Glycemic control in the intensive care unit assisted by Glycostat, a continuos central venous blood glucose measurement system with an algorithm giving advice on insulin infusion rate

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Primary Objective:To determine if the time in the desired glycemic range is equivalent by following the insulin infusion rate advice from the Glycostat algorithm compared to historical data in the ICU. The historical data for glycemic control...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON55181

Source
ToetsingOnline

Brief title
Glycemic control in the ICU assisted by Glycostat

Condition

- Other condition
- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
Hyperglycemia, Hypoglyceamia

Health condition

Intensive care - Glycemic control in the ICU

Research involving
Human

Sponsors and support

Primary sponsor: Medische Hulpmiddelen Industrie
Source(s) of monetary or material Support: Flowsion A/S;Denmark

Intervention

Keyword: continuos central venous blood glucose measurement system, Control Algorithm, Glycemic Control, ICU intensive care unit

Outcome measures

Primary outcome

Primary Objective:

To determine if the time in the desired glycemic range is equivalent by following the insulin infusion rate advice from the Glycostat algorithm compared to historical data in the ICU. The historical data for glycemic control includes at least 40 anonymous patients (with the same inclusion/exclusion criteria), which has been extracted extracted from EPIC (the hospital`s Healthcare Information System), or the NICE database and which has been analysed anonymously.

Secondary outcome

There are no secondary study parameters.

Study description

Background summary

Flowsion A/S (www.flowsion.dk) has developed the GlycostatTM system, intended

to continuously measure, record and track the blood glucose level (BGL) in critically ill patients i.e., those patients under intensive-care treatment within the operating rooms, emergency department, post-anaesthesia recovery unit and an Intensive Care Unit (ICU). In addition Glycostat has an algorithm which gives advice on the insulin infusion rate which -if adhered to- gives a good glycemic control.

Hyperglycaemia, which in the ICU patient population occurs very frequently due to an acquired stress induced insulin resistance, has long been known to be indicative of severity and poor clinical outcome (both mortality and morbidity). Two large prospective randomized controlled studies have shown that not only is hyperglycaemia indicative of poor outcome; treating these patients with large insulin doses to bring the glucose levels down to the normal range substantially reduces mortality and morbidity.

As a result of the two large studies by Greet Van Den Berghe more focus is being given to glucose control in the ICU setting. However, since the brain is dependent solely on glucose for its energy production there is a major concern about overdosing insulin and inducing hypoglycaemia, which may result in brain damage and death. As a consequence the target level for blood glucose is often increased above the normal range (i.e. 8.3 mM instead of 4.4 to 6.1 mM) as a compromise between the benefits of reducing blood glucose and the danger of hypoglycaemia.The recommendations regarding higher glucose concentration were partly founded on the findings of the socalled NICE Sugar study in which patients were given large amounts of insulin without frequent enough glucose concentration measurements. This resulted in increased mortality in the tight glycemic control group compared to the higher glucose concentration target of the control group.

Although the benefit of tight glycemic control has not been confirmed in more recently published work, there is general agreement that glycemic control is important and that continuous monitoring assisted by an algorithm would not only be beneficial for patients but might answer some of the outstanding questions within the area of tight glycemic control.

Regardless of the specific target range labour intensive frequent blood glucose measurements and calculations of the needed insulin infusion rate are required at the onset of insulin infusion therapy and until the patient is stabilized.

The most frequent manageable glucose monitoring in this early treatment window is twice per hour. Once the patient is stabilized typically blood glucose measurements are taken every four hours. Blood glucose is currently measured by drawing blood samples (either arterial, capillary, or venous) from the patient and using either a central laboratory analysis, a blood gas instrument or a stat laboratory analyzer placed locally in the ICU, or a point-of care (POC) glucose meter and strip (similar to the ones used by people with diabetes) to measure the concentration of BG. Manual blood sampling and BG measurements are usually continued 12 to 24 times per day over a several days period in order to monitor for changes in the patient*s response to insulin therapy and to ensure that

insulin is administered in accordance with patient feeding.

