Since the publication of a landmark randomised trial by Van den Berghe et al, tight glycaemic control has become a standard therapy in many intensive care units. It is also recommended as part of a treatment bundle to improve outcome from sepsis in the critically ill, and multicentre trials evaluating its impact in various groups of critically ill patients are either completed or ongoing. However, a major concern has been that undetected hypoglycaemic episodes could increase morbidity in critically ill patients. Two recent clinical trials (VISEP [Efficacy of volume substitution and insulin therapy in severe sepsis] and Glucontrol [comparing the effects of two glucose control regimens by insulin in intensive care unit patients]) were stopped early because of increased episodes of hypoglycaemia in the tight glycaemic control arms, and lack of clinical benefit.

Currently in intensive care, blood glucose level is usually monitored through intermittent sampling of capillary or arterial blood or more formal testing of whole venous blood in a central hospital laboratory. The intermittent and invasive nature of these investigations limits their usefulness in critically ill patients, in whom blood glucose concentration can change rapidly.

New technology has been developed that enables patients with diabetes mellitus to undertake continuous glucose monitoring. One such device is the Guardian REAL-Time continuous glucose monitoring system (Medtronic MiniMed, Northridge, Calif, USA), which comprises a subcutaneous glucose sensor containing the enzyme glucose oxidase along with a platinum wire electrode; enzymatic breakdown of glucose leads to a current proportional to the amount of glucose present. This process is very fast, with measurements made every 10 seconds and then aggregated to give a value on the glucose monitor every 5 minutes. The sensor is connected wirelessly to a glucose monitor.

No studies have evaluated the performance of this system in adult critical care patients. We aimed to evaluate the Guardian continuous glucose monitoring system, by comparing its results with those obtained by measurement of glucose concentration in capillary and arterial blood samples.

**Methods**

The study was conducted as a single-centre, prospective observational study in the ICU of the Royal Infirmary of Edinburgh, United Kingdom, between July and December 2006. This is an 18-bed mixed medical and surgical ICU in a university-affiliated hospital, which admits about 1100 adult patients annually. Ethical approval was obtained from the
multicentre research ethics committee, and written informed consent was gained from each patient’s next of kin.

**Study population**

All patients who underwent emergency admission to the ICU were considered for the study. Inclusion criteria were: patient requiring mechanical ventilation on admission or within 12 hours of admission to the ICU; and expected duration of ventilation of at least 24 hours. Exclusion criteria were: age less than 18 years; or patient moribund and not likely to survive more than 8 hours.

**Study protocol**

On recruitment, each patient had a Guardian continuous glucose-monitoring sensor placed in the subcutaneous tissue of the left or right lower quadrant of the abdomen. After the monitor’s required warm-up period of 2 hours and 20 minutes, it was calibrated with a capillary blood glucose sample taken from a fingertip in accordance with the manufacturer’s instructions.

All patients were managed with a tight glycaemic control policy that was well established at the time of the study (Appendix). Nursing staff were instructed to take blood samples for glucose measurement according to this protocol, and additional samples at their own discretion. Each time a capillary blood glucose sample was taken, a second sample was taken from the arterial line. The bedside point-of-care blood glucose machine (Accu-Chek Advantage, F Hoffmann-La Roche, Basel, Switzerland) was used to measure glucose levels in the capillary and arterial samples. This machine is checked every 12 hours with a standardised quality control solution.

The Guardian glucose value was ascertained simultaneously, so that each time a blood glucose sample was taken three sets of blood glucose measurements were available: capillary blood glucose, arterial blood glucose and Guardian blood glucose. Only the capillary blood glucose sample was used to alter the insulin dose, as dictated by the tight glycaemic control protocol.

The Guardian monitor stayed in situ for a maximum of 72 hours (the life of the sensor), or until the patient’s trachea was extubated, or the goal of therapy was changed to palliative care.

**Data analysis**

We assessed the agreement between glucose measurements obtained by the Guardian device and those obtained from capillary and arterial blood samples across the full range of blood glucose values, using the Bland and Altman method. Using an $\alpha$ error of 0.05 and a $\beta$ error of 0.1 to detect a difference of 1 mmol/L between the means obtained by different glucose sampling methods required 16 patients, which gave this study a power greater than 90%.

