Heterogeneity of Responses to Real-Time Continuous Glucose Monitoring (RT-CGM) in Patients With Type 2 Diabetes and Its Implications for Application

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OBJECTIVE—To characterize glucose response patterns of people who wore a real-time continuous glucose monitor (RT-CGM) as an intervention to improve glycemic control. Participants had type 2 diabetes, were not taking prandial insulin, and interpreted the RT-CGM data independently.

RESEARCH DESIGN AND METHODS—Data were from the first 12 weeks of a 52-week, prospective, randomized trial comparing RT-CGM (n = 50) with self-monitoring of blood glucose (n = 50). RT-CGM was used in 8 of the first 12 weeks. A1C was collected at baseline and quarterly. This analysis included 45 participants who wore the RT-CGM ≥4 weeks. Analyses examined the RT-CGM data for common response patterns—a novel approach in this area of research. It then used multilevel models for longitudinal data, regression, and nonparametric methods to compare the patterns of A1C, mean glucose, glycemic variability, and views per day of the RT-CGM device.

RESULTS—There were five patterns. For four patterns, mean glucose was lower than expected as of the first RT-CGM cycle of use given participants' baseline A1C. We named them favorable response but with high and variable glucose (n = 7); tight control (n = 14); worsening glycemia (n = 6); and incremental improvement (n = 11). The fifth was no response (n = 7). A1C, mean glucose, glycemic variability, and views per day differed across patterns at baseline and longitudinally.

CONCLUSIONS—The patterns identified suggest that targeting people with higher starting A1Cs, using it short-term (e.g., 2 weeks), and monitoring for worsening glycemia that might be the result of burnout may be the best approach to using RT-CGM in people with type 2 diabetes not taking prandial insulin.

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In a 12-month, prospective, randomized controlled trial of real-time continuous glucose monitoring (RT-CGM) in people with type 2 diabetes and not taking prandial insulin, we demonstrated that intermittent RT-CGM used for a period of 12 weeks was associated with a clinically significant reduction in A1C during the same period of time compared with premeal and bedtime self-monitoring of blood glucose (SMBG) and that the improvement in A1C was sustained for at least 40 weeks after the active intervention ended (1,2). Previous studies of RT-CGM for people with type 2 diabetes (3–5), although smaller and including mostly patients taking prandial insulin, have observed similar improvements in glycemia.

Owing to fluctuations around the mean, people with the same A1C can have different glycemic variability (6,7). Some researchers have proposed that higher glycemic variability may increase the risk for diabetes complications (8–10) through increased oxidative stress (11,12). However, these studies of RT-CGM in people with type 2 diabetes did not address whether glycemic variability was also reduced concomitantly with A1C and did not report whether there were different patterns of responses to using the device and when the responses might have occurred. Were responses immediate or gradual, temporary or sustained, marked or modest? These questions are important because their answers may inform clinicians how RT-CGM might be implemented in practice for people with type 2 diabetes who are not taking prandial insulin.

Thus, the present analysis sought to answer those questions through an in-depth investigation of each participant's raw glucose data from their RT-CGM and identification of common response patterns. This led to a new typology describing glucose responses, which we verified by statistical analyses of measures of mean glucose, glycemic variability, and patient engagement with the RT-CGM device.

RESEARCH DESIGN AND METHODS

Study design

This analysis used data from the study by Vigersky and colleagues (1), which has been previously described. Briefly, this was a 52-week, prospective, two-arm, randomized, controlled study that compared the short- (12-week) and long-term (40-week) relative effectiveness of RT-CGM and frequent SMBG. Those randomized to RT-CGM used a Dexcom SEVEN (Dexcom, Inc., San Diego, CA). RT-CGM use

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occurred in four periods (2 weeks on and 1 week off) over 12 weeks, for a total of 8 weeks of use. Those randomized to SMBG were asked to test their glucose before meals and at bedtime for 12 weeks as well as at times associated with the symptoms of hypo- or hyperglycemia. After the initial 12 weeks, all participants were asked to perform SMBG for the duration of the study as recommended by their usual provider. The study staff did not provide any care management, and the study participants' providers did not have access to the RT-CGM data. Follow-up study visits were performed at 3-week intervals during the first 12 weeks and every 3 months during the follow-up phase.