Since Glycostat is able to measure BG continuously and accurate, and is able to

calculate the insulin infusion rate which will give the best achievable glycemic control, Glycostat potentially can lower labour effort related to glycemic control as well as potentially will lead to improved glycemic control in the ICU, meaning more time in range, less hyper- and less hypoglycemic events, less fluctuation.

Study objective

Primary Objective:

To determine if the time in the desired glycemic range is equivalent by following the insulin infusion rate advice from the Glycostat algorithm compared to historical data in the ICU. The historical data for glycemic control includes at least 40 anonymous patients (with the same inclusion/exclusion criteria), which has been extracted extracted from EPIC (the hospital`s Healthcare Information System), or the NICE database and which has been analysed anonymously.

Study design

3. STUDY DESIGN
The enrolled patients are all part of the study group:
In the patients enrolled BGL will be controlled using the Glycostat measurement values, and the insulin infusion rate of Glycostat will be followed, if the ICU staff is of the opinion, that the insulin infusion advice looks reasonable and safe.

Insulin infusion will take place according to Glycostat advice only. The Glycostat measurement of blood glucose concentration is shown at all times on the large Glycostat touch screen display. In addition a trend curve on the screen shows the history of the patients BGL from the start until the 72 hours expires. The Glycostat BGL measurement will be checked 40 times within the 72 hours study duration (40 blood gas measurements per 72 hours) by comparison with the blood gas instrument measurement located in the ICU. That way it is secured that no severe hypoglycemic or hyperglycemic events can happen.
In case nurses do not follow the insulin infusion advice given by Glycostat - it is assumed it happens due to a substantiated medical reason which is to be noted.

The aim is to carry out the study during 180 days in total. Each patient is enrolled for 72 hours. The maximum number of blood samples needed for the study is 40 blood samples of 5 ml over 72 hours.

The study is a single site prospective, open-label, single arm clinical study.

All study group patients will receive a Glycostat intravenous probe placed in

the distal, proximal or medial lumen of their central venous catheter (CVC) already in place after they have been admitted to the ICU. All patients will be subjected to glucose measurements via a maximum of 40 blood gas measurements. Each blood sample will be 5 ml maximally. The Glycostat exposure will be 72 hours. The blood gas samples for the study will be evenly distributed over the 72 hours.

The historical patient data (BGL and insulin dosage) was extracted anonymously from EPIC (the hospital`s Healthcare Information System) or the NICE database, was analysed anonymously and is used to investigate if the algorithm in Glycostat is able to help control the glycemic level of the study group in a way equivalent to the normal practice of the clinic.
The inclusion and exclusion criteria apart from informed consent is the same for the study group as for the historical data.
Patients are in general anonymous to the sponsor. In case of the use of encrypted data GDPR is to be followed.

The ICU of the hospital has set the following target ranges for the patients in their glucose control protocol:
Non sepsis patients: Blood Glucose concentration larger than 4.5 mM, smaller than 6.5 mM
Sepsis patients: Blood glucose concentration larger than 4.8 mM, smaller than 8.3 mM

8.1 Study parameters/endpoints
8.1.1 Main study parameter/endpoint

The time in the desired glycemic range for the study group is calculated as the percentage of time inside a lower and upper blood gas boundary for all study objects. The lower and upper boundary will be set to 4.5 mmol/L and 6.5 mmol/L respectively for patients without sepsis and 4.8 mmol/l and 8.3 respectively for patients with sepsis. Data reported is the mean, rate of change, standard deviation, and confidence interval. Rate of change is calculated by differentiation of the blood glucose level with respect to time and the confidence interval is calculated based on the bootstrap percentile method.

The data is compared to historical data from the clinical site as stored in EPIC, the hospital*s Healthcare Information System, or from the NICE database. The historical data shows the time in range achieved for similar patients (same inclusion/exclusion criteria) as the study group patients. By comparing the time in range data of the historical data with the time in range data of the study group we intend to demonstrate equivalence in the time in range when the insulin infusion rate is guided by Glycostat.

