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SYMPOSIUM

Alarm Characterization for a Continuous Glucose Monitor That Replaces Traditional Blood Glucose Monitoring

Geoffrey McGarraugh, M.S.

Abstract

Background:
Continuous glucose monitoring (CGM) devices available in the United States are approved for use as adjuncts to self-monitoring of blood glucose (SMBG); all CGM alarms require SMBG confirmation before treatment. In this report, an analysis method is proposed to determine the CGM threshold alarm accuracy required to eliminate SMBG confirmation.

Method:
The proposed method builds on the Clinical and Laboratory Standards Institute (CLSI) guideline for evaluating CGM threshold alarms using data from an in-clinic study of subjects with type 1 diabetes. The CLSI method proposes a maximum time limit of ±30 minutes for the detection of hypo- and hyperglycemic events but does not include limits for glucose measurement accuracy. The International Standards Organization (ISO) standard for SMBG glucose measurement accuracy (ISO 15197) is ±15 mg/dl for glucose <75 mg/dl and ±20% for glucose ≥75 mg/dl. This standard was combined with the CLSI method to more completely characterize the accuracy of CGM alarms.

Results:
Incorporating the ISO 15197 accuracy margins, FreeStyle Navigator® CGM system alarms detected 70 mg/dl hypoglycemia within 30 minutes at a rate of 70.3%, with a false alarm rate of 11.4%. The device detected high glucose in the range of 140–300 mg/dl within 30 minutes at an average rate of 99.2%, with a false alarm rate of 2.1%.

Conclusion:
Self-monitoring of blood glucose confirmation is necessary for detecting and treating hypoglycemia with the FreeStyle Navigator CGM system, but at high glucose levels, SMBG confirmation adds little incremental value to CGM alarms.

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Author Affiliation: Abbott Diabetes Care, Alameda, California

Abbreviations: (BG) blood glucose, (CG-EGA) continuous glucose–error grid analysis, (CGM) continuous glucose monitoring, (CLSI) Clinical and Laboratory Standards Institute, (ISO) International Standard Organization, (SMBG) self-monitoring of blood glucose, (YSI) Yellow Springs Instrument

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Corresponding Author: Geoffrey McGarraugh, Abbott Diabetes Care, 1360 South Loop Road, Alameda, CA 94502; email address geoff.mcgarraugh@abbott.com

Introduction

Continuous glucose monitoring (CGM) devices are particularly attractive for managing blood glucose (BG) because of their potential to detect hypo- and hyperglycemia as they occur, which is impractical with self-monitoring of blood glucose (SMBG). Despite this advantage, all CGM devices available for use in the United States have been approved only as adjuncts to SMBG testing. The reason for this adjunctive status is that the margin of error in an isolated CGM glucose value is markedly greater than that in an SMBG result.

As the field of CGM has matured, more sophisticated methods of assessing CGM accuracy have been developed. Simply quantifying the error of isolated glucose readings is not a sufficient evaluation of CGM. Glycemia is a dynamic process that occurs over time and is best described in two dimensions: a glucose axis (providing actual glucose measurements) and a time axis (incorporating glucose measurements in the context of time). By providing glucose values over time, CGM tracks glycemic variation with both axes.

Continuous glucose–error grid analysis (CG-EGA)[1] is a good example of an established assessment method that takes into account the CGM information provided by both glucose and time axes. CG-EGA methodology is instructive for developing a CGM assessment tool. It is based on an intuitive understanding of how CGM data, specifically information provided by the CGM time axis about rate and direction of glucose change, can be used to improve clinical decision making.

An important insight of the CG-EGA is that additional information provided by the time axis can be used to overcome some of the deficiencies on the glucose axis. If the rate and the direction of glucose change reported by CGM are reasonably accurate, a correct clinical decision can be made with a less accurate instantaneous glucose value.

