The performance of flash glucose monitoring in critically ill patients with diabetes

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ABSTRACT

Objective: Frequent glucose monitoring may improve glycaemic control in critically ill patients with diabetes. We aimed to assess the accuracy of a novel subcutaneous flash glucose monitor (FreeStyle Libre [Abbott Diabetes Care]) in these patients.

Methods: We applied the FreeStyle Libre sensor to the upper arm of eight patients with diabetes in the intensive care unit and obtained hourly flash glucose measurements. Duplicate recordings were obtained to assess test–retest reliability. The reference glucose level was measured in arterial or capillary blood. We determined numerical accuracy using Bland–Altman methods, the mean absolute relative difference (MARD) and whether the International Organization for Standardization (ISO) and Clinical and Laboratory Standards Institute Point of Care Testing (CLSI POCT) criteria were met. Clarke error grid (CEG) and surveillance error grid (SEG) analyses were used to determine clinical accuracy.

Results: We compared 484 duplicate flash glucose measurements and observed a Pearson correlation coefficient of 0.97 and a coefficient of repeatability of 1.6 mmol/L. We studied 185 flash readings paired with arterial glucose levels, and 89 paired with capillary glucose levels. Using the arterial glucose level as the reference, we found a mean bias of 1.4 mmol/L (limits of agreement, –1.7 to 4.5 mmol/L). The MARD was 14% (95% CI, 12%–16%) and the proportion of measurements meeting ISO and CLSI POCT criteria was 64.3% and 56.8%, respectively. The proportions of values within a low-risk zone on CEG and SEG analyses were 97.8% and 99.5%, respectively. Using capillary glucose levels as the reference, we found that numerical and clinical accuracy were lower.

Conclusions: The subcutaneous FreeStyle Libre blood glucose measurement system showed high test–retest reliability and acceptable accuracy when compared with arterial blood glucose measurement in critically ill patients with diabetes.

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Excessive glycaemic variability and hypoglycaemia are associated with increased mortality risk in critically ill patients.[1,2] Achieving glycaemic stability is particularly challenging in critically ill patients with diabetes. In response to these challenges, there has been increasing interest in the use of subcutaneous or intravascular continuous glucose monitoring (CGM) devices. However, CGM systems require repeated calibrations and often need to be prematurely removed due to sensor or device-related problems. These issues cause prolonged data gaps.[3-5] In addition, the tubing and attached monitors interfere with nursing management and patient mobilisation.[5] Intravascular CGM sensors are also associated with thrombus formation and malfunction of the intravascular access, and may show limited accuracy when inserted in a peripheral vein.[6-8] Finally, the use of an intravascular CGM device carries a theoretical risk of infection.

The minimally invasive FreeStyle Libre flash glucose monitoring system (Abbott Diabetes Care) was recently approved for use in patients with diabetes.[9] The factory-calibrated subcutaneous sensor requires no additional calibrations and lasts 14 days. A handheld reader obtains glucose readings wirelessly by scanning the sensor up to every 15 minutes (hence the term "flash glucose").

Previous studies showed high accuracy for flash glucose monitoring when compared with capillary or venous glucose measurement in ambulatory patients with diabetes.[9,10] In contrast, flash glucose monitoring appears to systematically underestimate arterial blood glucose levels in patients undergoing cardiac surgery.[3] However, no study has assessed the performance of flash glucose measurements in critically ill patients with diabetes who are treated according to a liberal glycaemic protocol. We aimed to test the feasibility and accuracy of the FreeStyle Libre flash glucose monitoring system compared with routine glucose monitoring in such patients.

Materials and methods

Patients

The study was approved by the ethics committee at Austin Hospital, Melbourne, Australia (approval LNR/16/Austin/392) with a waiver for informed consent. Between 6 August and 18 October 2016, we studied eight consecutive patients with type 2 diabetes who were expected to remain in the intensive care unit for at least 48 hours. We collected their demographic data and data on their long-term therapy for diabetes, glycated haemoglobin (HbA_{1c}) level at admission,[11] lowest haematocrit, ICU admission diagnosis, and Acute Physiology and Chronic Health Evaluation

(APACHE) III score. As aspirin and vitamin C therapy may affect flash readings, we recorded long-term aspirin use, as well as treatment with aspirin and/or vitamin C during the study period. In addition, we recorded data on maximum vasopressor and insulin doses and patient outcomes.

