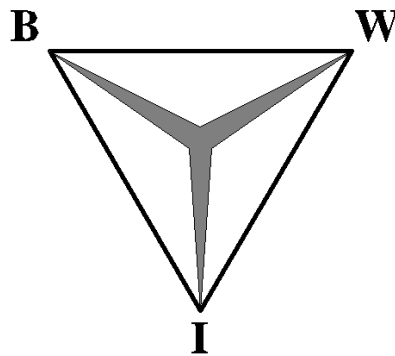
# ***Glucose management at the VUmc***

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**BMI Internship**

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## **Preface**

My name is Jasper de Boer, born in 1984 and I am studying Business Mathematics and Informatics (BMI) at the Vrije Universiteit in Amsterdam. The last part of the master BMI is the internship. I have done this internship at the VUmc (Vrije Universiteit medisch centrum), at the department Intensive Care Volwassenen (ICV) from October 2007 until May 2008. I have tried to find a way to keep the incidence of a critical low blood sugar level as low as possible, without an overall increase of the blood sugar level and higher incidence of very high blood sugar levels.

First of all I would like to thank the VUmc for giving me the opportunity to do this internship. Next I would like to thank the some people personally. First I want to thank my two supervisors at the VUmc: Rob Strack van Schijndel and Ronald Driessen. They gave me the freedom and assistance needed to do this research. I also want to thank Aad van der Vaart from the VU who supervised the internship, for his valuable guidance and comments, and I would like to thank René Bekker.

Furthermore, I would like to thank Mathijs Vogelzang, for his helpful responses to questions about the program GRIP, used for glucose management at the University Medical Center Groningen.

I hope the reader will enjoy this paper.

Amsterdam, June 2008

Jasper de Boer

## Executive Summary

Controlling the blood sugar level of intensive care patients is an interesting challenge. Every patient must be treated with the right amount of insulin and the insulin dose for a patient has to adjusted in the right way to let the blood sugar level stay in the target range. Several factors such as sudden changes in the illness of the patient or changes in the enteral and parenteral feeding can affect the blood sugar level. This research focuses on finding a good approach to prevent episodes of severe hypoglycemia and to keep the blood sugar level in a tight target range.

At the moment the VUmc is not using a protocol or formal guideline for the glucose management. Assessments are based on experience and intuition. With this approach the VUmc achieves a reasonable performance. Episodes of hypoglycemia occur in 0.19 % of all glucose measurements and in 3.0 % of all patients. The blood sugar level is in the target range (4-8 mmol/l) for 69.8 % of all measurements.

In the last couple of years a lot of research has been done in this area. With still some doubts about the benefits of tight glucose control a lot of studies are published about introducing a protocol for optimizing the glucose management. In the present study a lot of protocols are considered and the protocol used at the University Medical Center Groningen, the GRIP program, is found as the protocol with the best performance.

With GRIP, only 0.04 percent of the glucose measurements were beneath 2.2 mmol/l, which is approximately five times less frequent than the current performance at the VUmc. The blood sugar level of a patient is 67 percent of time in the target range (4-7.5 mmol/l), if the first 6 hours of stay are ignored this percentage is even 89 percent of time. This performance of GRIP is based on 2800 surgical ICU patients, at the VUmc the patient population consists of 6041 mixed ICU patients.

The significant lower incidence of episodes of severe hypoglycemia makes it attractive to introduce the GRIP program at the VUmc. When the advices of GRIP are compared with the insulin settings at the VUmc preceding a low blood sugar level, GRIP advises a lower insulin dose in 80 percent of the cases.

Introducing a protocol will make the performance of the glucose management more stable. The possibility of dangerous outliers will reduce and consulting a doctor is needed less often.

Therefore, the advice resulting of this study is to implement the algorithm behind the GRIP program at the VUmc. To ease the implementation of the rules of this algorithm, pseudocode is given in the appendix of this paper.

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# **1 Company**

## **1.1 VUmc**

The internship took place at the VU medisch centrum which is one of the eight university medical centers of the Netherlands. Because it is a university related medical centre, this hospital is especially developed to take care of medical research and offering education. [1]

The VU medisch centrum, also known as the VUmc, started officially in 2001 when the VUmc and the medical faculty of the Vrije Universiteit of Amsterdam started to work together. However, the VU hospital already opened its doors in 1966. Over the years the VU medical centre has developed towards the top 3 of the best Dutch science research centers.

## **1.2 Department ICV**

The department of the VUmc where the internship took place was the department ICV. At the department ICV (Intensive Care Volwassenen), the medical staff is concerned with the security and treatment of threatening vital functions, where the disfunctioning of the organ system can be recovered. Serious sick patients of age 18 and higher are treated using modern equipment and under continuous observation. On the ICV, a special trained team of nurses and doctors treats and observes the patients. Day and night, nurses and doctors are present in the room, making ICV more crowded than other departments.

Intensive care requires a high level of nursing handling. Both from the medical discipline and the nursing discipline there is research initiated, and both disciplines stimulate and help each other.

The Intensive Care Volwassenen is located at sections 6D, 7D. These locations have 14 and 12 beds operational, respectively. The department has a clear policy, based on protocols and guidelines. Continuum of care, optimal family company and a patient based admission- and dismissal policy are major goals of the department.

The admission- and dismissal policy is determined by the ICV. The ICV takes responsibility about qualitative and logistic aspects for periods before and after the admission at the intensive care.

## **2 Introduction**

### ***2.1 Introduction***

The human body breaks food down into organic compounds, one of which is glucose. The cells of the body use glucose as a source of energy for movement, growth, repair, and other functions. However, before the cells can use glucose, it must move from the bloodstream into the individual cells. This process requires insulin.

Insulin is produced by the beta cells in the islets of Langerhans in the pancreas. When glucose enters the bloodstream, the pancreas should automatically produce the right amount of insulin to move glucose into the cells. [2]

This right amount of insulin is not produced by patients with diabetes mellitus. Diabetes mellitus, often simply called diabetes, is a syndrome characterized by disordered metabolism and inappropriately high blood sugar (hyperglycemia) resulting from either low levels of the hormone insulin or from abnormal resistance to the effects of insulin coupled with inadequate levels of insulin secretion to compensate. [3] There are two types of diabetes mellitus. People with type 1 diabetes produce no insulin, while people with type 2 diabetes do not always produce enough insulin, due to insulin resistance or reduced insulin sensitivity, combined with reduced insulin secretion.

Patients with diabetes have high blood sugar levels and must be treated with insulin to keep the blood sugar level at a normal level. If hyperglycemia is not treated well, a condition called ketoacidosis (diabetic coma) could occur. Ketoacidosis develops when the body does not have enough insulin. Without insulin, the body cannot use glucose for fuel and the body has to break down fats to use for energy.

When the body breaks down fats, waste products called ketones are produced. The body cannot tolerate large amounts of ketones and will try to get rid of them through the urine.



Unfortunately, the body cannot release all the ketones, so that these build up in the blood. This can lead to ketoacidosis. Ketoacidosis is life-threatening and needs immediate treatment. [4]

Chronic elevation of blood glucose level leads to damage of blood vessels. This can cause many complications, such as retinopathy (eye), neuropathy (nerves) and nephropathy (kidney).

Also low blood sugar levels (hypoglycemia) can occur in people with diabetes who take insulin to keep their blood glucose levels in control. This may be caused by several factors, such as too much or incorrectly timed insulin, too much or incorrectly timed exercise (exercise decreases insulin requirements) or not enough food (specifically glucose-producing carbohydrates). [3]

Usually hypoglycemia is mild and can easily be treated by eating or drinking something with carbohydrate. But if hypoglycemia is left untreated, it can be damaging for the brain, which uses especially glucose as fuel. Consciousness can be altered or even lost in extreme cases, leading to coma, seizures, or even brain damage and death.

Patients with diabetes have to prevent hypoglycemia and eat enough carbohydrates to compensate the insulin dose. But they also must prevent hyperglycemia and take enough insulin. To find the right balance and keep the blood sugar level at a normal level, especially after big efforts such as sports, is sometimes difficult. Careful control and strict diets are needed to reduce the risk of long term complications.

In the intensive care unit (ICU) the glucose regulation is also an issue. Hyperglycemia and insulin resistance are common in critically ill patients, even if they previously did not have diabetes. Hyperglycemia in patients who did not have diabetes previously is often called stress hyperglycemia, because critical illness causes an increase of stress hormones (cortisol, glucagon, etc.) and cytokines. Another consequence of critical illness is a decrease of insulin secretion. Stress hyperglycemia is likely to be associated with at least

some of the same complications as hyperglycemia in true diabetes mellitus, such as poor wound healing and a higher infection rate. [5]

In the ICU patients are often fed with a stomach tube or intravenously (parenteral feeding). The carbohydrate intake over time is known and if it changes, the insulin dose can be adjusted in such a way that the glucose level will stay in the normal range. But it can occur that for some reason nutrition is stopped, and the nurses forget to adjust the insulin dose. This will cause hypoglycemia.

Insulin resistance and insulin sensitivity of a patient are changing during the time of stay at the ICU. The insulin dose has to be adjusted on time to keep a normal glucose content of the blood. There are also some drugs (corticosteroids, inotropes) which can affect the glucose level.

In conclusion, normoglycemia is not easy to obtain in the ICU setting and a lot of training and experience is needed. Normoglycemia is often defined as a glucose level between 4 and 8 mmol/l, but these boundaries are varying in the literature. A plasma glucose level beneath 4 mmol/l it is called hypoglycemia. A condition in which over 8 mmol/l of glucose circulates in the blood plasma is called hyperglycemia.

This paper is about the glucose management in the ICU. The goal is to avoid hyperglycemia and prevent episodes of severe hypoglycemia (< 2.2 mmol/l).

## **2.2 Literature**

There is an extensive literature about glucose management in the ICU . Traditionally, insulin was not administered until blood glucose exceeded 11 mmol/l, based on the rationale that such mild increases were not deleterious and tighter control might be complicated by life threatening hypoglycemia. Stress hyperglycemia was thought to be merely a marker of disease, rather than a risk-factor for complications or even mortality.

In a study by Van den Berghe and colleagues [6] it was shown that maintenance of normoglycemia with intensive insulin therapy largely prevented morbidity and reduced mortality of critically ill patients. These results were confirmed by an analysis performed by Krinsley, in which also a decrease in mortality was achieved with intensive insulin therapy [7].

As a result, professional organizations have recommended intensive insulin control in hospitalized patients and strict glycemia control is now routine practice during the postoperative period in intensive care patients. Especially for septic patients, guidelines now recommend using insulin to reduce high glucose levels [8].

Intensive insulin therapy is an aggressive treatment approach designed to keep the blood sugar levels close to a normal level, such as 4-8 mmol/l. Intensive insulin therapy requires close monitoring of blood sugar levels and frequent changes in dose of insulin to keep the blood sugar level at a normal level.

A disadvantage of lowering the glucose levels is the increasing risk of hypoglycemia, especially in sedated patients admitted to an intensive care unit. Intensive treatment of modest levels of hyperglycemia has resulted in hypoglycemia in various percentages of patients in the interventional studies. The rate of severe hypoglycemia increases from 0.8% (conventional treatment group) to 5.2% (intensive insulin treatment group) in the surgical Leuven study [6] and from 3.1% to 18.7% in the medical Leuven study [9]. In

both studies, hypoglycemia occurred more in patients who did not survive. Despite this risk, tight blood glucose control is nowadays advised for all patients with diabetes, as it is clear that glucose toxicity plays a major role in diabetic complications [10, 11].

However, as hypoglycemia was associated with mortality in both insulin therapy groups, it remained unclear whether this association was causal. More importantly, among hypoglycemic patients, mortality was lower in the intensive than in the conventional insulin therapy group. Fears of hypoglycemia and its imagined consequences, based on deeply rooted emotional belief rather than evidence, explain why hypoglycemia is often considered more dangerous than hyperglycemia in the critically ill [12].

Vriesendorp and colleagues [13] investigate the short-term consequences of hypoglycemia in the intensive care unit. This study was performed in a mixed medical/surgical intensive care unit. The aim was strict glycaemic control, with target glucose levels between 4.5-8 mmol/l. With this regime, 6.9 % of all patients experienced at least one episode of hypoglycemia. No association between incidental hypoglycemia and mortality was found. The authors acknowledge that the small sample size does not completely exclude the association of hypoglycemia with intensive care unit mortality. In three patients with possible hypoglycemia-associated coma or seizures, a causal role for hypoglycemia seemed likely, but could not fully be established.

The only adverse effect of intensive insulin therapy identified is hypoglycemia. Vriesendorp and colleagues [13] have indicated that incidental, brief episodes of hypoglycemia, when picked up rapidly and treated appropriately, are not likely to cause serious harm. However, hard evidence about the harm of episodes of hypoglycemia is still unclear.

Lately, Krinsley reached a different conclusion [14]. In the study it is demonstrated that even a single episode of severe hypoglycemia conferred an increased risk of mortality. The net benefit of intensive insulin therapy, however, far exceeded its deleterious effect. It can be interesting to determine the factors that predispose to severe hypoglycemia.

Vriesendorp and Krinsley both investigate these predisposing factors [14,15]. Some self-evident factors seemed to be associated with severe hypoglycemia, such as: prior diagnosis of diabetes mellitus, insulin treatment, discontinuation of nutrition without adjustment of insulin therapy and tight glucose control. However, also some more interesting factors are linked to hypoglycemia such as: sepsis, need for inotropic or vasopressor drugs, CVVH treatment with bicarbonate substitution fluid, renal insufficiency, mechanical ventilation and severity of illness.

Hypoglycemia has been the reason to stop a randomized multicenter trial on intensive insulin therapy in patients with severe sepsis or septic shock early, because of a potential for harm and lack of efficacy [16].

In the last years many studies are published about protocols for glucose control. After each glucose measurement, simple if-then rules or lookup tables yield an advice on how much insulin needs to be administered [6,7,17,18,19,20,21,22,23,24,25,26,27,28]. In section 5 these protocols are discussed.

There are different kinds of algorithms to manage the glucose levels with different levels of freedom for intuitive decisions. The highest level of freedom is a situation with only some guidelines for insulin doses and glucose infusions. A sliding scale protocol is a protocol with fixed insulin doses according to certain glucose ranges. In a dynamic scale protocol actions are based on some trend information. The decrease or increase of the glucose level is considered, and based on this change in combination with the current glucose level a new insulin dose is determined. These paper protocols are often implemented as an automated computer algorithm nowadays, but this reduces the insight of the rules and the impulse to ignore the protocol.

Studies using a dynamic scale protocol that combines a tight glucose target and the last two blood glucose values to determine the insulin infusion rate yielded the best results in terms of glycemic control, and reported low frequencies of hypoglycemic episodes [29].

Another overview of protocols is published in 2007 and showed the lack of consensus in the delivery of intravenous insulin infusions [30]. There was wide variability of practice in nearly every aspect of the management. It was concluded that the ideal insulin infusion protocol should achieve glycemic control in a reasonable timeframe, with minimal hypoglycemia, low operator error rate, and minimal nursing time required. Permission of “offprotocol” adjustments is also recommended.

The selection of a protocol requires careful investigation and must take the type of patient into account. One protocol may not suffice for all patients. However, it seems to be clear, that surgical ICU patients will benefit from the intensive insulin therapy. A big decrease in mortality is achieved for this group of patients. Patients undergoing cardiac surgery (especially diabetes) also benefit of normalizing glucose levels. Less wound infections are observed.

Another study [31] also mentioned the danger of “one protocol fits all”. Because of the differences of ICUs (patient groups, etc.), different institutions should carefully consider formal decision analysis of the possible benefits and risks of intensive insulin therapy in their patients before implementing a protocol.

Furthermore, most of the protocols do not incorporate relevant clinical data, such as changes of nutrition and systemic inflammatory status of the individual patient or administration of interacting medication, such as steroids. [32] Although a comparative study on outcome between continuous hydrocortisone and boluses of hydrocortisone does not exist, it seems prudent to administer hydrocortisone as a continuous infusion in septic shock patients in order to maintain normoglycemia in these patients as tight as possible. [33]

Following a protocol seems to have benefits, but there are some barriers to adopt the protocols in medical centers. [34] Significant barriers are the fear of hypoglycemia, the increase in nursing workload, the need to upgrade computer- based clinical information

systems to monitor and assess the safety and effectiveness of the glycemic control program, the lack of clinical and administrative resources, education and training for hospital staff, skepticism regarding the benefits of glycemic control, and a general resistance to change.

