Glycemic Outcomes in Adults With T1D Are Impacted More by Continuous Glucose Monitoring Than by Insulin Delivery Method: 3 Years of Follow-Up From the COMISAIR Study

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OBJECTIVE

This study assessed the clinical impact of four treatment strategies in adults with type 1 diabetes (T1D): real-time continuous glucose monitoring (rtCGM) with multiple daily insulin injections (rtCGM+MDI), rtCGM with continuous subcutaneous insulin infusion (rtCGM+CSII), self-monitoring of blood glucose with MDI (SMBG+MDI), and SMBG with CSII (SMBG+CSII).

RESEARCH DESIGN AND METHODS

This 3-year, nonrandomized, prospective, real-world, clinical trial followed 94 participants with T1D (rtCGM+MDI, $n = 22$; rtCGM+CSII, $n = 26$; SMBG+MDI, $n = 21$; SMBG+CSII, $n = 25$). The main end points were changes in A1C, time in range (70–180 mg/dL [3.9–10 mmol/L]), time below range (<70 mg/dL [<3.9 mmol/L]), glycemic variability, and incidence of hypoglycemia.

RESULTS

At 3 years, the rtCGM groups (rtCGM+MDI and rtCGM+CSII) had significantly lower A1C (7.0% [53 mmol/mol], $P = 0.0002$, and 6.9% [52 mmol/mol], $P < 0.0001$, respectively), compared with the SMBG+CSII and SMBG+MDI groups (7.7% [61 mmol/mol], $P = 0.3574$, and 8.0% [64 mmol/mol], $P = 1.000$, respectively), with no significant difference between the rtCGM groups. Significant improvements in percentage of time in range were observed in the rtCGM subgroups (rtCGM+MDI, 48.7–69.0%, $P < 0.0001$; and rtCGM+CSII, 50.9–72.3%, $P < 0.0001$) and in the SMBG+CSII group (50.6–57.8%, $P = 0.0114$). Significant reductions in time below range were found only in the rtCGM subgroups (rtCGM+MDI, 9.4–5.5%, $P = 0.0387$; and rtCGM+CSII, 9.0–5.3%, $P = 0.0235$). Seven severe hypoglycemia episodes occurred: SMBG groups, $n = 5$; sensor-augmented insulin regimen groups, $n = 2$.

CONCLUSIONS

rtCGM was superior to SMBG in reducing A1C, hypoglycemia, and other end points in individuals with T1D regardless of their insulin delivery method. rtCGM+MDI can be considered an equivalent but lower-cost alternative to sensor-augmented insulin pump therapy and superior to treatment with SMBG+MDI or SMBG+CSII therapy.

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Use of real-time continuous glucose monitoring (rtCGM) has emerged as a critical component of diabetes self-management for individuals treated with intensive insulin regimens, and it is now considered a standard of care for these patients (1–6).

Recent randomized clinical trials have demonstrated that use of rtCGM results in significant improvements in glycemic control and hypoglycemia and confers a higher quality of life to participants treated with multiple daily insulin injections (MDIs) compared with traditional self-monitoring of blood glucose (SMBG) (7–11). Similar improvements in A1C and hypoglycemia have also been observed in participants using rtCGM with insulin pump therapy (12,13). Significant reductions in severe hypoglycemia have also been observed in patients with type 1 diabetes (T1D) with problematic hypoglycemia who were treated with rtCGM in combination with either MDI (10) or insulin pump therapy (13). Importantly, a common observation in most rtCGM studies is that glycemic improvements and other benefits were dependent upon the persistence of sensor use (7–15).

Although randomized controlled trials (RCTs) are recognized as the highest level of evidence regarding the efficacy of rtCGM when used within tightly controlled settings, our understanding of the real-world use and benefits of rtCGM has been limited. Findings from RCTs often fail to reflect actual participant behaviors and resultant outcomes in real-world clinical practice (16–18). Moreover, there have been few long-term comparisons to evaluate the efficacy of rtCGM use in combination with the various insulin delivery methods (e.g., rtCGM + continuous subcutaneous insulin infusion [CSII] vs. rtCGM+MDI), and conclusive evidence of rtCGM benefits compared with SMBG has been sparse. Because diabetes management is primarily dependent on participant behavior, different research approaches are needed to more definitively assess these behavior-based interventions.

