Journal of Diabetes Science and Technology
Volume 6, Issue 2, March 2012

REVIEW ARTICLE

The Accuracy of Point-of-Care Glucose Measurements

Annette Rebel, M.D.,[1] Mark A. Rice, M.D.,[2] and Brenda G. Fahy, M.D., FCCM[2]

Abstract

Control of blood glucose (BG) in an acceptable range is a major therapy target for diabetes patients in both the hospital and outpatient environments. This review focuses on the state of point-of-care (POC) glucose monitoring and the accuracy of the measurement devices. The accuracy of the POC glucose monitor depends on device methodology and other factors, including sample source and collection and patient characteristics. Patient parameters capable of influencing measurements include variations in pH, blood oxygen, hematocrit, changes in microcirculation, and vasopressor therapy. These elements alone or when combined can significantly impact BG measurement accuracy with POC glucose monitoring devices (POCGMDs). In general, currently available POCGMDs exhibit the greatest accuracy within the range of physiological glucose levels but become less reliable at the lower and higher ranges of BG levels. This issue raises serious safety concerns and the importance of understanding the limitations of POCGMDs. This review will discuss potential interferences and shortcomings of the current POCGMDs and stress when these may impact the reliability of POCGMDs for clinical decision-making.

J Diabetes Sci Technol 2012;6(2):396-411

Introduction

The prevalence of diabetes mellitus continues to increase with approximately 12.9% of the population in the United States diagnosed with diabetes and an even larger portion (29.5%) estimated to be living in a prediabetic state.[1] Control of blood glucose (BG) in an acceptable range remains a target for diabetes patients in both the hospital and outpatient environments.[2] Glycemic control using an insulin infusion in critically ill patients requires frequent and rapid BG monitoring with devices available for bedside use.[3–7] The accuracy of the BG measurements plays an important role for treatment decisions when aiming for glycemic control. This article reviews the accuracy and limitations of current point-of-care glucose monitoring devices (POCGMDs).

Author Affiliations: [1]Department of Anesthesiology, College of Medicine, University of Kentucky, Lexington, Kentucky; and [2]Department of Anesthesiology, University of Florida College of Medicine, Gainesville, Florida

Abbreviations: (ADA) American Diabetes Association, (BA) Bland-Altman, (BG) blood glucose, (CLD) central laboratory devices, (FDA) Food and Drug Administration, (GDH) glucose-1-dehydrogenase, (GOX) glucose oxidase, (Hct) hematocrit, (ICU) intensive care unit, (ISO) International Organization for Standardization, (MBTH) meta[3-methyl 2 benzothiazoline hydrazine]N-sulfonyl benzene sulfonic acid, (NAD) nicotinamide adenine dinucleotide, (NADH) nicotinamide adenine dinucleotide (reduced form), (P_aO_2) blood oxygen content, (P_aCO_2) carbon dioxide tension, (PO_2) oxygen tension, (POC) point of care, (POCGMD) point-of-care glucose monitoring device, (PQQ) pyrroloquinoline quinone, (SMBG) self-monitoring of blood glucose, (YSI) Yellow Springs Instruments

Keywords: blood glucose, glucose error, glucose measurement, hypoglycemia, laboratory, point-of-care device

Corresponding Author: Brenda G. Fahy, M.D., FCCM, Department of Anesthesiology, College of Medicine, University of Florida, Florida, P.O. Box 100254, Gainsville, FL 32610; email address *ohall@anest.ufl.edu*

The accuracy of glucose monitoring depends on many aspects, including the device measurement mechanism, sample source and collection, and patient attributes. This review will summarize the details of measurement techniques and potential interferences that may alter these measurements to provide background for the subsequent discussion of device accuracy.

Glucose Monitoring Techniques

Point-of-care Glucose Monitoring Devices

During the 1970s, POCGMDs were originally designed for home self-monitoring of blood glucose (SMBG) for diabetes patients to improve glucose control during regular life activities. However, ease of use of a POCGMD and its rapid reporting of BG information led to its utilization in the inpatient setting, recognizing that POCGMDs might have certain limitations with this application. Depending on the specific glucose measurement technique of a POCGMD, the measurements can be influenced by various circumstances. Therefore, technical data are listed in **Table 1**, and the glucose measurement methodology will be briefly discussed.

Glucose Oxidase

This measurement technique uses glucose oxidase (GOX) as a catalyst for oxidation of glucose to gluconic acid and hydrogen peroxide; the amount of hydrogen peroxide produced is proportional to the glucose concentration in the blood sample. This change in the hydrogen peroxide concentration can be measured by using a color change as an indicator using a photometric technique or in newer devices, which rely on the production of an electrical current (amperometric technique).[8] The basic chemical pathways for the GOX reactions are shown in **Figure 1**.

Glucose-1-dehydrogenase

This measurement technique uses glucose-1-dehydrogenase (GDH) to convert glucose to gluconolactone with older devices using a coenzyme to convert nicotinamide adenine dinucleotide (NAD) to NADH (reduced form of NAD). The NADH concentration is measured and is proportional to the BG concentration. The NADH concentration can be measured using a photometric or amperometric technique. Newer POCGMDs use the coenzyme pyrroloquinoline quinone (PQQ) because of less sensitivity to ambient oxygen and electrochemical interference. However, this coenzyme has introduced a dangerous situation, as described later. The outline for the GDH PQQ reaction is shown in **Figure 1**.

Table 1.
Summary of Frequently Used POCGMDs

Company and devices	Method		Range (mg/dl)	Information
	Enzyme	Analysis		
Roche (Basel, Switzerland)				
AccuChek II	GOR	Photo		Discontinued
Accuchek Advantage	GDH	Amp	10–600	
AccuChek Compact Plus	GDH	Amp	10–600	
AccuChek Comfort	GDH	Amp		Discontinued
AccuTrend	GDH	Amp		Glucose/ lactate/ triglycerides
HemoCue (Cypress, California)	GDH	Photo		
Abbott/MediSense (Alameda, California)				
Precision QID	GOX	Amp	20–600	
Precision PCX	GOX	Amp	20–600	
FreeStyleFlash	GDH	Amp	20–500	
Optium	GDH	Amp	20–500	
Optium Xceed	GDH	Amp	20–500	
Bayer (Leverkusen, Germany)				
Elite XL	GOX	Amp	20–600	
Ascensia Contour	GDH	Amp	20–500	
LifeScan (Milpitas, California)				
OneTouch II/Ultra	GOX	Photo	0–600	
SureStep Pro/Flexx	GOX	Photo	0–500	
DDI Prodigy (Charlotte, North Carolina)	GDH	Amp		Voice controlled
Menarini GlucoMen PC (Berlin, Germany)	GOX	Amp	20–600	

GOR, glucose dye oxidoreductase mediator reaction; photo, photometric; amp, amperometric.