A large prospective, multicenter study is now well under way. The NICE-SUGAR study [35] is expected to randomize at least 6100 patients. The study is a cooperation of two studies, NICE and SUGAR. The Normoglycemia in Intensive Care Evaluation (NICE) study recruits patients in 20 ICUs in Australia and New Zealand. The study is joined by a group of Canadian investigators who will contribute data from an additional cohort of patients already committed to a study called Survival Using Glucose Algorithm Regulation (SUGAR). The NICE-SUGAR study will provide information on the effect of normoglycemia in a heterogeneous (medical and surgical) group of critically ill patients. Until the publication of NICE-SUGAR, sweeping recommendations for intensive insulin therapy to be applied to “all patients” seem premature and should be viewed with a healthy degree of scientific scepticism. [36]

In order to cut back the risk of hypoglycemia, glucose levels must be frequently measured. Each measurement calls for a decision on what action to take to keep glucose levels in the normal range. Intravenous insulin infusion with 1-4 hourly blood glucose measurements is recommended. With these sampling frequencies, implementation of tighter glucose control poses an important logistic challenge. [25]

To determine the interval between two glucose measurements, multiple factors have to be taken into account. [25] The interval is recommended to be small when blood sugar levels are unsatisfactory, and can be wider when the blood sugar levels are in the target range. Another factor is the amount of insulin. If the insulin dose is very high, frequent sampling is recommended. On the other hand, when a patient does not receive any insulin from pumps, glucose values can be measured less frequently. Frequent sampling is recommended when the admission of the patient is not long ago and when there are big changes of insulin dose.

Some other factors that affect the risk of hypoglycemia are the amount of administered glucose to the patient, whether steroids have recently been stopped, whether the patient had a hypoglycemic episode earlier and whether the glucose level fall back quickly. When the risk of an episode of hypoglycemia is high, frequent sampling is recommended.

The optimal situation is a situation where the glucose level is known every moment in time. With such continuous glucose monitoring, threatening episodes of hypoglycemia can be recognized and treated on time [38,39]. Such advances should offer the promise of more widespread and successful implementation of intensive insulin therapy. Hopefully, validated systems will become available soon and find their way to the ICU.



## ***2.3 Problem***

In the previous section the difficulties of glucose management in the ICU are considered. The ICU at the VUmc has its own approach to keep the glucose values in the target range.

In this paper we try to find a good approach to prevent episodes of severe hypoglycemia at the VUmc, which also avoids hyperglycemia. The right insulin dose for a patient has to be found and adjusted in the right way, when the blood sugar level is likely to leave the target range.

At the moment, the VUmc is not using a protocol or formal guideline for the glucose management. What is the best approach to keep the blood sugar level in the target range? Does the use of a protocol lead to better management and less episodes of hypoglycemia?

## ***2.4 Structure of the paper***

The paper is organized as follows: in section 3 the current situation at the VUmc about the glucose management and the data collection is described. In section 4 the data about the patients that experienced a 'hypo' are analyzed. A way to implement the results of the data analysis is the use of a protocol for glucose management. Different existing protocols are discussed in section 5 and the most promising protocol is compared with the current approach at the VUmc. Analyzing the results leads to conclusions about the problem. These conclusions are discussed in section 6. The paper ends with recommendations about the glucose management in section 7 and the references in section 8.

## **3 Framework**

In this section the current glucose management system at the VUmc is explained. First the data management is described and afterwards the current blood sugar policy at the VUmc is described briefly.

### ***3.1 Data collection ICV***

A lot of intensive care units use a Patient Data Management System (PDMS). A PDMS is designed to support intensive care units in the areas that are most sensitive to mistakes and errors: doctors' orders. A PDMS provides the registration of data for assessment of treatment outcome and production. It also supports easy access to the recorded data in its database.

The ICV section of the VUmc uses Metavision [40]. Metavision is a clinical information system, specially developed for critical care. Use of Metavision will result in a reduction of preventable medical mistakes and supports informed healthcare decisions, which assist in saving lives. Minute by minute data capture replaces illegible handwriting with printed information, offering a more complete data record.

Metavision automates labor-intensive tasks (such as score calculations), optimizes patient care and reduces the probability of errors. The system also has an event manager. The event manager enables users to pre-define multi-parametric conditions, which assist in the early detection of complex conditions. Metavision also has a form builder where flowcharts can be implemented with some programming to assist in the management of processes (e.g. the implementation of a flowchart assisting the glucose management).

A shortcoming of the current structure at the ICV department is the absence of direct coupling between the pumps running bedside of a patient and the PDMS. When a pump

is added or a pump rate is changed, this is not directly linked to the database. Nurses have to notify this in Metavision. Unfortunately, when a nurse is busy the registration is often delayed. Also the time of an event (change of pump rate for example) is not always registered exactly.

At the moment a lot of problems make direct coupling impossible. These problems are present both in technical and functional areas. There are very few medical centers in the world with a pump coupling that is completely correct.

There are different ways to measure the glucose values. Section 6D utilizes a blood gas analyzer. When blood gas is analyzed, the glucose value is also determined. The nurses register the resulting glucose values in Metavision by hand. The blood gas analyzer is mostly used to get results quickly to manage the mechanical ventilation in the right way. The reason why there is an analyzer at section 6D, but not at 7D is historical. Section 6D formerly was a surgical ICU with a lot of cardiosurgical patients, which require the most recent values for decision making, especially short after the operation.

On both sections there is another way to determine the blood sugar level: a glucose meter. A glucose meter is a medical device for determining the approximate concentration of glucose in the blood. A small drop of blood obtained by pricking the skin with a lancet is placed on a disposable test strip, which the meter reads and uses to calculate the blood glucose level. This way to analyze the glucose value is not often used.

All other measurements are done at the laboratory. The samples are sent to the laboratory with the pneumatic post. At the laboratory the blood sugar level is determined and registered in ZIS (the hospital information system). This system is linked to Metavision.

Glucose values are almost always determined together with other lab determinations. At an ICU blood is often sampled following a certain protocol (e.g. blood is sampled at fixed time intervals). The different ways of glucose sampling have comparable results.

### **3.2 Glucose management VUmc**

At the moment, there is no formal guideline for adjusting the pump rate of insulin at the ICU of the VUmc. The target range of the blood sugar levels is 4-8 mmol/l. In practice, the insulin pump rate is set to a higher rate when the blood sugar level rises above 8 mmol/l. This increase of insulin is often a slight change of 0.2-0.5 units per hour and sometimes a bolus of 2-4 units of insulin, given intravenously. The decision to change the insulin dose is commonly taken according to the actual blood sugar level in combination with the glucose measure before.

If the feeding is stopped or paused, the insulin dose will be halved or set to zero. This decision depends on the level of the insulin dose. There is no consistent regime for this, but the PDMS provides a warning when feeding is stopped and insulin dose is unchanged. When the given insulin dose over a day is higher than 1000 units, parenteral feeding is stopped if this was running, in order to achieve a decrease in insulin resistance.

A start of feeding or addition of a medication which increases the insulin resistance, is often anticipated. The pump rate of insulin is adjusted, or glucose values are sampled more frequently.

## 4 Data analysis

Since the start of the PDMS in May 2003, 6041 patients have been registered on the intensive care unit of the VUmc. From these patients, 183 patients experienced one or more episodes of severe hypoglycemia (3.0 %). There are 209,462 glucose measurements registered in the system, 248 of the registrations are beneath 2.2 mmol/l (0.19%).

From all glucose registrations, 69.8 % is in the target range of 4-8 mmol/l.

The performance measures are listed in table 1.

<b>Patients with hypoglycemia (&lt; 2.2 mmol/l)</b>	3.0 %
<b>Glucose values &lt; 2.2 mmol/l</b>	0.2 %
<b>Glucose values in target range (4-8 mmol/l)</b>	69.8 %
<b>Average number of glucose samples per patient per day</b>	6.2
<b>Mean value of all glucose measurements</b>	9.4
<b>Median value of all glucose measurements</b>	6.9

**Table 1. Performance measures of all registered patients at the VUmc**

### 4.1 Data 'hypo'-patients

There are 183 patients registered since the start of the PDMS with a glucose registration beneath 2.2 mmol/l. With a query on the database the patients are selected that experienced at least one episode of severe hypoglycemia and are treated with insulin as well. Patients with very strange glucose values, for example a blood sugar level of zero or a negative blood sugar level) are excluded, the same holds for patients with their only 'hypo' at admission. After this selection 143 patients are included in the study.

General information about the patients is shown in table 2. The hypo column describes the information about the study group: the 143 patients with a ‘hypo’. The ‘All’-column gives the information about all registered patients.

The APACHE II ("Acute Physiology and Chronic Health Evaluation II") score is a severity of disease classification system, one of several ICU scoring systems. After admission of a patient to an ICU, an integer score from 0 to 71 is computed based on several measurements; higher scores imply a more severe disease and a higher risk of death. [41]

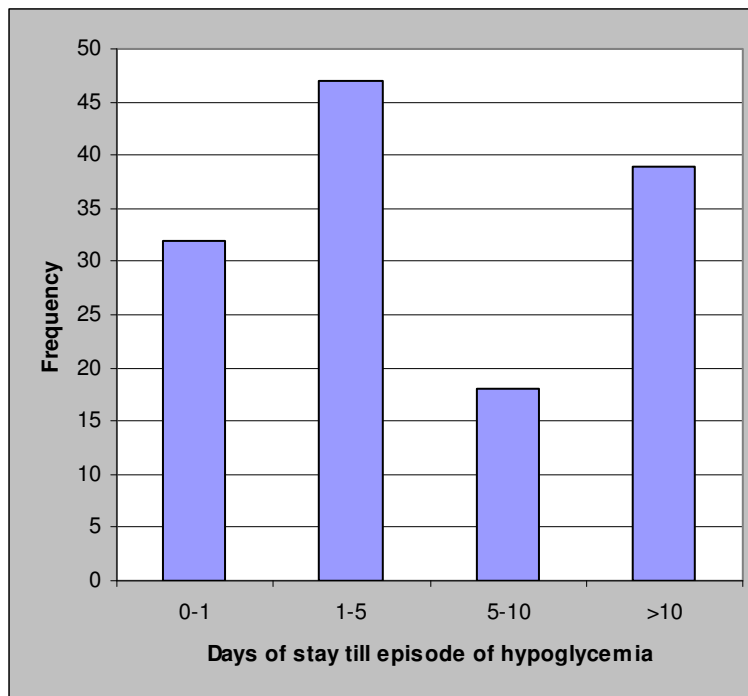
	<b>Hypo</b>	<b>All</b>
<b>Male (%)</b>	61.7 %	65.5 %
<b>Average age</b>	66.0	64.7
<b>Average APACHE II</b>	24.9	17.5
<b>Length of stay at time first hypo (days)</b>	Mean: 9.1 Median: 3.5	-
<b>Length of stay (days)</b>	Mean: 21.6 Median: 14.5	Mean: 5.58
<b>Mean glucose value at admission</b>	10.87	7.86
<b>Average number of glucose samples per patient per day</b>	7.3	6.2

**Table 2. General information about all hypo patients compared with the information of all patients**

At first sight, age and gender do not seem important risk factors for developing an episode of severe hypoglycemia. Patients that experienced a ‘hypo’ have on average a higher APACHE II score. It seems to be logical that patients that experienced a ‘hypo’ have a longer length of stay on average. When a patient stays longer, the blood sugar level of the patient is measured more often because of the longer stay.

The blood sugar level of patients with at least one 'hypo' is measured more often per day than other patients. When patients are at more risk for developing an episode of hypoglycemia, the blood sugar level is measured more frequent.

At admission, the glucose value is often high. The patient is set on an intensive insulin therapy immediately. It is difficult to find the right insulin dose in the beginning, because there is no history of insulin doses. To examine if there are more episodes of hypoglycemia at the first phase of stay, compared to the rest of the period of stay, a histogram (Figure 1) is made about the occurrence of hypoglycemia over time.



**Figure 1. Distribution of the episodes of hypoglycemia over time of stay**

The median length of stay of patients that experienced at least one episode of severe hypoglycemia is 14.5 days and the median length of stay at the moment of the first hypo was 3.5. After one day of stay, almost 25 % of all 'hypo'-patients already have had their first episode of hypoglycemia, after 5 days this percentage is almost 60 %.

The major part of the episodes of hypoglycemia is in the beginning of the stay, but there is also a significant part that occurs after a longer period of stay.

Most ICU patients are not able to take meals and are fed with a feeding pump. Some patients are able to feed themselves in the normal way, by oral intake. The registration of this oral intake is often not reliable, because patients can take half portions and not all intakes are registered.

In table 3 three groups of patients are distinguished. The eat group consists of patients that have some normal oral intake during the stay at some point of time, and experienced a ‘hypo’ after this point in time. The semi-eat group consists of patients that have some oral intake during the stay, but not before the episode of hypoglycemia. The last group (No eat) have not fed themselves in the normal way at all.

<b>Eat</b>	31 (21.8 %)
<b>Semi-eat</b>	47 (33.1 %)
<b>No eat</b>	64 (45.1 %)

**Table 3. Distribution whether patients are taking meals**

The 31 patients of the eat group are excluded from the study, because the registration of carbohydrates is not always reliable.

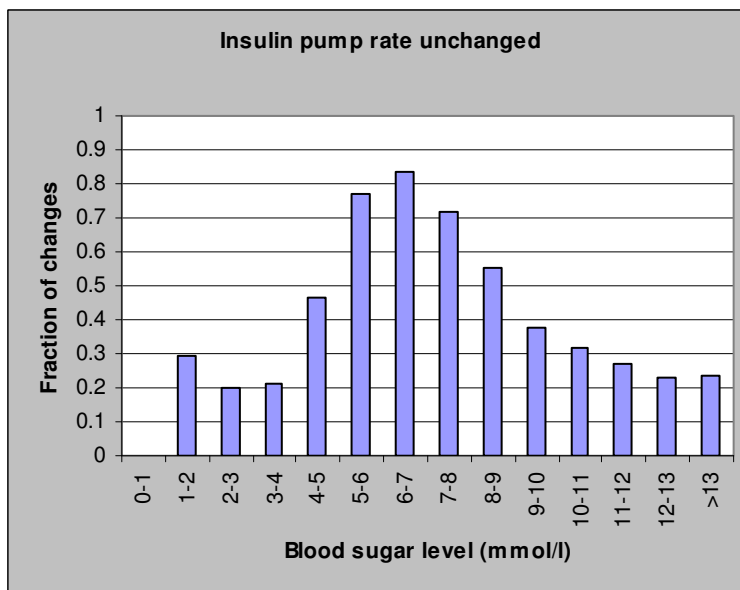
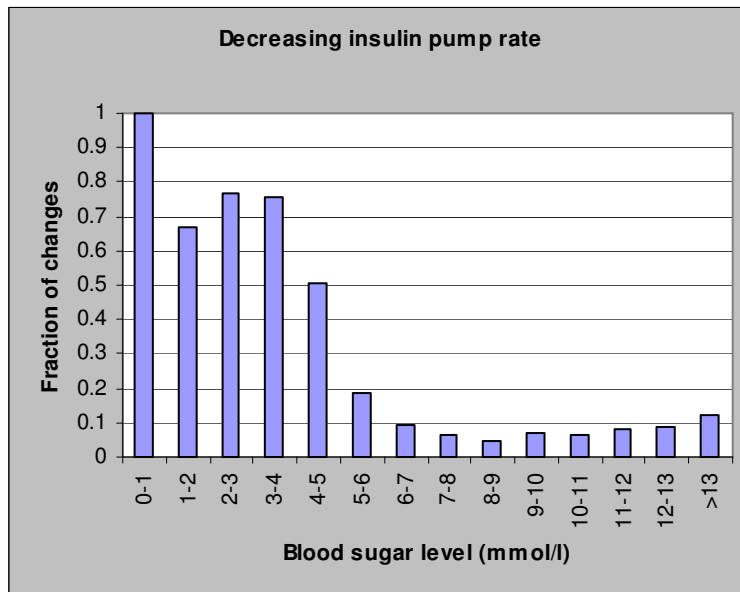
There are patients that have no insulin pump running around the period of the appearance of the episode of hypoglycemia. The hypoglycemia is caused by other factors than insulin treatment. Although all patients included in the study have an insulin pump running at some point in time, there are 17 patients in the study that have no insulin pump at the period preceding the ‘hypo’.

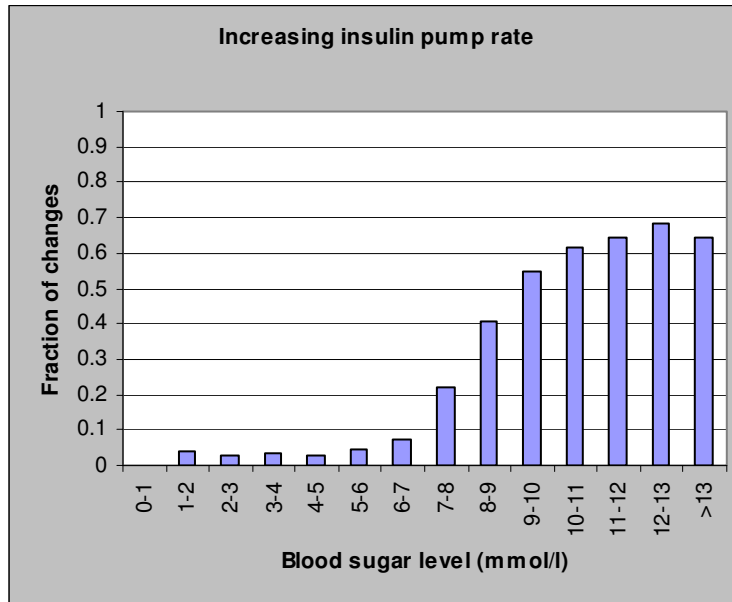
This study will focus on the patients that have an insulin pump running in the period preceding the episode of hypoglycemia.



