

Accuracy of bedside glucose measurement from three glucometers in critically ill patients*

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Objective: Implementation of strict glucose control in most intensive care units has resulted in increased use of point-of-care glucose devices in the intensive care unit. The aim of this study was to determine the reliability of point-of-care testing glucose meters among critically ill patients under intensive insulin treatment.

Design: Prospective observational study.

Patients: Intensive care unit and non-intensive care unit patients in a tertiary care teaching hospital.

Measurements: A glucose oxidase method was used to validate the point-of-care testing devices. Three different point-of-care testing devices, Accu-Chek Sensor (Roche Diagnostics), Precision (Abbott Diagnostics), and HemoCue were tested. Glucose measurements were performed in duplicate by an experienced technician under standardized conditions in the hospital's laboratory, using arterial (intensive care unit patients) and arterial or venous (non-intensive care unit patients) heparinized whole blood samples.

Main Results: A strong correlation was found between the glucose oxidase method and the Accu-Chek device ($r^2 = .9596$, $p < 0.001$). Mean absolute difference between the glucose oxidase and Accu-Chek was -0.32 mmol/L (95% confidence interval -0.84 to 1.48 mmol/L). Using the International Organization for

Standardization (ISO) criteria, 27 of 197 samples (13.7%) were inaccurate. In all samples that failed to meet the ISO criteria, glucose values measured by the Accu-Chek device were higher compared with the glucose oxidase method. In another set of experiments among intensive care unit patients, strong positive correlations were also found between the other point-of-care testing devices and the glucose oxidase method. However, paired samples from Accu-Chek, HemoCue, and Precision failed the ISO criteria in 9 of 82 (11.0%), 4 of 82 (4.9%), and 11 of 82 (13.4%) of cases, respectively. In non-intensive care unit patients paired samples from Accu-Chek, HemoCue, and Precision failed the ISO criteria in 3 of 120 (2.5%), 11 of 120 (9.2%), and 16 of 120 (13.3%) cases, respectively.

Conclusions: Under standardized conditions, glucose results from three point-of-care testing devices were inaccurate in both intensive care unit and non-intensive care unit patients. Among intensive care unit patients, inaccurate glucose readings were most frequently falsely elevated, resulting in misinterpretation of high glucose values with subsequent inappropriate insulin administration or masking of true hypoglycemia. (Crit Care Med 2008; 36:3062–3066)

KEY WORDS: glucose; insulin; point-of-care testing; hypoglycemia; intensive care unit; glucometry

Strict glycemic control may improve morbidity and mortality in intensive care unit (ICU) patients (1, 2). However, intensive glucose control is associated with a higher prevalence of hypoglycemia compared with conventionally treated patients (3). In the two Leuven studies, intensive insulin therapy resulted in hypoglycemia in 5.1% and 25.1% of patients (1, 2). In addition, the prospective, randomized multicenter Effi-

ciency of Volume Substitution and Insulin Therapy in Severe Sepsis trial and Glucontrol study were both stopped prematurely because of the high rate of hypoglycemia in the intensive treatment group (4). Among critically ill patients, detection of hypoglycemia is especially difficult because these patients are often sedated and incapable of communicating, thereby masking clinical symptoms and signs. Therefore, frequent glucose measurement is required to titrate the amount of insulin and detect episodes of hypoglycemia.

Most ICUs use a nurse-driven insulin infusion protocol, combined with frequent blood glucose measurements. For practical reasons, bedside glucometry is often used. Point-of-care testing (POCT) devices for glucose measurement are extensively used among diabetic patients in hospital and outpatient settings. Implementation of strict glucose control has resulted in an extended use of POCT glucose devices in

other areas of the hospital, such as the ICU and operating room. Few studies assessed the accuracy of bedside glucometry in the ICU setting, revealing conflicting results. The aim of this study was to determine the reliability of several point-of-care glucose meters among critically ill patients under intensive insulin treatment.