Both GOX and GDH measurement techniques present limitations. The GOX method is extremely specific for BG concentration. However, blood oxygen concentrations influence GOX devices, but not the GDH technique.[9,10] The potential influence of physically dissolved oxygen for the GOX reaction is shown in **Figure 1**. When there are high levels of dissolved oxygen in the sample (e.g., hyperoxia), oxygen is readily available for the GOX reaction and can cause an underestimation of blood glucose; conversely, hypoxemia may falsely elevate GOX

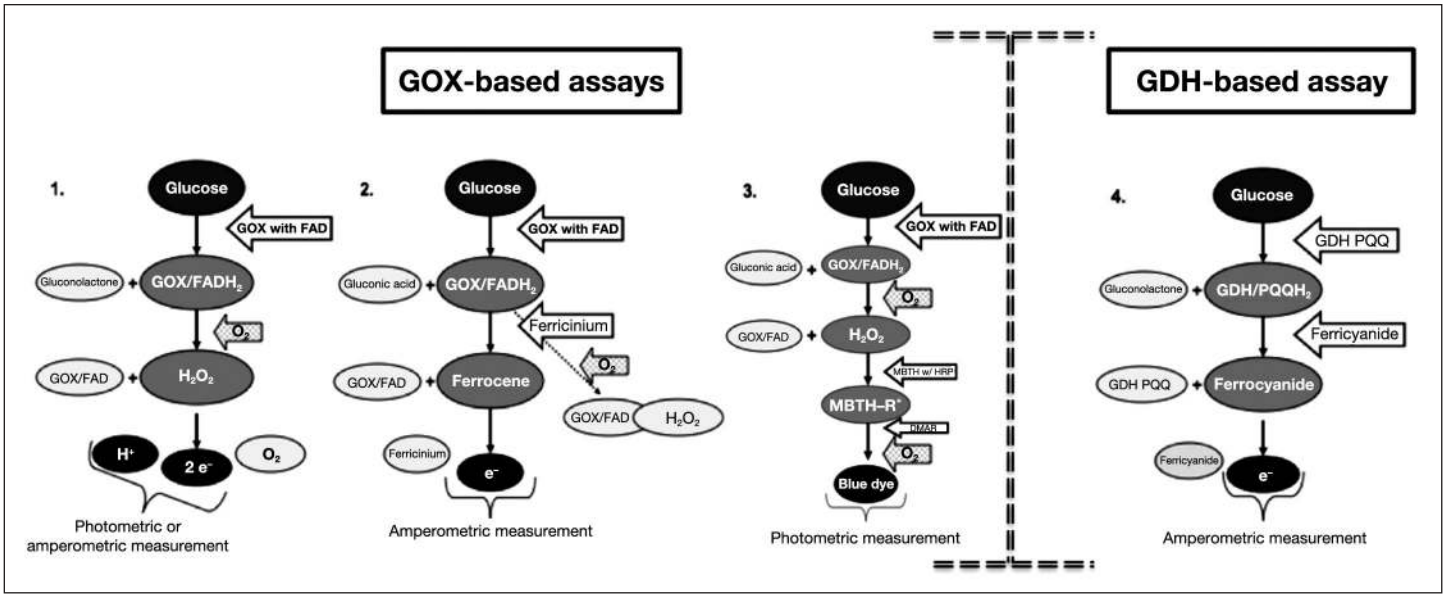

Figure 1. Basic chemical pathways for the glucose oxidase and glucose dehydrogenase-based glucose measurement.H2O2, hydrogen peroxide; FAD, flavin adenine dinucleotide; MBTH, meta[3-methyl 2 benzothiazoline hydrazine]*N*-sulfonyl benzene sulfonic acid; HRP, horseradish peroxidase; DMAB, dimethylaminobenzoic acid.[9]

glucose measurements. The significance of the oxygen influence is relatively small compared to other potential interferences.[9,11] The GDH technique using PQQ has limitations as well. This coenzyme reacts with other sugars (e.g., maltose, galactose, mannose, xylose, and ribose) and detects them as glucose; alternate techniques should be used when these other sugars are present.[12,13] The Food and Drug Administration (FDA) issued a public health notification in 2009, secondary to a number of deaths, for the use of the GDH-PQQ glucose monitor because of the potential fatal error related to the interference of other sugars with this methodology.[14] For example, icodextrin (a substance commonly used in peritoneal dialysis fluid) is broken down to maltose, which is reported as glucose with the GDH-PQQ POCGMDs. Because of this substance interference, the POCGMD overreports the BG level and, in some cases, can lead to critical treatment errors with significant consequences of hypoglycemia.

Drugs may interfere with both GOX and GDH glucose measurement methods, including but not limited to ascorbic acid and acetaminophen.[15,16] The presence of high doses of ascorbic acid has the potential to read falsely low in GOX- and GDH-based devices. Acetaminophen, in therapeutic concentrations, results in lower and higher glucose measurements with the GOX and GDH POCGMD techniques, respectively.[12]

Central Laboratory Devices

One comparison used for glucose devices is the central laboratory device (CLD) because of its higher accuracy, and studies assessing POCGMD accuracy often employ CLD. Measurement techniques of CLDs vary by device type, and most frequently utilize either the GOX or, more commonly, the glucose hexokinase reaction to measure BG concentration. According to a proficiency report surveying U.S. laboratories, the majority of CLDs use a hexokinase-based method, and the remaining facilities use GOX-based assays.[17] Glucose hexokinase phosphorylates glucose to glucose-6-phosphate which is then oxidized by glucose-6-phosphate dehydrogenase using NAD as a cofactor. This results in production of NADH, and the concentration is measured with a spectrophotometer (absorption 340 nm) to determine BG concentration.

The YSI (Yellow Springs Instruments, Yellow Springs, OH) has been used in many studies as a glucose reference. The YSI uses GOX to measure the hydrogen peroxide produced with an amperometric technique. However, in clinical practice, the YSI analysis has been replaced by multianalyte automated instrumentation. Rarely, a radioactive labeled isotope assay is used for instrument validation. Few laboratories still report YSI values.[17,18]

Sample Source and Collection Site

Methodologies involved with the collection site and storage can significantly impact BG measurements. At room temperature, glucose is metabolized by blood cells at a rate of 5–7% per hour.[19] Glycolysis is typically not an issue for a POC measurement, but can cause

falsely lower values in CLD results with delayed analysis. One should be cognizant of this when comparing results from both sources.

The CLD reports plasma glucose concentrations; POCGMD measurements typically involve whole blood samples with results usually internally converted to plasma values. Glucose concentrations are higher in the plasma than whole blood because the water content (and thus the glucose concentration) is higher in plasma than in erythrocytes.[20] The water content of the plasma can be affected by the concentration of other components. Hypertriglyceridemia and paraproteinemias decrease the water concentration in the whole blood sample, potentially causing a "pseudohypoglycemia," measured by POCGMDs.[20]

Sample source can also significantly impact glucose concentration measurements. Potential sampling sites include arterial, venous, or capillary (e.g., finger tips, ear lobes, etc.). As a general rule, the highest to lowest glucose concentration by sampling site is artery, capillary, and then venous.[21] The difference in glucose concentrations between capillary and venous blood can be altered by the patient's metabolic state, with insignificant differences in the absence of stress and fasting. In a critically ill patient, the presence of a hypermetabolic state and other stressors, including fasting, can cause significant differences between these values.[21,22] As an example, a critically ill patient with circulatory shock may exhibit a significant difference caused by increased glucose extraction and poor tissue perfusion.

