

Evaluation of a Continuous Glucose Monitoring System for Home-Use Conditions

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INTRODUCTION

The cost burden of diabetes is significant. In 2007, the total costs associated with the disease were estimated at \$174 billion (ADA 2008). Patients diagnosed with diabetes incur 2.3 times higher medical expenditures than those without the disease. Hypoglycemia severe enough to warrant third-party intervention results in mean costs exceeding \$1,000 per episode (Bullano 2005, Heaton 2003).

Several landmark trials have confirmed that tighter control of diabetes improves clinical outcomes (UKPDS Group 1998, DCCTRG 1993). The adoption of an intensive form of diabetes management can, however, come with increased risk, as was reported in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial (NHLBI 2008). There is speculation that the increased risk of

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ABSTRACT

Objective: To evaluate the safety and effectiveness of the FreeStyle Navigator Continuous Glucose Monitoring System when used by adult patients with type 1 or 2 diabetes requiring insulin in the home environment. **Research design and methods:** Multicenter, prospective study enrolling 137 subjects. This was a two-phase study consisting of 20 days of use ("masked period") without access to continuous glucose readings followed by 21 days of use ("unmasked period") with access to continuous glucose readings and glucose alarms. At the conclusion of the study, all subjects were asked to complete a User's Questionnaire. **Results:** A total of 11,487 paired continuous glucose sensor and blood glucose reference results from 961 sensors were evaluated; 77.2 percent were in Clarke error grid zone A and 19.6 percent were in zone B. Only 13.1 percent of the hypoglycemic and 0.5 percent of the hyperglycemic threshold alarms were false alerts. Subjects with type 1 diabetes demonstrated a 55 percent reduction in time spent with significant hypoglycemia (below 55 mg/dL) ($P < .0001$) from masked to unmasked periods. Their average number of hypoglycemic episodes (below 70 mg/dL) per day fell from 1.1 to 0.8 ($P < .0001$). Results from patient questionnaires demonstrated high levels of subject satisfaction and the ability to use and understand the system. **Conclusions:** FreeStyle Navigator Continuous Glucose Monitoring System is safe and effective, and results in a high level of subject satisfaction while used in the home setting. Utilization of continuous glucose monitors with alerts may result in cost offsets by reducing the number and severity of clinically significant events and assisting in the maintenance of optimal glycemic control.

Key words: diabetes, continuous glucose monitor, FreeStyle Navigator

cardiovascular death may be due to higher baseline cardiovascular risk; however, this has yet to be confirmed. Intensive management of diabetes would, therefore, require close monitoring of glycemic control with the goal of maintaining blood glucose levels within a defined optimal range (70–180 mg/dL) (ADA 2005).

Continuous glucose monitoring (CGM) provides greater information regarding glycemic control than

episodic blood glucose measurements. CGM has the ability to indicate a rate of change both in numeric form and through the use of prospective, directional trend arrows. In addition, alarms are activated when glucose levels approach critical hypoglycemic or hyperglycemic values. CGM provides the patient and health care provider with access to retrospective continuous glucose data over clinically relevant periods of

time (Garg 2006, Deiss 2006). These features result in systems that provide trend information that can guide treatment decision making.

This is a report of a study examining the accuracy of the FreeStyle Navigator Continuous Glucose Monitoring System (Abbott Diabetes Care, Abbott Park, Ill.) in the home environment and patient assessment of its use. The device and its performance in a clinical setting have been described previously (Weinstein 2007).

METHODS

This was a prospective, single-arm, multicenter study. Enrolled adult subjects with type 1 or type 2 diabetes mellitus who required insulin wore the continuous sensor on the upper arm or abdomen, as preferred, continuously for 40 days. CGM readings and alarms were not provided to the subjects during the first 20 days of wear (“masked period”), although a reading was automatically logged into the device’s memory every 10 minutes throughout the study period.

On day 21, the device was set to display glucose readings and to provide low and high glucose alarms (set at 65 and 300 mg/dL, respectively). This “un-masked” period continued for the final 20 days of the study, until final sensor removal on day 41. Subjects were instructed not to use CGM readings to make therapeutic deci-

sions regarding management of their diabetes without confirming blood glucose status through a traditional finger-stick blood glucose test.