The study recruited military health care beneficiaries from the Walter Reed Health Care System. Patients were eligible if they were 18 years or older, had a diagnosis of type 2 diabetes for at least 3 months, had an initial A1C ≥7% but ≤12%, were treated with diet/exercise alone or other glucose-lowering therapies, except prandial insulin, were able to independently measure and read fingerstick blood glucose levels, and were willing to perform SMBG. The study recruited 100 subjects, of which 50 were allocated to the RT-CGM group and 50 to the SMBG group.

Sample

The current analysis examined data from 45 of the participants of the RT-CGM group only who wore the RT-CGM (3 refused to wear it after randomization, and 2 wore it too infrequently to allow appropriate examination). We extracted the RT-CGM data for each participant in this group and selected the middle 3 days of each 7 days of use. We did this to ensure that each study participant had time to calibrate and adjust to the device, to minimize the number of sensor failures in the data more likely to occur toward the end of the sensor life span, and to obtain a comparable number of glucose readings for each period of RT-CGM use for each participant. These 3 days of data constituted a "cycle." There were 302 of a possible 360 cycles (84%) available for analysis (6.7 cycles per participant). If fewer than 3 days of data were available for a participant, we did not examine that cycle for this analysis.

Measures

The response patterns were derived from examination of the raw glucose readings data from the Dexcom SEVEN, which reports interstitial glucose results every 5 minutes. RT-CGM data often contain "gaps" in readings that interfere with the accurate calculation of certain measures of variability (13). Our data preparation involved imputing values to fill these gaps based on the duration of the gap and the difference between the blood glucose value before and after the gap.

The study summarized the RT-CGM glucose readings by calculating mean glucose, proportion below 70 mg/dL, and proportion above 240 mg/dL, standard deviation (SD), mean amplitude of glycemic excursion (MAGE; a measure that selects the major glucose swings and calculates the mean of the difference between consecutive glucose increases or decreases greater than 1 SD), continuous overlapping net glycemic action (CONGA; a measure that captures the SD of the difference in glucose levels using different time periods), and mean of daily difference (a measure of the difference between glucose values at the same time of day on consecutive days). There are multiple measures of quality of glycemic control, and each has its merits and deficiencies (14,15). However, many of the measures of glycemic control are highly correlated (14), and none is a gold standard, so this analysis focused on these few. The mean, SD, MAGE, and CONGA were calculated using EasyGV 8.6 software (16).

A1C was measured quarterly in the main clinical trial using a Roche/Hitachi cobas c system with a Tina-quant Hemoglobin A1C Gen.2 assay. As context for interpreting the RT-CGM data and patterns, we calculated the "change-from-baseline" in A1C by subtracting the baseline value from the 12-week value, and we estimated average glucose at baseline and 12 weeks (eAG_0 and eAG_{12}) using the following formula: (A1C × 28.7) – 46.7 (17).

As a proxy for participant engagement with the RT-CGM, we used the data on screen views embedded in the Dexcom SEVEN RT-CGM software to determine the average number of discrete episodes per day that study participants looked at the display on the RT-CGM receiver during the 3-day periods of their first and last cycles. To be counted as a discrete episode, display viewings had to be separated by at least 1 minute; thus, if a participant viewed multiple graphs in a brief period of time, clicking back and forth among them, this counted as a single episode.

Analysis

The analyses comprised several steps. First, we graphed each participant's "raw" glucose data for each cycle and juxtaposed those data with their measures of glycemic control (e.g., A1C, mean glucose, SD, MAGE, etc.) until several patterns emerged. This type of approach (called a health pattern approach), in which all of each individual's data are examined until patterns become apparent, has been used in life course and aging research to identify heterogeneity often obscured when researchers focus exclusively on measures of central tendency (18). To our knowledge, this approach has not been used in the area of glycemic variability research.

Second, to validate the response patterns identified in the first step, we conducted statistical tests of pattern-related differences over time in mean glucose levels, SD, MAGE, CONGA, proportion of readings below 70 mg/dL and proportion of readings above 240 mg/dL. We used multilevel models for longitudinal data.

