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ORIGINAL ARTICLES

Accuracy of a New Real-Time Continuous Glucose Monitoring Algorithm

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Abstract

Background:

Through minimally invasive sensor-based continuous glucose monitoring (CGM), individuals can manage their blood glucose (BG) levels more aggressively, thereby improving their hemoglobin A1c level, while reducing the risk of hypoglycemia. Tighter glycemic control through CGM, however, requires an accurate glucose sensor and calibration algorithm with increased performance at lower BG levels.

Methods:

Sensor and BG measurements for 72 adult and adolescent subjects were obtained during the course of a 26-week multicenter study evaluating the efficacy of the Paradigm® REAL-Time (PRT) sensor-augmented pump system (Medtronic Diabetes, Northridge, CA) in an outpatient setting. Subjects in the study arm performed at least four daily finger stick measurements. A retrospective analysis of the data set was performed to evaluate a new calibration algorithm utilized in the Paradigm® Veo™ insulin pump (Medtronic Diabetes) and to compare these results to performance metrics calculated for the PRT.

Results:

A total of $N = 7193$ PRT sensor downloads for 3 days of use, as well as 90,472 temporally and nonuniformly paired data points (sensor and meter values), were evaluated, with 5841 hypoglycemic and 15,851 hyperglycemic events detected through finger stick measurements. The Veo calibration algorithm decreased the overall mean absolute relative difference by greater than 0.25 to 15.89%, with hypoglycemia sensitivity increased from 54.9% in the PRT to 82.3% in the Veo (90.5% with predictive alerts); however, hyperglycemia sensitivity was decreased only marginally from 86% in the PRT to 81.7% in the Veo.

Conclusions:

The Veo calibration algorithm, with sensor error reduced significantly in the 40- to 120-mg/dl range, improves hypoglycemia detection, while retaining accuracy at high glucose levels.

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Abbreviations: (BG) blood glucose, (CLSI) Clinical and Laboratory Standards Institute, (CGM) continuous glucose monitoring, (DCCT) Diabetes Control and Complications Trial, (FoH) fear of hypoglycemia, (HbA1c) hemoglobain A1c, (MARD) mean absolute relative difference, (PRT) Paradigm REAL-Time, (SMBG) self-monitoring of blood glucose

Keywords: continuous glucose monitoring, hypoglycemia, insulin pump, sensor

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Introduction

The landmark Diabetes Control and Complications Trial (DCCT)[1,2] clearly demonstrated the benefits of treating to a target hemoglobin A1c (HbA1c) of 7.0% or less after reporting a vast decrease in morbidity and a slowed onset, or progression, of severe complications in a type 1 diabetes population. This outcome was attributed to reduced blood glucose (BG) levels through the use of intensive insulin therapy, which required self-monitoring of blood glucose (SMBG) levels at least four times a day.

However, fear of hypoglycemia (FoH) deters insulin-dependent patients from more aggressive management of their BG levels. In fact, before home blood glucose monitoring, physicians encouraged patients to aim for a higher-than-normal BG level—a phenomenon that has been reviewed extensively by Wild and colleagues.[3] In contrast, it has been demonstrated that patients who perform only SMBG with a customary BG meter with four daily finger stick measurements could miss up to 71% of hypoglycemic events, whereas testing up to seven times daily could miss 58% of events when compared to continuous glucose monitoring (CGM).[4]

Additionally, the ability of CGM to reduce HbA1c has been demonstrated, at least under clinical supervision.[5,6] The introduction of glucose sensors, therefore, has provided evidence indicating that CGM can indeed further reduce HbA1c levels and glycemic variability, with increased awareness to hypoglycemia, when compared to standard SMBG. Also, because the goal of intensive therapy diabetes management is to reduce HbA1c levels without increasing the incidence of hypoglycemia, then it is evident that CGM therapy can be very beneficial.