8.1.2 Other study parameters (if applicable)

Glycostat needs information on the body mass of the subjects in order for the algorithm to function. In addition Glycostat needs information on the insulin infusion rate. For the criteria please see page 39 chapter 10.2.

8.1.3 Randomisation, blinding and treatment allocation
There will be no randomization. The study will be conducted as an open-label single arm study.
The BGL of all patients enrolled into the study group will be controlled using the Glycostat measurement values. The insulin infusion rate recommended by Glycostat will be followed, if the ICU staff is of the opinion, that the insulin infusion advice looks reasonable and safe.

8.2 Study procedures
Before starting the clinical study Flowsion will arrange a - if necessary multiple - training session for all nurses and anaesthesiologists that are taking active part in the clinical study. The training will cover the general use of Glycostat including a practical demonstration and explicitly cover the point that the probe is to be inserted into the CVC under echographic guidance. Furthermore training will include the use of the CRF (Case Report Forms).
All anesthesiologist are trained in CVC catheter placement. All probes and catheters will be introduced with echo guidance and the tip of the probe and the CVC will be checked.
If new staff becomes involved in the study they will be trained by Flowsion before playing an active role in the study.

Remark: Before starting the system there are department settings which under regular circumstances are not to be changed by the operator, e.g. the unit mg/dl or mmol/L - this is due to different countries use different units.

Blood glucose level target setting:
The target setting will be a part of the training. Responsible for the setting is the PI or a person authorized by the PI to execute the target setting. The target used are those described by the document *insulin therapie_intensief*. This internal document of Sankt Antonius states:
Objective
• Treat hyperglycaemia in accordance with protocol by means of intravenous administration of insulin.
• Strive towards normoglycaemia (glucose levels of 4.5-6.5 mmol/l).
• Minimise hypoglycaemic episodes (glucose level <3.9 mmol/l).
• Patients with sepsis to have range levels of 4.8-8.3 mmol/L.

The start procedure is described in the IFU (Instruction for Use) for Glycostat. The startup sequence until calibration is shown on the Glycostat display. The procedure can be summarized as follows:
The Glycostat application is started on the base unit by double-clicking on the Glycostat app icon on the touch screen display.
A sound signal is heard. If the user hears it the user confirms on the touch

screen display
Glycostat then asks you to enter patient data as shown on the Patient ID screen. Please enter patient ID by means of the touch screen keyboard according to the procedure of your hospital
Next enter the patient*s body mass in kg and press Confirm on the touch screen
Next enter current insulin infusion rate in ml/hour and press confirm
Next it is time to install the Glycostat probe:
a. Open the Procedure Pack
b. Use the Glycostat Probe 20 or 16 cm package according to the length of the Arrow CVC in place. Inspect the packaging of the probe and introducer prior to opening to check the integrity of the packaging.
c. If no damage to the package, unpack the Glycostat Probe 16 or 20 cm package. Be aware that the probe and CVC introducer are provided sterile. Caution: Users should employ aseptic techniques throughout the insertion.
d. This step shall be carried out by a physician. Insert guide wire into distal lumen of the CVC all the way until the guide wire can be attached to the CVC luer connection. Move the guide wire in and out a couple of times in order to expand the CVC at the narrow places in the middle and at the distal tip. Dispose of the guide wire.
e. Next insert the probe into distal lumen of Central Venous Catheter of the patient by means of the CVC introducer. The probe must be introduced all the way until the luer of the probe can be screwed onto the luer connection of the CVC distal lumen.
Caution: The microdialysis probe can be inserted provided that the CVC is placed more than 2,5 cm from the atrium to avoid any risks to the patient. Insertion of the probe will take place with echographic guidance in the same way as to place a central venous catheter.That way it is ensured that the probe tip is placed in the correct place with no risk of harming the patient. All anaesthesiologists are trained in the echographic technique.