Third, we used multiple regression to regress change-from-baseline in A1C on response pattern, baseline A1C (to adjust for the strong effect of previous status often observed in health research), and their interaction (pattern × baseline A1C). This step indicated whether the response patterns differed in A1C outcome at 12 weeks and whether baseline A1C was associated with how participants responded to RT-CGM.

Fourth, we compared the screen viewings of the patterns at different time points using a nonparametric equivalent for ANOVA (Kruskal-Wallis analysis of ranks) and for paired *t* tests (Wilcoxon signed rank sum test). The statistical analyses used SAS 9.2 software (SAS Institute, Cary, NC). Data are presented as mean ± SD.

RESULTS—The 45 participants were a mean age of 55.8 ± 9.6 years, and the duration of diabetes was 8.7 ± 6.0 years. Mean BMI was 32.1 ± 5.9 kg/m^2. Twenty-nine (64.4%) were men, 23 (51.1%) were African American, and 17 (37.8%) were Caucasian. At baseline, 3 (6.7%) were managing their diabetes with diet and exercise only, 22 (48.9%) were taking oral medications and no other medications for their diabetes (such as insulin or exenatide), 16 (35.6%) were taking basal insulin alone or with oral medications, and 4 (8.9%) were taking

another injectable medication (such as exenatide).

Patterns

As of the first cycle of using the RT-CGM, 38 participants (84.4%) had RT-CGM glucose readings that were lower than what would be expected given their eAG_0 values, indicating a response to the intervention. Examination of the glucose readings within and across cycles suggested four common patterns of response. Figure 1 presents the RT-CGM glucose readings, by cycle, of one individual for each type of response. Reference lines are provided at 70 and 180 mg/dL, and eAG_0 and eAG_{12} are noted on the right and left of the graphs. We assigned descriptive names to the patterns.

The seven participants (15.6%) who had a favorable response but with high and variable glucose had greater numbers of readings exceeding the target reference lines in the figures than participants who fit the other three patterns. The 14 participants (31.1%) who fit the pattern of tight control had glucose readings that were almost entirely within the target range for all cycles. The worsening glycemia pattern in six participants (13.3%) was distinct from the others in that their readings were mostly within the target in cycles 1 and 2 but then became higher and more dispersed. For the 11 participants (24.4%), who had an incremental improvement, glucose readings improved such that their penultimate and ultimate values were lower than cycle 1. Seven participants (15.6%) had no response. A glucose graph is not shown for this pattern.

Validation of observed patterns

Baseline mean glucose ($P = 0.08$), SD ($P = 0.04$), MAGE ($P = 0.04$), CONGA ($P = 0.07$), and proportion of readings above 240 mg/dL ($P = 0.004$) were higher for participants who had a favorable response but with high and variable glucose versus the reference group (participants who had no response; Table 1). Baseline mean glucose ($P = 0.03$) and CONGA ($P = 0.07$) of participants who had tight control were lower versus participants who had no response. With respect to change over time, mean glucose ($P = 0.0001$), SD ($P = 0.08$), CONGA ($P = 0.0003$), and proportion of readings above 240 mg/dL ($P = 0.008$) increased over time for participants who had worsening glycemia, and mean glucose ($P = 0.02$), SD ($P = 0.02$), MAGE ($P = 0.08$), and CONGA ($P = 0.02$) decreased for participants who had an incremental improvement. Compared with participants who had a favorable response but with high and variable glucose, participants who had tight control had lower mean glucose ($P < 0.0001$), SD ($P = 0.0001$), MAGE ($P = 0.0003$), CONGA ($P = 0.0001$), and proportion of readings above 240 mg/dL ($P = 0.0001$) as of cycle 1.

Mean baseline and 12-week A1C was 8.4 ± 1.2% and 7.8 ± 1.1% for participants who had a favorable response but with high and variable glucose,