METHODS

Population. We performed a prospective observational study in ICU patients admitted to a tertiary care teaching hospital in Nijmegen, The Netherlands. The local Institutional Review Board waived the need for informed consent. Random arterial blood samples were collected from medical and surgical ICU patients. All patients were treated with continuous insulin infusion therapy aiming at blood glucose levels between 4.4 and 6.1 mmol/L according to the protocol by Van den Berghe et al. (1, 2). A nurse-driven dynamic insulin algorithm was used combining continuous intravenous insulin infusion with intravenous

*See also p. 3113.

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bolus injections. In the control group, random arterial or venous blood samples were collected from non-ICU patients admitted to a surgical, internal medicine, or cardiac care ward.

Glucose Measurements. In ICU patients, approximately 2 mL of blood was withdrawn in a heparinized syringe (Pro-Vent, Pulsator; Portex, Keene, NA) from an arterial catheter after 3 to 5 mL of waste blood was discarded. In non-ICU patients admitted to the cardiac care unit, internal medicine and surgical ward venous or arterial blood samples were collected in the heparinized syringe.

The hexokinase method is considered the gold standard for blood glucose measurement. For practical purposes, we used the glucose oxidase method to validate the different POCT devices. To validate the glucose oxidase method (RapidLab blood gas analyzer, Siemens Diagnostics, Deerfield, IL), we measured 32 samples from 32 ICU patients and compared the obtained results with the hexokinase

method (Aeroset, Abbott Diagnostics, Basel, Switzerland). Three different POCT devices, Accu-Chek Sensor (Roche Diagnostics, Abbott Park, IL), Precision (Abbott Diagnostics), and HemoCue were tested. The Accu-Chek uses plasma-referenced glucosedehydrogenase-pyrroloquinolinequinone test strips for glucose detection. The Precision uses glucose dehydrogenase-NAD⁺, and HemoCue uses modified glucosedehydrogenase for glucose measurement. Glucose measurements were performed in duplicate by an experienced technician under standardized conditions in the hospital's laboratory, using arterial (ICU patients) and arterial or venous (non-ICU patients) heparinized whole blood samples. All POCT devices were used as advised by the operator's manual.

Experiments. In a first set of experiments, we compared the performance of the Accu-Chek with the glucose oxidase method in 197 arterial blood samples of 85 random ICU patients. In a second set of experiments, we simultaneously compared the performance of the three POCT devices with the glucose oxidase method in 82 arterial blood samples from 53 random ICU patients. The population in the second set of experiments was different from the population in the first set. In a third set of experiments, these three POCT devices were simultaneously tested using 74 arterial or venous samples from 47 random non-ICU patients admitted to a surgical, internal medicine, or cardiac care ward.

Statistical Analysis. The means of duplicate measurements were used for statistical analysis. Results of paired measurements (glucose oxidase vs. Accu-Chek, glucose oxidase vs. Precision, and glucose oxidase vs. HemoCue) were analyzed. The Pearson correlation coefficient (*r*) between the different methods was determined by linear regression. A Bland-Altman graph was made plotting the absolute differences between paired samples against the averages of these samples. In addition, paired samples were evaluated using the International Organization for Standardization (ISO)

criteria. To meet these criteria, glucose values of >4.1 mmol/L test values had to be within 20% of reference values, and for glucose values ≤4.1 mmol/L test values had to be within 0.8 mmol/L of reference values, 95% of the time. Patient characteristics were compared with the Mann-Whitney U test for continuous or Chi-square test for categorical variables. A *p* value <0.05 was considered significant.

RESULTS

Correlation Between the Glucose Oxidase and Hexokinase Method. Correlation between the glucose oxidase and hexokinase method was good ($r^2 = .9948$, $p < 0.001$, data not shown). Mean absolute difference between the glucose oxidase and hexokinase method was -0.15 mmol/L (95% CI -1.24 to 0.94 mmol/L). All samples met the ISO criteria.