The hypo- and hyperglycemia alarm features of CGM devices are also made possible by the CGM time axis. Because SMBG provides a more accurate instantaneous glucose value than CGM, all CGM alarms currently must be confirmed by SMBG before treatment. Just as the CG-EGA used the time axis to overcome some of the error in the CGM glucose value, can the CGM time axis be leveraged to eliminate the need for confirmatory SMBG after a CGM alarm sounds? This report attempts to answer that question.

Based on an alarm analysis by the Diabetes Research in Children Network Study Group,[2] the Clinical Laboratory and Standards Institute (CLSI) created a standard for evaluating CGM alarms that makes use of the CGM time axis.[3] In the CLSI standard, hypo- and hyperglycemia are considered to be events that occur over time. An event is detected if an alarm occurs within ±30 minutes of the start of the event. This effectively defined the maximum allowable error on the time axis for CGM alarms. The guideline also suggested that ±15 minutes be considered as an optimum detection window.

Unfortunately, the CLSI standard allowed for no error on the CGM glucose axis, which is not appropriate for the evaluation of glucose monitors. To complete CLSI alarm analysis, an acceptable error on the CGM glucose axis must be incorporated. The standard of the International Standard Organization (ISO) for assessing the accuracy of SMBG devices (ISO 15197) defines an accurate measurement to be within ±15 mg/dl of a reference measurement for glucose levels <75 mg/dl and within ±20% of a reference measurement for glucose levels ≥75 mg/dl.[4] The acceptance criterion for SMBG performance is 95% accurate results. These limits were based on state-of-the-art glucose meters in 2003 and on their effectiveness for monitoring BG in patients with diabetes, as demonstrated in clinical outcome studies. The ISO 15197 definition of accuracy is nearly identical to the error grid analysis definition of clinically accurate, which was based on correct clinical decision making.

In this report, the ISO 15197 standard for SMBG was combined with the CLSI guideline for CGM to determine the CGM alarm performance required to eliminate confirmatory SMBG. The ISO 15197 standard for SMBG defined accuracy on the CGM glucose axis; the CLSI guideline for CGM defined the accuracy on the CGM time axis. Both 15- and 30-minute time windows were evaluated. A clinical study comparing a commercially available CGM to a laboratory reference was used to illustrate the alarm characterization.

Materials and Methods

Clinical Study

The clinical study has been described previously and conforms to the CLSI guideline for in-clinic studies with frequent reference readings.[3,5,6] Fifty-eight subjects with

type 1 diabetes were enrolled at three sites comparing the FreeStyle Navigator® CGM system Abbott Diabetes Care, Alameda, CA) to venous glucose measurements using the Yellow Springs Instrument (YSI) 2300 STAT Plus glucose analyzer (YSI Life Sciences, Yellow Springs, OH).

In the clinical study, two sensors were inserted into each subject, one at the back of the arm and one on the abdomen. Venous YSI measurements were taken at 15-minute intervals for a total of 50 hours for each subject. The subjects' clinic time was scheduled to incorporate the entire 5-day lifetime of the sensors. Insulin and glucose challenges were administered to assure hypo- and hyperglycemic conditions (Registration Number NTC00920881 on Clinicaltrials.gov). Raw CGM data were postprocessed using the FreeStyle Navigator TRU-Start™ calibration algorithm, which calls for calibration with SMBG 1, 2, 10, 24, and 72 hours after insertion of a 5-day sensor.

Analytical Methodology

Continuous glucose monitoring readings were paired with YSI values taken within the same minute, and YSI whole blood measurements were multiplied by 1.12 to obtain plasma equivalent values.[7] The start of a hypoglycemic event was defined by the first of multiple successive reference readings below the hypoglycemic threshold, and the end of the event was defined by two successive reference readings above the threshold. An exception was made for brief events involving a single reference point. To eliminate events caused by random error in the reference test, the single point was required to be >2 standard deviations beyond the threshold (e.g., using a standard deviation of 3 mg/dl for YSI glucose measurements <100 mg/dl, a single reference point 70-mg/dl hypoglycemic event required an YSI measurement <64 mg/dl). Alarms originated with the first CGM paired point below the hypoglycemic threshold and ended with two successive CGM paired points above the threshold. Hyperglycemic events and alarms were defined similarly, except that the YSI error for the single-point hyperglycemic event was a 3% coefficient of variation for glucose >100 mg/dl.