Blood oxygenation affects POCGMD glucose measurement techniques with GOX and not with GDH.[9–11] Although values may not differ significantly within the normal oxygen range, errors with GOX measurement techniques can be 15% or more when P_aO_2 (blood oxygen content) exceeds 100 mm Hg or falls below 44 mm Hg depending on the type of test strip and measurement method.[9,23] As shown in **Figure 1**, GOX test strips using peroxide/meta[3-methyl 2 benzothiazoline hydrazine] *N*-sulfonyl benzene sulfonic acid (MBTH) are less vulnerable to oxygen presence than the GOX/ferrocene method. On the basis of a comparative analysis of several POC test strips by Tang and colleagues,[11] using ±15% of reference value from CLD as tolerated error, the GOX/ferrocene strips had the highest glucose measurements outside of the error tolerances (20.1–31.6%), while 14.3% of the GOX/MBTH measurements were outside of the set limits. The impact of oxygen tension on accuracy worsened when blood glucose concentration fell below 100 mg/dl and the oxygen tension was above 100 mm Hg. Only one study investigated the influence of extremely low oxygen tension on POC glucose measurements and found that GOX-based techniques might be inaccurate at extremely low oxygen tensions (PO_2 less than 20 mm Hg).[23] Although the impact of oxygen tension on the overall accuracy of POCGMD in the cited studies can be minimal, it is not negligible. Therefore, it has been recommended to minimize the oxygen tension effect on glucose testing variability by using oxygen-insensitive test methods in critically ill patients with P_aO_2 >100 mm Hg or patients with unpredictable blood PO_2 levels.[11]

The impact of patient factors on POC glucose accuracy has been investigated by assessing POCGMDs during tight glycemic control for critically ill patients. The application of POCGMDs for glucose monitoring in critically ill patients is thus important with a detailed discussion covered later in this review. The FDA MAUDE (Food and Drug Administration Manufacturer and User Facility Device Experience) database has been searched for reports related to glucose monitors, revealing 189 records for the year 2011.[24] An inquiry of the FDA recall database indicated 30 recalls related to glucose monitors in the time frame 2004–2011.[24]

Based on the review of the databases mentioned earlier, the POCGMD technology is not always the cause of inaccuracy. Additional effects can come from sample sources, collection sites, and patient factors, and may include the glucose meter cleaning solution or the disinfectant wipe interfering with the measurement.[25,26]

Point-of-Care Glucose Monitoring Devices Accuracy

There are two ways to assess the accuracy of glucose measurement techniques: technical or clinical. Technical accuracy assesses the agreement between the measured and reference glucose values. Clinical accuracy judges how the differences in the measurements impact clinical decision processes. Both have clinical implications.

A review by Krouwer and Cembrowski[27] details the standards and statistical methods used to characterize accuracy of POCGMDs and highlight the different criteria acceptable for accuracy between standard organizations and professional societies (**Table 2**). In 1987, an American Diabetes Association (ADA) consensus statement recommended that the acceptable error for POCGMDs from all sources (user, analytical, etc.) should be less than 10% for glucoses ranging from 30 to 400 mg/dl at all times.[28]

This ADA consensus statement also recommended that glucose measurements should not differ more than 15% from values obtained by a laboratory reference method. The ADA decreased the maximum allowable analytical error to <5% in 1996.[29,30]

International Organization for Standardization (ISO) 15197 provided different recommendations in 2003.[31] These state that 95% of the individual glucose measurements compared to the reference measurements are required to be in the range ±15 mg/dl for values less than or equal to 75 mg/dl and ±20% for glucose values greater than 75 mg/dl.[30] This is the standard that the FDA normally uses as the goal for approval of POCGMDs. The standards set by the ADA (ADA 1987/1996), requiring all glucose measurements with POCGMDs to be within 5% of CLD values, were deemed technically unachievable by the International Federation of Clinical Chemistry and Laboratory Medicine.[19,27] Additionally, the ranges of error set by the technical standards and allowable error do not address the possibility that these errors might provide safety concerns for patients by decision-making being based on inaccurate glucose values.[19,31,32]

Because of these concerns, publications have reviewed the technical and statistical aspects of POCGMD glucose monitoring.[20,27,33,34] Several statistical and graphical options has been used to correlate POCGMD measurements with CLD values. One option to assess analytical error is to use bias plots, such as Bland-Altman (BA) plots. The BA plot graphs the difference between a candidate and a reference method plotted against the mean of the two measurements, where the candidate method is the method under validation. Therefore, the BA plot is a direct visualization of the difference between the two methods. Bias plots allow the analysis of bias and variation from reference of POCGMD measurement over a range of glucose concentrations.[35] However, information about the clinical significance of the error is not included in this type of analysis. The error grid plots accuracy in terms of the effect on clinical decisions. The recognized need for a more clinically oriented approach to ensure patient safety for evaluation and regulation accuracy of devices was addressed by Clarke and colleagues[36] in 1987, with these recommendations modified by Parkes and colleagues[37] in 2000, which is commonly called the consensus grid. Clarke and colleagues[36] developed the error grid to evaluate the accuracy of the clinical decision-making based on the measured glucose value. The grids define several zones: zone A, points with no clinical implication because of clinically accurate measurement; zone B, points still lead to accurate clinical decisions; zone C, misinterpretation of euglycemia as hyper- or hypoglycemia; and zone D/E, points lead to overestimation of hypoglycemia or underestimation of hyperglycemia. Decisions and/or interventions that were clinically inappropriate due to errors in glucose measurements were illustrated by the points located in zones C, D, and E. Parkes and colleagues[37] subsequently modified the Clarke error grid (shown in **Figures 2** and **3**) because of concerns of the proximity of the results in zone A (acceptable result) and zone D (dangerous result). Although the error grids of Clarke and Parkes have been used to explore the clinical accuracy and implications of POCGMDs, organizations responsible for establishing standards have yet to adopt this approach. The FDA commonly uses error grids in the approval process for a POCGMD.

On the basis of recent publications reviewing the difficulties of the technical and statistical aspect of

Table 2.
Acceptable Performance Criteria

Glucose range	ADA (1987)	ADA (1996)	FDA (1988)	ISO 15197 (2001)
<100 mg/dl	<10%	±5%	±20 mg/dl	At <75 mg/dl, 95% of measurements should be ±15 mg/dl; at >75 mg/dl, 95% of measurements should be ±20%
≥100 mg/dl	<10%	±5%	±20%	95% of measurements should agree with the reference method; the regression slope can only deviate by ±5%
	at 100% times	at 100% times	<100% of data	95% of data

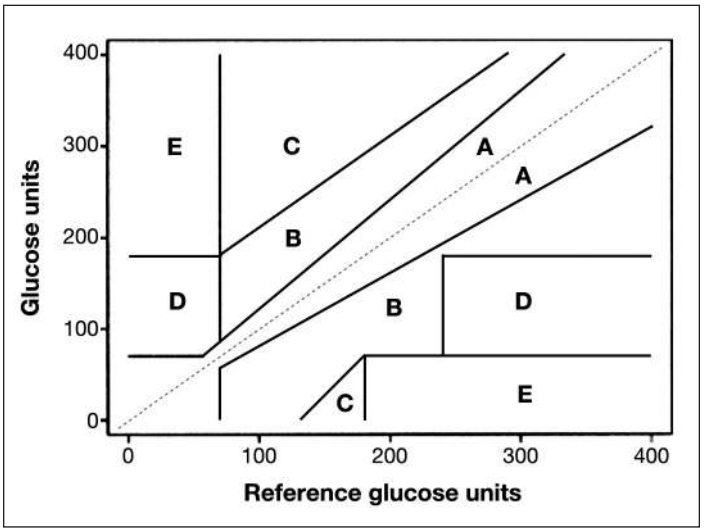

Figure 2. Clarke error grid.