This article focuses on the accuracy of CGM—specifically the accuracy of a new calibration algorithm. The motivation for improved accuracy is to enhance further the efficacy of CGM in lowering HbA1c, as already seen in several clinical studies. To date, the largest of these studies included 322 patients in a multicenter randomized control trial sponsored by the Juvenile Diabetes Research Foundation, which compared the efficacy of CGM to that of SMBG.[7] Overall, results demonstrated that CGM significantly improves glycemia over standard SMBG with a reduction of 0.5% in HbA1c, although results were not statistically significant in the adolescent population, likely due to poor adherence. Similarly, the European GuardControl Trial[8] evaluated the efficacy of CGM in a multicenter study that included 156 patients wearing the Guardian® RT monitor (Medtronic Diabetes, Northridge, CA). The outcome showed that subjects in the treatment arm decreased their HbA1c levels by an average of 1%—a 0.6% improvement over the control group using traditional SMBG—and HbA1c levels were reduced by 2% in over 26% of subjects.

In 2006, the first sensor-augmented insulin pump, Medtronic's Paradigm® REAL-Time (PRT) system, was launched, introducing the first platform with all of the required components communicating together, necessary for an ambulatory closed-loop artificial pancreas product.[9] The system is composed of a Paradigm® 522/722 insulin pump enhanced with the real-time CGM component, which utilizes the same calibration algorithm as the Guardian RT, Paradigm REAL-Time Revel™ system, and Guardian REAL-Time™ system. An early prototype of this system was tested in 20 type 1 diabetes subjects who wore the device for up to 2 years.[10] Study results demonstrated that participants achieved a mean reduction in HbA1c of 1.1% and that those subjects with levels greater than 7% had a 0.67 probability of reducing their level below this value in the first 3 months of use.

The STAR 1 study, sponsored by Medtronic Diabetes and conducted across seven centers, investigated the efficacy of the PRT system.[11] The primary objective of this study was to demonstrate a greater reduction of HbA1c levels in subjects placed on the PRT system. In the control group, the overall change in HbA1c from baseline was –0.58 ± 0.73%, whereas the change was –0.72 ± 0.69% in the PRT group, representing a 7% decrease for the control group and an 8.3% decrease for the PRT group. Compared to the 8.2% average HbA1c outcome from 30 university hospital centers[12] and the 8.0% DCCT HbA1c results,[13] subjects in the study achieved an average HbA1c of 7.68%. Final results revealed that 38% of patients in the CGM sensor-augmented group reached the 7% (or below) HbA1c target versus 19% in the control insulin pump group. Additionally, the PRT group showed a significant decrease in hypoglycemia area under the curve when compared to the control group, and the PRT group also included a higher percentage of adult and adolescent subjects reaching a target HbA1c value of less than 7.0%. This development is clinically meaningful because previous attempts to reduce HbA1c levels below the 7% mark in an adolescent population

have been unsuccessful due to an increased risk for hypoglycemia.[14,15] Furthermore, because the control group was not able to achieve this reduction, the lowered HbA1c levels attained by adults and adolescents in the PRT group were, in all probability, due to sensor usage.

From the previously detailed studies, it is evident that through CGM therapy patients can more effectively manage their BG levels and achieve an improvement in HbA1c, while reducing the risk of hypoglycemia and, possibly, anxiety associated with FoH. However, it is also evident that improved control through CGM requires a reliable and accurate glucose sensor with an effective calibration algorithm coupled with patient compliance.

Current commercially available CGM devices are progressively demonstrating greater accuracies.[16,17] In a multicenter study that included 58 subjects to evaluate the performance of the FreeStyle Navigator® (Abbott Diabetes Care, Alameda, CA), a mean absolute relative difference (MARD) of 12.8% was achieved over 5 days of sensor use with 80% sensitivity to hypoglycemia (<70 mg/dl). In a more recent study that included 72 insulin-dependent diabetic subjects wearing the SEVEN® system (DexCom, San Diego, CA), accuracy was evaluated over 7 days of sensor use, calibrating with capillary finger stick measurements. An overall MARD of 16.7% was achieved with 13.3% on day 7, which demonstrates that the DexCom 7-day system shows a significant improvement over the 3-day system, a development that is credited to new algorithm enhancements.

