A Pilot Study to Assess Clinical Utility and User Experience of Professional Continuous Glucose Monitoring Among People With Type 2 Diabetes

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IN BRIEF Glucose variability is a potential independent risk factor of poor clinical outcome among people with diabetes, with adequate measurement technically difficult and cumbersome. For this study, a novel 14-day continuous sensor was used to assess glucose variability among people with type 2 diabetes (T2D). The aim was to characterize glucose profiles for up to 2 weeks in T2D and to survey device utilization in a standard clinical setting and its potential to collect clinically meaningful data.

Achieving and maintaining A1C targets while avoiding hypoglycemia in medically treated individuals with diabetes is limited despite adherence to several patient-centered therapeutic strategies. This is because the simple measurement of A1C does not provide insight into the day-to-day glucose variability in individuals on different diabetes therapy regimens. Recent research has indicated that reduction of hypoglycemic risk is strongly associated with a reduction in glycemic variability (1,2). Severe hypoglycemia is not uncommon among patients with type 2 diabetes (T2D) across all levels of glycemic control and tends to be higher in patients with either near-normal glycemia or very poor glycemic control (3).

It has been suggested that a reasonable strategy to counter the increased risk of hypoglycemia in individuals with T2D is to minimize episodes of glucose variability (4). A new method, professional flash continuous glucose monitoring (CGM), is designed to address the challenges associated with collecting a full glycemic profile of up to 14 days and support clinical review of glucose patterns. The FreeStyle Libre Pro Flash Glucose Monitoring System (Libre Pro) (Abbott Diabetes Care, Alameda, CA) was approved for use in the United States by the U.S. Food and Drug Administration in 2016.

The Libre Pro monitors interstitial glucose via a disposable sensor and subcutaneous sensor filament adhered to the skin. The sensor is placed by a single-use applicator and activated by a quick wireless scan with a handheld reader. After a 1-hour warm-up period, the sensor takes automatic measurements of glucose every 15 minutes for up to 14 days without calibration by self-monitoring of blood glucose (SMBG). The device collects the interstitial glucose values and stores them for subsequent download at the end of the 14-day wear period. The data are blinded and are not seen by the patient wearing the device. At any time, the sensor may be wirelessly scanned in the clinic by a reader to download the acquired glucose readings. A reader with acquired data is connected to computer-based software by USB cable to generate summary reports, including the ambulatory glucose profile (AGP) report (5–9).

The purpose of this multicenter, prospective, single-arm, real-world, observational study was to examine the overall variability of glucose levels among people with T2D managed

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with different treatment modalities. The major drug classes included in the treatment guidelines of T2D were selected to provide exploratory information regarding the extent of glucose variability in different groups of study participants (10). Additionally, the study evaluated participant and clinical investigator perceptions of the system, including acceptability of device wear and software-generated data reports.

Materials and Methods

This study was conducted in compliance with the applicable International Council for Harmonisation guidelines, Good Clinical Practice, the Declaration of Helsinki, and regulatory requirements. The key inclusion criteria included age 18 years or older, T2D diagnosis with diabetes therapy for at least 6 months, and considered by investigator to be able to comply with study procedures. Exclusion criteria included known allergy to medical grade adhesive or isopropyl alcohol (to prepare skin site), or other skin condition at the sensor location. People with diabetes therapy involving multiple-drug combinations were excluded, as were women who were pregnant or attempting to conceive.

The therapy groups were selected from those in the joint position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) on the management of hyperglycemia in T2D (10). The noninsulin therapy study group was divided into the following subgroups: *1*) no medication, *2*) metformin monotherapy, *3*) sulfonylureas (SU), *4*) glucagon-like peptide 1 receptor agonists (GLP-1 RA), *5*) sodium–glucose cotransporter 2 inhibitors (SGLT2i), and *6*) dipeptidyl peptidase 4 inhibitors (DPP-4i) alone or in combination with an additional acceptable diabetes therapy. The two insulin therapy study groups were further subcategorized by those using basal insulin and premixed insulin, either alone or in combination with no more than two of SU, GLP-1 RA, or DPP-4i or other acceptable diabetes therapies. For all groups, the other acceptable additive diabetes therapies included metformin, thiazolidinediones, α-glucosidase inhibitors, bile acid sequestrants (colesevelam), or dopamine-2 agonists (quick-release bromocriptine). Groups were further selected by A1C levels: participants with an A1C between 6.0 and 12.0% for groups managed with education (n = 11), metformin (n = 12), SU (n = 25), basal insulin (n = 21), and premixed insulin (n = 18) and those restricted to an elevated A1C (7.5–12.0%) for DPP-4i (n = 6), SGLT2i (n = 4), and GLP-1 RA (n = 8). A1C measurements were performed at the beginning and end of the 14-day sensor wear period.