Glucose monitoring

We applied a FreeStyle Libre flash glucose sensor on the patient's upper arm, according to the manufacturer's directions. After a 1-hour warm-up, the flash reader was used to scan the sensor every hour to obtain a flash glucose value (Appendix Figure S1, online at cicm.org.au/Resources/Publications/Journal). To be able to assess the test–retest reliability, we obtained flash glucose recordings in duplicate, 15 minutes apart. The reference blood glucose level was measured by arterial blood gas analysis using the Radiometer ABL 825 blood gas analyser (Radiometer Medical) or by capillary blood analysis using the FreeStyle Optium Xceed point-of-care meter (Abbott Diabetes Care) as part of routine care. The reported percentage coefficient of variation (%CV) (micromode) for glucose analysed by the Radiometer ABL 825 (electrochemical) was 5.8% at 4.0 mmol/L, 3.9% at 9.0 mmol/L and 3.1% at 15.2 mmol/L. The reported %CV for glucose analysed by Optium Xceed (electrochemical) was 3.9% at 5.9 mmol/L and 4.4% at 21.2 mmol/L.[12] Flash glucose and blood glucose recordings were obtained and documented by the bedside nurses, who were instructed to guide glucose management based on blood glucose values only. The choice of reference method to guide such therapy was left to the discretion of the bedside nurse.

According to our unit protocol for patients with diabetes, we targeted blood glucose levels at 10–14 mmol/L, using intravenous or subcutaneous insulin to treat patients with glucose values above 14 mmol/L.[13,14] We defined hypoglycaemia as a blood glucose value below 4 mmol/L. Glycaemic variability was determined by the standard deviation of blood glucose concentration.

Statistical analysis

We analysed data using Stata/SE, version 11.2 (StataCorp). Continuous variables are expressed as medians with ranges, and categorical variables are expressed as frequencies with percentages. We quantified bias according to Bland–Altman methods.[15] We further determined numerical accuracy by calculating mean absolute relative difference (MARD), where a value < 14% represents acceptable accuracy, a value between 14% and 18% represents intermediate accuracy and a value > 18% represents poor accuracy.[5] Accuracy was also determined according to the International Organization for Standardization (ISO) criteria from 2013 (ISO 15197:2013)[16] and the Clinical and Laboratory Standards Institute (CLSI) Point of Care Testing 12-A3 (POCT12-A3) standard.[17] The ISO 15197:2013 criteria specify that 95% of results should be within 15% of a reference value ≥ 5.6 mmol/L and within ± 0.80 mmol/L of a reference value < 5.6 mmol/L. The CLSI POCT12-A3 standard specifies that 95% of results be within 12.5% of a reference value ≥ 5.6 mmol/L, and within ± 0.67 mmol/L of a reference value < 5.6 mmol/L.

Clarke error grid[18] (CEG) and surveillance error grid (SEG)[19] analyses were used to assess the magnitude of clinical risk from inaccurate flash glucose readings (clinical accuracy). We calculated the Pearson product moment correlation coefficient (*r*) and the coefficient of repeatability (CR) to assess relative and absolute test–retest reliability, respectively.[20]

Results

Patients and sensors

Characteristics of the eight study patients (two women and six men) are shown in Table 1. The median age was 72 years (range, 62–81 years), median APACHE III score was 73 (range, 33–142), median HbA_{1c} level was 7.1% (range, 5.8%–13.4%) or 54 mmol/mol (range, 40–123 mmol/mol), and median lowest haematocrit was 0.32 (range, 0.19–0.45). All patients had type 2 diabetes. Seven patients received norepinephrine and/or epinephrine infusion. We observed a median glucose variability of 3.1 mmol/L (SD, 0.1–5.8 mmol/L). One patient (Patient 8) experienced one hypoglycaemic episode (blood glucose level, 2.7 mmol/L). A flash glucose level of 3.2 mmol/L was recorded 2.5 hours before that episode. All patients were treated with aspirin before ICU admission and/or received aspirin in the ICU. No patient received vitamin C. Different staff members easily applied the eight sensors. Sensors remained in situ for a median of 57 hours (range, 4–187 hours) and were removed before ICU discharge. We observed no sensor-related complications.

Data points

We collected 289 blood glucose readings (195 arterial blood gas values and 94 capillary values) and 690 flash glucose readings (Figure 1). We identified 274 paired samples (185 paired with arterial blood glucose and 89 paired with capillary blood glucose) for assessment of accuracy and 484 duplicate flash glucose readings (taken 15 minutes apart) for calculation of test–retest reliability.