Similarly, this investigation evaluates the performance of a new glucose sensor calibration algorithm, now utilized in the Paradigm Veo™ insulin pump recently launched in Europe. The Veo calibration algorithm with enhancements is compared to that of the PRT by retrospective analysis of data collected during the STAR 1 clinical trial, with a range of performance metrics calculated for each system.

Methods

In the previously discussed STAR 1 trial—a randomized multicenter treat-to-target 6-month study in which continuous subcutaneous insulin infusion therapy, augmented with real-time CGM, was compared with standard SMBG and insulin pump therapy[11]—136 patients were enrolled across seven study centers. Ninety-six subjects were adults, of whom 57% were female, while 60% of the adolescent subjects were female. Patients were randomized into either a control arm wearing the Paradigm 715 insulin pump or a treatment group wearing the PRT sensor-augmented insulin pump. The primary end point of HbA1c reduction over a 26-week period was the healthy glycemic control goal for diabetes patients of below 7%. Subjects had to be insulin pump users for a period greater than 6 months and have HbA1c levels greater than or equal to 7.5%. Subjects in the study group were required to perform at least four finger stick measurements daily, uploading with the Paradigm Link® blood glucose monitor (Medtronic Diabetes) for the duration of the study. Subjects wore two sensors per week and tested HbA1c five times during the study.

Insulin pump and glucose sensor data were uploaded every 2 weeks over the Internet via the CareLink Clinical® application (Medtronic Diabetes). This investigation utilized BG and raw glucose sensor data acquired from the CGM arm of the study. The accuracy of two calibration algorithms was compared by a retrospective analysis of raw data. As the difference between calibration algorithms is purely mathematical, in that each algorithm uses the same data points with the same timing, a true point-to-point analysis can be performed between the two routines. Consequently, the PRT algorithm is applied retrospectively to raw data to ensure this consistency. As the commercial PRT algorithm does not have the benefit of predictive alerts, this retrospective analysis uses predictive alerts that are part of the Paradigm REAL-Time Revel system and Guardian REAL-Time system—devices not yet launched in the United States. However, all three devices have the same calibration algorithm. The predictive alerts utilize a Savitzky–Golay finite impulse response derivative filter to estimate the sensor glucose rate of change, which is multiplied by a prediction horizon of 5–30 minutes.

Sensors were worn for up to 3 days of use by 72 subjects in the study arm of the STAR 1 trial. A total of 7193 sensor downloads provided 90,472 paired BG and sensor measurements for retrospective analysis. Performance metrics were calculated for each glucose sensor calibration algorithm based on guidelines set forth by the International Organization for Standardization[18] and the Clinical and Laboratory Standards Institute (CLSI)[19] for continuous interstitial fluid glucose monitoring. Sensitivity and specificity were calculated for hypo- and hyperglycemia, defined as a single BG measurement below 70 mg/dl and above 240 mg/dl, respectively. Additionally, consensus[20] and Clarke[21] error grid analyses were performed for each algorithm.

Results

The performance of each calibration algorithm is presented in **Tables 1–6** for the range of metrics described previously. The PRT calibration algorithm is represented as bold following results of the Veo calibration algorithm. The aggregated error is shown in **Table 1**, with the error stratified by range in **Table 2**. The Veo algorithm outperforms the PRT algorithm, with the overall mean ± SD decreased by 0.25 ± 0.6 to 15.89 ± 16.89%, with a reduction in median error of 0.1 to 11.56%. The error is reduced further by 5.3 to 19.5% and 0.4 to 17.31% in the 40- to 80- and 80- to 120-mg/dl ranges. A slight error increase exists in the mid to upper ranges, with a 0.7% increase from 120 to 240 and 0.6% above this threshold.