f. Dispose of the CVC introducer.
g. Use the Consumable Kit package. Inspect the packaging prior to opening to check integrity of the packaging.
h. If no damage to the package, unpack the Consumable Kit package.
i. Connect luer locks of the probe onto the satellite.
j. Place the Front-end in the satellite.
k. Close the lid of the satellite.
l. Attach satellite to the patient according to normal practice of your ICU.
m. Insert Reagent Cassette into the Base unit.
n. Close the lid.
When all tasks above have been performed: Press Confirm on the screen

Warning: Do not pull the probe when attached to the CVC
Warning: Do not use the USB port while inserting the probe.
Caution: Be aware to place tubing in such a way that the risk of entanglement is reduced.
Caution: Control daily if leakage of reagents has occurred.

After confirmation, the system goes into Priming mode. This lasts 30-60 minutes

Next, the system informs that priming is complete. Press the button Initiate calibration

The calibration screen step 1 is shown on the display. Take a blood gas sample within 5 minutes to measure BGL. Press the Blood sample taken button.

Calibration screen 2 is shown on the display
Enter the blood gas glucose value in the shown units and press the Calibrate button

Remark: One cannot calibrate when hypoglycemia is present - it has a higher priority to eliminate the hypoglycemia than calibrating GLYCOSTAT.

Next the main screen with no BGL value is shown. Note: The blood BGL value measured by Glycostat is shown when the delay of 12 minutes has elapsed. Also note that due to this delay, the glucose value on the display is the value from 12 minutes ago.

Remark: Glycostat measures the central venous blood glucose concentration continuously with a delay of 12 minutes. Even though T1/2 of rapid insulin is 5 minutes, blood glucose concentration due to insulin infusion varies more slowly with typically not more than 2 mM in 20 minutes. If Glycostat measures such a high downward slope with blood glucose concentration being within the desired range, the algorithm will advise that insulin infusion is stopped. Advice to infuse insulin will then only be given when the blood glucose concentration trend is upwards again. Another advantage of the Glycostat device is that it measures the blood glucose continuously with a sample rate of 2 measurements per second. This gives the nurse an early indication of in which direction the blood glucose concentration is going and thereby allow her to make better decisions with respect to adjusting the insulin infusion rate compared to alternative methods where the blood glucose concentration is sampled at a much lower frequency.

1. When the delay of about 12 minutes has elapsed the BGL value is shown.
2. The system will attempt to regulate patient BGL to a target value which is the average of the upper and lower BGL control limits. This is obtained by providing insulin infusion rate recommendations. The regulation system will more aggressively drive the BGL towards the target value when the BGL is outside the control limits.
The recommended insulin infusion rate is shown on the display if it deviates more from the current insulin infusion rate than what is specified by departments settings..
3. If the insulin infusion rate is adjusted, change it on the system as well by pressing the Insulin Infusion Rate button. The screen will appear and the

insulin infusion rate can be entered. The recommended insulin infusion rate displayed will disappear if it does not deviate more from the entered insulin infusion rate than specified by department setting. In case nurses do not follow the insulin infusion advice given by Glycostat - it is assumed it happens due to a substantiated medical reason which is to be noted.

Remark: Advice is given to the nurse this is what Glycostat is allowed to from a regulatory point, eventhough closed loop control is the final goal. Meaning control in hospitals where the glucose measurement system controls the infusion pump. The risk if nurses do not follow the advice is that patients go hyper- or hypoglycemic. This can also happen when manual control is applied. The risk is lower for hypo- and hyperglycemia when using Glycostat because the glucose concentration is performed continuosly and alarms are given for hyper- and hypoglycemia. This is not the case with manual protocol in place.
There are log files of Glycostat records the Glycostat advice given by Glycostat, and it also records if the nurse reports infusion rate is changed or not.
In addition the CRF (Case report forms) require to note the insulin infusion rate displayed on Glycostat and the insulin infusion rate whenever a blood samples is taken for measurements under this study.