Participants wore two sensors, with one applied to the back of each upper arm, for a period of up to 14 days while going about normal daily activities, including any SMBG. The two sensors were worn to provide a redundancy to the data collection since the subjects were naive to sensor wear. Clinical staff applied the sensors and used a reader to initialize and upload the sensors. An evaluable participant had to have worn at least one sensor that contained at least 6 days of glucose data. Glucose readings were analyzed from the single sensor per participant that collected the most data. Mean sensor glucose was calculated along with time below, within, and above the range of 70–180 mg/dL. Glucose variability was evaluated by SD and coefficient of variation (CV).

AGP reports, including estimated A1C values, were reviewed by investigators. Estimated A1C utilizes the established conversion adopted by the ADA and EASD (11). Estimated A1C values were compared with 95% prediction limits (approximately ±15%) reported by the A1c-Derived Average Glucose (ADAG) Study Group (11).

Questionnaires were completed by participants regarding the insertion and sensor wear experience and by study investigators documenting assessment of the software reports of the glucose data, including the AGP. Investigators were asked to document a treatment decision based on the medical history and A1C of the patient and then document whether they would reconsider that decision based on the sensor glucose reports. Furthermore, the investigators were asked whether the glucose reports contained enough information to feel confident in making a change in therapy without the use of other data. These investigator responses were summarized for each treatment group. Device-related site symptom assessments and adverse events were tabulated for all participants.

Statistical analysis of the collected data involved four single-factor linear models that were evaluated for their relationship to CV of glucose: age, sex, baseline A1C, and duration of diabetes. Statistical comparisons across the therapy groups were performed by analysis of variance using SAS version 9.2 (SAS Institute, Cary, NC).

Results

Participant Characteristics

There were 115 participants with a sensor inserted, with 105 having at least 6 days of sensor glucose readings and 1 participant not completing the final clinic visit. Fifty-four (47%) participants were female, aged 59 ± 11.5 (mean ± SD) years, with BMI 34.2 ± 6.8 kg/m^2, 10.8 ± 8 years since diagnosis of T2D, and 3.4 ± 4.2 years on their current diabetes therapy (Table 1). Participants included 67 (59%) non-Hispanic white, 35 (31%) black or African-American, and 12 (10%) other (Asian, Native Hawaiian or Pacific Islander, or other) individuals. Mean A1C for all participants was 7.9 ± 1.5%.

Glucose Variability

Significant effects of age, sex, and duration of diabetes were found to be associated with glucose CV, while baseline A1C was not. Duration of diabetes had the largest mean effect, with an increase in CV of 0.5% for each year of diabetes (Table 2). CV

TABLE 1. Study Participant Characteristics

Sensor inserted, *n*	115
Completed final visit, *n*	114
Female, %	47
Age, years	59 ± 11.5
BMI, kg/m^2	34.2 ± 6.8
Non-Hispanic white, %	58.8
Black or African American, %	30.7
Other, %	10.5
Years since T2D diagnosis	10.8 ± 8
Years on current therapy	3.4 ± 4.2
A1C, %	7.9 ± 1.5
A1C, mmol/mol	63 ± 16

Data are mean ± SD unless otherwise indicated.