Accumulated electronic data were uploaded from the receiver by study research staff at scheduled clinical visits at enrollment, study initiation, days 6, 21, 41 and at a final follow-up date between 3 to 7 days after the last sensor was removed. At the end of the study, subjects were asked to respond to a user’s questionnaire. Responses were ranked on a Likert scale that utilized forced-choice responses from 1 (strongly agree) to 6 (strongly disagree). In addition to an average score determination, agreement was calculated as the percentage of subjects responding 1, 2 or 3.

Review boards at participating institutions approved the study protocol, and all subjects provided written consent before study participation.

ANALYSIS METHODS

The average of duplicate blood glucose test measurements were paired with a CGM reading, to provide paired quantitative comparisons during everyday activity. For the alarm analysis, categories were assigned to hypoglycemic alarms at the 65 mg/dL setting when paired CGM/blood glucose values were available: “true positive” if the CGM value was below threshold; “appro-

priate” if the CGM value was ± 15 mg/dL of threshold, and “false alarm” if the CGM value was ≥ 15 mg/dL above threshold. Respective categories were assigned to hyperglycemic alarms ≥ 300 mg/dL if the CGM blood glucose value was above the threshold (true), within 20 percent (appropriate), or >20 percent below the threshold (false).

Differences between CGM data collected on days 1–20 (masked data) and on days 21–41 (unmasked data) were assessed for duration, intensity and frequency of hypoglycemic (<70 mg/dL) and hyperglycemic (>180 mg/dL) episodes and total proportion of time spent outside the 70–180 mg/dL range.

RESULTS

Of the 137 subjects enrolled in the investigation, 123 completed the 40-day monitoring period. Fourteen subjects withdrew from the study either voluntarily for reasons unrelated to the study, or due to non-compliance with protocol demands ($n=8$) or difficulties handling the device ($n=6$). None of the discontinued subjects participated in the unmasked portion of the study. However, the glucose data available for the discontinued subjects were included in the paired point analysis. Demographic characteristics of the study population are summarized in Table 1.

Data from 961 sensors with 11,487 paired CGM blood glucose reference values were evaluated. Of the 11,487 paired points, 77.2 percent fell in the Clarke error grid zone A (clinically accurate), and 19.6 percent fell in zone B (clinically acceptable), indicating a high level of correspondence between the reference blood glucose measurements and the CGM results (Weinstein 2007). Low threshold alarm (65 mg/dL) performance analysis demonstrated that 13.1 percent of alarms were false, while the remaining alarms were either true (60.3 percent) or within 15 mg/dL of the blood glucose test result (26.6 per-

TABLE 1
Subject demographics

Characteristic	Result (N=137)
	Mean \pm SD (range)
Age (year)	48.6 \pm 13.0 (19-72)
Weight (lb)	180.0 \pm 37.1 (114-306)
BMI* (kg/m ²)	28.7 \pm 5.8 (18.9-52.6)
Approximate daily dose of insulin (units)	51.7 \pm 28.7 (12-160)
Race (percent)	
Caucasian	78.8
Asian	3.6
Multiracial	17.5
Black	0

*Body mass index

TABLE 2
Results of paired CGM/blood glucose value paired assessment

Group category	Glucose range (mg/dL)	Analysis	Masked mean (SD)	Unmasked mean (SD)	Difference P-value
Type 1	<55	Hours per day spent	0.55 (0.8)	0.25 (0.4)	<.001
	<70	Hours per day spent	1.42 (1.4)	0.83 (0.8)	<.001
	70–180	Hours per day spent	13.11 (3.6)	13.79 (3.8)	.0038
	>180	Hours per day spent	9.47 (4.2)	9.38 (4.1)	.7079
	<70	Number of episodes per day	1.1 (0.8)	0.8 (0.6)	<.0001
	>180	Number of episodes per day	2.5 (0.9)	2.7 (0.7)	.020
	<70	Average duration of episode (hrs)	1.0 (0.6)	0.7 (0.4)	<.0001
	>180	Average duration of episode (hrs)	3.9 (1.5)	3.5 (1.3)	.0025
Type 2	<55	Hours per day spent	0.15 (0.3)	0.20 (1.0)	.3676
	<70	Hours per day spent	0.62 (0.8)	0.69 (1.0)	.6520
	70–180	Hours per day spent	13.75 (5.5)	15.38 (4.1)	.0027
	>180	Hours per day spent	9.62 (5.8)	7.93 (4.4)	.0057
	<70	Number of episodes per day	0.5 (0.5)	0.6 (0.6)	.3861
	>180	Number of episodes per day	2.3 (0.6)	2.4 (0.7)	.1512
	<70	Average duration of episode	0.9 (0.7)	0.6 (0.5)	.1260
	>180	Average duration of episode	4.3 (3.2)	3.3 (2.0)	.0024