Table 3 provides the number of points within 20 and 30% of their respective paired BG values, or 20 mg/dl for BG values below 80 mg/dl. For the Veo algorithm, more than 8% additional points reside within both boundaries in the 40- to 80-mg/dl range—with an insignificant difference between the two algorithms in all other ranges—and the number of points processed by this new algorithm decreases at higher ranges.

The number of observed hypo- and hyperglycemic events, based on criteria for home-monitoring use, is reported in **Table 4**. The Veo algorithm detected 82.28% of the 5841 hypoglycemic episodes and 81.67% of the 15,851 hyperglycemic episodes. In contrast, the PRT algorithm detected 54.89 and 86.26% of all hypo- and hyperglycemic events, respectively. The new algorithm had a slightly lower specificity (96.36–98.32%) for hypoglycemia and a comparable specificity (~98%) for hyperglycemia. Sensitivity and specificity analyses for the Veo and Revel algorithms are illustrated with pie charts in **Figures 1** and **2**, respectively, for hypo- and hyperglycemic events. The pie charts are color coded to specify the percentage of events falling within particular limits. An additional category—accurate glucose—shows the percentage of events that fall within the error tolerance of the measuring reference

Table 1.
Aggregated Error[a]

Sensors	Pairs	MARD (SD)	Median
7193	90,472	15.89 (16.86) **16.14 (17.46)**	11.56 **11.65**

[a] The PRT calibration algorithm is represented as bold following results of the Veo calibration algorithm.

Table 2.
Error Stratified by Range[a]

	40–80 mg/dl	>80–120 mg/dl	>120–240 mg/dl	>240 mg/dl
Number of readings	10,655	18,420	45,655	15,742
MARD (SD)	19.5 (23.78) **24.8 (27.65)**	17.31 (18.84) **17.75 (19.02)**	14.88 (14.92) **14.16 (14.15)**	14.73 (13.17) **14.14 (12.64)**
Median	14.36 **18.19**	12.48 **13.21**	10.8 **10.38**	11.23 **10.73**

[a] The PRT calibration algorithm is represented as bold following results of the Veo calibration algorithm.

Table 3.
Number of Points within 20 and 30% of Their Respective Paired BG Values[a]

Comparative glucose (mg/dl)	Total number paired of readings	Within 20% or 20 mg/dl	Within 30% or 20 mg/dl
40–80	10,655	8,635 (81.04%) **7,765 (73%)**	8,849 (83.05%) **8,016 (75%)**
81–120	18,420	13,132 (71.29%) **12,960 (70%)**	15,451 (83.88%) **15,491 (84%)**
121–240	45,655	34,274 (75.07%) **35,291 (77%)**	40,254 (88.17%) **41,043 (90%)**
240–400	15,742	11,731 (74.52%) **12,074 (77%)**	13,933 (88.51%) **14,176 (90%)**
Overall	90,472	67,772 (74.91%) **68,090 (75%)**	78,487 (86.75%) **78,726 (87%)**

[a] The PRT calibration algorithm is represented as bold following results of the Veo calibration algorithm.

Table 4.
Number of Observed Hypo- and Hyperglycemic Events Based on Criteria for Home-Monitoring Use[a]

	Hypo events	Hyper events
Number of readings	5841	15,851
Sensitivity	82.28 **54.89**	81.67 **86.26**
Specificity	96.36 **98.06**	98.32 **98.64**
False positive rate	2.927 **1.619**	0.9579 **1.045**

[a] The PRT calibration algorithm is represented as bold following results of the Veo calibration algorithm.

device, which, in this case, is a home-monitoring BG meter. This error boundary for hypoglycemia is 70–85 mg/dl and 20% for hyperglycemia based on CLSI guidelines.[17] The charts illustrate the sensitivities reported previously, including the percentage of both threshold and predicted alerts for a 15-minute prediction horizon. Likewise, the specificities are shown for true and false threshold alerts. As the PRT algorithm does not include predictive alerts, but has the same calibration algorithm as the Revel and Guardian devices, its performance can be derived from **Figure 2** by only including threshold alerts in the calculations.