We used separate comparisons to assess agreement between capillary (“gold standard”) and Guardian blood glucose values, between arterial and Guardian blood glucose values, and between capillary and simultaneous arterial blood glucose values.

We calculated the bias between the methods of measurement (the mean difference between the methods) and upper and lower limits of agreement with 95% confidence intervals. If the limits of agreement are less than a predetermined level of clinical significance, then these methods of measurement can be used interchangeably. For the purposes of this study we selected a priori the level at which a difference became clinically significant as ±1 mmol/L. Correlation between the different methods using capillary blood glucose values as the gold standard was determined by linear regression.

<table>
<thead>
<tr>
<th>Table 1. Patient demographic characteristics, by primary diagnosis (mean [range], unless otherwise indicated)</th>
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<tr>
<td><strong>Sepsis</strong> $(n = 4)$</td>
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<tr>
<td>Age (years)</td>
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<td>Sex: no. of women (%)</td>
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<td>APACHE II score</td>
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<td>Highest SOFA score</td>
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<td>Inotrope use: no. of patients (%)</td>
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<td>Guardian versus capillary</td>
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APACHE = Acute Physiology and Chronic Health Evaluation. SOFA = Sequential Organ Failure Assessment.

* Included pulmonary embolism, asthma, epilepsy, pancreatitis and duodenal ulcer perforation.
The relationships between patient factors, variation in the number of readings taken, performance over time and the use of inotropic or vasopressor therapy were also analysed by analysis of variance (ANOVA) or paired t test, with a significance level of \( P < 0.05 \).

All statistical analyses were performed using SPSS version 12 (SPSS Inc, Chicago, USA).

Results
A total of 1101 glucose readings were obtained from 17 patients: 371 from the Guardian monitor, 373 from capillary blood samples, and 357 from arterial blood samples. Of these, 366 paired samples were available for comparing Guardian and capillary glucose values, 350 for comparing Guardian and arterial values, and 352 for comparing capillary and arterial values. The demographic characteristics of the patients studied are shown in Table 1.

Comparison of measurement methods
The correlation between Guardian and capillary blood glucose values was \( r^2 = 0.70 \) (\( P < 0.001 \)); between Guardian and arterial values was \( r^2 = 0.85 \) (\( P < 0.001 \)); and between capillary and arterial values was \( r^2 = 0.78 \) (\( P < 0.001 \)).

Overall, the bias for the Guardian versus capillary and arterial values suggested that the Guardian device tended to read higher values than blood analysis (bias, 0.4 to 0.6 mmol/L), but the difference was not clinically important. Limits of agreement were wide for comparison of Guardian versus both capillary and arterial values (about \(-3\) to \(+2\) mmol/L). This level of disagreement was clinically highly significant and exceeded the pre-set acceptable level of \( \pm 1\) mmol/L.

However, we also found wide limits of agreement between capillary and arterial values (\(-1.8\) to \(+2.3\) mmol/L). Bland and Altman plots are shown in Figure 1, and Bland and Altman comparisons between the methods are summarised in Table 2.

Analysis of glucose samples \( \leq 4.5\) mmol/L
Twenty-four capillary and 12 arterial blood samples showed glucose levels \( \leq 4.5\) mmol/L. Agreement between the methods of measurement under these conditions was poor for comparisons between all methods of measurements (Table 3). For four (17%) of the 24 capillary blood samples with glucose levels \( \leq 4.5\) mmol/L, the corresponding Guardian reading was 1.0 mmol/L or more higher than the capillary value. Similarly, for five (42%) of the 12 arterial samples with glucose levels \( \leq 4.5\) mmol/L, the corresponding Guardian reading was 1.0 mmol/L or more higher.

Analysis of patient factors
We studied the relationship of patient-specific variables with the differences found in paired glucose measurements.

There was no significant difference between groups stratified by APACHE II score, sex or inotrope use at any time (Table 4).
Analysis of individual patient data

The mean biases for capillary to Guardian, capillary to arterial, and arterial to Guardian glucose measurements were 0.67 mmol/L, 0.09 mmol/L and 0.62 mmol/L, respectively. This difference between groups was significant ($P=0.01$).