First Set of Experiments: Comparison of the Accu-Chek and the Glucose Oxidase Method. From June to July 2006, 197 random heparinized arterial blood samples were drawn from 85 medical and surgical ICU patients. Patient characteristics, disease severity score, and diagnosis at admission to the ICU are presented in Table 1. We did not differentiate between diabetic and nondiabetic patients. In each blood sample, the glucose concentration was measured simultaneously by the Accu-Chek and glucose oxidase method. A strong positive correlation was found between the glucose oxidase method and the Accu-Chek ($r^2 = .9596$, $p < 0.001$). Mean absolute difference between the glucose oxidase and Accu-Chek was -0.32 mmol/L (95% CI -0.84 to 1.48 mmol/L) (Fig. 1). Using the ISO criteria, 27 of 197 samples (13.7%) were inaccurate. These inaccurate samples were found over the entire range of blood glucose values (2.3–18.7 mmol/L). In all samples that failed to meet the ISO criteria, glucose values measured by the Accu-Chek were higher compared with the glucose oxidase method. We compared patients having inaccurate Accu-Chek glucose values with those whose Accu-Chek glucose values met the ISO criteria (Table 2). Patients with inaccurate Accu-Chek glucose values were significantly older (median 71 vs. 51 yrs, $p = 0.002$), had higher Simplified Acute Physiology Scores (median values 60.0 vs. 46.5, $p = 0.003$), and had a higher ICU mortality rate (57.1% vs. 26.8%, $p = 0.03$).

Second Set of Experiments: Comparison of POCT Devices and the Glucose Oxidase Method in ICU Patients. In a second set of experiments, we tested the

Table 1. Patient characteristics on admission to the intensive care unit (ICU)

Number of patients (n)	85
Male (n)	54
Age (yrs)	55 (38.0–69.3)
BMI (kg/m ²)	24.5 (22.5–27.1)
SAPS	49.0 (35.0–55.8)
APACHE II	21.0 (16.0–25.0)
Diagnosis at admission to ICU (n)	
Respiratory failure	8
Pneumonia	4
Sepsis	19
Trauma	20
Postsurgery	14
Cardiac arrest	3
Stroke	7
Other	10

BMI, body mass index; SAPS, Simplified Acute Physiology Score; APACHE II, Acute Physiology and Chronic Health Evaluation.

Values are expressed as median values (interquartile range), unless stated otherwise.

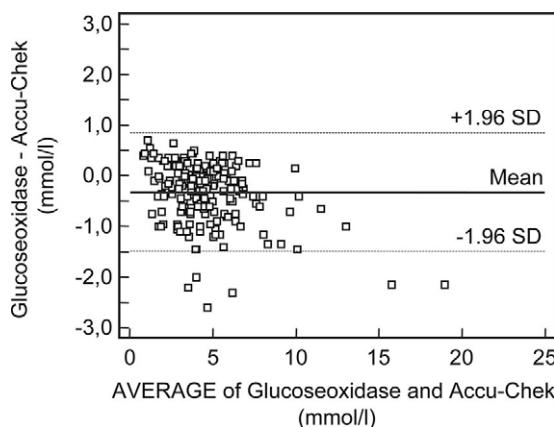


Figure 1. Bland and Altman plot of agreement between simultaneous glucose measurements by the Accu-Chek and glucose oxidase method in 197 arterial blood samples obtained from 85 random intensive care unit patients.