Numerical accuracy

The Bland–Altman plots are shown in Figure 2. Flash glucose readings were systematically lower than arterial blood glucose measurements (mean bias, 1.4 mmol/L; limits

Table 1. Patient and treatment characteristics of study patients with type 2 diabetes

Characteristic	All patients	Patient number							
		1	2	3	4	5	6	7	8
Age, years	72 (62–81)*	81	62	75	79	73	72	71	67
Sex	Ratio 6M:2F (75%:25%)	Male	Female	Male	Male	Male	Female	Male	Male
Body weight, kg	106 (60–130)*	60	60	69	108	103	109	126	130
APACHE III score	73 (33–142)*	133	61	66	105	79	51	33	142
HbA_{1c}, %	7.1 (5.8–13.4)*	7.4	6.9	6.5	na	13.4	5.8	12.7	7.1
Diabetes treatment									
Insulin only	2 (25%)†	Yes	No	No	No	No	No	No	Yes
Oral hypoglycaemics only	5 (62.5%)†	No	Yes	Yes	Yes	Yes	Yes	No	No
Insulin + oral hypoglycaemics	1 (12.5%)†	No	No	No	No	No	No	Yes	No
Receiving regular aspirin	3 (37.5%)†	Yes	No	No	No	Yes	No	No	Yes
Admission diagnosis	–	Cardiac arrest	Viral infection	Septic shock	Cardiac arrest	Pneum.	Pneum.	Stroke	CABG surgery
Mechanical ventilation	6 (75%)†	Yes	Yes	No	Yes	No	Yes	Yes	Yes
Maximum medication dose									
Norepinephrine, µg/kg/min	0.10 (0–0.39)*	0.09	0.05	0.27	0	0.10	0.39	0	0.14
Epinephrine, µg/kg/min	0 (0–0.19)*	0	0	0.19	0.07	0	0	0	0
Milrinone, µg/kg/min	0 (0–0.25)*	0	0	0	0	0	0.25	0	0
Insulin, U/h	6 (0–10)*	10	7	5	4	5	0	7	9
Mean BGL, mmol/L‡	13.1 (8.7–14.8)*	13.3	13.0	14.8	11.6	13.4	8.7	14.6	9.3
Glucose SD, mmol/L‡	3.1 (0.1–5.8)*	2.9	3.6	5.8	3.5	2.5	0.1	2.4	3.4
Hypoglycaemia‡§	1 (12.5%)†	No	No	No	No	No	No	No	Yes
Received aspirin in ICU	4 (50%)†	Yes	No	No	No	Yes	No	Yes	Yes
ICU length of stay, days	7 (2–14)*	14	9	5	8	6	2	4	8
Died in ICU	2 (25%)†	No	No	Yes	No	No	Yes	No	No

M = male. F = female. APACHE = Acute Physiology and Chronic Health Evaluation. HbA_{1c} = glycated haemoglobin. na = not available. Pneum. = pneumonia. CABG = coronary artery bypass graft. BGL = blood glucose level. SD = standard deviation. ICU = intensive care unit.
* Median (range). † *n* (%). ‡ Data based on reference glucose measurements only. § Defined as blood glucose level < 4 mmol/L.

of agreement, –1.7 to 4.5 mmol/L) and lower than capillary blood glucose measurements (mean bias, 1.9 mmol/L; limits of agreement, –2.6 to 6.5 mmol/L). Other estimates of numerical accuracy are shown in Table 2. When comparing flash glucose with arterial blood glucose values, we observed an MARD of 14% (95% CI, 12%–16%). Overall, 64.3% of flash glucose values met the ISO 15197:2013 criteria and 56.8% met the CLSI POCT12-A3 criteria. Numerical accuracy in the absence of vasopressor therapy, compared with numerical accuracy during vasopressor therapy, was not statistically different (Appendix Table S1). We observed a significantly higher MARD ($P = 0.049$) and a significantly lower proportion of accurate readings according to ISO 15197:2013 criteria ($P = 0.007$) and CLSI POCT12-A3 criteria ($P = 0.01$) when flash glucose was compared with capillary blood glucose.