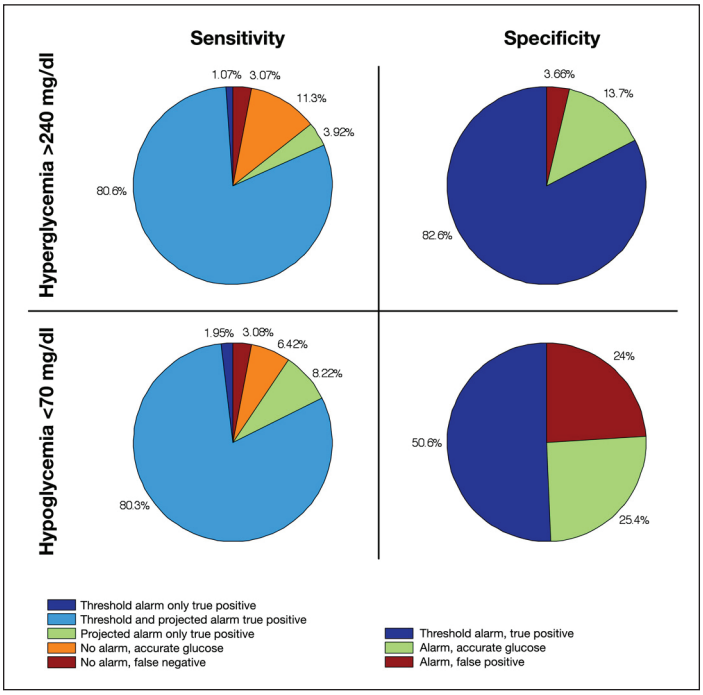

Figure 1. Veo algorithm sensitivity and specificity analyses for hypo- and hyperglycemic events.

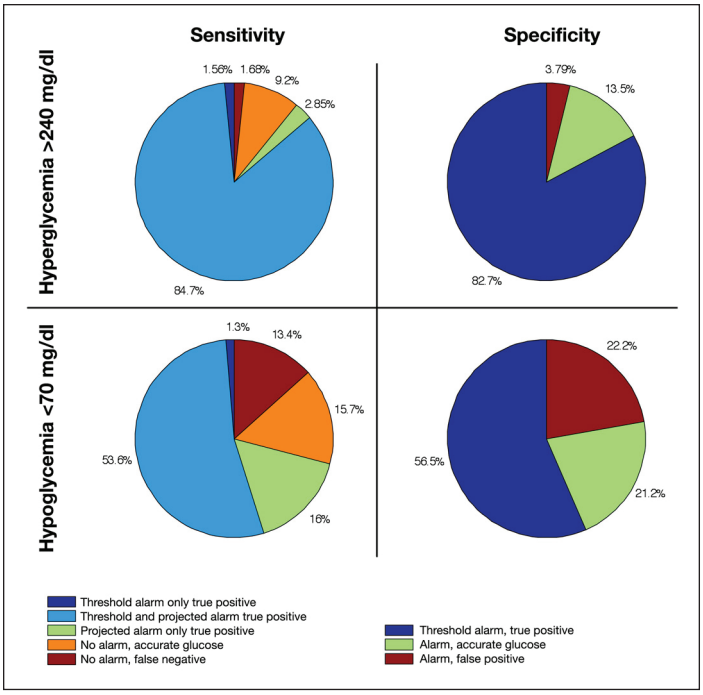

Figure 2. Revel and Guardian REAL-Time algorithm sensitivity and specificity analyses for hypo- and hyperglycemic events.

In the following alarm categories—threshold, threshold and projected, projected, no alarm accurate glucose, and false negative—when applying a 30-minute prediction horizon for hypoglycemia detection, the Veo algorithm generated accuracies of 2.62, 79.7, 11.4, 4.02, and 2.29%, respectively. Applying the same 30-minute prediction horizon to Guardian and Revel algorithms produced accuracies of 7.29, 47.6, 20.1, 13.8, and 11.3%, respectively.