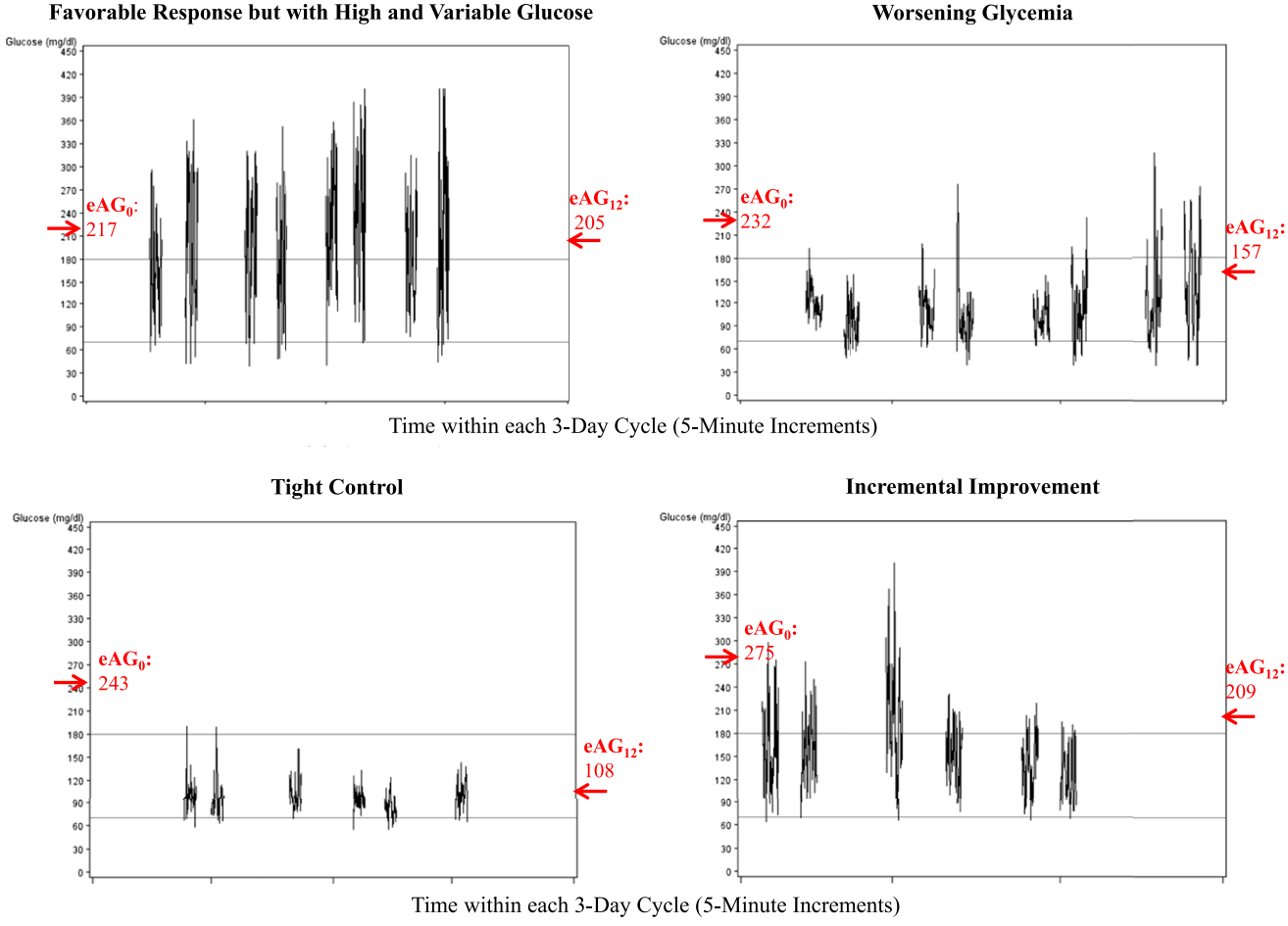

Figure 1—*Examples of main response patterns observed with RT-CGM. (A high-quality color representation of this figure is available in the online issue.)*