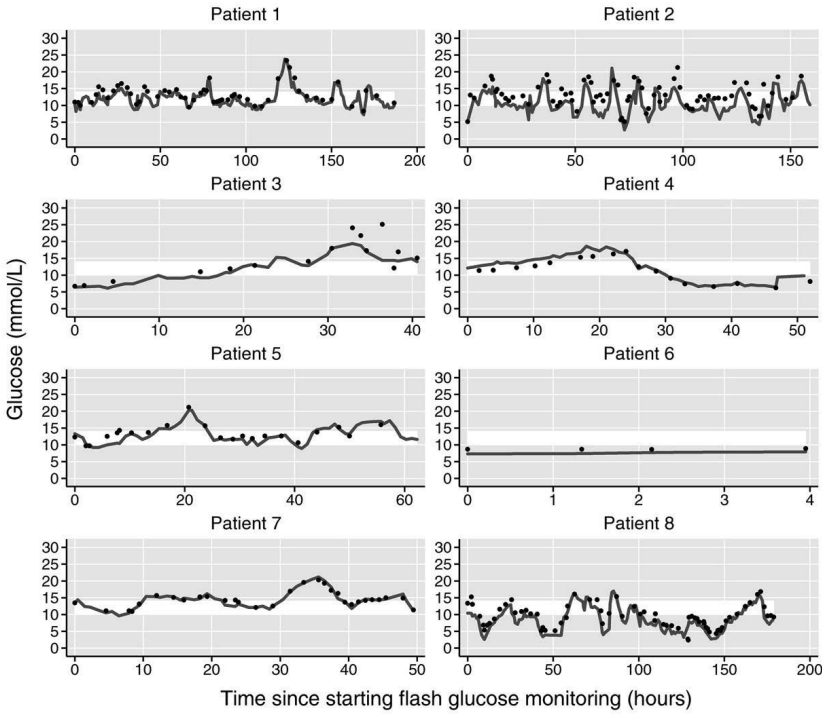
Clinical accuracy

On CEG analysis, using arterial blood glucose level as the reference, 97.8% of readings were found in zone A and B, and the remaining 2.1% in zone D (Table 2). On SEG analysis, 99.5% of readings were considered low risk (risk score ≤ 1.5) (Figure 3). The proportion of readings in CEG zone A and B (96.6%) and with a risk score ≤ 1.5 on SEG analysis (96.6%) was lower when capillary blood glucose level was used as the reference.

Test–retest reliability

When comparing the 484 duplicate flash glucose measurements, we observed a Pearson correlation coefficient of 0.97 (relative reliability) and a CR of 1.6 mmol/L (absolute reliability) (Appendix Figure S2).

Figure 1. Blood glucose and subcutaneous glucose concentrations of eight critically ill patients with type 2 diabetes



Black closed circles = arterial or capillary blood glucose levels. Navy solid line = subcutaneous glucose levels. White strip = target glucose range for patients with diabetes in the intensive care unit (10–14 mmol/L).

Discussion

Key findings

In eight critically ill patients with type 2 diabetes, of whom seven were receiving vasopressors, we assessed the accuracy of a minimally invasive, subcutaneous flash glucose monitor for up to 8 days in the ICU during a period of permissive hyperglycaemia. Compared with arterial blood glucose monitoring, flash glucose measurement showed acceptable numerical and clinical accuracy. We also observed a higher level of performance when flash glucose measurement was compared with arterial blood glucose level than with capillary blood glucose level. Irrespective of the reference method, the ISO 15197:2013 or CLSI POCT12-A3 criteria were not met. Finally, we found that the flash glucose test–retest reliability was high.

Relationship with previous studies

Our study was the first to investigate the performance of the FreeStyle Libre flash glucose monitoring system in critically

Figure 2. Bland–Altman plots showing agreement between flash glucose readings and arterial (upper panel) and capillary (lower panel) blood glucose readings