## 4.2 Insulin analysis

To gain some insight in the current actions of the nurses in the area of setting insulin pumps, it was examined which action is taken at different blood sugar levels. Is the pump rate increased, unchanged or decreased at a certain glucose value? Figures 2a, 2b and 2c give the percentages of these three different actions at different glucose ranges.





**Figure 2a. Decreasing insulin pump rate**  
**Figure 2b. Insulin pump rate unchanged**  
**Figure 2c. Increasing insulin pump rate**

The figures give an impression about the glucose management, and especially about the actions around insulin adjustments. Figure 2a shows that the insulin pump rate is often decreased, when the blood sugar level falls under 5 mmol/l. This confirms the prediction, with a target range of 4-8 mmol/l. Between 5 mmol/l and 9 mmol/l, the pump rate is often unchanged. And Figure 2c shows that the pump rate is set to a higher rate when the blood sugar level exceeds 9 mmol/l in most cases.

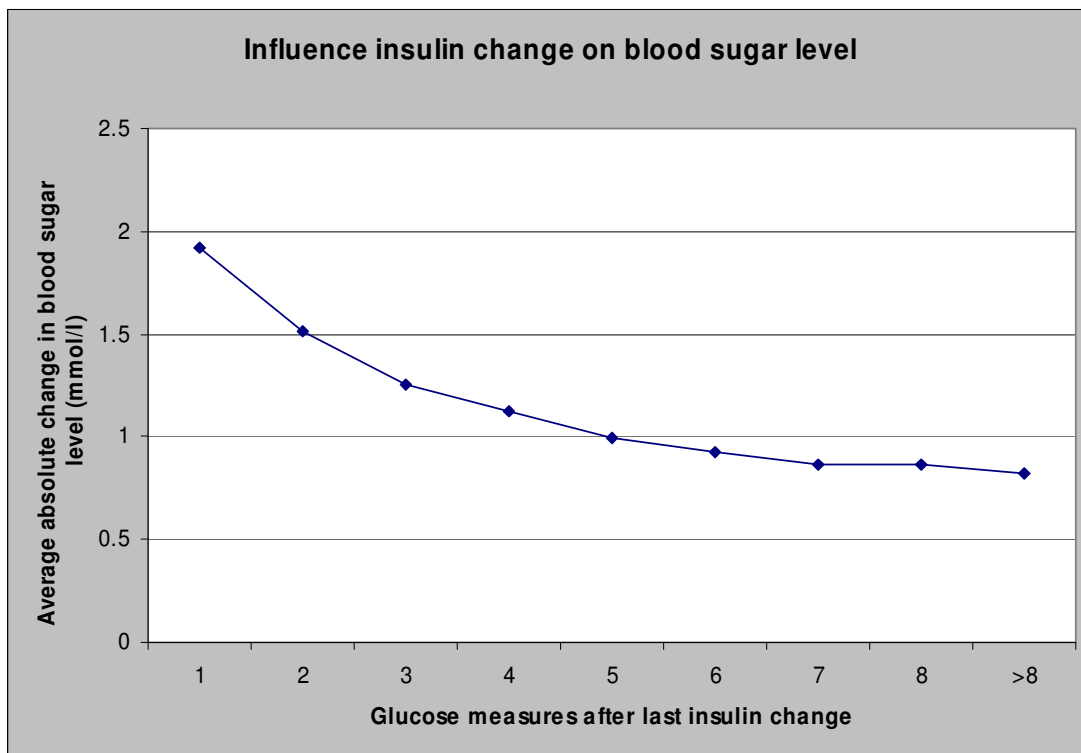
The results of the last bins are a bit misleading. When the blood sugar level is high sometimes a bolus of insulin is given. This flush of insulin causes a short elevate of the insulin dose. So after this elevation the insulin dose is decreasing, but the current blood sugar level is, although somewhat lower, still high in most cases. This will lead to a higher percentage of decreasing pump rates at high glucose values, but in reality the pump rate is not decreasing; only the insulin dose is decreasing.

The results of the first bins are also remarkable. In a few cases, the insulin dose is increased when the blood sugar level is under 3 mmol/l. In these cases, the insulin pump was not running, the pump has been stopped already, just before the point in time of the

glucose measurement. And after the ‘hypo’, the patient was treated with a glucose infusion and the insulin therapy was continued with a low dose of insulin.

It is clear that insulin has a negative influence on the blood sugar level. However, it is not clear what the scale of this influence is, and how long a change will influence the blood sugar level. How long a change will affect the blood sugar level can be investigated by comparing the change in blood sugar level after a change of insulin pump rate with the change in blood sugar level when the insulin pump rate is stable.

In Figure 3 the average absolute change in blood sugar level is displayed for different numbers of measurements after the last insulin change. The changes in blood sugar level are grouped by the number of glucose measurements since the change of the insulin pump rate. A value of one on the x-axis means that there is one glucose measurement after the last change of the insulin pump rate.

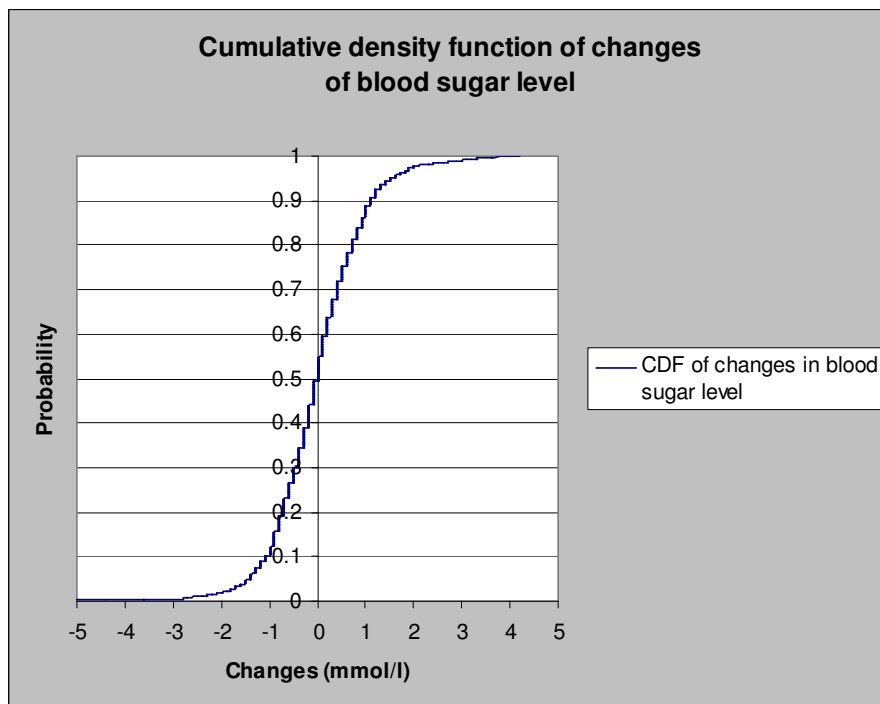


**Figure 3. Influence of a insulin change on blood sugar level**

The figure shows that the change of insulin affects the first glucose measurement the most. Every next measurement is less affected than its previous measurement. This means that when the blood sugar level is falling, because of a change in the insulin pump rate, the expectation will be that (with the same insulin dose) at the next measurement the blood sugar level is even lower. Although it is expected that every following measurement the decrease will be less, until the blood sugar level is stable again with some basal fluctuation.

The data are based on more than 10,000 glucose measures from the 'hypo'-patients. The line in the figure tends to go to a change of 0.8 mmol/l in a stable situation (over 8 measurements with a stable insulin pump rate).

Patients that are not on an insulin therapy (no insulin administered at all during the stay) should have an average change of blood sugar level that is similar to this stable condition. Twenty patients without insulin are considered. These patients had an average change of blood sugar level of 0.72 mmol/l between two measurements. The cumulative density function of all this changes is plotted in figure 4.



**Figure 4. Cumulative density function of changes of blood sugar level**

The figure is symmetric, negative changes occur with the same frequency as positive changes of the same absolute size. The blood sugar level of these patients that are not treated with insulin, changes less than 1 mmol/l per measurement in approximately 80 percent of the cases. But still in 20 percent of the cases the change is higher than 1 mmol/l per measurement, even without the influence of the change of an insulin pump rate. When a commonly used stringent target range of 4.4-6.1 mmol/l is used, this basal change is relatively high. Keeping the glucose value in the target range would be hard, when adjustments of the insulin pump rate influence the blood sugar level.

It is reasonable to assume that bigger changes of the insulin pump rate will lead to bigger changes in blood sugar level. This is first examined by determining the average absolute change in blood sugar level, when an insulin pump rate is adjusted. There are three categories of changes: small changes (changes between 0 and 0.5 insulin unit per hour), medium changes (changes over 0.5 insulin unit per hour toward 1 insulin unit per hour) and big changes (changes over 1 insulin unit per hour).

<b>Insulin pump change</b>	<b>Average absolute change in blood sugar level</b>
[0-0.5]	1.82
(0.5-1]	2.06
>1	2.29

**Table 4. Influence on blood sugar level of different scales of insulin changes**

Table 4 shows that a change has indeed more influence when the change in pump rate is higher. Only the first glucose measurement after a change is taken into account. This means that the average absolute change is measured as the absolute difference between the blood sugar level before the insulin change and after the insulin change.

The last analysis makes no difference between increasing and decreasing pump rates. To examine if there is a different impact on the blood sugar level in both cases, the actions are divided into two separate groups.

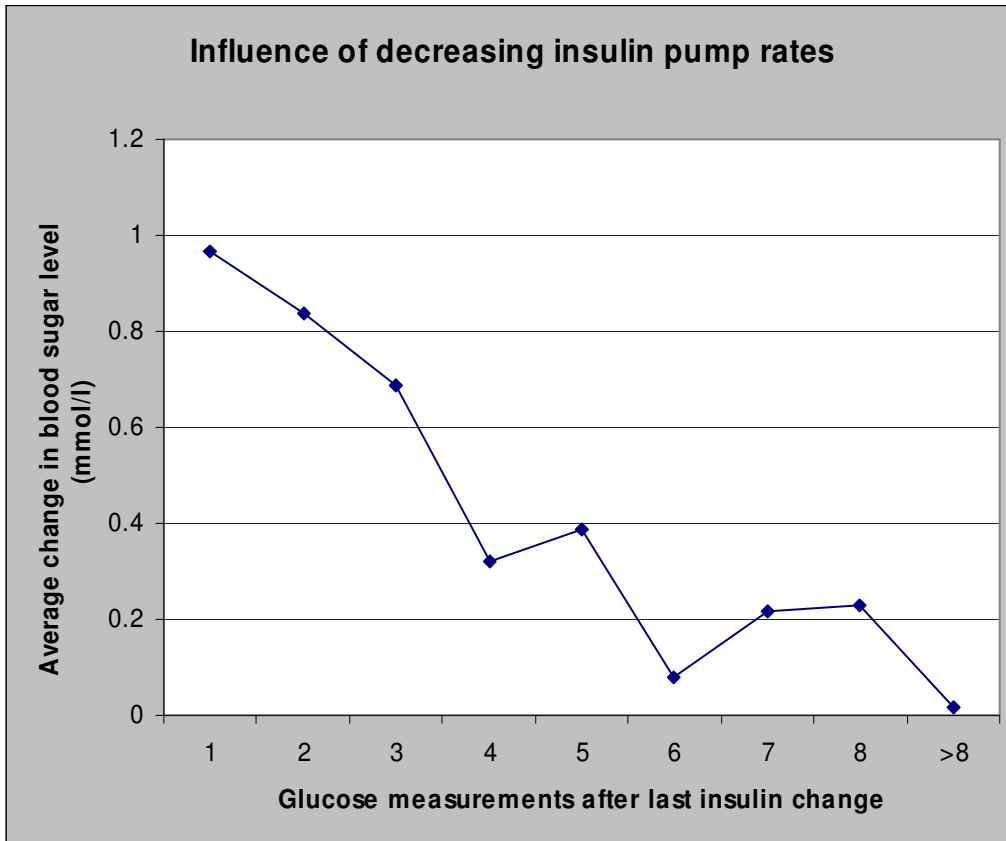
<b>Insulin pump change</b>	<b>Change of blood sugar level after lowering the insulin dose</b>	<b>Change of blood sugar level after elevating the insulin dose</b>
(0,0.5]	0.64	-0.49
(0.5,1]	1.23	-0.99
>1	1.56	-1.06

**Table 5. Comparison between the influence on blood sugar level of lowering and elevating the insulin dose**

The results in table 5 are surprising. In every of the three categories of changes, lowering the insulin dose has more impact on the blood sugar level than increasing the insulin pump rate. One of the reasons for this difference could be that stopping an insulin pump is sometimes coupled to adding a glucose infusion. This glucose infusion gives a boost to the increase of blood sugar level. But such a high dose of glucose is administered incidentally, so it is questionable if this can declare the difference.

To compare the effect of lowering the insulin pump rate and elevating the insulin pump rate in more detail, the average changes (real, not absolute) of both categories are displayed in two figures.

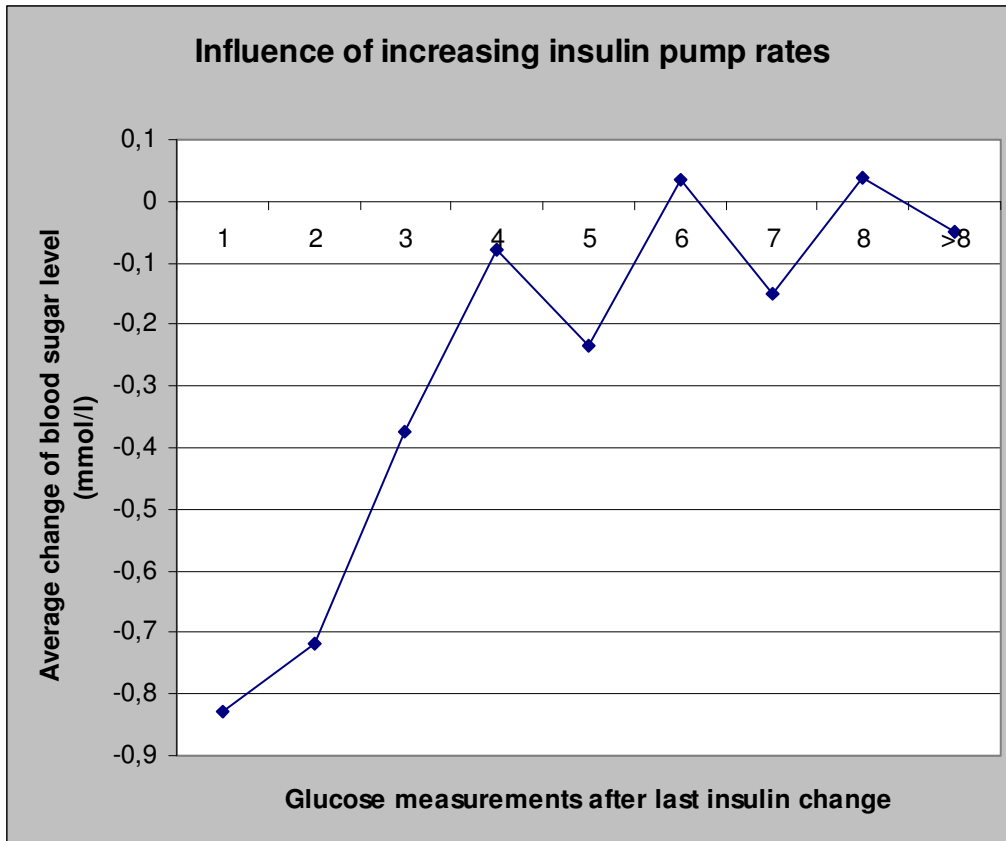
In Figure 5 the effect on the blood sugar level of lowering the insulin pump rate is shown.



**Figure 5. Influence on blood sugar level when insulin pump rate is lowered**

Roughly the same pattern as in figure 3 is seen. In figure 5 the averages are real and not absolute; consequently the line in the figure connects points with values that are somewhat lower than in figure 3. Negative values bring the average down. The line tends to go to zero, so the effect of the insulin change is eliminated after a long period of a stable insulin pump rate. The line is not as smooth as in figure 3. This is because of the fewer data available; there are fewer insulin pump decreases than there are insulin pump changes.