POCGMD glucose monitoring, the currently available standards are not meeting the needs of clinicians in certain environments (hyper- or hypoglycemia, intensive insulin therapy), and clinicians are concerned with the lack of agreement between POCGMD results with serum/plasma laboratory results.[20,27] With concerns that the current allowable errors could potentially harm patients, there has been a call for the development of more clinically relevant standards.[20,27,33,34]

Studies of Point-of-Care Glucose Monitoring Devices Accuracy

A Medline search was performed for the years 1990–2011 using the following key words: blood glucose, glucose meter, glucose error, glucose measurement, hypoglycemia, point-of-care device, tight glucose control, and insulin therapy. Review of this literature identified publications relevant to the evaluation of POCGMD accuracy. Characteristics of the relevant publications studying outpatients or hospitalized ward patients excluding intensive care unit (ICU) patients are listed in **Table 3**, with a study summary in **Table 4**. This search revealed publications that compared several POCGMDs to a reference CLD. Giordano and colleagues[38] compared seven commercially available POCGMDs with a reference method, finding only three devices had acceptable measurement accuracy. The remaining four devices consistently underestimated blood glucose levels of less than 100 mg/dl, raising concerns about the potential implications of unrecognized and thus untreated hypoglycemia. Chen and colleagues[39] blindly evaluated four POCGMDs to prevent any potential bias created by commercial pressure. Only two out of four devices performed with acceptable accuracy according to ISO standards; none achieved the ADA 1996 recommendations for POCGMD accuracy. All four POCGMDs showed less reliability with lower glucose values compared to normal or higher values. Cohen and colleagues[40] evaluated five POCGMD using the Clarke error grid; four of the five devices met criteria for accurate clinical decision-making. However, only one out of five devices met ADA 1996 accuracy standards.

Seven POCGMDs involving four different manufacturers were compared to a reference method (YSI) by Khan and colleagues.[41] Only one device met ADA 1996 performance requirements. Of major concern was the significant disagreement with reference values within the critical hypoglycemic range that could result in an adverse clinical decision. At the extremes of hyperglycemia and hypoglycemia, when compared to CLD, 61% of values

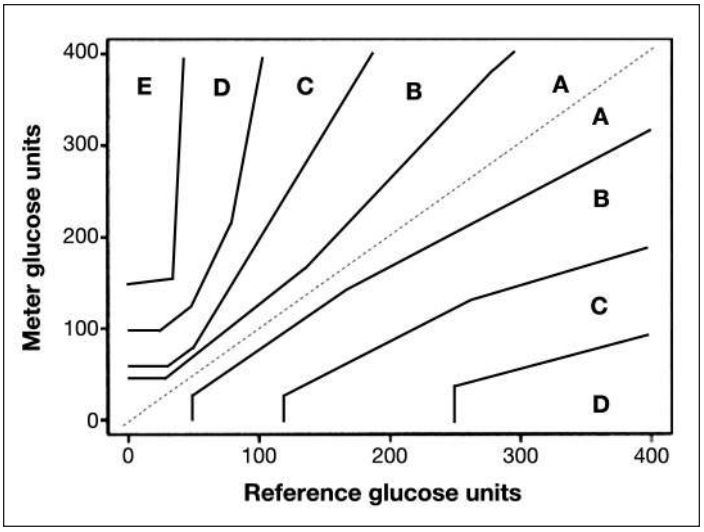

Figure 3. Parkes consensus error grid (printed with permission from the *Journal of Diabetes Science and Technology*).

differed by more than 10% from the reference method with an alarming 57% of measurements differing by more than 20% in the hypoglycemic range. This study emphasizes the shortcomings for accurate detection and thus treatment of hypoglycemia with POCGMDs.

In 2008, Thomas and colleagues[42] evaluated several POCGMDs not available in the United States. Four of the five devices were deemed accurate enough to be used in a clinical setting based on a Clarke error grid. However, only two of the five devices provided measurements with less than 20% variation from the reference method, with one device having less than 10% error.

Although the ADA and ISO guidelines have been published for over a decade, few POCGMDs meet these accuracy standards. Two examples of evaluations include (1) Sheffield and colleagues[43] studied four commercially available POCGMDs and reported that only two devices met ISO standard requirements and (2) Florkowski and colleagues[44] evaluated two POCGMDs, and although both passed ISO requirements, they failed to meet ADA 1996 recommendations.

One specific concern with POCGMDs is errors in the hypoglycemic range and the potential impact on clinical decision-making. When errors occur in the lower glucose ranges, it most commonly entails a report of a higher than actual blood glucose value. This can lead to a misdiagnosis of euglycemia when in fact hypoglycemia exists, placing the patient at risk for neurological sequelae because of a failure of early recognition or aggressive treatment of hypoglycemia.[38,39,41,45–50] Because of the importance of accurate glucose values in the hypoglycemic range, Stork

and colleagues[46] focused further evaluation of POCGMDs in these patients. While measurements in the euglycemic range were acceptable, measurement accuracy decreased significantly in the hypoglycemic range. In neonates, POCGMDs for hypoglycemia screening did not have the required accuracy.[47,50]

Although less frequent, POCGMDs can report a falsely low value. The error may result in treatment for hypoglycemic when, in fact, euglycemia actually exists; the hypoglycemia treatment with additional glucose may lead to hyperglycemia. These examples illustrate some of the limitations of current POCGMDs. The accuracy of POCGMDs in these studies rarely met ADA accuracy recommendations in the hypoglycemia range. These devices were originally designed for outpatient SMBG, not to accurately reflect hypoglycemia in hospitalized ward and critically ill patients, whose condition may mask signs and symptoms of hypoglycemia.