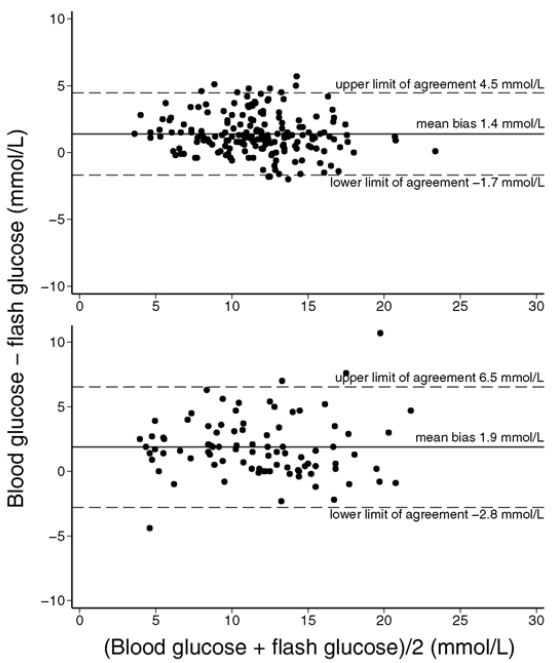


Table 2. Flash glucose measurement accuracy

Variable	Flash glucose v arterial BGL	Flash glucose v capillary BGL	*P*
Paired readings, *n*	185	89	
MARD, % (95% CI)*	14% (12%–16%)	20% (15%–25%)	0.049
ISO 15197:2013 criteria met, *n* (%)†	119/185 (64.3%)	42/89 (47.2%)	0.007
CLSI POCT12-A3 criteria met, *n* (%)‡	105/185 (56.8%)	36/89 (40.4%)	0.01
Clarke error grid zone, *n* (%)			0.097
A	136/185 (73.5%)	54/89 (60.7%)	
B	45/185 (24.3%)	32/89 (36.0%)	
C	0	0	
D	4/185 (2.1%)	3/89 (3.4%)	
E	0	0	

BGL = blood glucose level. MARD = mean absolute relative difference. ISO = International Organization for Standardization. CLSI POCT = Clinical and Laboratory Standards Institute Point of Care Testing. * < 14% represents acceptable accuracy; > 18% represents poor accuracy. † Number of flash glucose values within 15% of reference glucose ≥ 5.6 mmol/L and within 0.80 mmol/L of reference glucose < 5.6 mmol/L. ‡ Number of flash glucose values within 12.5% of reference glucose ≥ 5.6 mmol/L and within 0.67 mmol/L of reference glucose < 5.6 mmol/L.

ill patients with diabetes. However, Schierenbeck and colleagues compared flash glucose measurement with arterial blood glucose measurement for up to 48 hours in 24 patients after cardiac surgery (six of whom had diabetes).[3] In contrast to our study, they found the performance of the FreeStyle Libre system to be poor, with an MARD of 30.5%, a bias of 2.4 mmol/L and only 7% meeting the ISO 2013 criteria. Although it was not reported by the authors, perioperative hypothermia with poor subcutaneous tissue perfusion may explain the limited accuracy in their study.

Bailey and colleagues analysed 12 172 venous glucose reference results paired with flash glucose measurements in 72 ambulatory patients with diabetes and found an MARD of 12%.[9] Overall, 96.5% of readings were classified as accurate and a further 2.4% as benign errors not affecting decision making. Similar accuracy was found when capillary glucose level was used as the reference. Further, accuracy was stable during the 14 days of wearing the flash sensor and was unaffected by body mass index, age, type of diabetes, study site, insulin administration or HbA_{1c} level.

Ji and colleagues analysed almost 7000 flash glucose readings paired with venous blood glucose measurements in 45 ambulatory patients who required insulin for diabetes.[10] They also showed high numerical accuracy (MARD, 10.7%) and clinical accuracy (99.1% of readings within CEG zones A and B). In addition, accuracy persisted across all levels of glycaemia in these patients. In agreement with the study by Bailey and colleagues, Ji and colleagues showed similar accuracy when capillary or venous glucose measurement was used as the reference method.

We observed similar accuracy to that reported in the two studies comparing flash glucose measurement with arterial blood glucose measurement in ambulatory patients with diabetes. However, in contrast to those two studies, our comparison with capillary glucose level generated significantly lower accuracy. The fact that the haematocrit level was below normal in most of our patients may explain this, as previous studies have shown that blood glucose level is overestimated when measured by the FreeStyle Optium Xceed point-of-care meter when haematocrit levels are low.[21,22] Consequently, the capillary blood glucose level may be an inappropriate reference glucose method for critically ill patients.[23]