In addition, to assess whether any difference in performance in glucose methods could be explained by the varying number of glucose measurements taken from individual patients (range, 4–60), we analysed data taken at a similar time of day (09:00 ± 2 hours). For this cohort, the bias (and upper and lower limits of agreement) for capillary to Guardian, capillary to arterial, and arterial to Guardian glucose measurements were 0.6 mmol/L (−2.1 mmol/L), 0.2 mmol/L (−2.2 to 3 mmol/L) and 0.6 mmol/L (−2.1 to 2.25 mmol/L), respectively. No significant differences were found with any measurement comparison method (Table 4).

Analysis by patient condition

In patients with acute liver failure as the primary diagnosis, we found a statistically significant difference between Guardian and arterial blood glucose values ($P=0.02$), but not between Guardian and capillary ($P=0.24$) or capillary and arterial ($P=0.18$) values.

In patients with sepsis as the primary diagnosis, we found a significant difference between capillary and arterial blood glucose values ($P=0.02$), but not between Guardian and capillary ($P=0.58$) or Guardian and arterial ($P=0.05$) values.

Performance of the Guardian device over time

To assess whether the performance of the Guardian device changed over time, we analysed the data in three 24-hour time periods. We found that the bias (and lower and upper limits of agreement) for capillary versus Guardian glucose values at 24, 48 and 72 hours was 0.8 mmol/L (−2.3 to 3.5 mmol/L), 0 mmol/L (−2.3 to 2.3 mmol/L) and 0 mmol/L (−2.2 to 2.1 mmol/L), respectively. For arterial versus Guardian glucose level over the same periods, the bias (limits of agreement) was 0.7 mmol/L (−1.8 to 3.3 mmol/L), 0.5 mmol/L (−2.2 to 3 mmol/L) and 0.27 mmol/L (−1.71 to 2.25 mmol/L), respectively.

Over the 72 hours, the only significant difference was found in Guardian versus arterial glucose values ($P=0.01$).

Discussion

We found poor agreement between blood glucose measurements by the Guardian REAL-Time glucose monitoring...
device and measurements in both capillary and arterial blood samples by a point-of-care glucometer in critically ill patients undergoing tight glycaemic control. There was no systematic bias between the techniques, but the limits of agreement were too wide to support routine use. However, poor agreement was also found between capillary and arterial blood glucose measurements, suggesting that significant measurement error occurs in bedside glucose measurements.

We further analysed the data to determine whether patient factors could be a significant cause of the differences found between the different methods of glucose measurement. We found no difference in the groups when stratified by APACHE II score, sex, inotrope or vasopressor use, or varying number of glucose measurements taken in individual patients. However, there were significant differences in patients with specific diagnoses: between Guardian and arterial blood glucose values in patients with acute liver failure, and between capillary and arterial values in those with sepsis. The numbers in our study were small, and speculation about the reasons for these differences would be premature. Of additional concern was the difference found over time, and the inconsistency of the gap between the Guardian and the capillary and arterial glucose measurements by the Accu-Chek Advantage glucometer. Guardian glucose values showed no difference from arterial values in the first 48 hours, but a significant difference by 72 hours, suggesting that measurement error increases with the Guardian system towards the end of the sensor’s life span, although there was no such demonstrable difference between Guardian and capillary glucose measurements.

The statistically significant difference found when we assessed consistency of the gap between Guardian and Accu-Chek Advantage measurements between patients is also important. It suggests that the difference cannot be accounted for simply by applying a correction factor to Guardian values, thus introducing the risk of further measurement error.

Our study found poor agreement between all three methods of glucose analysis. This is important as many ICUs have adopted tight glycaemic control as a standard of care. The disagreement between methods suggests that patients could be exposed to hypoglycaemia as a result of measurement error. Recent trials of tight glycaemic control have raised concerns that hypoglycaemia could increase mortality in ICU patients treated with insulin as part of tight glycaemic control. In addition, other trials (VISEP and Glucontrol) were stopped early on safety grounds because of increased incidence of hypoglycaemia in the patients treated with tight glycaemic control.

Our study had several strengths. We analysed a large number of samples (over 300 paired samples) compared with other studies. The samples were tested under routine clinical conditions, so the results are applicable to “real world” ICU conditions. However, our data were collected from only 17 patients in a single centre, and so may not be generalisable to other critically ill populations. Another important weakness of our study was that few readings were in either the hyperglycaemic or hypoglycaemic range, and thus it is not possible to comment on the performance of the three methods of glucose estimation at these levels.