Studies of Point-of-Care Glucose Monitoring Devices Accuracy in Intensive Care Unit Patients

Critically ill patients offer additional challenges for POC glucose monitoring. Microcirculatory abnormalities may affect capillary sampling or may be receiving other therapies, including vasoactive and additional pharmacological

Table 3.
Selection of Publications Evaluating POCGMD Accuracy Measuring Glucose Levels

Author	Publication year	POCGMD(s)	Sample source	Study characteristics
Giordano *et al.*[38]	1989	AccuChek II	Cap	*n* = 27; accuracy at high altitude
		Diascan–S		
		ExacTech		
		Glucometer II		
		Glucoscan 3000		
		OneTouch		
		Tracer		
Ashworth *et al.*[51,a]	1992	HemoCue	Ven	*n* = 30; triglyceride influence; range 32.4–129.6 mg/dl
Wiener *et al.*[52]	1993	HemoCue	Ven	Hematocrit influence
Larbig *et al.*[53,a]	2003	Prestige IQ		*n* = 61; outpatient setting
Chen *et al.*[39]	2003	4 GOX brand POCGMD (meter A, B, C, D)	Ven	*n* = 461; range 10–600 mg/dl, hct 25–60%, normoxia
DIRECNET[45,a]	2003	OneTouch Ultra	Cap, ven	*n* = 91; children 3–17 years, outpatient setting
Singh *et al.*[54]	2004	SureStepFlexx	Ven	Accuracy evaluation
Dai *et al.*[55]	2004	EasyTouch	Cap	*n* = 516, range 42–555 mg/dl
Kendall *et al.*[56]	2005	Ascensia Confirm 10 disk system	Cap	*n* = 100, patient vs health care provider, self-monitoring accuracy; range 41.4–352.8 mg/dl
Stork *et al.*[46]	2005	HemoCue		*n* = 24 (500 measurements); hypoglycemic range (289 measurements)
Rao *et al.*[57]	2005	3 GOX meters	Ven	600 measurements, 50 at each hct level over Hct 30–60%; automatic hct correction
		Meter 1: GOX/Ph-m		
		Meter 2: GOX/Am-m		
		Meter 3: GOX/Am-m with hct correction		
Hawkins *et al.*[58,a]	2005	AccuChek Go		*n* = 120; whole blood sample (AC) vs plasma glucose (Optium)
		Optium		

Continued →

Table 3. Continued

Author	Publication year	POCGMD(s)	Sample source	Study characteristics
Cohen *et al.*[40,a]	2006	AccuChek Go	Cap	*n* = 49; clinic setting
		AccuChek Advantage		
		Optium		
		CareSense		
		GlucoMen PC		
Rosenthal *et al.*[47]	2006	Accutrend	Cap	*n* = 110 (122 samples); postnatal monitoring
Khan *et al.*[41]	2006	One Touch II	Cap, ven	*n* = 358; clinic setting
		Precision QID		
		Precision PCX		
		Elite XL		
		SureStepFlexx		
		AccuChek Advantage		
		AccuCheck Comfort C		
Rivers *et al.*[48,a]	2006	FreeStyleFlash	Cap, ven, finger vs forearm	*n* = 100; clinic setting; range 69–354 mg/dl
		One Touch Ultra		
Lippi *et al.*[49]	2006	Accuchek	Ven	*n* = 225 measurements; outpatient setting; range 2.2–22 mmol/liter
		One Touch II		
		Elite XL		
		GlucoMen PC		
Bellini *et al.*[50]	2007	HemoCue	Cap	*n* = 78; neonatal monitoring
Thomas *et al.*[42,a]	2008	FreeStyle Flash	Cap, ven	*n* = 202; clinic setting
		AccuChek		
		BD Logic		
		AccuChek Compact Plus		
		Ascensia Contour		
Karon *et al.*[16,a]	2008	Statstrip	Ven	*n* = 185 measurements; hematocrit influence; acetaminophen influence
		AccuCheck II		
		Precision PCx		
		SureStepFlexx		
Sheffield *et al.*[43,a]	2009	Optium	Cap, ven	*n* = 125; clinic setting
		DDI Prodigy		
		HDI True TrackSmart System		
		Hypoguard Assure		
Florkowski *et al.*[46,a]	2009	Roche Performa	Cap	*n* = 100; outpatient setting
		Optium Xceed (5s and 10s)		

Cap, capillary; Ven, venous
[a] Industrial sponsorship.

Table 4.
Selection of POCGMD Accuracy Data

Author	POCGMD(s)	Results	Conclusions
Giordano *et al.*[38]	AccuChek II	R = 0.98, underestimates BGlu by 20.6% at levels <100 mg/dl	The four out of seven tested POCGMD underestimated BGlu at <100 mg/dl. AccuChek performed best, followed by OneTouch. Measurements at high altitude increased the BGlu underestimation.
	OneTouch	R = 0.97, underestimates BGlu <100 mg/dl—overall reliable	
	Diascan–S	R = 0.93, underestimates BGlu at all levels—inconsistent measurements	
	Tracer	R = 0.94, overestimates BGlu <100 mg/dl, underestimates >250 mg/dl—scatter	
	ExacTech	R = 0.96, overestimates BGlu at all levels, especially <100 mg/dl	
	Glucometer II	R = 0.89, overestimates BGlu <100 mg/dl, underestimates >250 mg/dl	
	Glucoscan 3000	R = 0.87, underestimates BGlu at all levels, scatter—not consistent	
Ashworth *et al.*[51]	HemoCue	R = 0.947 with all measurements <5% of RM	Reliable and accurate POCGMD
		Triglyceride concentration affected glucose measurements	Correct for triglyceride concentration
		Hct 35–65% did not affect glucose measurement with HemoCue	Hct range did not affect the accuracy
Wiener *et al.*[52]	HemoCue	CV 1.8%	Hct range did not affect the accuracy
Larbig *et al.*[53]	Prestige IQ	R = 0.972 with 95.9% in Clarke A or B area	Reliable and accurate POCGMD
Chen *et al.*[39]	4 GOX brand POCGMD	Tested 4 brand POCGMDs—covering 90% of the market at the time	Meter A overestimated; meter D underestimated; only meter B and C fit ISO accuracy criteria, none met ADA criteria for accuracy
		A: R = 0.989; at high BGlu R = 0.977, at low BGlu R = 0.956; CV 2%	
		B: R = 0.988; at high BGlu R = 0.974, at low BGlu R = 0.952; CV 3.3%	
		C: R = 0.989; at high BGlu R = 0.982, at low BGlu R = 0.947; CV 3.5%	
		D: R = 0.975; at high BGlu R = 0.934, at low BGlu R = 0.900; CV 4.3%	
DIRECNET[45]	OneTouch Ultra	R = 0.97, 99% of measurements in Clarke A/B area. More variability at low BGlu; ISO criteria were met at 96% of venous samples but only at 84% of capillary samples	POCGMD less reliable at BGlu <70 mg/dl; ISO criteria were met with venous samples
Singh *et al.*[54]	SureStepFlexx	When compared nurse operator vs lab tech, both had <5% measurement error when compared to RM. However, inconsistent BGlu measurements with total error variability for nurse 0–21% and for lab tech 4–13%	Inconsistent measurements but not operator dependent
Dai *et al.*[55]	EasyTouch	R^2 = 0.957, 100% of measurements are in Clarke A or B zone	Reliable POCGMD
		Reading are consistent in all BGlu ranges: <100, 100–200, >200	
Kendall *et al.*[56]	Ascensia Confirm	Device vs RM R = 0.97, 92.3% of BGlu <5% of RM, 93% of values are in Clarke A zone, 7% in Clarke B zone; SMBG vs HCP R = 0.96	Reliable POCGMD, good accuracy in SMBG use
	10 disk system		
Stork *et al.*[46]	HemoCue	R in normoglycemia = 0.979	Not reliable during severe hypoglycemia
		R in hypoglycemia = 0.880, difference in BGlu between POCGMD and RM increased during hypoglycemia conditions	
Rao *et al.*[57]	3 GOX meters	At hct >50%, all POCGMD underestimated BGlu	Automatic Hct correction did not improve POCGMD accuracy
Hawkins *et al.*[58]	AccuChek Go	AC measures whole blood and has consistent BGlu bias +2.5%, 97% in Clarke A zone, 3% in Clarke B zone	Both devices perform satisfactory for clinical use, but AccuChek had better accuracy and consistency than Optium
	Optium	Optium measure plasma glucose, showed concentration-dependent bias with positive bias at low BGlu and negative bias at high BGlu; 94% of values in Clarke A zone, 6% in Clarke B zone	