The bias seen towards a lower glucose value with flash glucose monitoring may not reflect inaccuracy but the difference in measurement of glucose level before glucose consumption by cells (ie, arterial glucose level) compared with after glucose consumption by cells (ie, interstitial glucose level). Interstitial flash glucose level was thus systematically lower than circulating glucose levels. The magnitude of this difference may be dictated by the rate of glucose diffusion from blood to the interstitium and by the rate of glucose uptake by cells.[24] Glucose diffusion is determined by blood supply, which may have been impaired in our patients due to critical illness, vasopressor therapy or both. Simultaneously, glucose uptake by subcutaneous cells may be augmented because of exogenous insulin administration. Interstitial oedema, which is common in critically ill patients, may further dilute the subcutaneous glucose and contribute to an increased glucose gradient between blood and interstitium. Finally, a higher blood glucose level may increase the absolute difference between interstitial and arterial glucose levels. Brunner and colleagues found a mean difference (interstitial glucose level minus arterial glucose level) of –0.1 mmol/L (95% CI, –0.13 mmol/L to –0.07 mmol/L) in 174 medical ICU patients.[25] In contrast, interstitial glucose level slightly overestimated arterial glucose level in 50 patients treated in a mixed medical and surgical ICU (bias [arterial minus interstitial], –0.03 mmol/L [95% CI, –3.2 mmol/L to 3.1 mmol/L]).[4] However, tight glycaemic control was applied in those studies, which may explain a lower degree of bias than occurred in our patients, whose blood glucose levels were managed according to a more liberal control protocol. At this stage, it remains unclear whether the biologically relevant target of therapy should be the arterial or the interstitial glucose level.