4. The system needs to be calibrated daily using a measurement from a blood gas sample.. The time for daily calibration is specified by department setting. The count-down to calibration is shown in the top of the screen, but the system can always be calibrated if desired.
When it is time for calibration the user will be notified and the calibration is performed identically to the calibration during start-up.
If the system has not been calibrated in the last 26 hours the system will stop showing BGL measurements.

5. If the patient becomes hypoglycemic or hyperglycemic, alarms will appear.
6. The consumable should be changed every third day. A count-down is visible in the top of the screen. An alert and alarm will notify the user when it is time to change the consumable. For change of consumable, remove the probe from the patient and shut down the system by holding the power button depressed for ~5 seconds. When the screen is black you should disconnect the power supply from mains. Next, remove the Cassette from the Base unit, and dispose of the consumable according to department policy. If you want to continue using Glycostat for this patient perform a complete start
7. Glycostat is compared to measurement with BGA (blood gas analyzer) 40 blood samples @ 5 ml are drawn over 72 hours from the CVC and analyzed in the BGA. CRF`s are used to note the sample time and measurement value of blood glucose to receive so-called matched pairs (compared measurement with BGA and Glycostat measurement at the same time). BGA (blood gas analysers) are used to compare Glycostat measurement, since BGA are considered accurate enough for the use in the ICU, and it is more practical than sending all blood samples to the central

lab. Please be aware the the 40 measurements are to be analysed with BGA (blood gas analyzer) and not the POC devices and not the POC dives in use. In addition the CRF (Case report forms) require to note the insulin infusion rate displayed on Glycostat and the insulin infusion rate whenever a blood samples is taken for measurements under this study.

Remark: Since the nurses perform the blood gas measurements themselves, thus they have the results instantly and can compare them with the Glycostat display.

8. Study group: All patients enrolled are part of the study group and will be glycemically controlled using the Glycostat measurement values, and the insulin infusion rate of Glycostat will be followed, as long as the ICU staff is of the opinion, that the insulin infusion advice looks reasonable and safe. The ICU staff has the necessary information the remark above. In case the ICU staff decides not to follow the advice it has to be noted.

8.3 Withdrawal of individual subjects
Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.
Subjects where the patient consent have been given by a legal representative, will be asked to give consent - for the consent provided by their representatives as soon as they are in a condition to understand the information

8.4 Replacement of individual subjects after withdrawal
New patients are to be added instead of the patients that have withdrawn from the study to achieve the 20 patient enrollment in total.

8.5 Follow-up of subjects withdrawn from treatment
No follow up for patients withdrawn from the study foreseen.

8.6 Premature termination of the study
No premature termination of the study is foreseen.

8.7 Information regarding Glycostat ALARMS
Regarding the Glycostat alarms we refer to the research protocol chapter 8.7 Information regarding Glycostat alarms - since it includes pictures.

Study burden and risks

The enrolled patients will give up to 40 blood samples @ 5 ml over the72 hours duration of the enrolment. The associated infection risk and the blood loss are main disadvantages to the enrolled patients.
The clinical evaluation of Glycostat has shown that the device is capable of measuring BGL with an accuracy comparable to commonly used BGA devices. BGA (blood gas analysers) are considered accurate enough for the use in the ICU,

and it is more practical than sending all blood samples to the central lab. It offers the additional benefit to patients that measurement is continuous, and alarms are triggered as soon as a hyper- or hypoglycemic event is identified. Thus, ICU staff can recognize and react to patient blood sugar being too high or too low, making it more feasible for them to realize the clinical benefits of glycemic control.
In addition to its measuring function, Glycostat calculates a recommended insulin infusion rate to maintain patient BGL (Blood Gas Level) within upper and lower limits set by clinical staff. The current state of the art for controlling blood glucose concentration is done by looking at the latest manual blood glucose measurements and, via either a paper-based or computerized protocol, manually determine what insulin infusion rate should be applied. The algorithms are typically implemented as written instructions, with calculations performed bedside by ICU staff whenever a new glucose value is available (typically every 1-4 hours).
Computer-based algorithms aiming at providing the nursing staff insulin infusion rate advices have become commercially available, either as standalone software or as part of semi-automated insulin infusion devices. Studies have shown that computerized protocols perform better in terms of keeping patient BGL within defined limits than manual protocols.
By combining computerized insulin infusion rate advice with continuous blood glucose monitoring, Glycostat offers patients the benefit of maintaining BGL within defined limits, while avoiding hyper- or hypoglemic events, which are known in the field to be associated with complications and longer ICU stay and survival.