In figure 6 the influence on the blood sugar level when the insulin pump is set to a higher rate is displayed. The figure shows almost the same pattern as the previous figure, but because the pump rates are increased in this case, the average changes are negative instead of positive.



**Figure 6. Influence on blood sugar level when insulin pump rate is elevated**

An interesting note is that the average changes after a decrease of the insulin pump rate are always slightly higher than the changes after an increase of the insulin dose. This phenomenon was also present in table 5.

One explanation could be that the increases are on average on a somewhat different scale than the decreases. In table 6 the average change of the pump rates is given, the average is calculated over all changes.

	<b>Pump rate increase</b>	<b>Pump rate decrease</b>
<b>Average change</b>	1.05 IE/h	1.31 IE/h

**Table 6. Comparison of the average change of the insulin pump rate between lowering the insulin pump rate and elevating the insulin pump rate**



The table shows that the average decrease of the insulin pump rate is bigger than the elevation of the pump rate. A logical consequence is the bigger influence of a decrease of pump rate, noticed in the previous figures. The medical staff seems to be more cautious with an elevation of the insulin pump rate, because of the fear of hypoglycemia.

In the previous figures, a change of insulin seems to affect particularly the first three glucose measurements after the change. But the interval time between two measurements is always different. To get an idea about the interval times, the number of glucose measurements used in the last three figures is converted to average time intervals after the last insulin change. In table 7, the number of measurements after the last change ( $n$ ) with the corresponding average time in hours between the time of the last change and the current glucose measurement are displayed.

	$n = 1$	$n = 2$	$n = 3$	$n = 4$	$n = 5$	$n = 6$	$n = 7$	$n = 8$
<b>Average time after last change</b>	3.36 h	6.93 h	10.93 h	14.68 h	18.75 h	22.66 h	26.74 h	33.07 h

**Table 7. Average time after last change corresponding to measurement  $n$**

As noted before, especially the first three glucose samples after a change in insulin are affected by the change in insulin dose. According to table 7 this corresponds to approximately 11 hours on average. After the third glucose measurement the influence on the blood sugar level becomes negligible. A basal variability is left; according to figure 3 this basal absolute change of blood sugar level between two measurements is around 0.8 mmol/l.

The average sampling frequency at the VUmc is 6.2 times a day per patient. On average, approximately every 4 hours the blood sugar level is measured. Consequently, the basal absolute change of 0.8 mmol/l between two measurements is the basal absolute change of the blood sugar level in a 4 hour-interval, without the influence of insulin changes.

### 4.3 Cases

To give insight in the insulin settings around an episode of hypoglycemia, some of the patients that experienced an episode of severe hypoglycemia are observed in more detail. Insulin pump rates are plotted together with the glucose values and recent changes in feeding pumps or glucose infusions are discussed.

#### Case A: Repetition of high insulin pump rates

The patient of Case A is a 74 years old, female patient. In Figure 7 the glucose values and insulin pump rates of a fragment of four days for this patient are displayed. The patient has experienced an episode of hypoglycemia at March 14, 4:00. There were no recent changes in feeding pumps or glucose infusions.

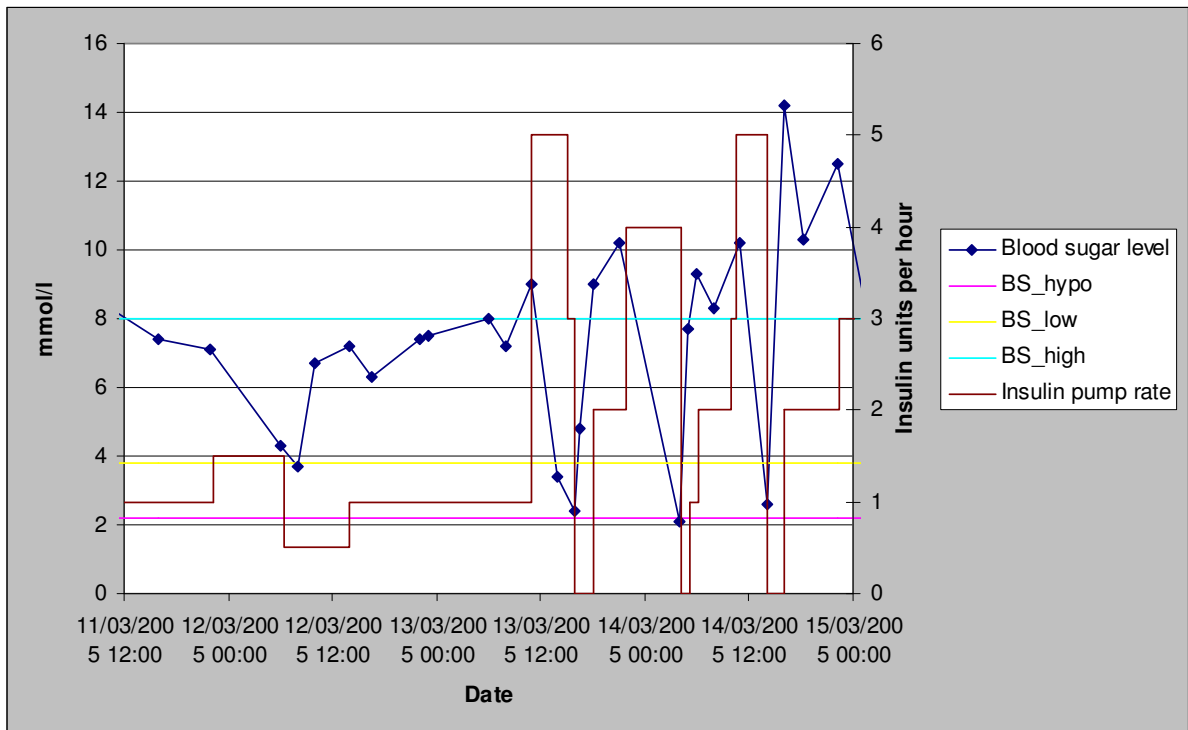


Figure 7. Blood sugar level pattern around a 'hypo' of the patient of case A

Three boundaries are plotted. BS\_hypo equals 2.2 mmol/l and represents the critical line of hypoglycemia. Beneath this line a patient experienced an episode of severe hypoglycemia. The BS\_low line equals 3.8 mmol/l, a common critical point that distinguishes normal glucose values from low glucose values. The BS\_high line equals 8 mmol/l and is the critical point that distinguishes high glucose values from normal glucose values.

The first days displayed in the figure, the patient is treated with an insulin dose around 1 unit per hour. At noon March 13, the blood sugar level exceeds the upper boundary of 8 mmol/l. The medical staff increases the pump rate enormously, from 1 unit per hour to 5 units per hour. The blood sugar level is falling steeply from 9 to 3.4 in 3 hours. The insulin pump rate is adjusted to 3 units per hour, but the blood sugar level is still decreasing. The medical team decides to stop the insulin pump to bring the blood sugar level in the target range again. After a few hours the blood sugar level is back to 9, which is too high. An insulin pump is started at a rate of 2 units per hour; the glucose level is still increasing so 3 hours later the insulin pump rate is set to 4 units per hour. Seven hours later, the patient experienced an episode of hypoglycemia and the running insulin pump is stopped and a dose of glucose 40 % infusion is administered.

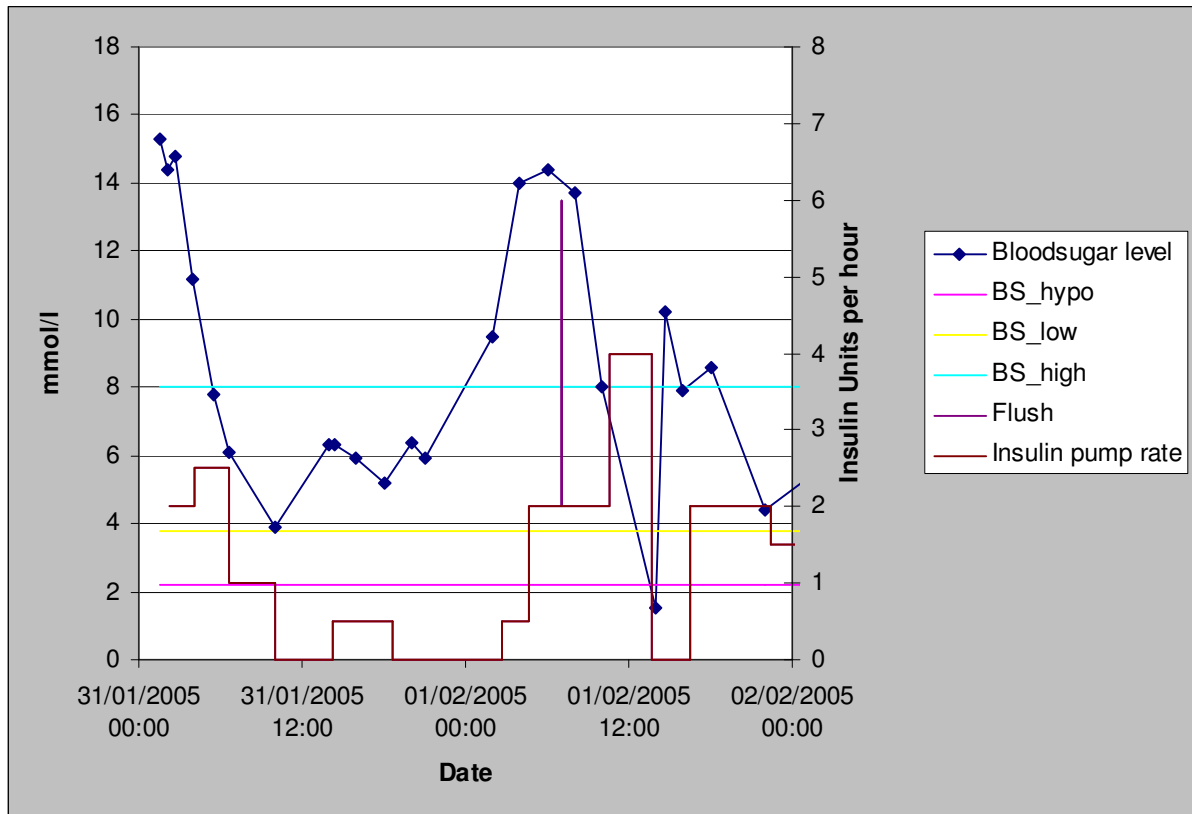
The period after the 'hypo' is interesting. The insulin pump is stopped and some glucose is administered. As a consequence the blood sugar level rises to 8. Insulin is started again and the right dose is searched. But again the high rate of 5 units per hour is found, which was harmful recently. Again the blood sugar level falls steeply, this time a value of 2.5 is reached and some glucose 40 % is needed to keep the patient on a normal blood sugar level.

A possibility to make the blood sugar pattern more clear is to support the medical staff with graphs about the glucose values and the insulin dose. The history of treatment can be detected easier, which can help in current decisions about the insulin pump rate.

## Case B: High Insulin

The patient of Case B is a male patient with the age of 78. In Figure 8 the glucose values and insulin pump rates of the first two days for this patient are displayed. The patient has experienced an episode of hypoglycemia at February 1, 14:00. There were no recent changes in feeding pumps or glucose infusions. The feeding pump started almost a day before the hypoglycemia.

The flush in the figure represents a bolus of 4 units of insulin; these 4 units are displayed above the current pump rate of 2 units per hour at that moment.



**Figure 8. Blood sugar level pattern around a 'hypo' of the patient of case B**

In this case the episode of hypoglycemia seems to be caused by an inappropriate elevation of the insulin pump rate. In the morning of February 1 2005, the blood sugar level falls steeply from around 14 mmol/l to 8 mmol/l. The blood sugar level is reaching

the target range; nevertheless the insulin pump rate is increased from 2 units per hour to 4 units per hour. The blood sugar level is still falling and this resulted in an episode of hypoglycemia.

Probably, the blood sugar level has not fall beneath the critical hypoglycemia boundary of 2.2 mmol/l if the insulin pump rate has not been increased. When the glucose value falls steeply it is recommended to measure the glucose values more frequent, especially when the insulin pump rate is even increased.

### Case C: Decreasing pattern

The patient of Case C is a 77 years old, male patient. The patient has experienced an episode of hypoglycemia at February 23, 6:00. There were no recent changes in feeding pumps or glucose infusions.

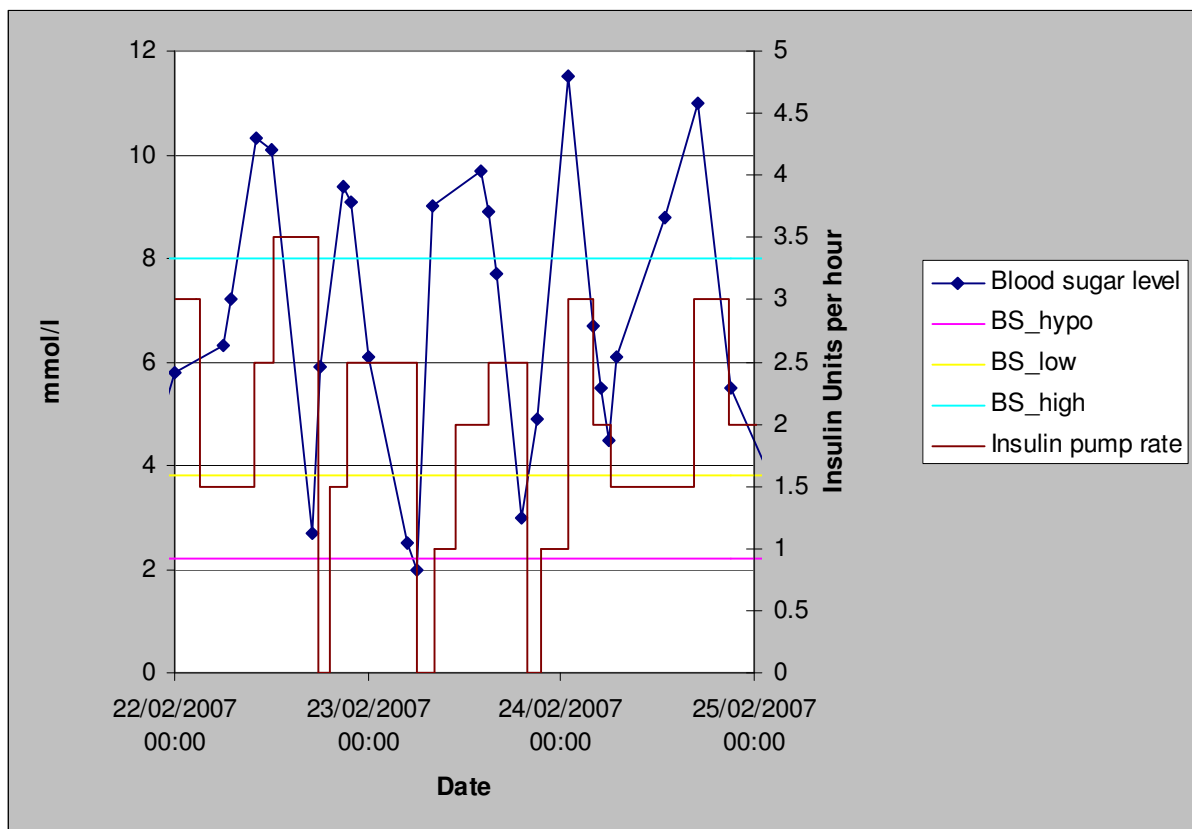


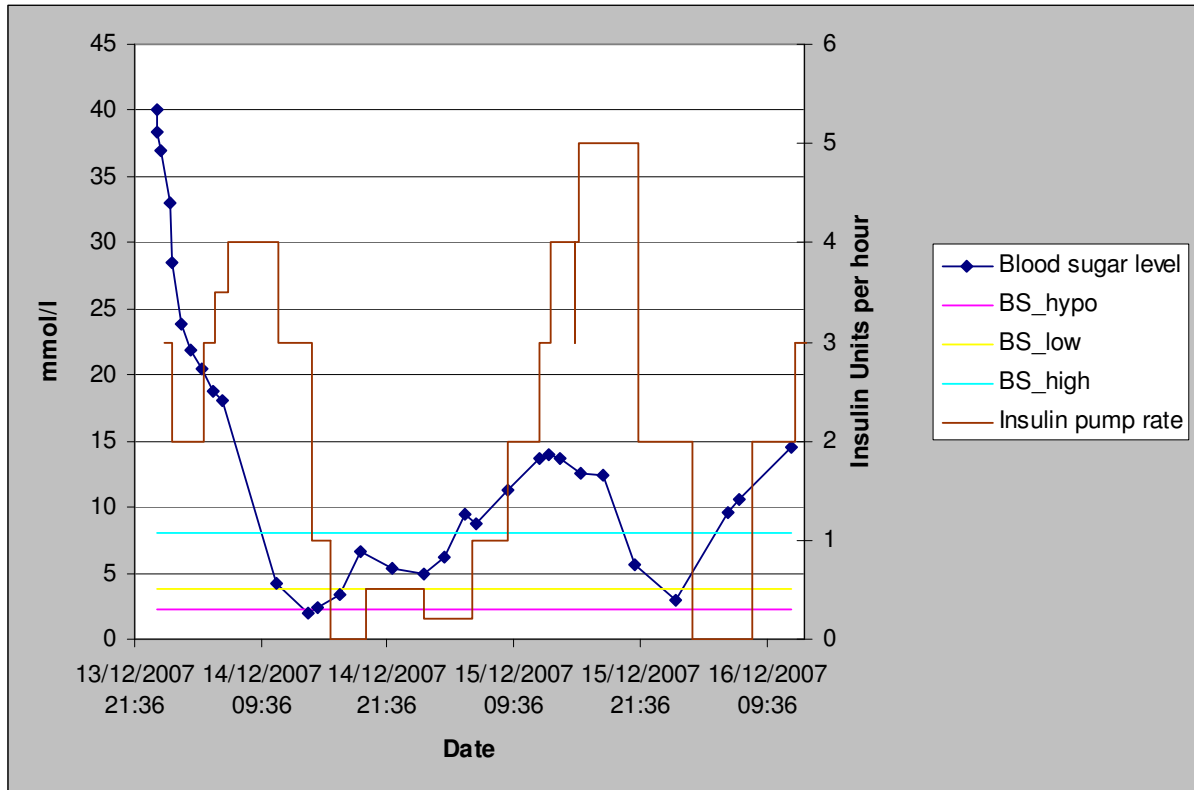
Figure 9. Blood sugar level pattern around a ‘hypo’ of the patient of case C

In Figure 9 the glucose values and insulin pump rates of a fragment of three days for this patient are displayed. In the evening of February 22, the blood sugar level rises from 2.7 to 9, because the insulin pump is stopped. An insulin pump is started again and when the rate is set to 2.5 units per hour, the blood sugar level is starting to fall. After two hours the blood sugar level is declining from 9 to 6.1, the pump rate is unchanged and 5 hours later the blood sugar level is 2.5. Although it is likely that the medical staff will stop the insulin pump at this moment, the insulin pump rate is unchanged and this leads to an episode of hypoglycemia one hour later.