Continued →

Table 4. Continued

Author	POCGMD(s)	Results	Conclusions
Cohen *et al.*[40]	AccuChek Go	$R = 1.06x + 0.12$; CV low 5.51%; CV high 3.26%	All POCGMD measured higher than RM. Only CareSense met ADA accuracy criteria (<5% error)
	AccuChek Advantage	$R = 1.03x + 0.29$; CV low 3.64%; CV high 2.62%; error range 6.5%	
	Optium	$R = 0.99x + 0.67$; CV low 4.36%; CV high 3.71%	
	CareSense	$R = 0.93x + 0.95$; CV high 2.83%; error range 4%	
	GlucoMen PC	$R = 1.15x + 0.03$; CV NA (no standard provided); error 15.5% (All measurements were in Clarke A or B zone)	
Rosenthal *et al.*[47]	Accutrend	From 122 measurements, 39 overestimated BGlu, 81 underestimated BGlu. $R = 0.68$; 17% of measurements were outside the 95% CI	Not reliable for neonatal BGlu screening
Khan *et al.*[41]	OneTouch II	Bias varied from –7.9% to 2.8%	AccuChek POCGMD showed lowest bias. However at hypoglycemia, BGlu differences >20% occurred in 57% of values, differences >10% in 61%
	Precision QID	Bias varied from –10.4% to –0.7%	
	Precision PCX	Bias varied from –17.0% to –5.2%	
	Elite XL	Bias varied from –30.6% to –6.1%	
	SureStepFlexx	Bias varied from –2.7% to 12.7%	
	AccuChek Advantage	Bias varied from –15.5% to –5.8%	
	AccuCheck Comfort C	Bias varied from –5.1% to 0.8%	
Rivers *et al.*[48]	FreeStyleFlash	72% of BGlu (finger), 64% (forearm) were within 10% RM value	FreeStyleFlash POCGMD measurements were more accurate than OneTouch. Finger capillary samples were more reliable than Forearm sampling
	OneTouch Ultra	57% of BGlu (finger), 36% (forearm) were within 10% RM value	
Lippi *et al.*[49]	AccuChek	Bias was –4.9 to 14.1%. GlucoMen and Elite POCGMD consistently overestimated BGlu and OneTouch consistently underestimated BGlu. OneTouch/AccuChek/Elite showed acceptable BGlu within 95% CI; GlucoMen BGlu 15% of measurements were outside of acceptable error tolerance level	No POCGMD met ADA accuracy criteria. AccuChek/OneTouch/ Elite XL were in the ISO accuracy recommendations
	OneTouch II		
	Elite XL		
	GlucoMen PC		
Bellini *et al.*[50]	HemoCue	$R = 0.905$, POCGMD overestimated BGlu by 16.7mg/dl (average)	Accuracy is dependent on birth weight. HemoCue cannot be used for neonatal BGlu screening
Thomas *et al.*[42]	FreeStyle Flash	BGlu within 10% of RM = 70%, Clarke A 97, B 4, C 0, D 0	Only FreeStyle Flash and Ascensia Contour measurements were within 20% accuracy criterias. Only FreeStyle flash fulfilled the <10% error tolerance
	AccuChek Advantage	BGlu within 10% of RM = 30%, Clarke A 75, B 23, C 1, D 1	
	AccuChek Compact Plus	BGlu within 10% of RM = 38%, Clarke A 70, B 29, C 1, D 1	
	Ascensia Contour	BGlu within 10% of RM = 46%, Clarke A 88, B 10, C 0, D 2	
	BD Logic	BGlu within 10% of RM = 48%, Clarke A 67, B 26, C 1, D 6 (All POCGMD had a tendency to read higher at low BGlu level)	
Sheffield *et al.*[43]	Optium	42% of BGlu varied <5% of RM, precision 9 ± 10 mg/dl	Optium was found to be the most accurate POCGMD with 94% of BGlu were in <20% agreement with RM. Only Optium and DDI Prodigy met ISO accuracy criteria
	DDI Prodigy	24% of BGlu varied <5% of RM, precision 11 ± 10 mg/dl	
	HDI True TrackSmart	13% of BGlu varied <5% of RM, precision 15 ± 18 mg/dl	
	Hypoguard Assure	29% of BGlu varied <5% of RM, precision 11 ± 16 mg/dl	

Continued →

Table 4. Continued

Author	POCGMD(s)	Results	Conclusions
Florkow-ski *et al.*[44]	Roche Performa	Bias 0.52%, 99% in Clarke A, 1% in Clarke B	<5% of POCGMD measurements were within 20% of RM values (ISO standard); ADA goals were not met
	Optium Xceed (5s)	Bias –2.78%, 98% in Clarke A, 2% in Clarke B	
	Optium Xceed (10s)	Bias –1.36%, 96% in Clarke A, 4% in Clarke B	

BGlu, blood glucose concentration; RM, reference method; GOX, glucose oxidase method; HCP, health care provider; *R*, regression coefficient; CI, confidence interval; CV, coefficient of variation.

agents, that interfere with POCGMD. Other factors that may impact accuracy of testing include significant variation in hematocrit (Hct), pH, and blood oxygen or carbon dioxide level. Hyperglycemia treatment for many critically ill patients requires intravenous insulin infusion to control blood glucose.[6,7,59,60] Accurate BG measurements are extremely important for patients on insulin infusions. Relevant publications of POCGMD evaluated in the critically ill patient are listed in **Table 5**.