2.1 Summary of known and potential risks and benefits
2.1.1 Clinical Background and Medical benefit
Glycostat is intended for use in critically ill adults in Intensive Care Units (ICUs), where it provides quantitative continuous monitoring of blood glucose level (BGL) and insulin infusion rate advice. The Glycostat Clinical Evaluation Report (IMDD Anex 8). includes a detailed summary of the clinical background for glucose monitoring and glycemic control in this patient population.
Routine patient management in ICUs involves avoiding complications of hyperglycemia (high blood glucose) and hypoglycemia (low blood glucose), which are common in critically ill patients. Hyper- and hypoglycemia are associated with a high risk for adverse clinical outcomes. Control of blood glucose in ICU patients to maintain it within prescribed boundaries is therefore crucial to avoid further complications.
Currently, there are several commercially available technologies to measure BGL in the ICU: Central Laboratory Devices (CLD), Handheld Point-of-Care (POC) devices and Blood Gas Analyzers (BGAs). CLDs represent the gold standard for accuracy, but have a longer turnaround time for results, as they are not located bedside. Handheld POCs and BGAs are therefore commonly used to measure patient BGL in the ICU. Of these devices, BGAs are generally more accurate. However, they all suffer from the drawback that glucose measurement is intermittent, not continuous, and increased measurement frequency results in

increased nurse workload. Hyper- or hypoglycemic events that occur between measurement points may not be recognized.
The advantage of continuous BGL measurement is that both hypo- and hyperglycemia events may not be missed and the nurse workload may be reduced. There are also several different commercially available systems for Continuous Glucose Monitoring (CGM), applying various technologies ranging from more invasive systems placed inside a blood vessel to less invasive subcutaneous systems. Subcutaneous systems have been tested in clinical studies with varying results. Their accuracy has been shown to be poor for patients with microcirculatory impairment.
Intravascular microdialysis, the method applied by the Glycostat device allows continuously blood glucose measurements without blood sampling. The method wa$ first experimentally described in 1996 and has been studied as part of the Eirus medical device (Maquet Critical Care, Solna, Sweden). This method is rnore invasive, a$ it requires a probe to be placed inside a blood vessel. Glycostat and Eirus both utilize the central venous catheter (CVC) which is routinely placed in intensive care patients.
The most important difference between Eirus and Glycostat is the diameter of the probe. The diameter of the Eirus probe is larger than the Glycostat probe. To use the Eirus probe one has to use the Eirus CVC whereas the Glycostat probe fits into the distal lumen of e.g. Edward CVC.
The basic principle of Eirus and Glycostat is the same: Microdialysis, which is well known and accepted for many years. Eirus has a larger dialysis membrane area than the Glycostat probe.
The clinical evaluation of Glycostat has shown that the device is capable of measuring BGL with an accuracy comparable to commonly used BGA devices. BGA (blood gas analysers) are used to compare Glycostat measurement, since BGA are considered accurate enough for the use in the ICU, and it is more practical than sending all blood samples to the central lab.
lt offers the additional benefit to patients that measurement is continuous, and alarms are triggered as soon as a hyper- or hypoglycemic event is identified. Thus, ICU staff can recognize and react to patlent blood sugar being too high or too low, making it more feasible for them to realize the clinical benefits of glycemic control, ln addition to its measuring function, Glycostat calculates a recommended insulin infusion rate to rnaintain patient BGL within upper and lower lirnits set by clinical staff. The current state of the art for controlling blood glucose concentration is done by looking at the latest manual blood glucose measurements and, via either a paper-based or computerized protocol, manually determine what insulin infusion rate should be applied. The algorithms are typically implemented as written instructions, with calculations performed
bedside by ICU staff whenever a new glucose value is available (typically every 1-4 hours).
Computer-based algorithms aiming at providing the nursing staff insulin infusion rate advices have become commercially available, either as standalone software or as part of semi-autornated insulin infusion devices. Studies have shown that computerized protocols perfcrm better in terms of keeping patient