Table 1—*Summary measures of glycemic quality, by response pattern*

	RT-CGM cycle								*P* value	
Pattern	1	2	3	4	5	6	7	8	Baseline	Change
Measure (mean)										
Favorable response but with high and variable glucose (*n* = 7)										
Mean (mg/dL)	174.6	177.8	171.4	171.4	188.3	173.9	174.3	177.1	0.080	0.704
SD (mg/dL)	46.8	55.9	50.3	46.5	49.1	45.4	50.8	51.2	0.040	0.623
MAGE (mg/dL)	107.5	118.6	96.8	101.0	103.9	93.7	97.8	104.6	0.043	0.141
CONGA (mg/dL)	153.3	160.1	151.0	150.3	167.1	153.5	155.4	159.3	0.072	0.645
<70 mg/dL (%)	1.3	2.7	1.2	2.2	0.2	1.1	0.3	2.0	0.270	0.853
>240 mg/dL (%)	14.5	18.9	14.1	12.1	19.9	13.3	13.8	15.4	0.004	0.746
Tight control (*n* = 14)										
Mean (mg/dL)	125.9	135.2	123.9	132.3	133.5	123.5	138	127.7	0.031	0.800
SD (mg/dL)	31.3	35.2	30.8	32.2	32.3	28.8	34.0	32.9	0.136	0.581
MAGE (mg/dL)	66.2	71.2	64.0	77.1	70.9	69.0	65.7	64.5	0.195	0.336
CONGA (mg/dL)	110.6	118.6	109.6	116.6	116.2	106.9	122.3	111.8	0.073	0.814
<70 mg/dL (%)	2.4	1.3	4.1	2.2	1.2	2.2	0.7	2.3	0.453	0.851
>240 mg/dL (%)	1.3	3.4	1.1	2.0	2.8	1.1	3.0	1.7	0.569	0.755
Worsening glycemia (*n* = 6)										
Mean (mg/dL)	138.1	145.8	151.3	153.2	174.1	175.7	165.9	204.7	0.210	0.0001
SD (mg/dL)	30.7	33.2	36.2	38.6	41.2	44.3	43.0	40.8	0.263	0.075
MAGE (mg/dL)	55.6	71.0	77.8	78.2	76.9	98.5	89.5	71.3	0.275	0.392
CONGA (mg/dL)	124.0	130.8	136.7	138.8	159.3	155.6	152.8	187.2	0.405	0.0003
<70 mg/dL (%)	0.3	5.8	0.7	1.9	0.5	2.9	2.7	1.4	0.551	0.741
>240 mg/dL (%)	1.7	4.0	3.9	4.8	8.7	15.8	7.9	28.2	0.274	0.008
Incremental improvement (*n* = 11)										
Mean (mg/dL)	165.7	149.3	147.8	144.5	132.0	128.1	131.7	130.7	0.674	0.015
SD (mg/dL)	38.4	38.3	41.5	37.3	34.3	33.1	31.1	28.7	0.725	0.019
MAGE (mg/dL)	71.7	75.3	87.4	86.6	76.3	74.7	64.1	61.4	0.939	0.078
CONGA (mg/dL)	148.0	132.8	130.5	130.1	116.1	112.2	115.5	114.9	0.479	0.018
<70 mg/dL (%)	0.0	1.9	1.5	0.6	2.1	1.1	3.1	2.0	0.084	0.187
>240 mg/dL (%)	6.7	3.6	5.5	6.1	1.9	0.9	1.3	0.2	0.493	0.182
No response (*n* = 7)										
Mean (mg/dL)	148.3	146.7	155.4	151.6	156.4	152.6	135.8	142.9	Ref	Ref
SD (mg/dL)	39.6	33.2	43.9	40.5	42.8	45.5	44.4	39.4	Ref	Ref
MAGE (mg/dL)	76.2	74.5	98.3	94.3	101.5	99.3	81.6	86.9	Ref	Ref
CONGA (mg/dL)	129.4	126.0	133.3	130.5	136.5	130.0	114.7	124.2	Ref	Ref
<70 mg/dL (%)	3.5	1.9	5.5	1.5	2.1	4.6	4.3	1.5	Ref	Ref
>240 mg/dL (%)	2.9	2.0	6.2	3.9	10.8	8.7	3.2	3.1	Ref	Ref

The *P* values are from separate mixed models for longitudinal data in which each measure of glycemic quality was regressed on a qualitative indicator for pattern, time (e.g., cycle 1), and an indicator for the interaction between pattern and time. The results produce an estimate and *P* value for the average baseline value or initial status for participants in each patterns, and an estimate and *P* value for the average rate of change per cycle of the participants who fit each pattern. "Ref" (Reference) means that this was the group against which the other groups were compared in the separate mixed models for longitudinal data.

