COMMENTARY

Continuous Glucose Monitor Use and Accuracy in Hospitalized Patients

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HOSPITALIZED PATIENTS EXPERIENCE hyperglycemia, hypoglycemia, and glucose variability. Hyperglycemia is associated with adverse outcomes such as increased infections, increased duration of hospitalization, and mortality. Therefore, clinical practice in hospitals and randomized clinical trials (RCTs) have attempted to safely and effectively improve hyperglycemia in hospitalized patients.^{1,2} These RCTs have used hourly bedside blood glucose meter (BGM) testing to guide insulin therapy. The availability and maturation of continuous glucose monitoring (CGM) has resulted in its increasing utilization in clinical research and practice. Although its initial use has been in patients who are clinically stable in supervised clinical research settings and outpatient studies, CGM is now being increasingly evaluated in hospitalized patients.³ The subpopulation most studied to demonstrate the impact of tight glycemic control on outcomes during and after hospitalization has been patients hospitalized for cardiac surgery.^{4,5} More recently, other populations such as those with total pancreatectomy with islet autotransplantation (TPIAT) are being studied as reported in this issue of the Journal.⁶ Patients with chronic pancreatitis undergoing TPIAT or total pancreatectomy without islet autotransplantation (TP) represent a growing cohort worldwide. Patients enrolled for TPIAT may be euglycemic or have various stages of hyperglycemia from impaired glucose tolerance to diabetes mellitus.⁷ Patients who are hospitalized for TP with normal glucose tolerance or mild glucose intolerance represent a dramatic example of patients who are potentially transformed from full capacity of endogenous insulin secretion to almost complete absence of C-peptide secretion. Islet autotransplantation (IAT) performed after TP has the potential to provide endogenous insulin secretion for a varying period of time depending on various factors.⁸

Forlenza et al.⁹ analyzed the accuracy of CGM in an RCT of tight glycemic control in patients who underwent TPIAT. Patients were randomized to a control arm treated with multiple daily injections of subcutaneous insulin and an experimental arm in which the intervention was closed loop control (CLC).⁹ Both groups received intravenous insulin for the first three postoperative days. Subjects were fed by a jejunal tube and switched to receive subcutaneous insulin starting about 3–4 days after the surgical procedure. Both

groups wore two CGMs during the study period. Whereas the CLC group used Medtronic Enlite 2 CGM, iPro2 CGMs were used in the control group. One CGM was used in the CLC group to dose insulin through the Medtronic paradigm insulin pump. The CLC algorithm is based on the proportional integrative derivative (PID) model and the algorithm version used was the Medtronic ePID 2.0.¹⁰ The backup CGM was used based on investigator discretion. During the RCT, investigators were concerned about edema in the anterior abdominal wall affecting CGM accuracy and consequently impacting the CLC algorithm. Therefore, they analyzed accuracy of CGM data in the seven patients who were randomized to CLC.

Measures to assess accuracy of BGM and CGM data have evolved over time. The Clarke error grid (CEG) was described to evaluate the accuracy of BGMs.^{11,12} This grid includes zones designated A–E. Zone A represents glucose measurements that are $\leq 20\%$ from a gold standard blood glucose (BG) measurement (Yellow Springs Instruments or YSI). Zone B represents data that are outside the 20% limit but resulting in benign errors of antihyperglycemic medication dosing. Zones C–E show increased degrees of inaccuracy compared with the reference glucose. Subsequently, the surveillance error grid (SEG) to analyze BGM data has been described.^{13,14} The SEG assigns a numerical risk to BGM data and thus improves quantification of risk associated with an inaccurate measurement of glucose. Mean absolute relative difference (MARD) between CGM measurement and another measure of glucose measurement such as YSI measurement of BG or BGM has been used as a measure of CGM accuracy since its inception.¹⁵ Forlenza et al. report measures of CEG and SEG in their report.⁶ They compare CGM data 10 min after YSI measurement with YSI data obtained every 30 min.¹⁶ The seven subjects in their study provide about 21 days of data. A total of 990 data points were thus evaluated using CEG and SEG. It is reassuring that 99% of these data were in zones A and B of CEG and 98% of data were in the no or low risk SEG subgroups. The article also provides valuable additional information. Per protocol, CGM was needed to be recalibrated if (i) absolute relative difference (ARD) was greater than 30% on a single occasion or (ii) ARD was $>20\%$ with two consecutive measurements or (iii) at investigators discretion.