TABLE 2. Glucose Variability by Age, Sex, Duration of Diabetes, and Baseline A1C

Model Effect	*P*	Mean Estimates
Age, years	0.0002	CV (%) = 13.4 + 0.2*age
Sex	0.0094	F (*n* = 54): 25.9% M (*n* = 60): 29.9%
Duration of diabetes, years	<0.0001	CV (%) = 22.6 + 0.5*duration
Baseline A1C, %	0.2985	Not applicable

was found to be a sensitive measure of glucose variability for each therapy regimen, accounting for 39% of the variation, indicating that the therapy groups differed the most in their glucose CV. Additionally, an increase in glucose variability was found across the therapy groups with the greatest glucose variability seen in the subgroups using insulin and SU (Table 3). The lowest glucose CV was found in the subgroup on no medication, followed by the DPP-4i and metformin subgroups. The highest variability was noted for the insulin groups, both premixed and basal insulin, as well as for the subgroup using an SU. Inspection of the 95% CI found the no-medication, DPP-4i, and metformin subgroups did not overlap with the SU (A1C 6.4–7.4%), basal insulin (6.0–12.0%), and premixed insulin (6.0–12.0%) subgroups.

AGP and A1C

While glucose collection in this study was limited to 14 days, good agreement of the estimated A1C and laboratory A1C was demonstrated. A total of 59% of 105 estimated A1C values fell within the 95% prediction limits (approximately ±15%) reported by the ADAG study. For example, at A1C 6.0%, the 95% prediction limits of estimated A1C are 5.1–6.9%, while at A1C 10.0%, the 95% prediction limits of estimated A1C are 8.4–11.5%. Examples of AGPs with estimated A1C values within these limits at these A1C levels are shown in Figure 1. These AGPs show the variety of glucose levels from day to day (width of the AGP bands) and during the day (rises and falls across the hours of the day). The four examples with A1C of 6.0% show two that have stable and consistent glucose levels (A1 and A3) and two AGPs with substantial fluctuations across the days and between days (A2 and A4). However, the example in A3 shows consistent, extended periods of hypoglycemia from the hours of 3:00 A.M. to 9:00 A.M., with nearly 90% of readings <70 mg/dL between 6:00 A.M. and 7:00 A.M. Example A4 shows a consistent rise midmorning as well as a larger rise in the evening that consistently drops during the night. The four AGPs of participants with A1C levels of 10.0% also display a wide variety of glucose levels across the day and from day to day. B2 is the most consistent and stable, remaining in hyperglycemia ~90% of the time. B1 is similarly hyperglycemic ~90% of the time but has distinct rise and fall patterns across the day as well as inconsistency from day to day. B4 has consistent hyperglycemic patterns but with occasional periods of glucose within the target range of 70–180 mg/dL. The AGP in B3 has the most extreme glucose variability, with periods of consistent hypoglycemia overnight and hyperglycemia during the day. These AGP patterns provide crucial clinical insights beyond those possible with A1C alone.

Patient Questionnaires

Responses in the patient questionnaires revealed that the participants reported a high degree of satisfaction with sensor insertion and wear. Participants predominantly (*n* = 113) reported the sensor was comfortable, easy to wear, fit well into their life, and did not interfere with daily activities (Table 4). A large majority (87.6%) of participants agreed that they did not feel any discomfort under their skin while wearing the sensor, while only a small number (5.3%) disagreed. Approximately three-quarters (77.0%) reported believing that other people did not notice their sensor, while a small minority (14.1%) disagreed and considered it noticeable by others.

Investigator Questionnaires

Investigators were asked to complete a questionnaire aimed at assessing the value of data reports in assisting them in initiating therapy changes, including the initiation of multiple daily injections of insulin, and the potential for influencing provider confidence in therapy decisions. As therapy became