8.7 ± 1.4% and 6.7 ± 0.7% for tight control, 8.9 ± 0.9% and 7.6 ± 0.3% for worsening glycemia, 8.5 ± 1.5% and 7.1 ± 0.9% for incremental improvement, and 7.5 ± 0.4% and 7.6 ± 0.7% for participants who had no response. With the exception of participants who had no response, the amount of decline in A1C tended to be higher among participants who had higher baseline A1Cs. However, the nonparallel lines in Fig. 2 show that the amount of decline at increasing levels of A1C differed by response pattern. For example, participants who had tight control had a *cumulative* decline in 12-week A1C of 0.45 percentage points for every 0.5% increase in baseline A1C ($P = 0.02$). Participants who had an incremental improvement had a cumulative decline of 0.25% for every 0.5% increase in baseline A1C ($P = 0.03$).

Screen views

During their first cycle, the number of discrete times per day that the participants viewed the display did not differ by glucose response pattern ($P = 0.82$) (Fig. 3). As of their last cycle, however, the number differed ($P = 0.05$), with participants who had tight control having the most views (23 per day), followed by participants who had an incremental improvement (15 per day). Participants who had worsening glycemia had the lowest number of views by their last cycle (5 per day). Differences in views over time were trends for participants who had worsening glycemia ($P = 0.06$) and significant for those who had tight control ($P = 0.04$), with the former viewing the display less often over time and the latter viewing it more often.

No other participant characteristics aside from A1C and screen views were significantly associated with glucose

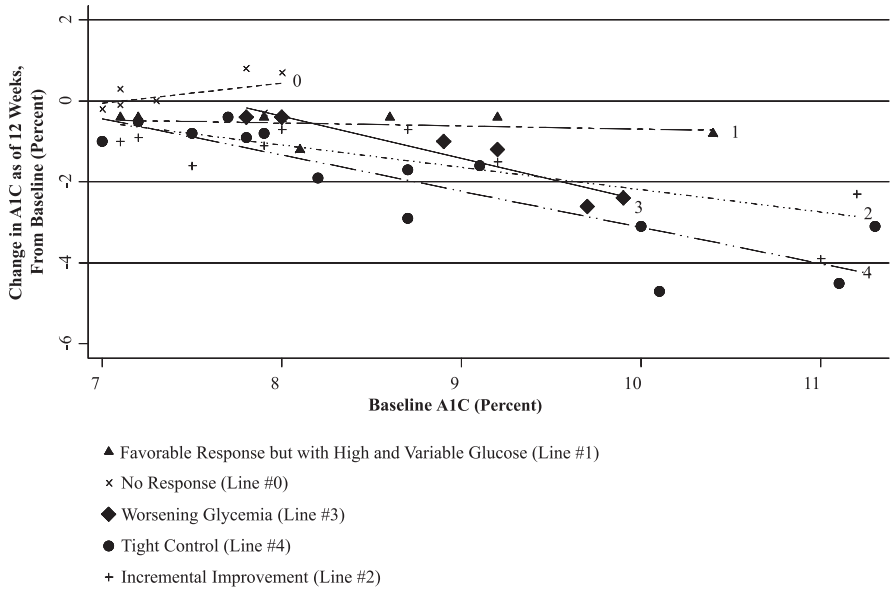

Figure 2—*Change in A1C as of 12 weeks by baseline A1C for each response pattern. Figure is a scatterplot of each response patterns' change in A1C and baseline A1C overlaid with a prediction plot to show the trends. To minimize the text in the figure, we assigned the patterns arbitrary numbers and the numbers are shown at the end of each line in the figure. The lines for each pattern start and end at their minimum and maximum data points in the scatterplot.*

response patterns (data not shown). Diabetes distress (as measured by the Problem Areas in Diabetes scale) was highest for those who had worsening glycemia and lowest for those who had tight control, but these differences were not statistically significant at baseline ($P = 0.11$) or 12 weeks ($P = 0.09$).

CONCLUSIONS—RT-CGM is known to be a useful management tool for people with type 1 diabetes (19–21) and people with type 2 diabetes taking prandial insulin (22). Recent reports have suggested that the improvement associated with the use of RT-CGM may result from the information it provides about the effects of physical activity and dietary choices, stress, medications, environment, and sleep, among other things (5,23–25). In the present analysis, we questioned whether the use of RT-CGM may also lead to a reduction in glycemic variability and how long it takes for its effects to be apparent. To address these questions, we identified and validated the major patterns of response to RT-CGM, using data from the largest clinical trial to date of RT-CGM versus SMBG alone in people with type 2 diabetes not taking prandial insulin. To our knowledge, the health pattern approach used here to identify heterogeneity often missed in analyses of central tendency has not been applied to research on RT-CGM data. Thus, the patterns and the descriptive names we assigned them are new in this literature.