BGL within defined limits than manual protocols. By combining computerized insulin infusion rate advice with continuous blood glucose monitoring, Glycostat offers paiients the benefit of maintaining BGL within defined limits, while avoiding hyper- or hypoglemic events, which are known in the field to be associated with complications and longer IGU stays.

2.1 .2 Justification and/or risk benefit analysis for individual risks

During risk assessment it was possible to implement risk control measures that lowered the risk of harm to an acceptable level as defined by Flowsion. Howevet for the following hazards lhis was not possible. ln the following table justification for proceeding with the design and production of Glycostat despite residual risks being in the 'medium' category is provided.

HAZARD# DESCRIPTION RESIDUAL RISK (RPN2) JUSTIFICATION

RA-42 lnsufficient cleaning and bad hygiene can cause cross contamination and thereby infection of patients and operators. 6 (medium) This is not different from any other equipment used in the ICU environment. There is no indication that Glycostat causes greater risk than any other equipment introduced via a CVC.

RA60 Wrong and too high glucose value entered during calibration. This can cause undetected severe hypoglycemia during BGL monitoring. 8 {medium) Two risk control measures are implemented to reduce risk as far as possible. Benefit of device exceeds residual risk. Measure 1: The system is set up to only calculate the calibration factor when reference value is below 25 mM. Higher values will result in an alert and a message saying that reference glucose concentration is higher than 25 mM and therefore out of range. Measure 2: The training material shall include information about the importance of entering the correct glucose reference value used for calibration.

RA-157 Wrong and too low glucose value entered during calibration, This can cause undetected severe hyperglycemia during BGL monitoring. 8 {medium) Two risk ccntrol measures are implemented to reduce risk as far as possible. Please see RA-60 (above)Benefit of device exceeds residual risk.

RA-176 Patient has very high BGL and the operator increase the insulin infusion rate beyond the recommendation provided by Glycostat. I (medium) Device does not control the insulin infusion rate pump and therefore cannot prevent the op¤rator to make wrong decisions.

RA-151 PatienVstaff trips over the wires and tubing from base unit to satellite resulting in bruises/fraetures/dislocations. 6 (rnedium) Hazard it is not limited to the Glycostat device. Patients/staff will generally move carefully around the patient in ICU settings.

RA-152 PatienUstaff trips over the power adapter cable resulting in bruises/fracturesldislocations. 6 imedium) Hazard it is not limited to the Glycostat device. Patients/staff will in generally move carefully around the patient in ICU settings.

RA-182 Operator does not notice visual alarm. 8 (medium) Risk control measure ensures that alarm$ are both visual and auditory.

The alarm will only be overheard if department is understaffed or attending more important situations.

URA-21 Distractions in the ICU result in the user not noticing alarm. 8 (medium) Risk control measure ensures that alarms are both visual and auditory. The alarm will only be overheard if department is under$taffsd ar attending more important situations.