In addition, we used capillary and arterial blood glucose measurements by the bedside point-of-care glucometer instead of the central laboratory, as this is the routine practice in our ICU. This may be important, as significant measurement errors have been described using different types of blood sample (capillary, arterial or venous) and different devices (point-of-care glucometer or glucose analysis on the blood gas analyser). For example, Khan and colleagues studied a range of point-of-care glucose meters from different manufacturers, and found that their accuracy in the hypoglycaemic range varied markedly from that of the central laboratory. Other researchers, such as Arias-Rivera et al, found that arterial blood glucose measurements were comparable to plasma glucose levels measured in the central laboratory, but there were significant differences between capillary blood glucose measurements and the plasma glucose levels. Furthermore, Kanji et al compared glucose measurements by three different methods (glucose meter analysis of capillary blood, glucometer analysis of arterial blood and arterial blood gas machine measurement of arterial blood) with a central laboratory-derived glucose level. They found good agreement between arterial blood measurements (by both the glucometer and blood gas analyser) and central laboratory results, but bedside glucometer measurement using capillary blood samples performed significantly less well. In particular, only 26.3% of capillary readings during periods of hypoglycaemia were accurate when compared with measurements in the central laboratory.

In contrast, in a study comparing capillary blood glucose levels measured by glucometer and contemporaneous arterial blood glucose levels measured by a multichannel blood gas analyser, Kulkarni et al found that the two methods agreed well, but that disagreement became more pronounced in patients treated with inotropes. A similar study by Lacara et al also found good agreement between point-of-care testing of capillary, central venous and arterial blood glucose samples compared with central laboratory testing. Finally, Karon et al studied the accuracy of a bedside glucometer in a population of postoperative cardiac intensive care patients who were treated with tight glycaemic control, and found that capillary whole blood values correlated best with laboratory values.
The current literature on glucose monitoring methods in critically ill patients is therefore conflicting. It is apparent that significant differences are attributable to the method of glucose measurement used. This becomes increasingly important given the relatively narrow range of glucose levels targeted by tight glycaemic control regimens.

There are few studies of the use of continuous glucose monitoring systems in critically ill adults. However, the previous version of the Guardian continuous glucose monitoring system (CGMS Gold, Medtronic MiniMed, Northridge, Calif, USA) has been evaluated in critically ill patients. The main difference between this device and the version used in our study is the latter’s ability to provide real-time glucose readings; the previous version required the data to be downloaded to a computer for later review.

Chee and colleagues' evaluated the CGMS system in five critically ill patients and attempted to use it in a closed-loop fashion, but manual intervention was required in four of the five patients due to the variation in arterial compared with CGMS glucose measurements. Goldberg et al' evaluated the CGMS in 22 patients at risk of hyperglycaemia in a medical ICU: 98.7% of readings were within the clinically acceptable range. Corstjens et al" evaluated the CGMS Gold system and compared it to arterial blood glucose measured with the ICU blood gas machine. The blood gas analyser had previously been validated as accurate when compared with contemporaneous samples measured in the central laboratory. They analysed 165 paired samples and found both the CGMS and arterial samples measured on the point-of-care machine performed well, as analysed by the method of Clarke error grid analysis. However, they also found wide limits of agreement when comparing the blood gas analyser glucose measurements to those of the CGMS Gold system (−2.4 to 2 mmol/L) and the point-of-care bedside glucometer (−2.5 to 2.5 mmol/L), which is consistent with our findings.

Research on the CGMS in paediatric cardiac intensive care showed that it performs well at both high and low blood glucose levels, with varying temperature and with inotrope use.

The continuous glucose monitoring device has been evaluated in non-critically ill populations. Wilhelm et al studied the performance of the CGMS under conditions of rapidly changing glucose levels in 12 adults with type 1 diabetes. They found no significant difference between the CGMS and the capillary blood glucose measurements. The device also performed well in studies assessing the risk of undetected nocturnal hypoglycaemia. Guillod et al studied 88 patients with type 1 diabetes with the CGMS Gold system over 6–9 months. The CGMS was found to reduce the risk of hypoglycaemia by 75%.