Five patterns emerged from the interpretation of the raw RT-CGM data in the first phase of our analysis; four of these indicated a response to the technology, apparent in eAG_0 versus mean glucose as of cycle 1 and lower A1C at the end of repeated RT-CGM cycles. The most common responses were tight control and incremental improvement, both of which were characterized by sustained limited glucose variability. Statistical analyses of various summary measures of glycemic quality, including A1C, mean glucose, SD, MAGE, CONGA, and the proportions of glucose readings below 70 mg/dL and above 240 mg/dL confirmed that the patterns differed. Patient engagement, as measured by screen views, was highest among participants who had tight control, increased over time for these participants, and decreased for participants who had worsening glycemia. The pattern of worsening glycemia—which occurred after an initial improvement in glucose control (based on comparison of eAG_0 with baseline A1C) and coincided with a reduction over time in screen views—might have been due to participant burnout or stress.

The response patterns identified suggest an approach for using RT-CGM as part of a treatment plan for people with type 2 diabetes not taking prandial insulin. First, the early response for four of the five groups suggests that the RT-CGM primarily augments motivation, a concept seen in behavioral economics research. We speculate that it augmented motivation because the feedback was timely (26,27), so participants did not have to wait 3 or more months for an A1C test to get feedback about lifestyle choices that modify their glucose. Therefore RT-CGM might be used for a relatively short period of time, such as just two rather than eight cycles. Future research is needed to determine the most effective "dose" or amount of RT-CGM use for people with type 2 diabetes; for example, short-term, repeated use of RT-CGM throughout the year, or annually.

Second, some of the participants had an incremental improvement over eight cycles, suggesting that some patients might benefit from longer-term use of RT-CGM. Whether supplementation with clinical interpretation of the RT-CGM data and/or structured diabetes education to facilitate problem solving may have additional benefits is not clear.

Third, because baseline A1C was lowest among participants who had no response, RT-CGM might be best reserved for people who have higher starting A1Cs. Alternatively, clinicians might use instruments to evaluate their patients' risks of diabetes burnout, stress, frustration, and/or readiness to change to be more selective in who might benefit from the use of RT-CGM, even those with lower baseline A1Cs.

Paired SMBG testing also may be a useful behavioral or motivational tool (28) and has been effective in improving A1C results in studies using a structured testing approach to guide therapy (29–31). However, SMBG potentially misses the apex and nadir of glucose in response to a particular choice or event, and cannot provide immediate feedback without numerous self-tests, which is costly and patients are loathe to do it. Compared with RT-CGM, the scant data SMBG provides makes it more a reactive than proactive tool. For the purpose of activating change in this cohort, short-term RT-CGM use might be best, in conjunction with paired SMBG testing afterward or providers' usual recommendations for SMBG.

A limitation of this study is that the participants were not asked to use the CGM masked. Thus, we did not have information about their glycemic variability before they started using the CGM