TABLE 3. Glucose Measures by Study Group

A1C Range	Therapy	*n*	Mean Glucose (mg/dL)	SD (mg/dL)	CV (%)*	Time <70 mg/dL (hours/day)	Time 70–180 mg/dL (hours/day)	Time >180 mg/dL (hours/day)
6.0–7.4%	SU	15	118	35	29.8 (26.9–32.6)	2.2	20.1	1.7
	Basal insulin	10	118	40	33.4 (28.7–38.2)	2.2	19.7	2.1
	Premixed insulin	8	138	48	35.8 (27.1–44.5)	2.4	16.2	5.5
6.0–12.0%	No medications	10	152	31	20.7 (16.7–24.6)	0.2	17.0	6.7
	Metformin	15	144	34	22.6 (19.1–26.0)	0.8	17.1	6.1
7.5–12.0%	SU	12	192	50	26.7 (22.4–30.9)	0.5	10.2	13.3
	GLP-1 RA	9	159	38	23.8 (19.2–28.3)	0.8	14.8	8.4
	DPP-4i	6	201	44	21.9 (19.8–24.1)	0.1	11.7	12.2
	SGLT2i	4	157	43	27.3 (21.2–33.3)	0.2	17.5	6.2
	Basal insulin	12	182	59	32.8 (26.9–38.7)	0.7	12.2	11.1
	Premixed insulin	10	170	57	33.9 (29.7–38.1)	1.4	13.5	9.1

*Data are mean unless otherwise indicated. *Mean (95% CI).*

more complex, there was more agreement regarding the value of the data to guide therapy considerations. For example, for premixed insulin with A1C >7.5%, 100% of the investigators indicated that the reports encouraged reconsidering treatment and that they contained enough information to make changes confidently (Table 5). For less intensive treatments, such as no medication or metformin alone, the glucose reports did support treatment reconsideration, but at a lower rate. For those patients on basal insulin only or premixed insulin with A1C >7.5%, the majority of the reviews of the glucose reports led to consideration of initiating multiple daily injection therapy.

Adverse Outcomes and Symptoms

There were nine adverse events recorded during the study; none were serious or device related. Thirteen of 115 (11%) participants had 1 or more of 19 sensor insertion site symptoms (Table 6). Sensor insertion site symptoms included slight edema (five participants), mild pain (four participants), itching (three participants), erythema (three participants), and mild bleeding (one participant). There were no instances of bruising, infection, induration, or rash.

Discussion

The role of personal CGM in patients with diabetes is increasingly recognized as a vital tool in the management of this disorder. Recent guidelines are clear in their recommendations for the use of CGM in patients with type 1 diabetes (T1D) (12). However, there is not yet a consensus for the use of personal CGM in those with T2D, although studies have shown benefits of using CGM in patients with T2D (13,14). The International Consensus on Use of Continuous Glucose Monitoring recommended that CGM should be considered in conjunction with A1C for glycemic status assessment and therapy adjustment in all patients with T1D and patients with T2D