performance of Accu-Chek in relation to two other POCT glucose devices (HemoCue and Precision), in critically ill patients using 82 arterial blood samples from 53 random ICU patients. Glucose measurements were simultaneously performed using the three different POCT devices and the glucose oxidase method. A strong correlation was found between the POCT devices and the glucose oxidase method, with highly significant correlation coefficients of $r^2 = .9433$, 0.9744 , and 0.9587 ($p < 0.001$), respectively, for the Accu-Chek, HemoCue, and Precision

devices. The mean differences between the Accu-Chek and the glucose oxidase method was -0.1 mmol/L (95% CI -1.80 to 1.60 mmol/L) (Fig. 2A), between the HemoCue and the glucose oxidase method was -0.15 mmol/L (95% CI -1.24 to 0.94 mmol/L) (Fig. 2B), and between the Precision and the glucose oxidase method was 0.1 mmol/L (95% CI -1.40 to 1.50 mmol/L) (Fig. 2C). Paired samples from the Accu-Chek, HemoCue, and Precision failed the ISO criteria in 9 of 82 (11.0%), 4 of 82 (4.9%), and 11 of 82 (13.4%) cases, respectively (Table 3). The

inaccuracies in blood glucose values based on the ISO criteria in the three POCT devices occurred in the range from 2.1 to 17.2 mmol/L glucose.

Third Set of Experiments: Comparison of POCT Devices and the Glucose Oxidase Method in Non-ICU Patients. In a third set of experiments, we tested the performance of POCT devices among 47 noncritically ill patients using random samples. Venous and arterial whole blood samples were analyzed simultaneously using the three different devices and the glucose oxidase method. A strong correlation was found between the POCT devices and the glucose oxidase method, with highly significant correlation coefficients of $r^2 = 0.963$, 0.971 , and 0.973 ($p < 0.001$), respectively, for the Accu-Chek, HemoCue, and Precision devices. The mean differences between the Accu-Chek and the glucose oxidase method was 0.1 mmol/L (95% CI -1.0 to 1.1 mmol/L) (Fig. 3A), between the HemoCue and the glucose oxidase method was 0.1 mmol/L (95% CI -1.1 to 1.4 mmol/L) (Fig. 3B), and between the Precision and the glucose oxidase method was -0.51 mmol/L (95% CI -1.64 to

Table 2. Clinical characteristics of intensive care unit (ICU) patients with accurate and inaccurate International Organization for Standardization (ISO) criteria using the Accu-Chek

	Accurate ISO Criteria (n = 71)	Inaccurate ISO Criteria (n = 14)	p
Male (n)	45 (63.4%)	9 (64.3%)	0.601
Age (yrs)	51 (35–66)	71 (56–75)	0.002
BMI (kg/m ²)	24.5 (22.5–26.6)	25.0 (23.0–27.1)	0.781
SAPS	46.5 (32.3–54.0)	60 (50.0–63.0)	0.003
APACHE II	21.0 (15.5–24.5)	24.0 (17.0–29.0)	0.122
Died in ICU (n)	19 (26.8%)	8 (57.1%)	0.030

Values are expressed as median values (interquartile range) unless stated otherwise.

SAPS, Simplified Acute Physiology Score; BMI, body mass index; APACHE, Acute Physiology and Chronic Health Evaluation.