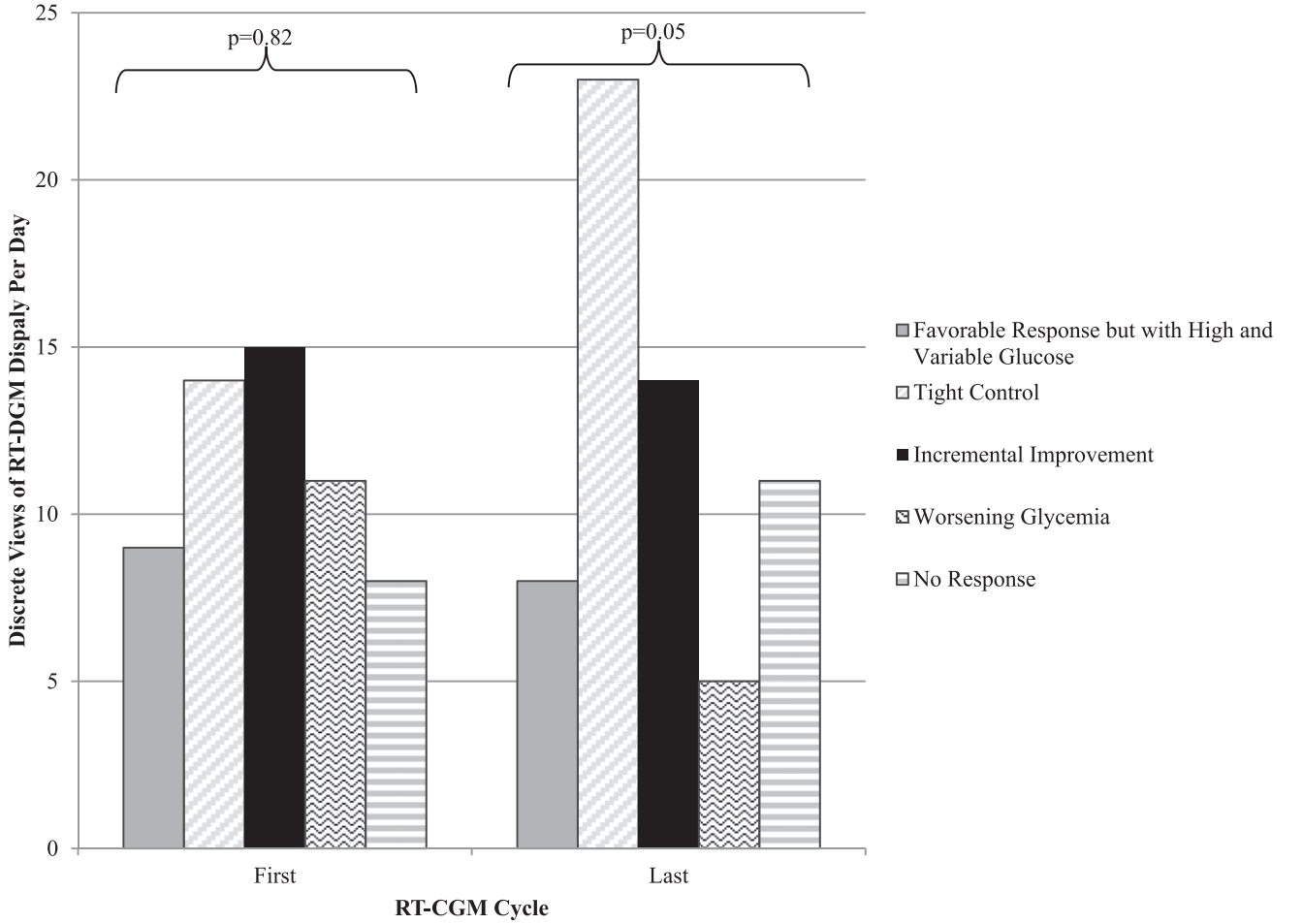

Figure 3—*Discrete views of the RT-CGM display per day first and last available cycle, by response pattern.*

real-time. However, given the early change in mean glucose as indicated by a comparison of eAG_0 and mean glucose at the first cycle, it is unclear whether a period of wearing a masked CGM would have provided a sufficient benchmark; the act of wearing the device might have been enough to change behavior. Future research might quantify the placebo effect of simply wearing a CGM device by applying a health pattern approach to characterize the glucose patterns of people who wore a masked device for multiple cycles. Another limitation of this study, as noted previously (1,2), is that it did not collect information on the participants' self-care behaviors before, during, and after use of the RT-CGM, so we cannot provide information about whether participants made changes based on their perceptions of the RT-CGM data and what those changes might have been.

In summary, we found that patients with type 2 diabetes and not on prandial insulin respond in different ways to RT-CGM data, leading to the possibility that certain subgroups of patients may be targeted in order to most effectively use this technology.

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S.J.F. performed the analyses and wrote the manuscript. S.J.S. and M.S.W. conducted the literature search and reviewed drafts of the manuscript. M.C. assisted with analyses. N.E. reviewed drafts of the manuscript. R.A.V. performed the analyses and reviewed drafts of the manuscript. S.J.F. 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.

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