The study CGMs were recalibrated 8.3 times per day. Since the study used two CGMs with the intent of using one CGM to drive automated insulin delivery with the second serving as backup, the frequency of use of the second CGM was also reported. The use of the second CGM occurred 1.4 times per day during the study period. Calibrations of CGMs in ambulatory care or the free living environment have been performed during times of stable glucose states. The current study reports MARD at different glucose ranges and during different rates of change of glucose. It is reassuring that MARD at high glucose concentrations was small and acceptable. The MARD in hypoglycemic range was high but the analysis is limited by the percentage of data points in this category being 0.8% of the 990 readings. The MARD during different rates of glucose change is characterized by high variability ($SD \geq \text{mean}$). It is also a concern that the high variability occurred with limited distribution of rate of change of glucose during the study period. The limited distribution for rate of change of glucose for this data set is not surprising, considering that subjects were fed by jejunal tubes, had limited physical activity, and were clinically stable.

CGM use has the potential to improve glycemic control during hospitalization and, therefore, has been studied by other research groups. In the hospitalized patient, CGM readings can be affected by various clinical factors such as postoperative edema, various medications, severity of illness, and abnormal body temperature. Therefore, it is important to assess the accuracy of CGM with rigorous statistical techniques. Schuster et al. assessed accuracy of Medtronic Guardian real-time (RT) CGM in 24 subjects in surgical in-

tensive care units (ICUs)⁵ and reported MARD of 22 mg/dL with 71.3% and 27.6% of CGM data in zones A and B of CEG, respectively. Siegel et al. assessed accuracy of CGM in 60 patients admitted for cardiac surgery.³ Two CGMs (Medtronic Guardian RT CGM and FreeStyle Navigator; Abbott) were placed in each patient a day before surgery and compared with arterial BG measured every 2 h during the first 24 h after surgery. MARD for the Navigator and Guardian CGMs was 11% and 14%, respectively. More recently, in the REGIMEN trial,¹⁷ 35 patients admitted in the medical ICU were randomized to microdialysis-based glucose sensor RT-CGM (GlucoDay_S; A. Menarini Diagnostics) or blinded CGM (GlucoDay CGM, control group). BG was checked using a BG analyzer (Rapidlab[®]1265; Siemens) every 1–4 h. On CEG, 98.6% measurements were in zones A and B. MARD was observed to be 11.2%. We searched clinicaltrials.gov for evaluating accuracy of CGM in hospitalized patients and summarized registered studies in Table 1. The number of registered studies that are ongoing is limited. Up-to-date information about several registered studies is not available and analyses for accuracy appear to be limited in scope based on the registration information.

In conclusion, the study by Forlenza et al. provides the first report of SEG analyses in CLC studies. The study also provides data about important variables such as frequency of backup CGM use, recalibration frequency, and MARD in different glucose ranges and at different rates of change. These end points should be included in future reports of hospital CGM use. The data set could be further analyzed to provide information about the CGM consequences of CLC when CGM data are located in different risk zones on CEG

TABLE 1. STUDIES EVALUATING CGMS REGISTERED ON CLINICALTRIALS.GOV²⁰

<i>Study/no. of centers/country</i>	<i>Patient population/ design/No. of patients</i>	<i>CGM used</i>	<i>Accuracy measurement methods</i>	<i>Comments</i>
NCT01301053/Single/US	ICU/RCT/20	Dexcom SEVEN PLUS and G4	Feasibility study, no accuracy analysis stated.	Last updated 2011
NCT00694473/Single/US	ICU and surgery/ single group/65	Freestyle Navigator	MARD	Last updated 2012
NCT00878891/Single/France	CABG/RCT/45	RT-CGM versus blinded CGM (GlucoDay)	MARD	Last updated July 2015
NCT01995994/Single/S Korea	ICU >72 hours/ single arm/23	Medtronic Guardian	MARD	Last updated 2015
realNCT02296372/ Single/Germany	ICU/single group/30	MEDTRONIC SENTRINO [®] and Edwards GlucoClear [®] systems.	Not stated.	Last updated November 2014
NCT00996099/ Single/Czech Republic	Cardiac surgery/ single arm/24	Not stated	Error grid analysis	Last updated August 2009
NCT01992965/ Single center/China	ICU/RCT/140	Not stated	Not stated	Last updated May 2014
NCT01942902/ Single center/India	ICU/single group/30	GlySure continuous intravascular glucose monitoring system	Not stated	Last updated November 11, 2013
NCT02421107/Single center/United Kingdom	ICU/single group/40	Glucose monitoring system (GlySure)	MARD	Last updated April 2015

CGM, continuous glucose monitoring; MARD, mean absolute relative difference; RCTs, randomized clinical trials.

and SEG. Complete analyses of CGM data from the primary and backup CGM would also be useful especially to design future studies. Glucose variability in days 4–7 after TPIAT when subjects are fed by a jejunal tube is low. The effect size of CLC in such circumstances is small. Given the high cost of running such studies, whether further studies of CLC are needed after TPIAT is an interesting and important issue. How important tight glucose control is to facilitate engraftment of infused islet product needs to be studied further in human recipients. The concept that tight glucose control facilitates islet engraftment in human subjects is a speculation from studies of small animals.^{18,19} Rigorous accuracy analyses from CGM used in the control arm would have provided additional important information.

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