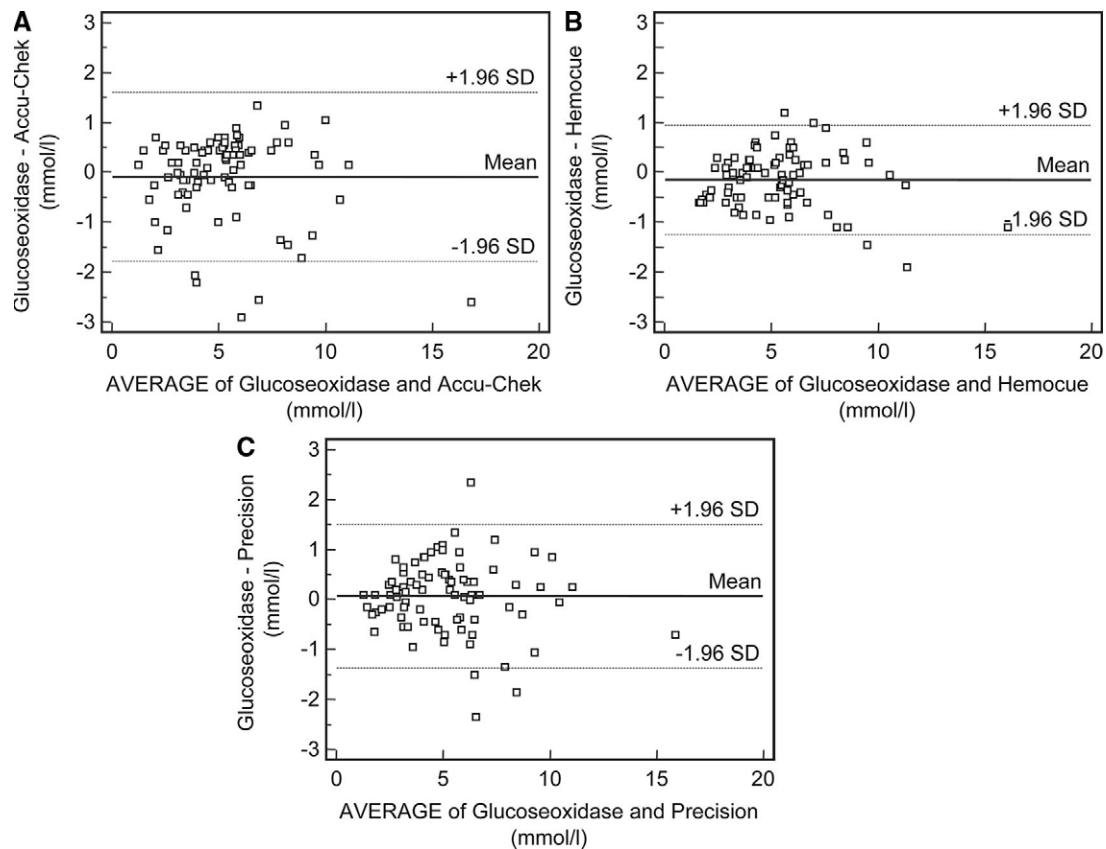


Figure 2. Bland and Altman plot of agreement between simultaneous glucose measurements by the Accu-Chek and glucose oxidase method (A), HemoCue (B), and Precision (C) method in 82 arterial blood samples obtained from 53 random intensive care unit patients.

0.63 mmol/L) (Fig. 3C). Paired samples from the Accu-Chek, HemoCue, and Precision device failed the ISO criteria in 3 of 120 (2.5%), 11 of 120 (9.2%), and 16 of 120 (13.3%) cases, respectively (Table 3). The inaccuracies based on the ISO criteria in the three POCT devices occurred in the range of 1.2 to 13.4 mmol/L glucose.

DISCUSSION

The present study demonstrates that glucose measurement in ICU patients using any of the three tested POCT devices studied can be inaccurate and potentially

dangerous. We also show that different results are obtained among ICU and non-ICU patients. Among ICU patients, inaccurate glucose readings were most frequently falsely elevated, and occurred over the entire range of blood glucose values. Patients with inaccurate POCT glucose results were significantly older, had a higher disease severity score, and a higher ICU mortality compared with patients with accurate glucose values. In non-ICU patients, inaccuracy was mainly observed in the lower range of blood glucose values.

In studies to date, the tendency of the POCT devices has been to overestimate

the reference standard (5–8). These studies compared capillary (fingerstick) glucose measurements using POCT devices with arterial blood gas samples using the glucose oxidase method. A general conclusion from these studies is that although there may be a statistically significant agreement between methods, the accuracy of glucose measurement using POCT has been unacceptable in critically ill patients. The inaccuracy has been even more evident in patients suffering from shock and requiring vasopressors. Studies comparing glucose levels in arterial blood samples have yielded conflicting results. Acceptable results were found between the blood gas analyzer and POCT device in critically ill patients by Corstjens et al. (9). Others found only a 70% agreement between POCT devices and the laboratory reference standard method (7). Agreement in this study was not based on absolute or relative differences between samples, but the tested methods were considered appropriate if both measurements resulted in the same intervention as dictated by the local insulin infusion protocol.