Low Glucose Alarms

Although there is no universal agreement on the glucose level that defines hypoglycemia, 70 mg/dl is generally accepted as mild hypoglycemia that should be treated and was used as the hypoglycemic threshold for this analysis. If a CGM is reading high by any margin, it will not activate an alarm set at 70 mg/dl when BG is 70 mg/dl. If, however, the CGM device is allowed the +15-mg/dl margin of error suggested by the ISO 15197 standard, it would still be considered accurate if the alarm set for a 70-mg/dl threshold sounded when BG was 55 mg/dl. With respect to error in the opposite direction, the CGM will activate a false alarm when it is reading glucose levels low. Allowing the –15 mg/dl margin of error, an alarm set for a 70-mg/dl threshold would still be considered accurate if it sounded when BG was ≤85 mg/dl. Thus, applying the ISO 15197 standard for glucose accuracy, an accurate CGM alarm set at 70 mg/dl must detect BG ≤55 mg/dl, and the glucose level when the CGM alarm sounds must be ≤85 mg/dl. Using the ISO 15197 acceptance criterion of 95% accuracy, the percentage of inaccurate alarm results must be ≤5% (i.e., the percentage of undetected events ≤55 mg/dl plus the percentage of false alarms >85 mg/dl must be ≤5%).

Continuous glucose monitoring devices approved to date cannot meet the ISO 15197 glucose accuracy criterion for instantaneous glucose; that is, current CGM devices cannot instantaneously detect hypoglycemia with an accuracy equivalent to SMBG. However, the CGM time axis has not yet been invoked to overcome the deficiencies in the glucose axis. The CLSI guideline, which allows up to ±30 minutes for the detection of glycemic events, provides the limit for error on the time axis. Incorporating the CLSI time constraint, the CGM must provide an accurate alarm for detection within ±30 minutes of the start of the event. In effect, this allows CGM ±30 minutes from the time BG descends into hypoglycemia to produce an accurate alarm.

Presumably, treatment would be performed immediately after an alarm sounds. Blood glucose must be in the desired range (≤85 mg/dl) for treatment to be correct; therefore, a time window for alarm activation should not be allowed when determining false alarms. The procedure for evaluating the 70-mg/dl low glucose alarm accuracy was, therefore, as follows:

1. Determine the percentage of BG levels of 55 mg/dl that were not detected 30 minutes after the start of the event.
2. Determine the same value with a 15-minute time frame.
3. Determine the percentage of alarms that occur with BG >85 mg/dl (false alarms).
4. Sum the percentage of BG levels <55 mg/dl that were not detected and false alarms >85 mg/dl for each time interval.
5. The sums must be ≤5% for adequate accuracy.

When using a 70-mg/dl alarm threshold to detect BG of 55 mg/dl (step 1 just given), the time window for

detection should be extended beyond 15 or 30 minutes on the negative side. When the alarm is set for 70 mg/dl, even a perfectly accurate CGM would activate an alarm before the 55-mg/dl event. If an alarm is not false, it is unnecessary to place a tight time limit on early detection because the early alarm correctly indicates the requisite treatment of the impending hypoglycemia. **Figure 1** is an extreme example, but occurrences with small excursions beyond –15 or –30 minutes should also be expected.

As an independent verification of alarm analysis, CG-EGA was performed on CGM results at the beginning of each 70-mg/dl event and each 70-mg/dl threshold alarm.