We recently reported findings from the Comparison of Sensor-Augmented Insulin Regimens (COMISAIR) study, a 1-year, nonrandomized, real-world study that assessed the efficacy of long-term use of sensor-augmented insulin regimens (SAIR)—rtCGM combined with either CSII (sensor-augmented pump [rtCGM+CSII]) or MDI (rtCGM+MDI)—on glycemic control compared with the addition of CSII (SMBG+CSII) or MDI (SMBG+MDI) among 65 individuals with T1D (19). At study end, significant A1C reductions from baseline were observed in both the SAIR groups (rtCGM+CSII: −1.1% [−12.0 mmol/mol], $P = 0.0025$; rtCGM+MDI: −1.3% [−14.2 mmol/mol], $P = 0.0034$). Although SMBG+CSII use also led to a significant A1C reduction (0.5% [5.5 mmol/mol]), no significant reductions were seen in the SMBG+MDI group. The increase from baseline in average number of boluses per day was significantly greater in the rtCGM+CSII and rtCGM+MDI groups (3.2 and 2.2, respectively, both $P < 0.0001$) compared with SMBG+CSII (0.6, $P = 0.08$). No increase was seen in the SMBG+MDI group. Importantly, significant reductions in percentage of time in hypoglycemia (<70 mg/dL [<3.9 mmol/L]) were observed only in the SAIR groups, from 8 ± 4% to 6 ± 3%, $P < 0.01$.

In the current follow-up study, we investigated the effects of SAIR interventions on glycemic control and treatment persistence among a larger participant cohort after 3 years, providing further supportive evidence for the use of rtCGM in the management of T1D.

RESEARCH DESIGN AND METHODS

The COMISAIR-2 study was the 3-year follow-up of the COMISAIR trial (19), which compared the efficacy of the long-term use of SAIR regimens among individuals. Participants were recruited from the participant population treated at the 3rd Department of Internal Medicine, 1st Faculty of Medicine, Charles University. This report includes results from an additional 29 participants whose complete 1-year data were not available at the conclusion of the initial COMISAIR trial. The study was approved by an independent ethics review board and conducted in accordance with the Declaration of Helsinki (20). All subjects provided written informed consent before enrollment.

Inclusion criteria were as follows: age >18 years, >2 years T1D duration, A1C 7.0–10% (53–86 mmol/mol), treated with analog insulins, willingness to use sensors >70% of the time or perform SMBG four or more times per day, and willingness to participate in a 4-day training program at baseline. Exclusion criteria were as follows: use of rtCGM within the previous 3 months, ketoacidosis within the previous 3 months, concomitant therapy influencing glucose metabolism, pregnant or planning pregnancy, and demonstrated nonadherence to current treatment regimen.

Procedures

Enrolled participants were scheduled for a total of 15 clinic visits (baseline, at week 2, and then at months 1, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, and 36). A detailed description of the study procedures was previously published (19).

At the initial visit, investigators confirmed eligibility and initiated professional CGM (iPro2; Medtronic, Northridge, CA) in all participants for 6 days. Throughout the study, participants in the groups not using SAIR had professional CGM every 3 months. Participants then attended a structured 4-day training program that addressed basic insulin administration skills, including timing and dosing of preprandial insulin, prevention of hypoglycemia, and theoretical and practical carbohydrate counting. Participants were encouraged to use flexible insulin dosing.

During training, all treatment modalities (rtCGM+MDI, rtCGM+CSII, SMBG+MDI, and SMBG+CSII) were introduced to participants. In collaboration with study clinicians, participants selected their treatment modality according to their individual needs and preferences. Investigator influence on participant decisions was minimal (6% of cases), and no participant was discouraged from using one of the SAIR regimens. Participants in the SAIR and CSII groups completed theoretical training on the relevant devices, followed by treatment initiation and practical training (including insulin adjustment) with investigators.