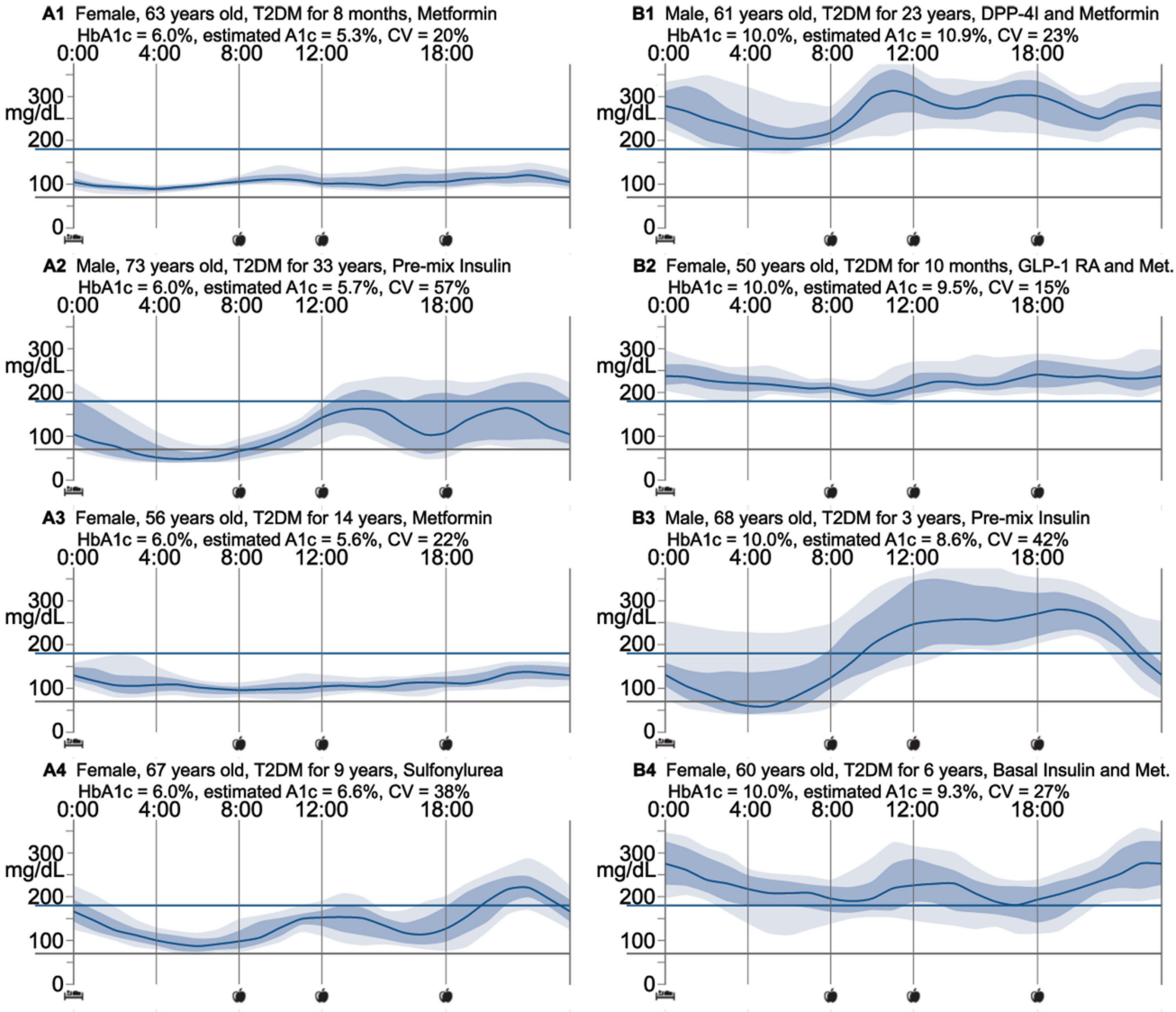

FIGURE 1. Comparison of AGP at the same laboratory A1C (A1–A4 = 6.0%, B1–B4 = 10.0%). Met, metformin.

TABLE 4. Participant Questionnaire Summary (*n* = 113)

Question	Strongly Agree	Agree	Neither Agree nor Disagree	Disagree	Strongly Disagree
The sensor was comfortable to wear.	56.6	39.8	0.9	2.7	0.0
The sensor was easy to wear due to its small size.	53.1	40.7	3.5	2.7	0.0
I believe that other people did not notice that I was wearing a sensor.	46.9	30.1	8.8	10.6	3.5
While wearing the sensor, I did not feel any discomfort under my skin.	57.5	30.1	7.1	4.4	0.9
This sensor did not get in the way of daily activities.	50.4	40.7	1.8	5.3	1.8
This sensor fit in well with my life.	48.7	41.6	5.3	4.4	0.0

Data are %.

treated with intensive insulin therapy who are not achieving glucose targets, especially if the patient is experiencing problematic hypoglycemia (15). The committee also recommended that "CGM data should be used to assess hypoglycemia and glucose variability" (15). Professional (retrospective or "blinded") CGM has been used in the

TABLE 5. Investigator Questionnaire Summary

Q1: Does review of the subject's glucose reports cause you to reconsider the treatment changes?					
Q2: Does the information presented in the glucose reports contain enough information for you to feel confident in making a change in therapy without the use of other data (i.e., no blood glucose data, no meal data, no activity/exercise, etc.)?					
Q3: For basal/premixed insulin users: Does review of the subject's glucose reports change your view of when to initiate multiple daily injections of insulin?					
A1C Range	Therapy	*n*	% Agree		
			Q1	Q2	Q3
6.0–7.4%	SU	15	60	67	
	Basal insulin	10	55	73	44
	Premixed insulin	8	88	100	50
6.0–12.0%	No medications	10	27	55	
	Metformin	15	43	71	
7.5–12.0%	SU	12	33	100	
	GLP-1 RA	9	33	67	
	DPP-4i	6	67	83	
	SGLT2i	4	50	50	
	Basal insulin	12	50	83	75
	Premixed insulin	10	100	100	50