cent). Analysis of the hyperglycemic threshold alarm (300 mg/dL) demonstrated that 0.5 percent were false alerts, while the remaining alarms were either true (89.9 percent) or within 20 percent of the blood glucose test result (9.6 percent).

The glycemic events and time spent in hypoglycemic (<70 mg/dL), euglycemic (70–180 mg/dL) and hyperglycemic ranges (>180 mg/dL) are listed in Table 2. Comparing the masked and unmasked periods, all subjects combined demonstrated a significant ($P<.001$) decrease in the time spent in hypoglycemia (<70 mg/dL) with the average amount of time per 24 hours decreasing from 1.23 hours to 0.80 hours.

Subjects with type 1 diabetes mellitus demonstrated a significant ($P<.001$) reduction in the time spent below the two predefined hypoglycemia (55 and 70 mg/dL) thresholds (–55 percent and –42 percent, respectively). The average number of hypoglycemic episodes per day decreased significantly (1.1 to 0.8; $P<.001$) as did the average duration of the episodes (1.0 hour to 0.7 hour;

$P<.001$) and the average magnitude of the excursions (54.7 mg/dL to 58.4 mg/dL; $P<.001$). There also was significant improvement in the average duration of each episode of hyperglycemia (>180 mg/dL) (3.9 hours to 3.5 hours; $P=.0025$) and the mean number of hours per day spent in the target glycemic range of 70 to 180 mg/dL (13.75 to 15.38; $P=.0027$).

Among subjects with type 2 diabetes mellitus, the duration of time spent in hyperglycemia improved in the unmasked phase. The time spent in the euglycemic range increased by 12 percent ($P=.0027$) and the time spent in hyperglycemia (>180 mg/dL) decreased by 18 percent ($P=.0057$). The measures of hypoglycemia were largely unchanged in the unmasked phase.

Safety and insertion site findings

There were no unanticipated adverse device effects reported for the study. However, two adverse events related to the device were reported: two occurrences of itching lasting more than seven days reported by the

same subject, each of which resolved and did not require medical treatment. All the other adverse events ($n=15$) were transient and unrelated to the device or study.

The one serious adverse event reported occurred in a subject who experienced an episode of severe hypoglycemia and lost consciousness. The subject was administered glucagon and recovered completely. The subject had a history of regular severe hypoglycemia and the episode was deemed unrelated to either the study device or study procedure.

Examination of the sensor insertion sites indicated that 17.4 percent of subjects experienced some arm bruising. Other possible insertion effects assessed (erythema, edema, rash, bleeding, pain or itching) were reported by <5 percent of subjects.

Study questionnaire

Questionnaire results were available from 131 subjects. The results of the study questionnaire (Table 3) demonstrated high levels of subject satisfaction and the ability to use and understand the system. Subjects in-

dicated that the device was easy to learn (115/130), the glucose alarms were easy to interpret (117/125), and the device helped them to understand their blood sugars (121/129).

DISCUSSION

This study demonstrated the safe and effective use of the FreeStyle Navigator Continuous Monitoring System by adults with type 1 or type 2 diabetes mellitus in a home-use setting. The participants in the study reported a high level of satisfaction and

ease of use of the FreeStyle Navigator system and an ability to understand the alarm features.