High Glucose Alarms

There is no universally accepted threshold for the treatment of hyperglycemia. As a result, a range of treatment levels must be considered. Another consideration is the time lag associated with the treatment of high glucose with subcutaneous insulin. If the therapeutic goal is to avoid BG levels >180 mg/dl, a lower value of BG (e.g., 140 mg/dl) might be the appropriate level to allow time for insulin to take effect after treatment.

Relating alarm accuracy to the ISO 15197 standard for glucose for high alarms is similar to the process used for low alarms. A CGM reading too low is unable to detect high glucose, and if the CGM device is reading glucose levels high, it will produce false alarms. To meet the ±20% accuracy standard, a high alarm must be able to detect a glucose event 20% higher than the alarm setting, and an alarm must occur when BG is no more than 20% lower than the alarm setting. Using a threshold alarm setting of 180 mg/dl as an example, the alarm must detect events of 216 mg/dl (180 mg/dl +20%), and an alarm is considered false if BG is <144 mg/dl (180 mg/dl –20%).

The time limit for detecting high glucose events in the CLSI guideline is the same for high alarms as for low alarms. Therefore, the procedure for the accuracy calculation was similar to that used for the low glucose alarm. The high alarm was characterized at 140, 180, 240, and 300 mg/dl. Alarm performance results were also compared to CG-EGA for consistency.

Results

Low Glucose Alarms

With a 70-mg/dl threshold setting at the 15-minute optimum time, detection of 70 mg/dl was 53.7%, and detection of 55 mg/dl was 62.2%, leaving 37.8% of 55-mg/dl events undetected (**Table 1**). At the 30-minute maximum time, results were better, with 64.0% detection of 70 mg/dl and 70.3% detection of 55 mg/dl, leaving