In this case, a clear decreasing pattern is observed. An insulin pump rate of 2.5 units per hour first causes a decrease of 3 mmol/l within 2 hours. Although the current glucose value at that moment is 6.1, which is perfectly in the target range, it is reasonable that the blood sugar level will be firmly lower 5 hours later because of the decreasing pattern. And indeed it was firmly lower, but the glucose value of 2.5 does not worry the medical staff.

#### **Case D: Steep decrease in blood sugar level and slight change in insulin pump rate**

The patient of Case D is a male patient with the age of 58. In Figure 10 the glucose values and insulin pump rates of the whole period of stay for this patient are displayed. The patient has experienced an episode of hypoglycemia at December 14, 14:00. There were no glucose infusions running. The feeding pump started two hours before the hypoglycemia.



**Figure 10. Blood sugar level pattern around a ‘hypo’ of the patient of case D**

The blood sugar level of this patient is very high at admission. The right dose of insulin is trying to achieve in the first hours. In the morning of December 14, the glucose value decreases steeply from around 18 to 4.2 within 5 hours. The medical staff is scared about this steep fall in combination with a low glucose value and decreases the insulin pump rate from 4 units per hour to 3 units per hour. But the change was still not cautious enough and it leads to an episode of hypoglycemia 3 hours later.

Two hours before the ‘hypo’ a feeding pump was started. But this boost of carbohydrates could not prevent the episode of hypoglycemia.

## 4.4 Decreasing patterns

As shown in the cases of last section, there are different indicators for achieving an episode of hypoglycemia. Although it is hard or even impossible to prove what the exact reasons are for developing a ‘hypo’, there are three factors that can be a serious indicator. The first one is a clear decreasing pattern (case C and case D). The second one is an out of proportion high amount of insulin (case A and case B), often coupled with a sampling frequency that is too low. The last factor is a change or stop of nutrition, without adjusting the insulin dose (at the VUmc the PDMS gives a warning in the case nutrition is stopped). The indicators of episodes of hypoglycemia are listed in table 8.

Besides the three factors mentioned above, two other categories are present in the table. The ‘hypo’ of a patient gets into the category “No Insulin” when the patient has no insulin pump running during the development of an episode of hypoglycemia. The category “Unclear” stands for episodes of hypoglycemia that looks unexplainable or at least not explainable for the whole part.

<b>Decreasing pattern</b>	36 %
<b>High insulin</b>	7 %
<b>Stop/Pause Nutrition</b>	6 %
<b>No Insulin</b>	16 %
<b>Unclear</b>	35 %

**Table 8. Indicators of the episode of hypoglycemia**

Whether the ‘hypo’ is explainable or not, is very subjective. In a case with such a steep decrease as in case D, the episode of severe hypoglycemia looks explainable. But when the blood sugar level is falling from 7 mmol/l to 5.5 mmol/l within 4 hours for example and the insulin dose is continued to be stable, can it be expected that the glucose value 4 hours later is beneath 2.2 mmol/l? The percentages of table 8 therefore are questionable, but the exact percentages are not important for giving a first impression about the



possible reasons for developing a ‘hypo’. In section 5 the actions of the insulin adjustments are compared with protocols used in other medical centers, to get more information if a ‘hypo’ possibly was preventable.

Around half of the episodes of hypoglycemia seem to be explainable, with a clear decreasing pattern as the major factor. It can be interesting to examine the patterns preceding a ‘hypo’.

To investigate the pattern of glucose values in the phase preceding an episode of severe hypoglycemia, the last two glucose values before hypoglycemia are considered.  $G_0$  is defined as the blood sugar level at the point in time of the hypoglycemia.  $G_{-1}$  is the glucose value of the measurement before the hypoglycemia, and  $G_{-2}$  the glucose value of the measurement before  $G_{-1}$ . There are different scenarios conceivable.

**Scenario 1:** Increasing or stable:  $G_{-1} \geq G_{-2}$

**Scenario 2:** High decreasing:  $G_{-1} < G_{-2}$  and  $G_{-1}, G_{-2} \geq 7.5$

**Scenario 3:** High/Low decreasing:  $G_{-1} < G_{-2}$  and  $G_{-1} < 7.5$  and  $G_{-2} \geq 7.5$

**Scenario 4:** Low decreasing:  $G_{-1} < G_{-2}$  and  $G_{-1}, G_{-2} < 7.5$

**Scenario 5:** Unknown pattern:  $G_{-1}$  or  $G_{-2}$  unknown

In table 9 the occurrence of the different patterns is listed.

<b>Scenario 1:</b> Increasing or stable	25.7 %
<b>Scenario 2:</b> High decreasing	11.8 %
<b>Scenario 3:</b> High/Low decreasing	24.3 %
<b>Scenario 4:</b> Low decreasing	34.6 %
<b>Scenario 5:</b> Unknown pattern	3.7 %

**Table 9. Blood sugar level pattern before the episode of hypoglycemia**

When factors such as feeding pumps, glucose infusions, illness of the patient and drugs as steroids are ignored, it can not be expected that the patient experienced a 'hypo' in scenario 1 at  $G_0$  or the insulin pump rate must be set very high. But most cases of this category of 'hypo' seem to be unexplainable.

Scenario 2 is only alarming when there is a big decrease in blood sugar level. A decrease is desirable because the blood sugar level has to fall into the target range again, but when the blood sugar level is falling steeply one has to be cautious.

Scenario 3 and 4 are the interesting categories. These patterns cover almost 60 percent of the patterns leading to an episode of severe hypoglycemia. In scenario 3 the blood sugar level falls back into the target range as desired, but when the decrease of blood sugar level is significantly high, the insulin dose has to be adjusted. The mean decrease of blood sugar level in this scenario between  $G_{-1}$  and  $G_{-2}$  that leads to a 'hypo' was 4.6 mmol/l. When the insulin dose is unchanged with such a big decrease, there is a significant probability that the glucose value will reach the critical hypo level.

The same reasoning yields for scenario 4. In the case of this scenario the insulin dose has to be adjusted with even more concern. A short sampling interval is recommended, especially when the glucose value is fast decreasing.

In scenario 5, there is no history known about the blood sugar level pattern. The first insulin setting appears to be too high with a 'hypo' as a consequence.

It is important to recognize a clear decreasing pattern. In the current situation at the VUmc the medical staff is aware of this, but there is no assistance by the system in the shape of a warning when the blood sugar level is decreasing towards a 'hypo'.

To get a better insight in the pattern of the blood sugar level, it could be an option to add a graphical display to the system. The medical staff can watch over the pattern and intervenes when a clear decreasing pattern is on its way to the critical 'hypo' line.

## 5 Protocols

To detect decreasing patterns and assist in the glucose management a protocol could help the medical staff to determine the right insulin pump rate. An advantage of a protocol is the lower required know-how about the glucose management for the nurses; a good implemented protocol includes all the needed information and consulting doctors is needed less. When the protocol works properly, wrong assessments by doctors are replaced by right calculations of the protocol. On the other hand a protocol could handle wrongly when the patient is a very special case.

In this section several protocols are compared. The results at the VUmc are compared with the best protocol from the literature, to investigate if the use of a protocol can be recommended.

### ***5.1 Comparing the protocols***

Nowadays a lot of medical centers are using some kind of protocol (paper or computerized) to achieve a good glucose management. As referred in the literature section: “studies using a dynamic scale protocol combining a tight glucose target and the last two blood glucose values to determine the insulin infusion rate yielded the best results in terms of glycemic control and reported low frequencies of hypoglycemic episodes.” [29]

Almost all protocols that are currently used consider the last two blood glucose values to determine the next insulin pump rate. There are at least some rules that consider the glucose value before the last one, to recognize decreasing patterns or determine whether the blood glucose level is stable.

Since the Leuven studies [6,9] were published most medical centers are targeting for tight glucose control. The exact optimal target range is not known at the moment, a lot of research is running about this subject [35]. Some aim for tighter control (target 4.4–6.1 mmol/l) and others aim for less stringent control with a target range of 4-8 mmol/l or close to that range.

In table 10 the performance measures of the VUmc are listed.

	<b>Approach</b>	<b>Target</b>	<b>Hypo</b>	<b>Results</b>	<b>Patients</b>
<b>VUmc</b>	No Protocol	4-8 mmol/l	0.19 % BG < 2.2 3.0 % patients < 2.2	69.8 % in 4-8 Median 6.9	6041 ICU patients

**Table 10. Info and performance of the current glucose management at the VUmc**

The VUmc does not use a protocol for the glucose management and the target range is 4-8 mmol/l. With this approach only 0.19 % of all glucose measurements were under the critical point of 2.2 mmol/l. When this is seen in the view of number of patients, a percentage of 3.0 % of all patients experienced an episode of hypoglycemia. This data are based on 6041 ICU patients with an admission to the ICU in the period of May 2003-February 2008.

From all glucose measurements 69.8 % of the samples are within the target range. Measurements have a mean of 9.4 and a median of 6.9. The average sampling frequency is 6.2 per patient a day.

To compare this performance with other intensive cares, outcomes of studies from other medical centers implementing intensive insulin protocols are given in table 11, BG stands for blood glucose measurements and the glucose values given in the table are in mmol/l.

	<b>Year</b>	<b>Target</b>	<b>Hypo</b>	<b>Results</b>	<b>Patients</b>
<b>Yale</b> [17]	2004	5.5-7.7	0.3 % BG < 3.3	66 % in 4.4-7.7	52 Medical ICU patients
<b>Delft</b> [18]	2006	4.5-7.5	0.05 % BG < 2.2	53.1% in 4.5-7.5	179 Mixed ICU patients
<b>Mayo</b> [7]	2004	< 7.7	0.34 % BG < 2.2	70 % BG < 7.7 Mean BG: 7.2	800 Mixed ICU patients
<b>Bath</b> [26]	2005	5.1-7.2	3 BG < 2.2	Median 6.2	27 ICU patients
<b>SPRINT</b> [20]	2006	4.2-6.1	0.5 % BG < 3.3	61.7 % in 4.2-6.1	19 ICU patients
<b>Spain</b> [21]	2007	5.6-7.8	2 BG < 2.2	55.5 % in 5.6-7.8	50 ICU patients
<b>Australia</b> [22]	2006	4.4-6.1	14.3 % of patients < 2.2	48.5 % in 4.4-6.1	70 Mixed ICU patients
<b>Zimmerman</b> [23]	2004	4.4-8.3	7.1 % of patients < 2.2	61 % in 4.4 – 8.3	168 Cardiothoracic ICU patients
<b>GlucoStabilizer</b> [24]	2007	4.4-6.1	0.4 % BG < 2.7	61 % in 4.4-6.1 Mean BG: 5.9	2398 ICU patients
<b>Groningen</b> [25]	2005	4-7.5	0.05 % BG < 2.2	78 % of time in 4-7.5	179 surgical ICU patients
<b>Leuven</b> [6]	2001	4.4-6.1	5.2 % BG < 2.2	Mean morning BG 5.7 ± 1.1	765 Thoracosurgical ICU patients
<b>Brunkhorst</b> [16]	2005	4.4-6.1	12.1 % of patients < 2.2	Mean morning BG 6.2	247 patients with sepsis
<b>Kanji</b> [27]	2004	4.5-6	4 % of patients < 2.2	11.5 ± 3.7 h/day in 4.5-6	50 ICU patients requiring insulin
<b>OLVG</b> [28]	2005	4-7	0.1 % of time < 2.5	54.2 % of time in 4-7	484 ICU patients

**Table 11. Info and performance of different published studies about improving glucose management**

The protocols used in Groningen [25] and Delft [18] had very few episodes of hypoglycemia. In these studies only 0.05 % of all glucose samples are under the critical point of 2.2 mmol/l. According to the results of the glucose management, besides again the protocol used in Groningen, the SPRINT protocol [21], the GlucoStabilizer study [24] and the Yale protocol [17] are promising.

The SPRINT study has some limitations. Only 19 patients were involved in the study and a very high sampling frequency was used. Every two hours the glucose value is measured, with even an increasing frequency when the glucose value is not in the normal range the last three measurements.

The GlucoStabilizer study also has a high sampling frequency. An initial interval of one hour is determined, which is expanded when the glucose values are stable in the target range. Such sampling frequencies are significantly higher than the frequency of glucose measurements at the ICU of the VUmc. From most studies the exact average sampling frequency is not known, but in table 12 a few frequencies are listed.

	<b>Glucose samples per patient per day</b>
<b>VUmc</b>	6.2
<b>Groningen [25]</b>	4.9
<b>Delft [18]</b>	3.4
<b>Kanji [27]</b>	11.3
<b>Leuven [6]</b>	> 6
<b>SPRINT [21]</b>	> 12

**Table 12. Sample frequencies of different studies**

The computerized protocol used in Groningen, the GRIP algorithm, seems to have very strong performance: a low incidence of severe hypoglycemia (0.05 %), a high percentage of glucose values within the target range (78 % of time in 4-7.5) and a relatively low sampling frequency (4.9). The patients involved in the study were surgical ICU patients.

At the VUmc the percentage in the target range is 69.8 % of all glucose measurements with even a wider target (4-8 mmol/l). A ‘hypo’ occurs four times more often at the VUmc. In the study at Groningen only 179 patients were involved, the reliability of the results could be less than the results at the VUmc.

Another protocol with good performance is the protocol used in the study in Delft [18]. This protocol also has very few episodes of hypoglycemia; the occurrence of a ‘hypo’ is four times lower than at the VUmc, with a low sampling frequency. The performance (53.1 % of measurements in the target range) looks worse than the performance with GRIP and at the VUmc, but the target range is smaller (4.5-7.5 mmol/l). The protocol is based on simple if-then rules and is easy to implement. But this study is based on only 179 patients and the performance looks inferior to GRIP.

Recently, a study [42] is published about GRIP with a larger patient population. The patients in the study are specified in three categories: surgical, thoracic and neurosurgical ICU patients. Table 13 shows the performance outcomes for this larger study.

<b>Groningen [42]</b>	2008	4-7.5	0.04 % BG < 2.2 0.86 % of patients < 2.2	67 % of time in 4-7.5	2800 mixed surgical ICU patients
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**Table 13. Info and performance of the glucose management with GRIP**

In comparison with the small research study of GRIP, the percentage of time that the glucose values are in the target range is somewhat lower. In the larger study the blood sugar level of the patients is in the target range only 67 percent of the time. This performance is comparable with the performance at the VUmc, although the target range at the VUmc is somewhat wider.

The performance measure of 67 percent of time is an average over all patients, where every patient has the same weight factor. For every patient this performance is determined and the average is taken over the whole bunch. A patient who stays only a few hours and a patient who stays 30 days are equally weighted. At the VUmc the

percentage is based on all glucose measurements, every measurement is equally weighted and the length of stay of a patient has no influence.