TABLE 6. Sensor Site Symptoms

Symptom	Severity	Occurrences	Participants (*n* = 115)
Bleeding	Mild	1	1
Edema	Slight	4	2
	Slight with defined edges	3	3
Erythema	Well-defined redness	4	3
Itching	Mild	3	3
Pain	Mild	4	4
Bruising	Any	0	0
Infection	Any	0	0
Induration	Any	0	0
Rash	Any	0	0
All		19	13

clinical setting to provide insight into glucose patterns in patients with T1D and T2D. However, despite availability, there has not been widespread adoption of the use of professional CGM in the clinical setting. Use of the Libre Pro system in this study provided "blinded" or retrospective CGM data for analysis of glucose patterns in patients with T2D. This retrospective review of CGM data (i.e., professional CGM) is in contrast to "real-time" personal CGM, which allows for patient direct access to the glucose data. However, there have been recent studies that have called into question the efficacy of recommending SMBG in all patients with T2D, especially those on oral medications without significant risk for hypoglycemia (15–20).

In this study, the Libre Pro system was used to collect professional ("blinded") CGM data for evaluation of glucose patterns in patients with T2D treated with a variety of therapies, including standard oral diabetes medications, basal insulin, and premixed insulins. Professional CGM assisted in the discovery of undetected events of hyperglycemia and hypoglycemia, provided an illustration of glycemic control in parallel with hemoglobin A1C levels, and identified the extent of glucose variability in these study groups. As shown in Figure 1, the AGP reports illustrate the additional clinical benefit of examining the glucose profile as an adjunct to the laboratory A1C, as there were examples of clinically important variations across the day at both in-target and above-target A1C levels.

A notable finding of this study was that 59% of 105 estimated A1C values fell within the 95% prediction limits (approximately ±15%) reported by the ADAG study, which was lower than the 89.95% reported in the original ADAG study report (11). Importantly, the current study utilized 14 days of continuous glucose data collected for estimated A1C calculation, while the ADAG study collected 2–3 days of CGM data repeated four times over a 12-week period. It is also noteworthy that hemoglobinopathies, drug therapies, and comorbidities (anemia, chronic kidney disease, or liver disease) were not excluded in the current study and may have contributed to the discrepancy. The wide prediction limit intervals emphasize the phenotypic variations between average glucose and glycated hemoglobin across individuals.

Glucose variability has been associated with microvascular complications and coronary artery disease in individuals with T2D (21). It has been suggested that actionable insights can be derived from CGM with clear, easy-to-understand glucometrics, representing the display and analysis of glucose data. This analysis could then provide insights

into the variety of patient behaviors, choices, and actions that contribute to diabetes control (12). Significant effects of age, sex, and duration of diabetes were found to be associated with glucose variability, while baseline A1C was not. Glucose variability was also found to differ between therapy groups, with increased variability associated with the use of insulin and SU (Table 2). This study found increased glucose variability (by 128 to 284%, i.e., one to three times) across all T2D therapy groups compared to reports in healthy subjects (22,23). Those with the most elevated variability approach that reported in T1D (24). The independent predictors of glucose variability among people with T2D is an interesting research topic for further study.

One of the major challenges facing providers working with patients with T2D is determining when to change or intensify therapies. Currently, most medical providers and diabetes educators rely on SMBG data and results of hemoglobin A1C levels to determine whether adjustments or modifications to a patient's diabetes management plan is either warranted or necessary. However, frequency of blood glucose checks is highly variable and depends on patient initiative as well as adequate insurance reimbursement for the cost of blood glucose test strips. CGM systems (both personal and professional) that diminish or eliminate the burden of monitoring and potential for user error, such as fingerstick calibrations, have the best opportunity for providing data that can be confidently used to guide therapy decision-making and promote the achievement of target glucose and A1C levels with reduced events or risk for serious hypoglycemia (12,21,25).