Over 14 hours of data is illustrated in **Figure 3** for rates of change in excess of 1 mg/dl/min, and greater rates on the decline. The 330-mg/dl calibration sample before hour 28 resulted in the PRT algorithm overreading proceeding low glucose levels and consequently failing to detect the 59-mg/dl (PRT = 81 mg/dl) hypoglycemic event at hour 34, whereas the Veo algorithm detected the event several hours before the meter indicated a hypoglycemic episode.

Clarke and consensus error grid analyses are presented in **Tables 5** and **6**. Results are comparable—with greater than 97% of all readings in the A + B zones of the consensus error grid for both algorithms and in all ranges, with the exception of the PRT algorithm in the 40- to 80-mg/dl range. In this range, the new algorithm shows a 4% improvement. No points reside within the E zone of the consensus error grid for either algorithm. Similarly, results are comparable throughout most ranges for Clarke error grid analysis, with the exception of low

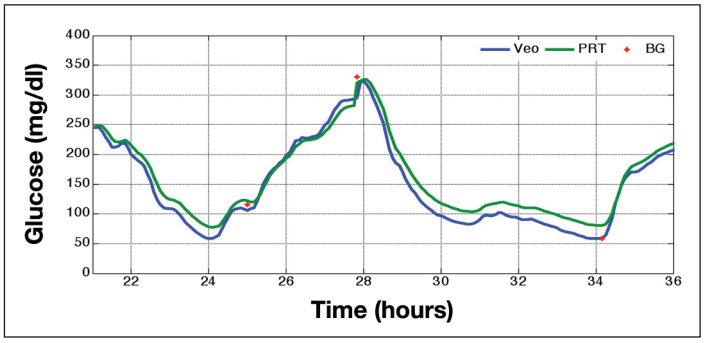

Figure 3. Sensor tracings for PRT and Veo calibration algorithms.

BG levels in the 40- to 80-mg/dl range. In this instance, the new algorithm has more than a 13% improvement with 89.81% of paired points in the A + B zones. Both algorithms have approximately 96% of all values in the clinically accurate and benign (A + B) zones for the complete range. Overall, there are only 0.18 and 0.12% points in the E zone of the Clarke error grid for Veo and PRT algorithms, respectively, which could lead to erroneous treatment of hypo- or hyperglycemia.

Discussion

The Paradigm Veo calibration algorithm is more accurate in the 40- to 80- and 81- to 120-mg/dl ranges, and it consequently detected significantly more hypoglycemic events. Sensitivity analysis of hypoglycemic events produced accuracies of 82.3% compared to the 54.9% detected by the PRT algorithm. Predictive alerts, with a 30-minute prediction horizon, detected 94% of all hypoglycemic events. It would, thus, be expected that an increase in sensitivity in the lower glucose ranges would result in a balanced decrease in accuracy at higher glucose ranges. However, accuracy at higher glucose ranges was affected only marginally—an expected development, as the new algorithm attempts to produce an even error distribution across the dynamic range of the sensor, reflective of the insignificant sensitivity difference for hypo- and hyperglycemia. Increasing accuracy at low blood glucose levels, therefore, while maintaining accuracy at high glucose levels, essentially broadens the dynamic range of the glucose sensor system; this is evident in **Figure 3**.

Table 5.
Consensus Error Grid Analysis[a]

		Consensus error grid zones					
Comparative glucose (mg/dl)	Total sensor readings	A + B	A	B	C	D	E
40–80	10,655 (11.78%)	97.13% **93.15%**	84.21% **77.90%**	12.91% **15.25%**	2.52% **6.35%**	0.36% **0.50%**	0% **0%**
81–120	18,420 (20.36%)	99.08% **98.76%**	75.75% **76.83%**	23.32% **21.93%**	0.85% **1.17%**	0.07% **0.07%**	0% **0%**
121–240	45,655 (50.46%)	98.96% **99.24%**	72.60% **75.69%**	26.36% **23.55%**	1.04% **0.76%**	0% **0%**	0% **0%**
240–400	15,985 (17.67%)	97.94% **98.21%**	76.87% **78.47%**	21.08% **19.74%**	1.90% **1.70%**	0.16% **0.09%**	0% **0%**
Overall	90,472 (100%)	98.59% **98.24%**	75.35% **76.66%**	23.24% **21.58%**	1.33% **1.67%**	0.08% **0.09%**	0% **0%**

[a] The PRT calibration algorithm is represented as bold following results of the Veo calibration algorithm.