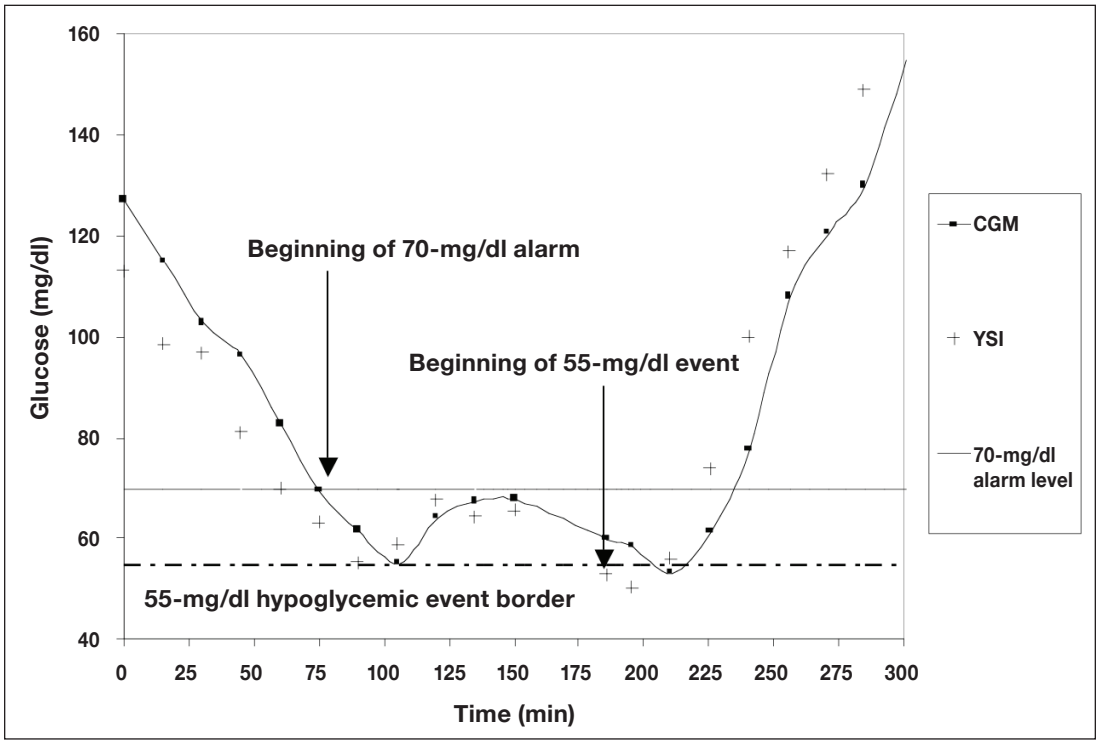

Figure 1. Early detection of a 55-mg/dl event with a 70-mg/dl alarm. The alarm occurs >100 minutes before the event, but it is not a false alarm and correctly indicates the requisite treatment of hypoglycemia.

Table 1.
Hypoglycemia Detection with Low Glucose Alarms

Detection at 70-mg/dl threshold		
Detection time	15 minutes	30 minutes
70-mg/dl events detected	53.7% (109/203)	64.0% (130/203)
55-mg/dl events detected	62.2% (46/74)	70.3% (52/74)
55-mg/dl events not detected	37.8% (28/74)	29.7% (22/74)
False alarms at 70-mg/dl threshold		
False alarms >70 mg/dl	35.2% (62/176)	
False alarms >85 mg/dl	11.4% (20/176)	
Alarm inaccuracies at 70-mg/dl threshold [a]		
	49.2%	41.1%

[a] Alarm inaccuracies are the sum of percentages of 55-mg/dl events not detected and false alarms >85 mg/dl.

29.7% of 55-mg/dl events undetected. The percentage of false alarms was 35.2% for BG >70 mg/dl and 11.5% for BG >85 mg/dl. Combined inaccuracies were 49.2% for 15 minutes and 41.1% for 30 minutes, which was far in excess of the ≤5% allowed by ISO 15197.

The performance of CG-EGA indicated that 61.2% of CGM values at the start of 70-mg/dl events were clinically accurate, 0% were benign errors, and 38.8% were clinical errors (**Table 2**). Clinically accurate values produce correct treatment; benign errors lead to no treatment or mistreatment with benign consequences; and clinical errors induce, fail to treat, or exacerbate hypo- or hyperglycemia. At the sounding of alarms, CGM values were 89.0% clinically accurate, 9.8% benign errors, and 1.2% clinical errors. Alarm analysis and CG-EGA indicated that CGM was not sufficiently accurate to replace SMBG.

High Glucose Alarms

At a 140-mg/dl threshold with a detection time of 15 minutes, the detection of 140-mg/dl events was 78.7%. The detection of events 20% higher (168 mg/dl) was 97.3%, leaving 2.7% of 168-mg/dl events undetected (**Table 3**). At the maximum 30-minute detection time, the detection of 140-mg/dl events was 89.6%. The detection of 168-mg/dl events was 98.9%, leaving 1.1% of 168-mg/dl events undetected. The percentage of false alarms with BG <140 mg/dl was 17.2%; the percentage of false alarms with BG levels 20% lower (112 mg/dl) was 2.1%. The combined inaccuracies were 4.8% for 15 minutes and 3.2% for 30 minutes; both were within the ≤5% ISO 15197 limit.

Table 2.
CG-EGA of CGM at the Beginning of Hypo- and Hyperglycemic Events and Alarms