**Methods to assess accuracy of continuous glucose monitoring:** Many studies of the CGMS use Clarke error grid analysis to assess the performance of the device. In this method, the difference between the sensor reading and the glucose meter reading is plotted on a chart split into Zones A to E, representing areas of clinical risk. Results are plotted in zones of different significance: points in Zone A have no clinical implications (clinically accurate measurement), and points in Zone B lead to an appropriate clinical decision. Only points lying in Zones C, D and E would lead to inappropriate intervention or lack of intervention. Zone C means misinterpretation of euglycaemia for hyper- or hypoglycaemia (unnecessary overcorrection is possible). Points in Zones D and E mean overestimation of hypoglycaemia or underestimation of hyperglycaemia, which may lead to dangerous treatment. Despite this analysis technique being widely used, a limitation is that even very poorly performing monitors can achieve most of their data in Zones A and B (clinically acceptable), thus leading to the erroneous conclusion that the device is accurate. We used the method of Bland and Altman to plot our results, because the a-priori limits of ±1 mmol/L that we set as clinically acceptable are more stringent than those found acceptable using the Clarke error grid method. This becomes particularly important when considering critically ill patients treated with tight glycaemic control, where the target glucose range is small (4.4–6.1 mmol/L).

**Conclusions**

Our findings do not support the use of the Guardian continuous glucose monitor in an unselected group of adult critically ill patients. Of additional concern, there was significant lack of agreement in blood glucose levels obtained from the most commonly used samples: arterial and capillary blood samples. It is important when training ICU staff responsible for monitoring patients’ blood glucose to emphasise the non-interchangeability of capillary and arterial blood samples using point-of-care machines. The weight of published evidence supports the use of arterial over capillary blood for the accurate measurement of blood glucose level, but further studies are required to allow firm recommendations in critically ill patients. Recent trials of tight glycaemic control have not comprehensively shown that it is of benefit to critically ill patients, and thus morbidity from hypoglycaemia could be important in these patients. There may be a role for the Guardian continuous glucose monitoring system as an early warning device for detecting hypo- or hyperglycaemia, but due to the lack of readings in our study in these ranges, we cannot at present recommend this device for that use. Further studies are needed to assess the optimal method of blood glucose monitoring.
analysis in critically ill populations, and to assess the use of continuous glucose monitoring systems as tools to detect covert hyper- or hypoglycaemia in our patients.

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References
Appendix. Protocol for tight glucose control at the Royal Infirmary of Edinburgh, United Kingdom

Critical Care Directorate - Blood Glucose Control
(All Patients)

Start: Measure Blood glucose
NB if initial BM < 4.4 mmol/l, straight to 'hypoglycaemia' box

Measure blood Glucose 4 hourly

4.4 – 7.0 mmol/l

Insulin 2u/hr

7.1 – 9.0 mmol/l

Insulin 4u/hr

>12.0 mmol/l

No insulin

Increase infusion by 1 unit/hr

Measure blood glucose hourly

What is the blood glucose?
(If < 4.4 straight to 'Hypoglycaemia' box)

7.1 – 9.0 mmol/l

4.4 – 7.0 mmol/l

>9.0 mmol/l

Stop Insulin
Give 20ml 50% dextrose IV or 50ml 20% dextrose peripherally
Check BM in 20 min Call doctor

If BM falls whilst within target range, halve insulin rate
Otherwise keep insulin rate same
1 hourly BM for 4 hours
2 hourly BM for 4 hours
Then 4 hourly

Stop insulin
Recheck BM in 1 hour

< 3.5 mmol/l

HYPOGLYCAEMIA

3.5 – 4.3 mmol/l

- Insulin 50 units Actrapid® in 50ml 5% glucose do not run without a glucose source
- Glucose Source - while insulin running, MUST have one of the following:
  - enteral feed or TPN (≥50ml/hr) OR
  - RIE 5% glucose as per protocol 80ml/hr
  - WGH 0.45% Saline in 4% glucose 80ml/hr
  - SJH 10% glucose 20ml/hr
- If insulin restarted after having been stopped, go to 'what is blood glucose' box, start at previous rate as long as blood glucose more than 7
- If glucose falls by more than half after any dose adjustment, halve insulin rate
- Any patients on peritoneal dialysis must have all BM's checked on blood gas any doubt check formal lab glucose

Author Dr M Geddes May 2003
Reviewed by Dr B Cook April 2007
Next Review April 2009