The impact of Hct on the POCGMD accuracy in critically ill patients has received attention. Some studies documented the influence[16,51,52,57,61–64] of Hct variation, especially when acute anemia develops in certain patient populations (e.g., cardiac surgery),[61,62,64] while others report accuracy over a wide range of Hcts.[51,52,63] Newer POCGMDs correct for Hct variation with several amperometric methods, involving a new technique called dynamic electrochemistry.[65,66] There are certainly numerous possible interferences with these techniques, which may be similar to those recently documented for Hct POC measurements, which use similar methodology.[67]

Blood oxygen content (P_aO_2), carbon dioxide tension (P_aCO_2), and blood pH changes all can impact glucose measurement accuracy. Dissolved blood oxygen can interfere with the GOX assay as previously detailed.[9,11,23] All POCGMD methods rely on enzymatic activity with function potentially affected by changes in blood pH and P_aCO_2. Louie and colleagues[62] studied the influence of P_aO_2, P_aCO_2, and pH with POCGMDs using GOX and GDH technology. Neither POCGMD using GOX or GDH technology were affected by P_aCO_2 or pH, and the POCGMD using GDH was unaffected by P_aO_2. However, the GOX POCGMD was sensitive to oxygen tension, consistently reporting lower than actual BG value when P_aO_2 levels exceeded 150 mm Hg. However, Lacara and colleagues,[63] using a multifactorial regression model in a small patient population (n = 42 patients), found that plasma P_aCO_2 contributed to the difference between CLD and POC glucoses in critically ill patients after Hct correction. In summary, the influence of carbon dioxide tension on the POCGMD accuracy remains controversial and is most likely minimal.

The influences of peripheral edema, hypotension, vasopressor, or catecholamine therapy on POCGMD accuracy in critically ill patients had been the subject of several investigations.[21,63,68–73] Kanji and colleagues[68] investigated the influences of peripheral edema and vasopressor therapy on POC glucose monitoring. Disagreement was defined when CLD and POCGMD results led to different treatment decisions based on an institutional insulin therapy protocol. Compared to arterial sampling, capillary sampling was less accurate for glucose measurements in critically ill patients, especially in the hypoglycemia range.[68,70] With fast changing BG values, the time constant for capillary blood may be quite long and could be a contributor to inaccuracy under these circumstances.[74] Fewer than 80% of the capillary samples were in agreement with the CLD measurement. When hypotension was present, this agreement further decreased to less than 70%. With the presence of edema or when patients were receiving vasopressor medications and BG levels were <80 mg/dl, only 25% of the capillary POCGMD measurements and less than 55% of arterial POCGMD measurements were accurate when compared with CLD results (**Figure 4**).[68] Focusing on patients with low perfusion indices and requiring vasopressor therapy, Desachy and colleagues[71] noted disagreement between POCGMD and CLD in more than 15% of capillary samples. These measurement discrepancies correlated with low tissue perfusion index, generalized mottling, and hypotension. These influences were noted in older investigations by Atkin *et al.*[22] and Sylvain *et al.*,[73] where hypotensive patients' capillary blood glucose values were inaccurate. The time constant of the capillary blood space may contribute to this discrepancy, as lower perfusion may lengthen the time

Table 5.
Selection of Publications Evaluating POCGMD Accuracy Measuring Glucose Levels on Critically Ill Patients

Author	Publication year	POCGMD (s)	Patient collective	Sample source	Findings
Maser *et al.*[61]	1994	AccuChek II	*n* = 50, hematocrit correction	Ar, cap	Ar > cap samples by 30 mg/dl, decrease to 10 mg/dl if hematocrit corrected. Cap samples are up to 21 mg/dl from CLD values. Potential for incorrect insulin dosing if both ar and cap samples are used in ICU patients
Louie *et al.*[62]	2000	SureStepPro Precision G	*n* = 247; influence of paO_2, $paCO_2$, pH, hct	Ar	POCGMD accuracy between 91% and 95% (Pre) and 98–100% (SSPro); hct influence on glucose measurement accuracy
Ray *et al.*[75]	2001	OneTouch	*n* =10	Ar	Study range 86.4–392.4 mg/dl. POCGMD remained ±41.4 mg/dl of certainty
Kanji *et al.*[68]	2005	AccuChek	*n* = 30; influence of peripheral edema, vasopressor therapy	Ar, cap	POCGMD meet CLD measurement in 69.9% (ar) and 56.8% (cap), the reliability is less in hypotension. CLD agreement is achieved in <80% of samples, during hypotension <70% of samples
Finkielman *et al.*[69]	2005	SureStepFlexx	*n* = 197; influence of hypotension (retrospective)	Ar, cap	Difference between CLD and POCGMD 8–9 mg/dl, no influence of MAP or vasopressor therapy
Karon *et al.*[76]	2007	AccuChek	*n* = 20; s/p CABG under insulin therapy and inotropic medications	Ar, cap, ven	Cap measurements were more accurate than ar or ven samples. A total of 78/96 measurements were within 10% of CLD. More positive bias at glucose levels >160 mg/dl
Lacara *et al.*[63]	2007	SureStep Pro	*n* = 49; influence of Hct, $paCO_2$, MAP 56–130 mmHg	Ar, ven	Ar and ven samples less bias than cap sampling. POCGMD did not differ from CLD measurements at range 52–281 mg/dl. No influence of Hct, paCO2, or MAP
Critchell *et al.*[77]	2007	AccuChek	*n* = 80; MICU pt	Cap	Cap measurements were not reliable with variation of 8.6 ± 18.6 mg/dl from CLD, 19% of values were >5% from CLD level
Hoedemaekers *et al.*[78]	2008	AccuChek Precision HemoCue	Critically ill pt under insulin therapy vs non-ICU pt	Ar (ICU), ar, ven (non-ICU)	All three POCGMD are less accurate in ICU pt than in non-ICU pt. HemoCue more accurate than AccuChek or Precision
Petersen *et al.*[79,a]	2008	AccuChek	*n* = 144; MICU pt	Ar, cap, ven	POCGMD had a positive bias 12.6–16.2 mg/dl compared to CLD, ar and ven are less variable than cap. Cap sample 3/144 severely underestimated CLD glucose.
Slater-MacLean *et al.*[70]	2008	SureStepFlexx AccuChek FreeStyle	*n* = 60; influence of vasopressor and insulin therapy	Ar, cap	AccuChek POCGMD with higher level of bias. In all three POCGMD ar samples more reliable than ven or cap measurements
Desachy *et al.*[71]	2008	AccuChek	*n* = 85; critically ill pt in shock	Cap	Low tissue perfusion correlates with value discrepancy between POCGMD and CLD. A total of 7% discordant values—cap samples not accurate
Cook *et al.*[64]	2009	SureStepFlexx	*N* = 67; critically ill pt	Cap, ven (CVL)	Range 62–247 mg/dl, CVL samples 15% differ >20% from CLD, cap samples 21% differ from CLD. Discrepancies improved with hct correction
Meynaar *et al.*[80]	2009	AccuChek	*n* = 32; critically ill pt	Ar	Average 11 mg/dl difference between POCGMD and CLD, POCGMD accuracy better at high glucose levels. Mostly POCGMD is underestimating glucose level
Fekih-Hassen *et al.*[72]	2010	AccuChek	*n* = 43; influence of catecholamine therapy	Cap, ven	POCGMD and CLD difference >40 mg/dl in 29% without catecholamine therapy and 40% in patients with catecholamine therapy. Cap glucose monitoring not reliable during catecholamine therapy

MAP, mean arterial blood pressure; ar, arterial; cap, capillary; ven, venous; pt, patients; vs, versus; CVL, central venous catheter.
[a] Industrial sponsor for study.

constant. Catecholamine administration to critically ill patients also influences POC glucose. Fekih-Hassen and colleagues[72] investigated the accuracy of two capillary sampling sites in critically ill patients being administered catecholamines compared to hemodynamically stable patients not receiving these drugs. In critically ill patients receiving catecholamines, the POCGMD and CLD measurements differed from 29% to 40%. Even in hemodynamically stable patients, there was less than acceptable POCGMD accuracy with capillary sampling.[72] When comparing the performance of three POCGMDs in critically ill patients compared with noncritically ill patients, Hoedemaekers and colleagues[78] found all three devices to be less accurate in the critically ill patients. When inaccurate, the POC glucose levels were most often falsely elevated, with the potential for inappropriate insulin administration and/or masking "true hypoglycemia." The use of insulin infusions to manage BG levels in critically ill patients demands monitoring to be precise, reliable, and frequent.