This and other studies show that CGM enables better glycemic control in patients with type 1 or 2 diabetes mellitus who require insulin (Garg 2006, Deiss 2006, DirectNet 2007, Bode 2005, Bode 2004, Hirsch 2007). It is logical to assume that improved glycemic control may result in improved outcomes and the potential for decreased use of medical intervention over the long term. However,

in the absence of long-term, large, randomized controlled studies of CGM, clinical and economic benefits must be extrapolated from available data.

The potential for economic benefit with use of CGM in carefully selected patient populations is high. Reduced variability in glycemic control may lead to decreased use of acute care services for hypoglycemia in the short-term. In the long term, financial savings may result from improved clinical outcomes and decreased use

TABLE 3
Results of subject questionnaire

Questions	Overall percent in agreement* n=131	Mean score
Appearance		
General appearance of the on-body device is acceptable	76.3	2.7
Overall size of the on-body device is acceptable	63.4	3.0
The receiver size and shape is acceptable	73.3	2.8
Receiver display and function		
The system is easy to carry around with me	79.4	2.6
The system is easy to learn	88.5	2.0
The receiver display is easy to read	88.4	2.0
The receiver menus are easy to follow	88.5	1.9
The menu choices are satisfactory	84.6	2.2
It is easy to change the settings in the Navigator	90.2	1.9
It is easy to review reports and glucose history	90.3	1.9
It is easy to understand messages and alarms on the receiver	88.5	2.0
It is easy to interpret glucose alarms	93.6	1.7
The information from the system helps understand blood sugars	93.8	1.7
General		
Blood glucose tests with the FreeStyle test strips in the Navigator are easy	87.7	1.9
Waiting 10 hrs for the system to show real data is acceptable	46.2	3.6
Calibrating the system at 10/12/24/72 hours is acceptable	60.0	3.1
I found insertion site choices acceptable	80.0	2.2
The system performed without errors	53.1	3.5
Adhesive performance		
The adhesive is comfortable on my skin	83.2	2.2
The adhesive does not peel away from my skin prematurely	69.2	2.9
The adhesive is removed from my skin with minimal pain	91.6	1.9
General wear		
The transmitter is comfortable during normal activity	76.3	2.5
The transmitter is comfortable during sleep	73.3	2.6
Ease of application		
The mount is easy to apply to the skin	96.9	1.6
The inserter is no more painful than doing a finger-prick	80.2	2.2
The bleeding from the insertion is acceptable	81.7	2.2

* Response ranked as 1, 2 or 3 on a scale of 1 (strongly agree) to 6 (strongly disagree)

of expensive medical procedures, hospitalizations, and ancillary services due to consistently controlled hemoglobin A_{1c}.

These improvements may also lead to direct and indirect financial benefits to health plans through improved National Committee for Quality Assurance (NCQA) quality improvement ratings (Performance measurement 2008). NCQA accreditation ratings of health plans are used by employers, unions, and other purchasers of health care to assess how well managed care plans perform in delivery of care to members using objective outcomes and process measures criteria. Comprehensive diabetes care is an important set of performance measures as collected and reported through NCQA's Healthcare Effectiveness Data and Information Set (HEDIS) and has a significant degree of influence on the overall score that a plan receives. Employers, consumers, regulators, and health plans turn to NCQA accreditation as the gold standard in evaluating health care quality (Performance measurement 2008).

The NCQA overall accreditation rating allows a health plan to differentiate itself from other plans in overall and disease-specific quality of care. This helps plans retain and grow their enrollment. Another important aspect is the frequency of NCQA-sponsored onsite evaluations. Facilities with better accreditation ratings are evaluated less frequently than plans with low ratings, thereby reducing significant administrative burden resulting in direct savings.

In order to ensure appropriate utilization of this technology, managed care organizations (MCOs) need to establish clear medical eligibility criteria in order to easily identify appropriate patients for CGM like the FreeStyle Navigator system. MCOs typically employ prior authorization mechanisms to ensure that approval for payment of devices are for patients who have a clinical need and

who are likely to find the device easy to use and tolerable. Initial selection criteria may be most appropriate for the following subpopulations: patients who have experienced recurrent hypoglycemia; "brittle" patients who are frequently in and out of emergency departments or physician offices due to severe events; ongoing failure of improving glycemic outcomes despite participating adequately in their self-management plan through consistent blood glucose testing; women with type 1 diabetes who are planning for pregnancy; and newly diagnosed patients who can incorporate the technology early into their disease course or who would benefit in periods of therapeutic transition from the additional information CGM provides. A more advanced criteria list could be expanded to include patients with severe hypoglycemic unawareness, patients who have failed to adhere to medical treatment plans due to poor compliance with medications and inconsistent blood glucose monitoring, and patients experiencing comorbid complications or depression that may interfere with expected clinical outcomes.