Table 3. Inaccurate International Organization for Standardization (ISO) criteria in intensive care unit (ICU) and non-ICU patients

Setting	Test Device	Inaccurate ISO Criteria	Test Value Higher	Test Value Lower	p^a
ICU	Accu-Chek	9/82 (11.0) ^b	9/82 (11.0)	0/82 (0)	0.006
	HemoCue	4/82 (4.9)	4/82 (4.9)	0/82 (0)	0.12
	Precision	11/82 (13.4)	5/82 (6.1)	6/82 (7.3)	0.002
Non-ICU	Accu-Chek	3/120 (2.5)	2/120 (1.7)	1/120 (0.8)	0.25
	HemoCue	11/120 (9.2)	10/120 (8.3)	1/120 (0.8)	0.002
	Precision	16/120 (13.3)	16/120 (13.3)	0/120 (0)	<0.001

^a p value compared with glucose oxidase method; ^bValues in parentheses indicate percentage.

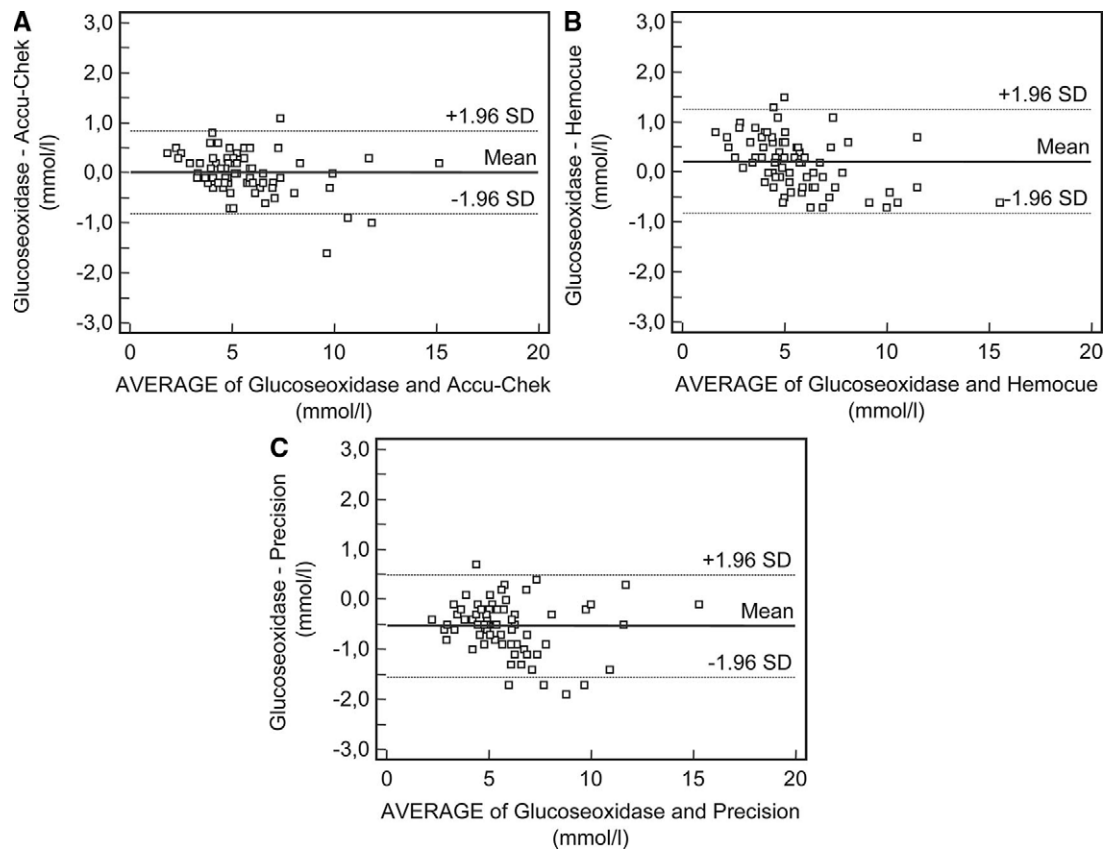


Figure 3. Bland and Altman plot of agreement between simultaneous glucose measurements by the Accu-Chek and glucose oxidase method (A), HemoCue (B), and Precision (C) method in 74 arterial and venous blood samples obtained from 47 random non-intensive care unit patients.

From these studies, it remains unclear whether different sampling methods, devices used, or both contribute to the observed inaccuracy. In most studies, two differently obtained blood samples were compared. Moreover, most of the previous studies compared bedside results obtained by nurses using POCT devices with blood-gas analysis performed in the hospital's laboratory. Using the methodology applied in these studies, preanalytical errors may interfere with the results. In our study, preanalytical bias was minimized. Comparisons between the different methods were performed simultaneously using a single blood sample, thereby abolishing the potential influence of sampling methods and avoiding aging of the specimens with concomitant secondary changes in glucose levels. All samples were measured in duplicate within the central laboratory facilities under standardized conditions and performed by an experienced laboratory technician. The results of the present study indicate that the observed inaccuracies are mainly due to the POCT device itself.

The mechanism underlying the differences in glucose values between the different POCT systems and the glucose oxidase method in critically ill patients is unknown. Accu-Chek uses the glucosedehydrogenase-pyrroloquinolinequinone method for glucose determination, which is not specific for glucose. This method misinterprets maltose, icodextrin (which is converted to maltose), galactose, and xylose as glucose, leading to erroneously elevated glucose levels (10). None of our patients used products containing these sugars (e.g., peritoneal dialysis solutions). In addition, Tang et al. (11) demonstrated that a large number of drugs commonly used in the treatment of critically ill patients, such as acetaminophen, dopamine, and mannitol, interfered with a number of POCT test systems. Although a large number of our patients were treated with acetamino-