CG-EGA rating	Beginning of events	Beginning of alarms
70-mg/dl low alarm		
Clinically accurate	61.2% (123/201)	89.0% (154/173)
Benign error	0% (0/201)	9.8% (17/173)
Clinical error	38.8% (78/201)	1.1% (2/173)
140-mg/dl high alarm		
Clinically accurate	90.7% (451/497)	93.2% (483/518)
Benign error	7.0% (35/497)	4.8% (25/518)
Clinical error	2.2% (11/207)	1.9% (10/518)
180-mg/dl high alarm		
Clinically accurate	90.1% (475/527)	93.2% (497/533)
Benign error	0.2% (1/527)	3.9% (21/533)
Clinical error	9.7% (51/527)	2.8% (15/533)
240-mg/dl high alarm		
Clinically accurate	95.3% (328/344)	93.4% (370/396)
Benign error	0.9% (3/344)	5.6% (22/396)
Clinical error	3.8% (13/344)	1.0% (4/396)
300-mg/dl high alarm		
Clinically accurate	98.2% (161/164)	88.8% (182/205)
Benign error	0.0% (0/164)	9.3% (19/205)
Clinical error	1.8% (3/164)	2.0% (4/205)
All high alarms[a]		
Clinically accurate	93.6%	92.2%
Benign error	2.0%	5.9%
Clinical error	4.4%	1.9%

[a] Percentages at each high alarm level were averaged.

The performance of CG-EGA indicated that 90.7% of CGM values at the start of 140-mg/dl events were clinically accurate, 7.0% were benign errors, and 2.2% were clinical errors (**Table 2**). At the sounding of alarms, CGM values were 93.2% clinically accurate, 4.8% benign errors, and 1.9% clinical errors.

Results were similar at the 180-, 240-, and 300-mg/dl alarm levels. At all glucose levels, high alarms met the accuracy requirement at the 15- and 30-minute detection times. The CG-EGA clinical errors (with one exception) and the alarm inaccuracies were both in the range of 1–5% for the high glucose alarms.

Table 3.
High Glucose Detection with High Glucose Alarms

Detection time	15 minutes	30 minutes
Detection at 140-mg/dl threshold		
140-mg/dl events detected	78.7% (395/502)	89.6% (450/502)
168-mg/dl events detected	97.3% (535/550)	98.9% (544/550)
168-mg/dl events not detected	2.7% (15/550)	1.2% (6/550)
False alarms at 140-mg/dl threshold		
False alarms <140 mg/dl	17.2% (92/534)	
False alarms <112 mg/dl	2.1% (11/534)	
Alarm inaccuracies at 140-mg/dl threshold [a]		
	4.8%	3.2%
Detection at 180-mg/dl threshold		
180-mg/dl events detected	74.9% (399/533)	86.7% (462/533)
216-mg/dl events detected	98.0% (443/452)	99.6% (450/452)
216-mg/dl events not detected	2.0% (9/452)	0.4% (2/452)
False alarms at 180-mg/dl threshold		
False alarms <180 mg/dl	24.2% (136/561)	
False alarms <144 mg/dl	1.6% (9/561)	
Alarm inaccuracies at 180-mg/dl threshold [a]		
	3.6%	2.0%
Detection at 240-mg/dl threshold		
240-mg/dl events detected	70.4% (247/351)	86.0% (302/351)
288-mg/dl events detected	97.4% (191/196)	98.5% (193/196)
288-mg/dl events not detected	2.6% (5/196)	1.5% (3/196)
False alarms at 240-mg/dl threshold		
False alarms <240 mg/dl	30.0% (123/410)	
False alarms <192 mg/dl	1.5% (6/410)	
Alarm inaccuracies at 240-mg/dl threshold [a]		
	4.0%	3.0%
Detection at 300-mg/dl threshold		
300-mg/dl events detected	72.8% (126/173)	88.4% (153/173)
360-mg/dl events detected	100.0% (55/55)	100.0% (55/55)
360-mg/dl events not detected	0.0% (0/55)	0.0% (0/55)
False alarms at 300-mg/dl threshold		
False alarms <300 mg/dl	35.3% (76/215)	
False alarms <240 mg/dl	3.3% (7/215)	
Alarm inaccuracies at 300-mg/dl threshold [a]		
	3.3%	3.3%
Detection for all high glucose alarms [b]		
Alarm threshold events detected	74.2%	87.7%
Threshold +20% events detected	98.2%	99.2%
Threshold +20% events not detected	1.8%	0.8%
False alarms for all high glucose alarms [b]		
False alarms at alarm threshold	26.7%	
False alarms at threshold –20%	2.1%	
Alarm inaccuracies for all high glucose alarms [b]		
	3.9%	2.9%

[a] Alarm inaccuracies are the sum of percentages of "threshold +20% events not detected" and "false alarms at threshold –20%."
[b] Percentages at each high alarm level were averaged.