Conversely, there may be patients who are inappropriate candidates for continuous glucose monitor technologies. For example, patients who either do not have the cognitive ability to utilize the device or interpret the data may not be appropriate candidates. Likewise, patients who are resistant to any technology to improve their care — whether due to compliance issues, emotional issues, or pure stubbornness — are not good candidates for CGMs.

One group of patients which payers may not consider as candidates may actually be the ones who need it most: patients who are able to control their diabetes through traditional methods have a proven track record of compliance and persistency with their prescribed regimens. These patients may benefit from CGMs as it

has been shown that a downside of intensive diabetes management is the risk of hypoglycemia. In fact, one study demonstrated that individuals who performed an average of nine fingerstick measurements per day, which is much higher than patients in a naturalistic setting, experienced two hours per day in a hypoglycemic state (Bode 2005). Equipping these patients with CGMs may not only make good clinical sense as they are likely to respond to the alerts, but also may be cost-effective through the reduction of potential hypoglycemic events. Additionally there is potential for reduced costs related to finger-sticks and their associated morbidity.

Many MCOs operate sophisticated disease state management programs relying heavily on the initial judgment of case managers. The recommendation of these case managers and/or physician reviewer specialist (e.g., diabetologist) for a CGM are likely to influence the decision to reimburse for a CGM.

From the prescribing physician perspective, patients who have the right tools to make adjustment decisions independently and with a high degree of accuracy can free up time for other patients. This is especially important for doctors under a capitated arrangement where there are financial incentives for keeping patients in control with fewer interventions.

Cost efficiencies of CGM systems will only become fully apparent with long-term use and the development of outcomes data. However, short-term benefits will become evident through improvements in acute outcomes, such as decreased hypoglycemic episodes, while long-term benefits, such as improvement in macrovascular disease, will require longer study in larger populations. With this goal in mind, all health care professionals involved in patient care must be well versed in both the technical application of the CGM system as well as the clinical interpretation of

data and glycemic management. An initial time investment on the part of the clinical management team to learn about the systems, careful patient selection and proper patient/caregiver education will contribute to a high degree of patient compliance, and long-term glycemic control through continuity of use.

A novel mechanism for providing patients with additional cost-effective services is seeing patients in groups in addition to individual office visits. One study found that patients seen in groups of 10 to 20 by a physician and two nurse specialists provided more contact time while reducing the frequency of individual office visits (Terry 1997). CGM training and follow-up may be particularly well suited for group programs as patients can discuss success strategies with other CGM patients and health care professionals.

TAKE AWAY POINTS

The FreeStyle Navigator has been proven to provide accurate interstitial fluid glucose data on a continuous basis. This enables the patient or health care provider to respond to changes in glycemic status more frequently than with random sampling provided by SMBG.

The FreeStyle Navigator Continuous Glucose Monitoring System is easily managed by and appropriately designed for use by adults with diabetes who require insulin. It is differentiated by its functionality including frequency of measurements and unique alert system. From a clinical perspective, it meets the conditions of a viable CGM technology as it is accurate, easy to use, and well tolerated.

Use of a CGM system may provide the opportunity for improved glucose control for patients with diabetes through reductions in glucose variability resulting in short- and long-term improvements in A_{1c} control.

Benefits associated with use of CGM in appropriate patient popula-

tions extend beyond short-term improvements in glycemic control to the potential for meaningful improvement in long-term outcomes, improved NCQA accreditation ratings, and decreased cost of care by reducing the number of clinically significant and costly hypoglycemic and/or hyperglycemic episodes.

Managed care must balance the new benefits that CGMs provide in the management of diabetes with the need to provide quality care that is cost effective.

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