Table 6.
Clarke Error Grid Analysis[a]

		Clarke error grid zones					
Comparative glucose (mg/dl)	Total sensor readings	A + B	A	B	C	D	E
40–80	10,655 (11.78%)	89.81% **76.53%**	74.80% **59.28%**	15.01% **17.24%**	0.09% **0.14%**	9.91% **23.05%**	0.19% **0.28%**
81–120	18,420 (20.36%)	99.47% **99.48%**	69.06% **67.77%**	30.41% **31.71%**	0.53% **0.52%**	0% **0%**	0% **0%**
121–240	45,655 (50.46%)	98.96% **99.18%**	75.07% **77.05%**	23.89% **22.13%**	0.83% **0.69%**	0% **0%**	0.21% **0.13%**
240–400	15,985 (17.67%)	92.78% **93.58%**	74.56% **76.24%**	18.22% **17.34%**	0.53% **0.40%**	6.43% **5.86%**	0.27% **0.16%**
Overall	90,472 (100%)	96.89% **95.57%**	73.72% **72.92%**	23.17% **22.66%**	0.63% **0.54%**	2.30% **3.76%**	0.18% **0.12%**

[a] The PRT calibration algorithm is represented as bold following results of the Veo calibration algorithm.

The Veo algorithm is more sensitive to fast glucose excursions, with a decreased filter delay (≈5 minutes), reducing the overall signal processing delay to 3.5 minutes and providing a much faster response time to rapid glucose excursions. The range of intrinsic delays for other CGM devices currently on the market was reported previously by the authors.[22]

It should be noted that STAR 1 data used in this investigation were acquired in an outpatient setting and evaluated retrospectively using standards for home monitoring. In this setting, accuracies are generally lower as error measurements are generally made at the maximum time duration following calibration. In contrast, evaluating sensor performance from frequent sampled in-clinic studies with laboratory reference measurements taken every 15 minutes, the sensor error is generally 3–4% lower with more accurate samples acquired by professionals.

Conclusion

Fear of hypoglycemia is a common emotion experienced by people with type 1 diabetes, often discouraging a greater intensive management of their BG levels in order to achieve better glycemic control. Features available with the Paradigm Veo, such as alerts and the low glucose suspend function, can help mitigate serious hypoglycemia, where insulin delivery is suspended beyond a predetermined threshold. While most CGM devices provide threshold and predictive alarms to warn the user of impending or occurring hypo- or hyperglycemic episodes, widespread adoption of these features is often hampered by low accuracy and false alerts. Therefore, increased accuracy, specifically at low blood glucose levels, is advantageous.

The Paradigm Veo calibration algorithm demonstrates performance improvement over the current PRT system, with accuracy improved in nearly all performance categories. Hypoglycemia sensitivity is increased by greater than 50%, with 90.5 and 94% of all hypoglycemic events detected for prediction horizons of 15 and 30 minutes, respectively. The mean error in the low glucose range is decreased by approximately 5%, and the sensor signal is more reactive to fast glucose excursions. Furthermore, sensor signal processing delays are reduced considerably in the Veo algorithm. This reduction in time delay provides earlier and more accurate alerts, where hypoglycemia can be detected and predicted sooner, thereby enhancing patient safety and affording more time to self-treat potential reactions.

Disclosure:

D. Barry Keenan, Raymond Cartaya, and John J. Mastrototaro are employees of Medtronic MiniMed.

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