Discussion

According to this low glucose alarm analysis and CG-EGA, the FreeStyle Navigator CGM system's low alarms were not sufficiently accurate for the detection of hypoglycemia, but the combination of CGM and SMBG can be very effective. Increasing the alarm threshold of the CGM device can increase the detection of hypoglycemia significantly.[6] The higher alarm setting will induce a higher number of false alarms, but all alarms should be confirmed by SMBG to ensure that only true hypoglycemia is treated. In effect, CGM is used for detection, and SMBG is used for treatment decisions. Thus, for hypoglycemia, the FreeStyle Navigator CGM system and SMBG are both necessary for successful detection and treatment. This suboptimal alarm performance, however, has its costs. The irritation of false alarms and additional finger stick tests will cause some patients to choose the convenience of low alarm settings over the safety of higher settings.

Alarm inaccuracies for high glucose alarms were within the ≤5% constraint of the ISO 15197 standard at both maximum and optimum detection times. The CG-EGA also indicated that clinical errors were at a suitably low level and that clinical accuracy was high. Both analyses suggest that SMBG is not necessary for the detection of hyperglycemia.

Implications of this finding should be closely examined. Clearly the CGM is superior to SMBG for the detection of hyperglycemia. The CGM device provided a high detection rate within 15 and 30 minutes, which cannot be matched with SMBG. The strength of SMBG is not detection; its strength is providing an instantaneous glucose value, which is ideal for determining treatment. Although alarm analysis suggests that the number of CGM false alarms is acceptably low at 2–3%, it does not necessarily follow that the CGM glucose at the time the alarm sounds is sufficiently accurate to determine treatment. The CG-EGA at the time alarms sound can be used to evaluate CGM treatment accuracy.

Because the performance for all high alarms was nearly the same, the combined CG-EGA results for all high alarm levels are a good summary of CGM performance (**Table 2**): 92.2% clinically accurate, 5.9% benign errors, and 1.9% clinical errors. SMBG performing within the ISO 15197 standard should produce >95% clinically accurate results; therefore, SMBG confirmation could improve treatment decisions by a small margin. It is questionable, however, whether the inconvenience and cost of SMBG confirmation are worth the small incremental gain.

The CGM time axis allows the capability for an additional class of alarms, the predictive alarm, which warns the user of impending hypo- or hyperglycemia. It is relatively straightforward to assess the detection capability of these alarms from clinical study data, i.e., did an alarm occur prior to an event. However, a complete alarm characterization requires an evaluation of false alarms, which is far from straightforward for predictive alarms. By the traditional definition, all predictive alarms are false. To see if a prediction was correct, it is possible to see into the future of a clinical study retrospectively, but the simple linear extrapolations of the current generation of CGM predictive alerts cannot claim to foresee the future. While this problem is not intractable, there cannot be a complete characterization of predictive alarms until there is a consensus agreement on what constitutes a predictive false alarm.

Conclusion

The proposed method for determining CGM threshold alarm accuracy considers error on both the CGM glucose axis and the time axis to provide a complete analysis of this type of CGM alarm. FreeStyle Navigator CGM system threshold alarms tested with this method were not sufficiently accurate for detecting hypoglycemia without SMBG confirmation. High glucose, however, was reliably detected, and SMBG confirmation provided only a small incremental improvement to treatment decisions.

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Disclosure:

Geoffrey McGarraugh is an employee of Abbott Diabetes Care, manufacturer of the FreeStyle Navigator® glucose monitoring system.

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