An additional goal of the study was to determine whether the FreeStyle Libre Pro system could be efficiently utilized in a standard clinical setting and allow a medical provider to collect meaningful data that would have a "real-world" impact on their patients. As is seen in Table 4, providers were asked their opinions with regard to their confidence in the data collected by the system and the impact that these data had on a possible decision to make adjustments to the patient's diabetes management plan. A majority of all providers confirmed in question 2 that the CGM data collected over 2 weeks by the device was by itself enough information to make possible therapy changes without the need for corroborating data such as blood glucose data, meal data, or activity/exercise logs. This is an important advance for improving clinical therapy decisions without undue patient burden. Furthermore, as seen in question 1, the CGM data collected led providers to recommend changes in the patient's diabetes management plan 50–100% of the time if the patient had been using a therapy that was identified as having higher CV (SU, basal insulin, premixed insulin). Of note, over a quarter of providers determined that their patients on no medications needed therapy changes based on the results of the 2-week CGM data collected. Moreover, nearly half to three-quarters of the providers polled indicated that the data from the 2-week CGM would have led them to recommend advancement to mealtime insulin (Table 5, Q3). The use of the FreeStyle Libre Pro system in this patient population could have led to a significant number of therapeutic changes in diabetes management with relatively less burden to the patient because no SMBG data was required (6,21). The results of the questionnaire indicated that the providers were confident recommending these changes without large amounts of patient-reported data. Thus, the use of the device could potentially improve clinical efficiency and maximize opportunities for meaningful therapeutic adjustments in a busy clinical practice.

This study introduced the use of a novel, retrospective CGM device that requires no fingerstick calibration during the 14-day sensor wear. The system was well accepted both by individuals wearing the glucose sensor and by health care providers who utilized analyzed data to confidently adjust or initiate medical therapy in broad groups of patients with T2D. The simplicity of this device, coupled with the ease of use in real-word medical practices and the comprehensiveness of the collected glucose data, supports the expanded use of this device in multiple clinical settings. The small sample size of the current study could be considered the main limitation. However, this was a pilot study that was able to identify important differences in glucose variability between therapy groups, indicating opportunities for large clinical studies.

Conclusion

Glucose variability was found to differ by age, sex, and duration of diabetes among people with T2D. Duration of diabetes had the largest mean effect, with an increase in CV of 0.5% for each year of diabetes. Increased variability was also associated with the use of insulin and SU. The AGP was found to be clinically acceptable to review T2D profiles, with over half of care providers stating they would consider treatment changes after review of their subjects' sensor profiles. This illustrates the need for patients and their health care providers to have access to data that can give insight into glucose variability, as these data can affect therapy decisions. Additionally, the participants found the sensor acceptable and comfortable to wear.

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Duality of Interest

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Merck, Novo Nordisk, and Sanofi; and has ownership interest in Novo Nordisk. E.E.W. has received research support from Abbott; serves on advisory boards for Abbott, Boehringer Ingelheim, Eli Lilly, and Voluntis; and consults for Boehringer Ingelheim and Eli Lilly. T.D.D. has received research support and serves on an advisory board for Abbott. D.F.K. serves on speakers' bureaus for Abbott, AstraZeneca, Boehringer Ingelheim, Dexcom, Eli Lilly, Janssen, Novo Nordisk, and Valeritas; serves on advisory boards for Abbott, Dexcom, Eli Lilly, Intarcia, Janssen, Novo Nordisk, and Sanofi; has received research support from Abbott, AstraZeneca, Dexcom, Eli Lilly, Lexicon, and Novo Nordisk; and has ownership interest in Dexcom. R.R.H. serves on advisory boards for AstraZeneca, Boehringer Ingelheim, Elcelyx, Intarcia, and Janssen; consults for Alere, AstraZeneca, Boehringer Ingelheim, Intarcia, Ionis, Janssen, REMD, and Sanofi; and has received research support from Abbott, AstaReal, Eli Lilly, Hitachi, Lexicon, Novo Nordisk, and Viacyte. R.A.H. is a full-time employee of Abbott. No other potential conflicts of interest relevant to this article were reported.

Author Contributions

K.M. wrote the manuscript and researched the data. J.R.U., E.E.W., T.D.D., D.F.K., and R.R.H. reviewed and edited the manuscript and researched the data. R.A.H. reviewed and edited the manuscript. K.M. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation

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