phen and other possible confounding drugs, no clear relation between use of these agents and the occurrence of inaccurate glucose values could be found (data not shown). No interference in POCT glucose measurements was observed when blood samples were diluted using different concentrations of a plasma expander (Voluven, Fresenius Kabi, Hamburg, Germany) or total parenteral nutrition (data not shown). We speculate that the inaccuracy of the POCT devices may result from an unknown confounder interacting with the enzymes on the test strips. Alternatively, the glucose metabolism may be altered in critically ill patients, resulting in glucose breakdown products that are misinterpreted as glucose.

We also observed inaccuracies among non-ICU patients. The performance of Accu-Chek was better among non-ICU patients (<5% inaccuracies) in comparison with ICU patients (>10% inaccuracies). In contrast, the HemoCue device showed the best performance among our ICU patients (<5% inaccuracies) and worse performance in non-ICU patients (>10% inaccuracies). In non-ICU patients, most inaccuracies resulted in an overestimation of glucose values in comparison to the glucose oxidase method. These differences among the three tested devices and among the various patient groups indicate different performance characteristics between groups. These results show that glucose POCT devices should be thoroughly compared with the reference method used in one's own laboratory before implementation in patient care.

In conclusion, this study clearly shows that, under standardized conditions, glucose results from the three POCT devices evaluated were frequently inaccurate in critically ill ICU patients. Among ICU patients, the inaccurate glucose readings were most frequently falsely elevated, resulting in misinterpretation of high glu-

cose values with subsequent inappropriate insulin administration or masking of true hypoglycemia. Although these POCT devices seem attractive because of simple handling and rapid results, they should not be used in ICU patients.

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