High blood sugar levels are mostly observed in the beginning of the stay; these high blood sugar levels have more impact with the determination of performance at the study about GRIP. When the first six hours of stay are ignored, the average percentage of time in the target range with GRIP was 89 percent, a very high percentage.

The occurrence of severe hypoglycemia is almost the same as in the smaller study; the incidence of a 'hypo' is even a little less frequent. At the ICU of the VUmc, the incidence of episodes of severe hypoglycemia is five times higher than at this larger study with GRIP.

The sampling frequency in this larger study is significantly higher than the smaller research study. On average, the blood sugar level was measured 5.9 times a day per patient, one measurement per day more than in the small study. This sampling frequency is still low, according to other published protocols and similar to the frequency at the VUmc.

The average APACHE II score of the patients that are involved in the larger GRIP study is 14. This is not very different from the average APACHE II score of 17.5 from the population at the VUmc.

In the larger study is proven that GRIP provides safe and efficient glucose regulation in routine intensive care practice.



## 5.2 GRIP

In this section a short description of the algorithm for adjusting the insulin pump rates in the study by Vogelzang et al. [25] is described. The source code of the whole program has free access at: <http://grip-glucose.sf.net>. The algorithm is based on the following formula:

$$\Delta I = (1 + 0.25I_{-4h}) \cdot (0.2 \cdot (G_0 - G_{target}) + 0.3 \cdot \Delta G_{-4h})$$

### **Formula 1. Base formula for calculating the recommended insulin adjustment**

In this formula,  $\Delta I$  is the recommended change of the insulin pump rate.  $I_{-4h}$  stands for the average insulin pump rate over the 4 hours preceding the last glucose measurement  $G_0$ . The parameter  $G_{target}$  is the target glucose value, in the study this value is set to 6.5 mmol/l. The last variable,  $\Delta G_{-4h}$ , is the glucose value between the last glucose measurement and the glucose value 4 hours before  $G_0$  (linearly interpolated when the blood sugar level is not measured 4 hours ago).

The first term of the formula ensures that when a patient receives a high dose of insulin, the suggested changes for the insulin pump rate are larger than when the current insulin dose is low.

The formula only considers data about the last 4 hours. Interesting information before is ignored and also the fluctuations within the last 4 hours are not taken into account. It was decided to use this interval, because of its robustness to sudden changes. In case of a sudden increase or decrease in insulin sensitivity due to some clinical event unknown to GRIP, the preceding glucose and insulin values become less relevant, or in the worst case even misleading to the recommendation algorithm. When the blood sugar level is

sampled sufficiently often the short lookback time makes quick adaption to new situations possible.

If a feeding pump is changed significantly, the advised pump rate will be increased or reduced proportionally. To improve user acceptance, recommendations lower than 0.3 units of insulin per hour are converted to no insulin. Some other major restrictions are a maximum increase of insulin per hour and a maximum pump rate of 10 units per hour due to the saturation of the effect of insulin.

When the blood sugar level is under 3 mmol/l, the 'hypoglycemia advice' is given, which consists of an intravenous glucose dose, an insulin pump rate of zero, and prompt notification of the attending physician. The attending physician is also consulted when the glucose values are very high ( $> 15$  mmol/l) or quite low ( $< 4$  mmol/l).

The algorithm is based on the use of continuous insulin infusion and does not recommend boluses of insulin. This decision is also made because of the saturation effect. Reference is made to a study which concluded that continuously infused insulin is more effective than boluses of insulin [43].

The GRIP program also gives advice about the time of the next glucose measurement.

This algorithm is considerably more complex. To describe the algorithm that calculates the desired time of the next glucose measurement we consider 4 factors: the risk of hypoglycemia, the blood sugar levels, the amount of insulin and some final checks.

When the risk of hypoglycemia is high, a short interval is recommended. Some factors that increase the risk of hypoglycemia:

- decreasing feeding pump
- the amount of administered glucose to a patient
- stopping of steroids
- recent history of episode(s) of hypoglycemia

Some factors about the glucose values that influence the interval of measurements:

- high and low glucose values will cause a short interval advice
- when glucose values are in the target range, a longer interval will be advised
- when changes of blood sugar levels make it likely that the future glucose value will be out of the target range, the interval between measurements is advised to be short.

Also the amount of insulin has its influence on the advice of the interval between two glucose measurements. When a patient is treated with a high dose of insulin, a shorter time interval till the next measurement will be recommended than when the patient is treated with a low dose of insulin.

There are also some final checks to get some extra safety in the blood glucose management:

- if a patient was admitted less than 12 hours ago, the maximum interval is set to 4 hours
- if insulin changed by more than 3 units per hour, the maximum interval is set to 1.5 hours
- if insulin changed by more than 1.5 units per hour, the maximum interval depends on whether insulin was under 5 units per hour, etc.
- the maximum advised glucose sampling interval is 12 hours
- the minimum advised interval is 30 minutes

This complex algorithm is described in detail in Appendix I. These rules do not bring the sampling frequency to an inappropriate high level. The average sampling frequency of 5.9 is satisfactory. The average number of measurements per patient per day is similar to the current average at the VUmc.

Acceptance by nurses was excellent at the University Medical Center Groningen, with minimal training needed. The orders of GRIP could be overruled at the discretion of the physician at any time, or a patient could be taken out of GRIP altogether. This happened structurally with patients who had recovered enough to be taking meals. The compliance of the medical staff in relation to recommended insulin pump rates and glucose measurement frequency is very high. Patients were on GRIP-ordered pump rates 97 percent of time.

### **5.3 Cases**

Although the study with the computerized protocol in Groningen included only surgical ICU patients, it is not unlikely that the protocol will have a reasonable performance in the ICU of the VUmc.

To give a first impression of using such a protocol, historical actions of the medical staff at the VUmc are compared with advice from the computerized protocol used in Groningen (GRIP). The advices from this section are not the real advices from GRIP, formula 1 is implemented, with  $G_{target} = 6.5$  mmol/l, but some side restrictions, such as changes in glucose intake and the special calculation for the initial advice for the first four hours after admission are not taken into account. The same cases as in section 4.3 are considered.

#### **Case A: Repetition of high insulin pump rates**

In table 14 information about the period around the episode of hypoglycemia of the patient is displayed. The change of insulin rate based on the glucose values and insulin rate of the medical staff from the VUmc are given and also the advice resulting from the calculations of the GRIP algorithm is listed.

The main differences between the actions of the VUmc and the advice of the GRIP program are the large increases of pump rate at the VUmc and the somewhat slighter

increases of the GRIP program because of the limited increase of units insulin per hour per change. Another difference is the more decisive action in GRIP when the blood sugar level is decreasing very fast. The decrease in the afternoon of March 13 is advised to be treated with an insulin stop, at the VUmc the pump rate is decreased by ‘only’ 2 units per hour.

<b>Date</b>	<b>Glucose Value</b>	<b>Current Insulin</b>	<b>Action VUmc</b>	<b>Advice GRIP</b>
13/03/2005 11:00	9	1	+ 4	+ 1.2
13/03/2005 14:00	3.4	5	- 2	- 5.0*
13/03/2005 16:00	2.4	3	- 3	- 3.0*
13/03/2005 16:30	4.8	0	+ 0	+ 0.0
13/03/2005 18:00	9	0	+ 2	+ 1.4
13/03/2005 21:00	10.2	2	+ 2	+ 1.5
14/03/2005 04:00	2.1	4	- 4	- 4.0*
14/03/2005 05:00	7.7	0	+ 1	+ 1.0
14/03/2005 06:00	9.3	1	+ 1	+ 1.5
14/03/2005 08:00	8.3	2	+ 0	+ 1.5
14/03/2005 10:00		2	+ 1	
14/03/2005 10:34		3	+ 2	
14/03/2005 11:00	10.2	5	+ 0	- 1.0
14/03/2005 14:00	2.6	5	- 5	- 5.0*

**Table 14. Case A: comparison of the historical insulin setting at the VUmc and the proposed insulin setting with GRIP around the ‘hypo’**

**\* A physician is consulted**

However, the episode of hypoglycemia in the early morning of March 14 is not mainly caused by the high amount of insulin, but the main reason seems to be that there is no glucose measurement for seven hours. This interval between measurements is very large considering the change of insulin of 4 units per hour over the last 4 hours. It is

recommended to have a high sampling frequency after such big changes in the insulin dose.

The actions taken in the morning of March 14 look also incomprehensible. The insulin pump rate is elevated twice without a registered glucose value just before the change. The pump rate is set to 5 units per hour, an even higher dose than the dose that caused a 'hypo' a few hours before.

### Case B: High Insulin

In table 15 the same sort of table as the previous one is given. The data are from the period preceding the episode of hypoglycemia.

Date	Glucose Value	Current Insulin	Action VUmc	Advice GRIP
31/01/2005 20:00	6.4	0	+ 0	+ 0.3
31/01/2005 21:03	5.9	0	+ 0	+ 0
01/02/2005 02:00	9.5	0	+ 0.5	+ 1.5
01/02/2005 04:00	14	0.5	+ 1.5	+ 1.5
01/02/2005 06:00	14.4	2	+ 1	+ 1.5
01/02/2005 07:00		3	Bolus of 2 units	
01/02/2005 08:00	13.7	3	+ 0	+ 1.5
01/02/2005 10:00	8	3	+ 1	- 3.0
01/02/2005 14:00	1.5	4	- 4	- 4.0*

**Table 15. Case B: comparison of the historical insulin setting at the VUmc and the proposed insulin setting with GRIP around the 'hypo'**

**\* A physician is consulted**

Most interesting of this table is the difference in action of the medical staff of the VUmc and the advice of GRIP at the glucose measurement before the episode of hypoglycemia. At the VUmc the insulin pump rate is increased, probably because of the somewhat high

glucose value of 8 mmol/l. But because of the big decrease of blood sugar level, GRIP advised a decrease of insulin pump rate of 3 units per hour which implies stopping of the insulin infusion. This action seems to be rigorous considering the current glucose value of 8 mmol/l. Nevertheless the advice of GRIP looks safer than the increase of the insulin pump rate at the VUmc.

**Case C: Decreasing pattern**

Table 16 represents the data from the period preceding the episode of hypoglycemia of the patient of case C.

<b>Date</b>	<b>Glucose Value</b>	<b>Current Insulin</b>	<b>Action VUmc</b>	<b>Advice GRIP</b>
22/02/2007 17:00	2.7	3.5	- 3.5	- 3.5*
22/02/2007 18:00	5.9	0	+ 1.5	+ 1.0
22/02/2007 21:00	9.4	1.5	+ 1	+ 0.6
22/02/2007 22:00	9.1	2.5	+ 0	+ 1.0
22/02/2007 00:00	6.1	2.5	+ 0	- 1.3
22/02/2007 05:00	2.5	2.5	+ 0	- 2.5*
22/02/2007 06:00	2	2.5	- 2.5	- 2.5*

**Table 16. Case C: comparison of the historical insulin setting at the VUmc and the proposed insulin setting with GRIP around the ‘hypo’**

**\* A physician is consulted**

This table shows that GRIP can recognize a decreasing pattern. When the blood sugar level falls down to 6.1 mmol/l the advice of GRIP is a decrease of 1.3 units per hour of insulin. At the VUmc the insulin pump rate is unchanged and even when the blood sugar level become 2.5 mmol/l the pump is unchanged. At that moment, GRIP recommends a stop of the insulin pump which seems to be a logical action with such a low glucose value.

### Case D: Steep decrease in blood sugar level and slight change in insulin pump rate

The following table (table 17) consists of the data from the first hours of stay of the patient of case D.

Date	Glucose Value	Current Insulin	Action VUmc	Advice GRIP
13/12/2007 23:45	40	0	+ 0	No advice
14/12/2007 00:00	37	0	+ 3	No advice
14/12/2007 01:05	28.5	3	- 1	No advice
14/12/2007 02:00	23.8	2	+ 0	- 2.0*
14/12/2007 03:00	21.9	2	+ 0	- 2.0 *
14/12/2007 04:00	20.5	2	+ 1	- 2.0*
14/12/2007 05:00	18.7	3	+ 0.5	- 2.0*
14/12/2007 06:00	18.1	3.5	+ 0.5	+ 0.6*
14/12/2007 11:00	4.2	4	- 1	- 4.0
14/12/2007 14:00	2	3	- 2	- 3.0*

**Table 17. Case D: comparison of the historical insulin setting at the VUmc and the proposed insulin setting with GRIP around the ‘hypo’**

**\* A physician is consulted**

The advices of GRIP in the early morning of December 14 are surprising. The advice is a stop of insulin even if the glucose values are excessive (>20 mmol/l). This is a consequence of the enormous decrease in blood sugar level. In the formula that calculates the recommended adjustment of the insulin pump rate, the decrease of the blood sugar level has more impact on the adjustment than the current glucose value. In this case this seems to be misleading, because the high glucose values are needed to be treated with insulin. But to prevent that the advices from this period are followed uncritically, the attending physician is consulted when the glucose values are very high (> 15 mmol/l) which is the case.



The big decrease in blood sugar level preceding the episode of hypoglycemia leads to a stopping advice from GRIP. At the VUmc, the insulin pump rate is adjusted with only 1 unit per hour.

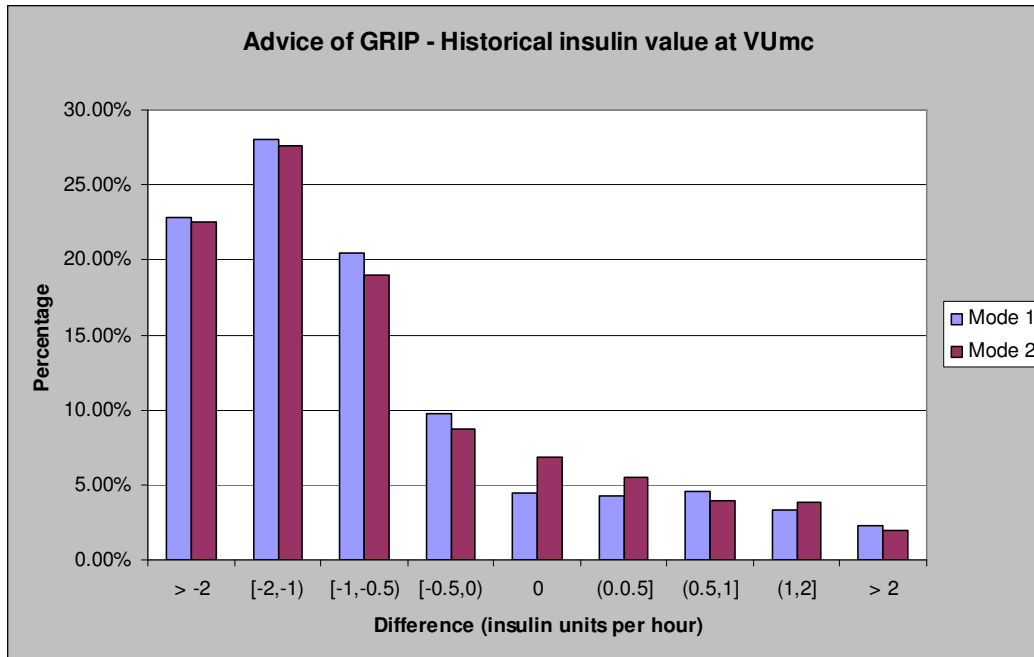
## **5.4 GRIP versus VUmc**

To get an overall view on the differences between the historical actions at the VUmc and the advices of GRIP in the period preceding an episode of hypoglycemia, the periods preceding all glucose values beneath 4 mmol/l are evaluated. Patients from the Eat-group, patients with no insulin pump running preceding the ‘hypo’ and patients with a ‘hypo’ related to a stop or big change in feeding/glucose infusions are excluded from this evaluation. After excluding these patients, 82 patients remain.

There are different ways to compare the historical insulin settings at the VUmc with the advice of GRIP. One can choose to compare the advice of GRIP with the insulin dose that is given to a patient in the next hour after the measurement which was the trigger for the advice of GRIP. Another way is to compare the advice of GRIP with the insulin pump rate at the VUmc at the glucose measurement following the glucose measurement which was the trigger for the advice of GRIP.

Most of the time, the historical insulin values of both manners will be the same, because the insulin pump rate is practically only changing after a glucose measurement. However, sometimes the medical staff decided to change the insulin pump rate before a new glucose measurement is done.

The different ways to compare will be denoted as Mode 1 (the first way, comparing the insulin rate an hour after the last glucose measurement) and Mode 2 (the second way, comparing the advice by the insulin pump rate at the next glucose measurement). The differences between the historical amount of insulin the patients at the VUmc were treated with and the advices of GRIP are displayed in figure 11.