The following risks and measures to control the risks have been added only due to remarks from MEC-U from a previous application, since these risks are considered *low*.
URA-37 - Operator makes a typing error when entering patient information - Wrong patient ID entered; Hazard: Algorithm uses wrong input value and thereby calculates a too high or too low insulin infusion rate advice. Harm: Severe hypoglycemia or severe hyperglycemia - Risk 4(low) - Risk control measures: 1. Severe hypoglycemia alarm 2. Severe hyperglycemia alarm 3. The system shall only accept body masses between 30 kg and 200 kg
URA-38 - Operator makes a typing error when entering patient information - Wrong body mass entered; Hazard: Algorithm uses wrong input value and thereby calculates a too high or too low insulin infusion rate advice. Harm: Severe hypoglycemia or severe hyperglycemia - Risk 4(low) - Risk control measures: 1. Severe hypoglycemia alarm 2. Severe hyperglycemia alarm 3. The system shall only accept body masses between 30 kg and 200 kg
URA-39 - Operator makes a typing error when entering patient information - Wrong value for current insulin infusion rate entered - Hazard: Algorithm uses wrong input value and thereby calculates a too high or too low insulin infusion rate advice. However, if a wrong value is entered this problem will be resolved next time the insulin infusion rate is changed (as the operator changes it on the display each time). Harm: Severe hypoglycemia or severe hyperglycemia - Risk 4 (low) - Risk control measures 1. Severe hypoglycemia alarm 2. Severe hyperglycemia alarm 3. Insulin infusion rate entered by the user shall be between 0 and a configurable maximum insulin infusion rate. There are several risk control measures in place that will effectively mitigate the risk related to algorithm malfunction. First of all there are alarms for severe hypoglycemia and for severe hyperglycemia. Furthermore, Glycostat offers the additional benefit to patients and caregivers that its measurement is continuous so that actual blood glucose numerical values can be seen on the Glycostat screen at all the times. In adition trend curves and insulin infusion rate advice is shown on the Glycostat screen. This represents an improved risk situation compared to the present situation with manual blood sampling and related intermittent blood glucose sampling values with the potential to miss hypo- / hyperglycemic event within between intermittent blood sampling glucose measurements.

2.2 Acceptability of overall residual risk
The residual risk associated with the Glycostat device has been reduced as much as possible. Some risks remain that cannot be further reduced. As described in section 6.4,2 above, some of these are inherent to devices in the ICU and would thus also be present if another device than Glycostat was used.
Residual risks in the low category will not result in any significant health

issues or the probability of these are only theoretical and unlikely to occur in the product lifetime. Post Market Surveillance will provide input to the iterative process of risk management. In this connection the probability of occurrence might be reevaluated.
The clinical evaluation of Glycostat did not identify any side effects associated with the clinical use of the device or equivalent devices. It also did not identify any hazards that have not boen considered in the risk assessment and reduced as far as possible through the rask management process. The overall residual risk is outweighed by the Medical Benefit. For this reason, the Overall Residual Risk is acceptable, and there is no single risk that precludes the release or the continued production of the device. Information on residual risks has been disclosed to the user in the patient consent form.

Contacts

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:
• Male and Female subjects, age >= 18 years, <= 85 years
• ICU patients (any type) with an Arrow 3, 4 or 5 lumen central venous catheter in place (CVC in situ not for study,
but part of standard practice)
• Clinical parameters (vital signs, medical history, and physical examination) not clinically significant or unstable as
determined by the principal investigator.
• Informed consent obtained before any activities related to the investigation from the patient or their legal representative
•Require IV infusion of insulin to control their blood glucose level

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
• Known or suspected allergy to device material
• Not eligible to receive IV insulin
• ICU patients without Arrow 3 lumen or 4 or 5 lumen central venous catheter in place
• Previous participation (defined as participation on Day 1) in this trial.
• Acute and/or severe chronic illness or history of any illness that, in the opinion of the Investigator, might pose additional risk in applying the Glycostat probe to the subject
• Participation in another investigational study within 30 days prior to investigation start
• Surgery or trauma with significant blood loss within the last 2 months prior to application of the micro dialysis probe
• Subject with mental incapacity or language barriers precluding adequate understanding or co operation, who is unwilling to participate in the study or who, in the opinion of the Investigator, should not participate in the study.
In case a legal representative receives the patient information and provides the patient consent the subject may be in included.
• Patients unwilling to participate

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	20
Type:	Anticipated

Medical products/devices used

Generic name:	GLYCOSTAT
Registration:	Yes - CE intended use

Ethics review

Approved WMO

Date:	03-12-2021
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL75148.100.21