Several studies have investigated POCGMDs during intensive insulin therapy in critically ill patients.[70,76,78] Capillary samples in one study showed acceptable accuracy during intensive insulin therapy in normotensive and euglycemic patients after cardiac surgery.[76] Two other studies found POCGMDs to have significant inaccuracies in critically ill patients.[70,78] Hoedemaekers and colleagues[78] tested three POCGMDs in ICU patients; all devices failed to meet ISO standards in hypoglycemic samples. Using simulation modeling, Karon and colleagues[81] defined performance criteria for using glucose meter technology for tight glucose control with insulin infusions, stating that POCGMDs that operate within a 15% total allowable error tolerance would be acceptable. The current criteria allow 20%. With these limitations, these authors concluded that POCGMDs were ill-suited to monitor glucose during intensive insulin infusion in critically ill patients. Sampling arterial blood rather than capillary blood may reduce measurement variability and inaccuracies[70] because of the variable time constant in the capillary sample, and the use of different sites might explain some discrepancies in POCGMD compared to CLD. When initiating intensive insulin therapy, close attention should be paid to potential sources of error, including sample source, measurement techniques, and patient factors. All these factors should be taken into consideration when making treatment decisions. Blood glucose concentration should be measured frequently (at minimum hourly) during intensive insulin therapy in critically ill patients, and when values obtained from POCGMD pose a patient safety risk, those values should be confirmed by CLD.

Conclusion

Accuracy can be defined as the variation from the reference value. When assessing laboratory values for glucose, the testing method is accurate if the measurement is within acceptable error compared to the reference method. Within the range of hypoglycemia, if the values reported by the POCGMD are inaccurate (e.g., reported higher than actual values), this inaccuracy could lead to failure to recognize and treat life-threatening values or even

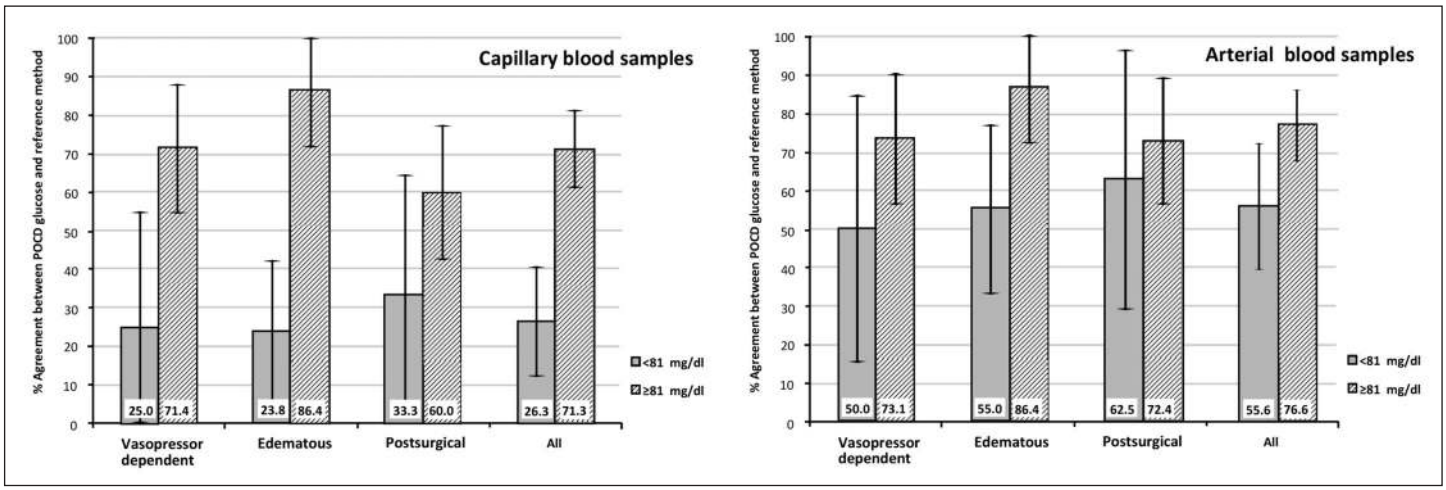

Figure 4. POCGMD glucose measurement agreement with reference method during hypoglycemia versus nonhypoglycemia in critically ill patients. The POCGMD glucose measurement were said to agree with the reference method (CLD) if both measurements resulted in a similar clinical intervention. A total of 118 paired observations were analyzed (all), divided into three groups: vasopressor-dependent (n = 36: hypoglycemia n = 8, nonhypoglycemia n = 28), edematous (n = 43: hypoglycemia n = 21, nonhypoglycemia n = 22), and postsurgical (n = 39: hypoglycemia n = 9, nonhypoglycemia n = 30). Data are presented as mean with 95% confidence interval. For the statistical analysis, please review the original data source.[68]

more worrisome result in a different treatment (e.g., increasing insulin infusions) that could pose a serious patient safety risk. The importance of accuracy for clinical treatment assesses whether the measurement value is within a range close enough to the actual value that the clinical approach to therapy remains the same. The current ADA device recommendations for SMBG with POCGMDs include the following: (a) achieve and maintain glycemic control, (b) prevent and detect hypoglycemia, (c) avoid severe hyperglycemia, and (d) facilitate diabetes therapy adjustment to lifestyle changes (activity, diet changes, etc.). The accuracy requirements set by the professional organizations are still rarely met by POCGMDs. With outpatients and other hospitalized noncritically ill patients, most clinicians appear satisfied with POCGMD accuracy when glucose values avoid the extremes of hypoglycemia and hyperglycemia. This is because, in the range of normal glucose, the accuracy in this range is typically acceptable for clinical decision-making. For the care of critically ill patients, accuracy becomes more important as some of the early signs present with hypoglycemia and hyperglycemia may be difficult to detect in this patient population due to decreased mental status, sedatives, and other patient conditions. For optimal glucose control in high-demand states in critically ill patients, POCGMD technology has yet to provide a high enough degree of accuracy and reliability that leads to appropriate clinical decision-making. Continuous glucose monitoring devices based on invasive, minimal invasive, or noninvasive methodology are being developed to improve blood glucose monitoring.[82] Available technology, including future advances and current limitations, has been reviewed by Vaddiraju and colleagues.[83] Development of a meter with accuracy equal to CLDs should continue to be the industry goal.

Acknowledgment:

The authors would like to thank Pamela Knight for her assistance with manuscript preparation.

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