**Figure 11. Differences between the advices of GRIP and the historical insulin settings at the VUmc before episodes of hypoglycemia**

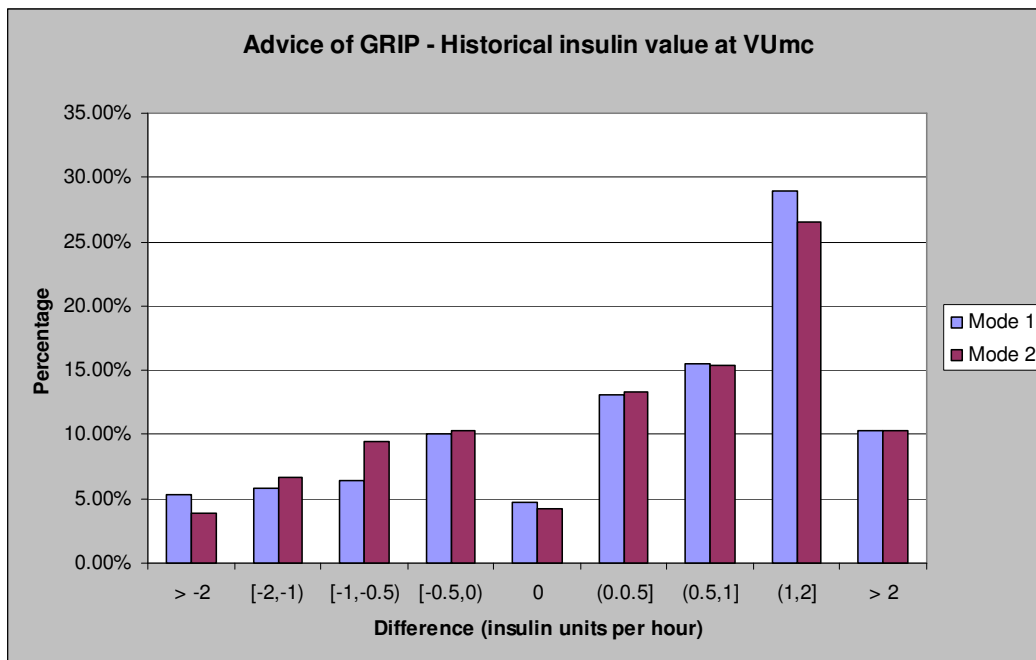
The results shown in figure 11 are promising. The advices of GRIP before episodes of hypoglycemia (< 4 mmol/l) are in approximately 80 percent of the cases lower than the insulin dose that is given in the situation at the VUmc. At more than 50 percent of all episodes of hypoglycemia GRIP advises an insulin pump rate that was more than 1 unit per hour lower than the dose given at the VUmc. It is reasonable to assume that with advised pump rates that were significantly lower most episodes of hypoglycemia were prevented or at least less severe. Around 70 percent of all low blood sugar levels are advised by GRIP to be treated with an insulin pump rate that was more than 0.5 unit of insulin lower.

Although in most cases the advice for the insulin pump rate is lower than the insulin dose that caused the episode of hypoglycemia, in 15 percent of the cases GRIP advises an insulin dose that is higher than the pump rate used at the VUmc. An even higher rate of insulin could lead to episodes of hypoglycemia that are more severe. There is even a small percentage (2 %) where the advice is over 2 insulin unit higher than the insulin dose at the VUmc that was enough to cause an episode of hypoglycemia.

However, when these specific cases are considered in more detail, the worries are taken away. The advice is only based on the blood sugar levels and the insulin pump rates, glucose infusions and feeding pumps are not taken into account. In the real GRIP algorithm these factors have influence, but in the more simple model used in the previous sections these factors are not taken into account.

In most cases where the advice of GRIP is more than 1 unit of insulin per hour bigger than the insulin pump rate at the VUmc, this wrong advice can be explained when other influences as glucose infusions and changes in feeding pump rates are considered.

The use of GRIP seems to reduce the incidence of episodes of severe hypoglycemia, but it is also important that episodes of hyperglycemia are prevented. To investigate if GRIP is also able to give the right advice when the blood sugar level is becoming high, again insulin settings from the past at the VUmc are compared with the advices of GRIP. This time the developing of all high glucose values ( $>10$  mmol/l) are considered. The insulin pump rate at the VUmc preceding such a high value is compared with the advice of GRIP.



**Figure 12. Differences between the advices of GRIP and the historical insulin settings at the VUmc before episodes of hyperglycemia**

The same two ways to determine the difference as in the previous figure are used. The results are shown in figure 12. In most cases, the recommended insulin pump rate is higher than the insulin dose used at the VUmc.

An advice that is more than 2 units per hour of insulin higher than the historical insulin value at the VUmc is less frequent than expected following the trend of the bins. This because of the restriction of GRIP, that elevation of the insulin dose is restricted to a maximum amount. With a higher amount of insulin, the glucose value will be lower. The episodes of hyperglycemia at the VUmc would be closer or in the target range when a higher amount of insulin was registered.

It does not look like the use of GRIP worsens the performance of the glucose management. Adjusting the insulin pump rate seems to be recommended at the right time to keep the blood sugar level in the target range. The performance measures of GRIP mentioned earlier stated this.

GRIP also advises about the time of the next measurement, this is an extra safety measure for the developing of an episode of hypoglycemia, because when the risk of a 'hypo' is high a high sampling frequency is recommended to keep track on the pattern of the blood sugar level.

In the phase preceding glucose values that were outside the target value at the VUmc, GRIP gives advices that would improve the glucose management. A lot of measurements should be in the target range when the advices of GRIP were followed. But on the other hand, it is not known in how many cases the advice of GRIP was worse than the insulin setting at the VUmc. However, the incidence of episodes of severe hypoglycemia is five times higher at the VUmc than the incidence with the use of the computerized protocol GRIP and the glucose values of patients are not more often in the target range at the VUmc.

## 6 Conclusion

After the landmark study from Van den Berghe in 2001 [6] a lot of ICUs started a tighter glucose control. There was concern about this tight control because of the higher occurrence of episodes of severe hypoglycemia. More recent guidelines and protocols are more advanced and are aware of the risk of hypoglycemia, but at the same time prevent excessive high blood sugar levels.

The best target range for the glucose values in an ICU is currently unclear. The landmark study targeted for glucose values within 4.4-6.1 mmol/l, but a less stringent range of 4-8 mmol/l is also often used. The latter target range is used at the VUmc. On average, 69.8 percent of the glucose measurements are in the target range at the VUmc. Only 0.19 % of the glucose samples are beneath 2.2 mmol/l, indicating an episode of severe hypoglycemia. Three percent of the patients experienced at least one episode of severe hypoglycemia during their stay at the ICU.

There are different risk factors for achieving an episode of hypoglycemia. Although it is hard or even impossible to prove what the exact reasons are for developing a 'hypo', the data indicate three different scenarios. The most frequent pattern is a clear decreasing blood sugar level, falling towards the critical 'hypo'-line, when the insulin pump rate is adjusted too late. The second one is an out of proportion high amount of insulin often coupled with a sampling frequency that is too low. The last pattern is a change or stop of nutrition without adjusting the insulin dose.

The glucose management at the VUmc is based on experience and intuition and no formal guideline or protocol is used. The use of such a protocol probably can prevent episodes of severe hypoglycemia by giving the right insulin advice.

In the last years many studies were published about glucose management in the ICU. The approaches in the studies vary in many aspects. Studies using a dynamic scale protocol

that combine a tight glucose target and the last two blood glucose values to determine the insulin infusion rate yielded the best results in terms of glycemic control and reported low frequencies of hypoglycemic episodes.

Each study discussed another kind of patient population, which makes the numerical results difficult to compare. The performance of the current approach at the VUmc was on average not worse than protocols used in published studies and it even outperforms most of them. However, in the cases section it is seen that on individual level, there are some incomprehensible actions at the VUmc. With the use of a protocol, the performance would be more constant and wrong assessments could be reduced.

The best protocol found in the literature was GRIP, a computerized protocol used in Groningen. Only 0.04 percent of the glucose measurements were beneath 2.2 mmol/l. At the VUmc the occurrence of episodes of severe hypoglycemia is approximately five times higher. The blood sugar level of a patient is 67 percent of time in the target range (4-7.5 mmol/l). When the first 6 hours of stay are ignored this percentage is even 89 percent of time. The patient population of the study consists of 2800 surgical ICU patients, which seems to be large enough to base justified conclusions on.

Although the population of the patients at the VUmc (mixed ICU patients) differs from the population in Groningen (surgical patients), we now make a comparison of the two approaches.

The average sampling frequency in Groningen is 5.9 per patient per day; at the VUmc the sampling frequency is similar: 6.2 glucose measurements per patient per day. A higher frequency of glucose measurements will make the glucose management easier, but it will lead to significant more costs in terms of nursing effort and supplies.

When the developing of all low glucose values ( $< 4$  mmol/l) of the patients with at least one episode of hypoglycemia are considered, the insulin settings at the VUmc are in approximately 80 percent of the cases higher than the insulin dose advised by GRIP. At more than 50 percent of all episodes of hypoglycemia GRIP advises an insulin pump rate that was more than 1 unit per hour lower than the dose given at the VUmc. One has to notice that not all restrictions of GRIP are implemented in the simplified model used for the determination of the recommendations in this paper.

A lot of episodes of hypoglycemia seem to be preventable with the use of GRIP. On the other hand, one can not say in how many cases the advice of GRIP will cause a 'hypo' that was not achieved with the insulin settings at the VUmc. However, the incidence of episodes of severe hypoglycemia is five times higher at the VUmc than the incidence of a 'hypo' with the use of the computerized protocol GRIP.

GRIP also advises about the time of the next glucose measurement. This improves the safety because the time interval until the next measurement is smaller if there is more risk to develop an episode of hypoglycemia.

The use of a computerized protocol seems to be a safe and efficient approach for a good glucose management. The blood sugar level can be kept in the target range most of the time and the incidence of episodes of severe hypoglycemia is very low with the correct use of a good protocol. The glucose management could be improved at the VUmc with the use of a protocol according to the significantly lower incidence of episodes of severe hypoglycemia.

## 7 Recommendations

To improve the glucose management at the ICU of the VUmc a few recommendations are described in this section.

At first, it looks helpful to support the medical staff with graphs about the glucose values and the insulin dose. When the blood sugar level is declining, it is important to recognize such a decreasing pattern, especially when the blood sugar level tends to the ‘hypo’ line of 2.2 mmol/l. The VUmc medical staff is already aware of this, but there is no assistance by the system in the form of a warning when the blood sugar level is decreasing towards a ‘hypo’.

To get a better insight in the pattern of the blood sugar level, adding a graphical display to the system could help. The history of treatment can then be observed, and this can help in current decisions about the insulin pump rate. The medical staff can watch the pattern and intervenes when a clear decreasing pattern is on its way to the critical ‘hypo’ line.

However, the best results will be achieved with the implementation of a good working protocol that advises about the right dose of insulin. Besides the insulin pump rate recommendation, another way to improve the glucose management is to give advice about the time of the next glucose measurement. When the risk of an episode of severe hypoglycemia is high, frequent sampling is needed to treat the patient with the right dose of insulin.

The best protocol found in the literature was GRIP. In a large study the incidence of episodes of hypoglycemia was five times lower than at the VUmc. GRIP is released under an open source license and is free to use and improve by anyone in the future. At the ICU of the VUmc, where a PDMS is already operational, the use of GRIP might introduce double data entry. However, this can easily be resolved by either letting GRIP query the PDMS for information or by integrating the GRIP rules into the PDMS (if it is



possible to add code within the PDMS). At the VUmc these rules can be implemented with the development of a form with the form builder of Metavision.

The major problem of GRIP is the complexity of rules behind the total algorithm. To get good results, the program has to be implemented in total. The recommended insulin pump rate and the time interval between the glucose measurements are determined according to a lot of rules. All rules can be determined from the source code. In appendix I they are described in pseudocode.

The best approach to improve the glucose management and reduce the incidence of episodes of severe hypoglycemia in the current situation seems the implementation of the algorithm behind GRIP to determine the insulin advice and the proposed interval to the next measurement. With a relatively low sampling frequency, the blood sugar level will be more stable. The possibility of dangerous outliers will reduce and consulting a doctor is needed less frequently.

It is important to implement such a protocol with enough safety measures, as long as doubts remain about the potential benefits of tight glucose control. Insulin administration should be intravenous and continuous, and guided by a dynamic scale protocol. Periodical monitoring of performance and incremental modification of the protocol leads to best results. [44]

Despite the clinical success of implementing an insulin infusion protocol, there are several barriers that can thwart introducing a protocol. Possible barriers are the fear of hypoglycemia, insufficient nursing staff to patient ratios, lack of administrative and physician support, various system and procedural issues, and resistance to change. Key steps to overcome the barriers include building support in all disciplines of the staff and make them aware of the clinical and economic benefits of improving glycemic control, setting realistic goals, selecting a validated insulin infusion protocol, and internally marketing the success of the protocol. [45]

The implementation of GRIP at the University Medical Center Groningen was excellently accepted by nurses, with minimal training needed. The advice of GRIP can be overruled at the discretion of the physician at any time, and a patient can be taken out of GRIP altogether. This happened structurally with patients who had recovered enough to be taking meals.

## 8 References

[1] VU medisch centrum. <http://www.vumc.nl/>

[2] Diabetes information, insulin. <http://www.fda.gov/diabetes/insulin.html>

[3] Wikipedia. Diabetes Mellitus. 2007

[4] American diabetes association, hyperglycemia. <http://www.diabetes.org/type-1-diabetes/hyperglycemia.jsp>

[5] McCowen KC, Malhotra A, Bistrian BR. Stress-induced hyperglycemia. *Crit Care Clin* 2001;17:107–124.

[6] Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R. Intensive insulin therapy in critically ill patients. *New Engl J Med* 2001; 345: 1359-1367

[7] Krinsley JS. Effect of an intensive glucose management protocol on the mortality of critically ill adult patients. *Mayo Clin Proc* 2004, 79(8):992-1000.

[8] Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, Gea-Banacloche J, Keh D, Marshall JC, Parker MM, Ramsay G, Zimmerman JL, Vincent JL, Levy MM. Surviving Sepsis Campaign Management Guidelines Committee: Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med* 2004, 32(3):858-873.

[9] Van den Berghe G, Wilmer A, Hermans G, et al: Intensive insulin therapy in medical intensive care patients. *N Engl J Med* 2006; 354: 449-461

[10] The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of longterm complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993; 329: 977–986

[11] UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998; 352:837–853

[12] Van den Berghe G. First do no harm...Hypoglycemia or hyperglycemia? *Crit Care Med* 2006 Vol. 34, No. 11

[13] Vriesendorp TM, DeVries JH, van Santen S, et al. Evaluation of short-term consequences of hypoglycemia in an intensive care unit. *Crit Care Med* 2006; 34:2714–2718

[14] ] Krinsley JS, Grover A. Severe hypoglycemia in critically ill patients: risk factors and outcomes. *Crit Care Med* 2007 Oct 35(10):2262-7

[15] Vriesendorp TM, van Santen S, DeVries JH, et al. Predisposing factors for hypoglycemia in the intensive care unit. *Crit Care Med* 2006; 34:96–101

[16] Brunkhorst FM, Kuhnt E, Engel C, MeierHellmann A, Ragaller M, Quintel M, Weiler N, Gründling M, Oppert M, Deufel T, Löffler M, Reinhart K. Intensive insulin therapy in patient with severe sepsis and septic shock is associated with an increased rate of hypoglycemia – results from a randomized multicenter study (VISEP). *Infection* 2005; 33 (Suppl 1): 19

[17] Goldberg PA, Siegel MD, Sherwin RS, Halickman JI, Lee M, Bailey VA, Lee SL, Dziura JD, Inzucchi SE. Implementation of a safe and effective insulin infusion protocol in a medical intensive care unit. *Diabetes Care*. 2004; 27: 461-467

[18] Meynaar IA, Dawson L, Tangkau PL, Salm EF, Rijks L. Introduction and evaluation of a computerised insulin protocol. 2006 Intensive Care Med DOI 10.1007/s00134-006-0484-z: 591-596

[19] Barth MM, Oyen LJ, Warfield KT, Elmer JL, Evenson LK, Tescher AN, Kuper PJ, Bannon MP, Gajic O, Farmer JC. Comparison of a nurse initiated insulin infusion protocol for intensive insulin therapy between adult surgical trauma, medical and coronary care intensive care patients. BMC Emergency Medicine 2007, 7-14.

[20] Lonergan T, Le Compte A, Willacy M, Chase JG, Shaw GM, Wong XW, Lotz T, Lin J, Hann CE. A simple insulin-nutrition protocol for tight glycemic control in critical illness: Development and protocol comparison. 2006. Diabetes Technology & Therapeutics. Volume 8, Number 2, 2006.

[21] Salaverría Garzón I, Cruz Acquaroni MM, Raigal Caño A, Alonso Garcia A, Sánchez Rodriguez P. Implementation and evaluation of a protocol for continuous insulin perfusion in critical patients. Med Intensiva. 2007; 31(9): 485-490.