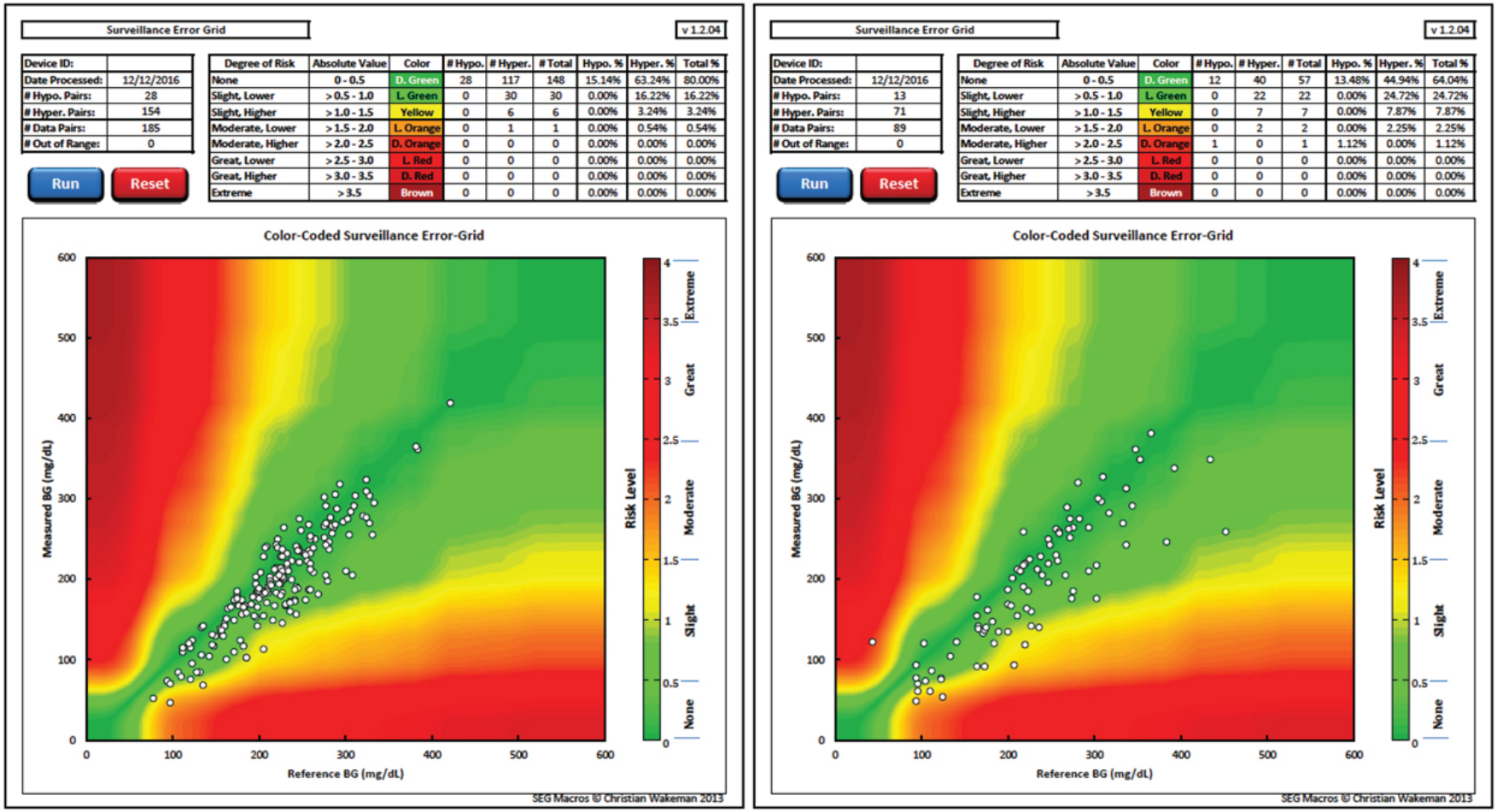
Study implications

Our study findings imply that subcutaneous glucose monitoring for up to 8 days using the FreeStyle Libre system is feasible and provides readings with sufficient numerical and clinical accuracy in critically ill patients with diabetes. The system is user-friendly and carries a minimal risk of complications, which makes it an attractive alternative to other CGM systems. Although the flash system is not truly continuous, readings can be obtained every 15 minutes with minimal effort. Flash glucose measurement slightly, but systematically, underestimated arterial glucose levels in our study. Such underestimation may be advantageous because it decreases the risk that hypoglycaemia will be undetected and may reflect measurement in a different biological compartment, rather than being inaccurate in itself. In contrast, a mild degree of hyperglycaemia can also be missed, but there is no strong evidence of clinical risks of mild to moderate hyperglycaemia in critically ill patients with diabetes.[13] Importantly, despite there being a time-lag between arterial and subcutaneous glucose levels, and despite high arterial glucose variability in most of our patients, the flash system generated subcutaneous values with high accuracy relative to arterial blood glucose levels.

Strengths and limitations

Our study has several strengths. We evaluated flash glucose measurement in critically ill patients with diabetes and

Figure 3. Surveillance error grid analysis comparison of subcutaneous flash glucose and blood glucose measurements*



* Comparison of flash glucose level (measured blood glucose level) with arterial (left panel) and capillary (right panel) blood glucose level (reference blood glucose level). Glucose values are stated in mg/dL; to convert to mmol/L, multiply by 0.05551.

with moderate to severe premorbid glycaemic control (HbA_{1c} level, 5.8%–13.4%), high glycaemic variability and prevalent vasopressor support, who were being managed according to a liberal glucose protocol. This was a previously unexplored population for this purpose. We also performed multiple assessments of numerical and clinical accuracy, as recommended in the literature. Finally, we provided robust measures of test–retest reliability using almost 500 duplicate flash glucose readings.

Our study has some limitations. We only included eight patients, but seven were receiving vasopressors, and we analysed almost 300 paired samples to determine accuracy. We did not evaluate the potential clinical benefits of flash glucose monitoring on glycaemic control. However, we provide preliminary evidence of sufficient accuracy to explore the potential utility of this system in a future randomised controlled trial. We did not examine whether the flash glucose sensor impaired image quality during computed tomography scanning, and this potential limitation should be assessed. Furthermore, clinicians must be aware that magnetic resonance imaging is likely to preclude the use of the FreeStyle Libre sensor. Finally, we did not compare flash glucose measurement with the gold standard of central laboratory glucose measurement. However, measurement of blood glucose levels with blood gas analysers such as the one we used has similar accuracy to laboratory glucose measurement.[26]

Conclusions

Flash glucose monitoring is feasible and offers the ability to measure the glucose level every 15–60 minutes with a reader and without the skin puncture necessary for capillary testing or the cost of arterial measurements. Our findings suggest that it may be sufficiently accurate to use as a complement to intermittent arterial glucose monitoring in critically ill patients with diabetes. Its tendency to underestimate arterial glucose level is also likely to offer protection from hypoglycaemia. Finally, the level of accuracy and safety observed and the likely added value of frequent flash glucose monitoring to improve glycaemic control justifies exploration in a future randomised controlled trial.

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Competing interests

We declare that we have no competing interests. The manufacturer of the FreeStyle Libre (Abbott) was not involved in the study design, study execution or interpretation or reporting of study results, nor did the study receive any financial support from Abbott.

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