[22] Mitchell I, Knight E, Gissane J, Tamhane R, Kolli R, Leditschke IA, Bellomo R, Finfer S, et al. A phase II randomised trial of intensive insulin therapy in general intensive care patients. 2006 Critical Care and Resuscitation, Volume 8, Number 4: 289-293.

[23] Zimmerman CR, Mlynarek ME, Jordan JA, Rajda CA, Horst HM: An insulin infusion protocol in critically ill cardiothoracic surgery patients. Ann Pharmacother 2004, 38:1123-1129.

[24] Juneja R, Roudebush C, Kumar N, Macy A, Golas A, Wall D, Wolverton C, Nelson D, Carroll J, Flanders SJ. Utilization of a Computerized Intravenous Insulin Infusion Program to Control Blood Glucose in the Intensive Care Unit. 2007 Diabetes Technology & Therapeutics, Volum 9, Number 3: 232-240.

- [25] Vogelzang M, Zijlstra F, Nijsten MWN. Design and implementation of GRIP: a computerized glucose control system at a surgical intensive care unit. 2005 BMC Medical Informatics and Decision Making 2005, 5:38
- [26] Laver S, Preston S, Turner D, McKinstry C, Padkin A. Implementing intensive insulin therapy: development and audit of the Bath insulin protocol. Anaesth Intensive Care. 2005 Feb;33(1):140
- [27] Kanji S, Singh A, Tierney M, Meggison H, McIntyre L, Hebert PC. Standardization of intravenous insulin therapy improves the efficiency and safety of blood glucose control in critically ill adults. 2004 Intensive Care Med 30:804–810
- [28] Rood E, Bosman RJ, van der Spoel JI, Taylor P and Zandstra DF. Use of a computerized guideline for glucose regulation in the intensive care unit improved both guideline adherence and glucose regulation. 2005 J Am Med Inform Assoc. 12:172–180.
- [29] Meijering S, Corstjens AM, Tulleken JE, Meertens JHJM, Zijlstra JG and Ligtenberg JJM. Towards a feasible algorithm for tight glycaemic control in critically ill patients: a systematic review of the literature. Critical Care 2006, 10:R19
- [30] Wilson M, Weinreb J, Soo Hoo GW. Intensive Insulin Therapy in Critical Care: A review of 12 protocols. 2007 Diabetes Care 30: 1005-1011
- [31] Egi M, Bellomo R, Stachowski E, French CJ, Hart G, Stow P, Li W and Bates S. Intensive Insulin Therapy in Postoperative Intensive Care Unit Patients: A Decision Analysis. 2006 Am J Respir Crit Care Med Vol 173: 407–413

[32] Pachler C, Plank J, Weinhandl H, Chassin LJ, Wilinska ME, Kulnik R, Kaufmann P, Smolle KH, Pilger E, Pieber TR, Ellmerer M and Hovorka R. Tight glycaemic control by an automated algorithm with time-variant sampling in medical ICU patients. 2008 Intensive Care Med DOI 10.1007/s00134-008-1033-8.

[33] Weber-Carstens S, Deja M, Bercker S, Dimroth A, Ahlers O, Kaisers U, Keh D. Impact of bolus application of low-dose hydrocortisone on glycaemic control in septic shock patients. 2007 Intensive Care Med 33:730–733

[34] Anger KE, Szumita PM: Barriers to glucose control in the intensive care unit. 2006 Pharmacotherapy 26:214–226.

[35] The NICE – SUGAR Study Investigators. The Normoglycemia in Intensive Care Evaluation (NICE) (ISRCTN04968275) and Survival Using Glucose Algorithm Regulation (SUGAR) Study: development, design and conduct of an international multi-center, open label, randomized controlled trial of two target ranges for glycaemic control in intensive care unit patients. Am J Respir Crit Care Med 2005; 172: <http://ajrccm.atsjournals.org/cgi/data/172/11/1358/DC1/1>

[36] Bellomo R and Egi M. Glycaemic control in the intensive care unit: Why we should wait for NICESUGAR. 2005 Mayo Clin Proc 80:1546–1548

[37] Tomky, Donna: Detection, Prevention and Treatment of Hyperglycemia in the Hospital. Diabetes Spectrum, Volume 18, Number 1, 2005; 39-44

[38] Mebis L, Gunst J, Langouche L, Vanhorebeek I and Van den Berghe G. Indication and practical use of intensive insulin therapy in the critically ill. 2007 Curr Opin Crit Care 13:392–398.

[39] Krinsley JS, Zheng P, Hall D, et al: ICU validation of the OptiScanner, a continuous glucose monitoring device. Crit Care Med 2006: 34:A67

[40] Clinical Information Systems for Critical Care. <http://www.imd-soft.com>

[41] Wikipedia. APACHE II. 2007

[42] Vogelzang M, Loef BG, Regtien JG, Van der Horst ICC, Van Assen H, Zijlstra F, Nijsten MWN. Computer-assisted glucose control in critically ill patients. Intensive Care Med 2008: DOI 10.1007/s00134-008-1091-y

[43] Prigeon RL, Røder ME, Porte D, Kahn SE. The effect of insulin dose on the measurement of insulin sensitivity by the minimal model technique. Evidence for saturable insulin transport in humans. J Clin Invest 1996, 97(2):501-507.

[44] Vogelzang M and Ligtenberg JJM. Practical aspect of implementing tight glucose control in the ICU. 2007 Current Opinion in Clinical Nutrition and Metabolic Care, 10: 178-180.

[45] Kelly LJ and Furnary AP. Implementing an intravenous insulin protocol in your practice: Practical advice to overcome clinical, administrative, and financial barriers. 2006 Semin Thorac Cardiovasc Surg 18: 346-358.

[46] Vanhorebeek I, Langouche L, Van den Berghe G. Tight blood glucose control: What is the evidence? Crit Care Med 2007 Vol.35, No.9: 496-501

[47] Van den Berghe G. Review: Saving lives with insulin in the ICU. International Journal of Obesity (2002) 26, Suppl 3, S3-S8

[48] Texas Diabetes Council Managed Care Work Group. IV Insulin Infusion Protocol for Critically Ill Adult Patients in the ICU Setting. 2007 Publication Number: E45-12063



[49] Chase JG, Shaw GM, Wong XW, Lotz T, Lin J, Henn CE. Model-based glycaemic control in critical care: A review of the state of the possible. *Biomedical Signal Processing and Control* 1 (2006) 3-21

[50] Goldberg PA, Roussel MG and Inzucchi SE. Clinical results of an updated insulin infusion protocol in critically ill patients. 2005 *Diabetes Spectrum* Volume 18, Number 3: 188-191.

## Appendix I

In this appendix, the proposed program GRIP [31] is described in more detail than is done in section 5.2. Pseudocode is given to make implementation of the program easier. The appendix contains two subparts, in the first subpart the algorithm is described that determines the recommended change in insulin dose and in the second subpart the algorithm that determines the proposed interval to the next glucose measurement is described.

### ***A. Insulin recommendation***

The change of the insulin pump rate recommended by GRIP is based on the following formula.

$$\Delta I = (1 + 0.25I_{-4h}) \cdot (0.2 \cdot (G_0 - G_{target}) + 0.3 \cdot \Delta G_{-4h})$$

This formula is the base calculation of the advised adjustment of the insulin pump rate, but the amount of glucose intake and some restrictions can change the recommended insulin pump rate. The algorithm for the insulin pump rate advice is described with pseudocode.

#### **Pseudocode**

$G_0$  = glucose value of last glucose measurement

$G_{target} = 6.5$

```

Method main() {

if  $G_0 > 25$  then
    return advice = No advice

if  $G_0 < 3.5$  or  $G_0 > 15$  then
    return advice = Call doctor

if  $G_0 < 3$  then
    return advice = intravenous glucose dose and insulin rate of zero

return advice = calcAdvice()

}

```

---

```

Method calcAdvice() {

if no glucose values known then
    return 0

if patient's admission is shorter than 4 hours ago then
    initialAdvice = initialAdvice()

 $I_{-4h}$  = average insulin dose over last 4 hours

if glucose value of a patient  $\leq 3$  in the last 4 hours then
     $I_{-4h} = 0.5 * I_{-4h}$ 

currentIntake = current total glucose intake (ml/hr)
oldIntake = average total glucose intake over last 4 hours (ml/hr)
relativeGlucose = currentIntake/oldIntake

if last 24 hours no glucose intake then
    relativeGlucose = 1

if oldIntake and currentIntake are both  $< 1$  then
    relativeGlucose = 1

if relativeGlucose  $< 0.8$  then
     $I_{-4h} = (relativeGlucose / 0.8) * I_{-4h}$ 

 $G_{-4h}$  = glucose value 4 hours ago (linearly interpolated when needed)

if  $G_{-4h} < 6$  then
     $G_{-4h} = 6$ 

 $\Delta G_{-4h} = G_0 - G_{-4h}$ 
pumpdifference =  $(0.2 \cdot (G_0 - G_{target}) + 0.3 \cdot \Delta G_{-4h})$ 

```

```

if pumpdifference > 1.5 then
    pumpdifference = 1.5

pumpdifference = (1+0.25 $I_{-4h}$ ) * pumpdifference
insulinAdvice =  $I_{-4h}$  + pumpdifference
insulinAdvice = adviceAfterRestrictions(insulinAdvice)

if initialAdvice ≥ insulinAdvice then
    insulinAdvice = initialAdvice

return insulinAdvice

}

```

---

Method initialAdvice(){

```

if  $G_0 < G_{target}$  then
    return 0

if BMI > 30 then
    obese = 1
else
    obese = 0
end if

if patient has diabetes then
    diabetes = 1
else
    diabetes = 0
end if

if reason of admission of the patient is a liver transplantation then
    liver_tx = 1
else
    liver_tx = 0
end if

insulinResistance = 0.5 + 0.2 * obese + 0.1 * diabetes + 0.31 * liver_tx
initialAdvice = insulinResistance *  $G_0 - G_{target}$ 
return adviceAfterRestrictions(initialAdvice)

}

```

---

Method adviceAfterRestrictions(double advice){

```

temp =  $G_0 - 3.5$ 

if  $G_0 < 3.5$  and advice > 0 then
    return 0

```

```

if (temp*temp) < advice then
    advice = temp*temp

advice is rounded to one decimal

if advice > 10 then
    advice = 10

if advice < 0.3 then
    advice = 0

return advice

}

```

---

## ***B. Determination proposed interval to the next measurement***

The time interval until the next measurement is calculated in three different ways, the minimum of these three results is taken to determine the time interval.

The three algorithms are: hypo-risk interval algorithm, glucose-based algorithm, insulin-based algorithm.

### Hypo-risk interval algorithm

The hypo-risk interval algorithm tries to estimate the current risk of hypoglycemia. The algorithm consists of several subparts: recent history of low glucose values, decreasing pattern, recent stop of steroids, amount of insulin and amount of registered glucose intake. The several subparts all have a certain factor which results in a formula that determines the risk of hypoglycemia:

After the calculation of all factors, the risk of hypoglycemia results in a value from 0 to 1.

HypoRisk	1	0.9	0.8	0.7	0.6	0.5	0.4	0.3	0.2	0.1	0
Time interval (hours)	0.5 h	1 h	1.5 h	2 h	3 h	4 h	6 h	8 h	12 h	16 h	24 h

**Table I. Minimum time interval according to a certain risk of hypoglycemia**

The time interval corresponding to the current *HypoRisk* results in the time interval of the hypo-risk interval algorithm (linearly interpolated).

### Glucose-based algorithm

Every glucose value is coupled to a time interval.

Glucose value (mmol/l)	3.5	4	5	6	7	8	9	10
Time interval (hours)	2 h	4 h	8 h	12 h	12 h	7 h	4 h	2 h

**Table II. Minimum time interval according to a certain glucose value**

The time intervals corresponding to the current glucose value and the extrapolated glucose value 4 hours in the future are determined (linearly interpolated). The minimum of these two time intervals is taken and it results in the time interval of the glucose-based algorithm.

### Insulin-based algorithm

Every insulin pump rate is coupled to a time interval.

Insulin (units/hour)	10	5	4	3	0.3	0
Time interval (hours)	1 h	4 h	6 h	8 h	8 h	24 h

**Table III. Minimum time interval according to a certain insulin pump rate**

The time interval corresponding to the current insulin pump rate results in the time interval of the insulin-based algorithm (linearly interpolated).

Now that the three results from the different algorithms are known, the minimum can be determined. After this, some final checks are done in the shape of some restrictions to the interval. The algorithm is described with pseudocode.

### **Pseudocode**

```
Method main() {
    if no glucoses known then
        return intervalAdvice = 0

    intervalAdvice = min(hypoRiskInterval(), glucoseInterval(),
        insulinInterval())
```

```

if patient admitted < 12 hours ago then
    intervalAdvice = min(4, intervalAdvice)

if patient has a glucose value < 4 in the last 4 hours then
    intervalAdvice = min(4, intervalAdvice)

newInsulin = advised insulin pump rate
oldInsulin = average insulin dose over last 4 hours
difference = newInsulin - oldInsulin

if difference > 3 then
    intervalAdvice = min(1.5, intervalAdvice)

if difference ≥ 1.5 or difference ≤ - 1.5 then
    if oldInsulin < 5
        intervalAdvice = min(3, intervalAdvice)

if (difference ≥ 1 or difference ≤ - 1) and oldInsulin < 5 then
    intervalAdvice = min(4, intervalAdvice)

if difference ≥ 0.5 or difference ≤ - 0.5 then
    intervalAdvice = min(6, intervalAdvice)

return intervalAdvice = max(min(intervalAdvice, 12), 0.5)

}

```

---

```

Method hypoRiskInterval() {

newInsulin = advised insulin pump rate
insulinFactor = min(1, newInsulin/2.5)

recentEnteral = current enteral glucose intake (ml/hr)
oldEnteral = enteral glucose intake 4 hours ago (ml/hr)
recentParenteral = current parenteral glucose intake (TPN + glucose
infusions) (ml/hr)
stomachRetention = current stomach retention over the last 6 hours

enteralGlucose = min(recentEnteral, oldEnteral) * 6 - stomachRetention

enteralFactor = 0.6 * enteralGlucose/500
enteralFactor = min(max(enteralFactor, 0), 0.6)
parenteralFactor = min(1, recentParenteral/(300/24))
glucoseIntakeFactor = max((enteralFactor + parenteralFactor) * 0.8,
max(enteralFactor, parenteralFactor))
if glucoseIntakeFactor > 1 then
    glucoseIntakeFactor = 1

glucoseIntakeFactor = 1 - glucoseIntakeFactor

if steroids stopped in last 24 hours then
    steroidsStopped = 1
else
    steroidsStopped = 0
end if

```

```

 $I_{-4h}$  = average insulin dose over last 4 hours
recentInsulin = min(1,  $I_{-4h}$ /10)
steroidFactor = steroidsStopped * recentInsulin

min3d = lowest glucose value in last 3 days
min12h = lowest glucose value in last 12 hours

if min3d > 3.5 then
    min3d = 0
else
    min3d = (3.5 - min3d)/3.5
end if

if min12h > 3.5 then
    min12h = 0
else
    min12h = (3.5 - min12h)/3.5
end if

hypoHistoryFactor = (min3d + min12h)/2

glucoseDecreaseIndex = 1 - (extrapolGlucose(2) - 2)/4
glucoseDecreaseIndex = min(max(glucoseDecreaseIndex,0), 1)
glucoseDecreaseFactor = 0.8 * glucoseDecreaseIndex

hypoRisk = insulinFactor * (glucoseIntakeFactor + steroidFactor +
hypoHistoryFactor + glucoseDecreaseFactor)/2

hypoRisk = min(hypoRisk, 1)

HR(x) = linear interpolator function, a hypoRisk x gives the
corresponding interval according to table I

return HR(hypoRisk)

}

```

---

```

Method glucoseInterval() {

 $G_0$  = glucose value of last glucose measurement
 $G_{+4h}$  = extrapolGlucose(4)

G(x) = linear interpolator function, a glucose value x gives the
corresponding interval according to table II

return min (G( $G_0$ ), G( $G_{+4h}$ ))

}

```



---

```
Method insulinInterval() {  
  
newInsulin = advised insulin pump rate  
I(x) = linear interpolator function, a insulin dose x gives the  
corresponding interval according to table III  
  
return I(newInsulin)  
  
}
```

---

```
Method extrapolGlucose(double hours) {  
  
 $G_0$  = glucose value of last measurement  
 $G_{-1}$  = glucose value of the measurement before  $G_0$   
 $t_0$  = moment in time of  $G_0$   
 $t_{-1}$  = moment in time of  $G_{-1}$   
  
if  $t_0 - t_{-1} < 30$  minutes then  
    return 4  
  
return  $G_0 + \frac{G_0 - G_{-1}}{t_0 - t_{-1}} * \text{hours}$   
  
}
```

---