Participants using SAIR were encouraged to make self-adjustments to their treatment using rtCGM values (hyperglycemia and hypoglycemic alerts and trends) and to incorporate results of SMBG into treatment changes. Participants in non-SAIR groups were encouraged to measure their blood glucose at least four times per day. All participants were instructed to use only the study

Table 1—Baseline characteristics

Characteristic	rtCGM + MDI (n = 22)	rtCGM + CSII (n = 26)	SMBG + CSII (n = 25)	SMBG + MDI (n = 21)	P value
Male (%)	59	50	48	52	0.89
Age (years)	32.6 ± 11.5	32.3 ± 9.9	33 ± 9.3	35 ± 15	0.95
Duration of diabetes (years)	13.7 ± 9.8	14.6 ± 7.8	13.4 ± 8.4	13.5 ± 8.8	0.86
A1C (mmol/mol)	66.6 ± 10.0	66.5 ± 10.2	67.3 ± 9	67 ± 8.6	0.95
A1C (%)	8.2 ± 0.9	8.2 ± 0.9	8.3 ± 0.8	8.3 ± 0.8	0.92
Mean sensor glucose (mmol/L)	10.5 ± 1.4	10.3 ± 1.5	10.4 ± 1.6	10.4 ± 1.3	0.89
BMI (kg/m^2)	26 ± 4	25 ± 4	25 ± 3	25 ± 3	0.91
Body weight (kg)	76.6 ± 14	72.5 ± 15	74 ± 11	73.7 ± 13	0.96
Total daily dose of insulin (units)	48.1 ± 15	46.2 ± 11.5	46.7 ± 11.4	48.8 ± 13.5	0.93
Relative proportion of bolus insulin (%)	48.7 ± 3.9	48.7 ± 4	50.1 ± 4.4	50 ± 4.4	0.61
No. of boluses/day (n)	3.9 ± 0.9	3.8 ± 0.8	3.8 ± 0.9	3.8 ± 0.7	0.99
Frequency of SMBG/day (n)	3.7 ± 1	3.7 ± 1.2	3.8 ± 1.1	3.6 ± 1	0.95

Values are presented as mean ± SD.

blood glucose meter provided to them for all SMBG measurements taken during this trial.

At each clinic visit, participants were screened for adverse events, sensor insertion sites were inspected (SAIR participants), and data from all rtCGM systems, insulin pumps, and blood glucose meters were downloaded for analysis.

Glucose Monitoring Devices

Participants in the CSII group wore one of two types of insulin pumps: MiniMed Paradigm Veo (Medtronic) and Animas Vibe (Animas Corporation, West Chester, PA). Participants in the rtCGM+CSII subgroup used either the MiniMed Paradigm Veo System with Enlite sensors (Medtronic) or Animas Vibe system with Dexcom G4 sensors (Dexcom, San Diego, CA). The subgroup of participants who selected rtCGM+MDI therapy used a Dexcom G4 rtCGM system. The iPro2 was used for glucose monitoring in all participants at baseline and every 3 months in SMBG participants. All participants were provided with a personal blood glucose meter (OneTouch [LifeScan, Milpitas, CA] or CONTOUR LINK [Bayer Diabetes Care, Basel, Switzerland]), which was used for diabetes self-management purposes and calibration of rtCGM. We highlighted to participants the importance of regular downloading and review of the data from rtCGM devices and insulin pumps. A bolus calculator was set for all participants with insulin pumps.

Outcomes

The primary end point was the difference in A1C between the groups after 3 years of follow-up. Secondary end points were as follows: change in glycemic variability (expressed as the total SD of blood glucose, average daily glucose from CGM, and percentage of time spent in range 70–180 mg/dL [3.9–10.0 mmol/L]), percentage of time <70 mg/dL (<3.9 mmol/L), rtCGM usage (SAIR groups), change in average number of boluses per day, and incidence of hypoglycemia.

Measures

A1C values were measured at the baseline and then every 3 months until study end. A1C was analyzed by a high-performance liquid chromatography method on a Variant II analyzer (Bio-Rad, Hercules, CA). The normal reference range of A1C in our laboratory is 4.0–6.0% (20–42 mmol/mol). Initially, all patients were monitored by professional CGM for 6 days. Then, throughout the study, subjects in the groups not using rtCGM were assessed by professional CGM for 6 days every 3 months.

Severe hypoglycemia was defined as an episode requiring assistance from another person or neurological recovery in response to restoration of plasma glucose to normal. Ketoacidosis was defined as an episode of hyperglycemia (>252 mg/dL [>14 mmol/L]) with low serum bicarbonate (<15 mmol/L), low pH (<7.3), or both together with either ketonemia or ketonuria that required treatment in a health care facility.

Statistical Analysis

The basic characteristics of each group were analyzed using nonparametric tests (Kruskal-Wallis and ANOVA). The data of repeated measurements (obtained every 3 months) such as the mean glucose levels, time in/below target range, and glycemic variability were compared using a linear mixed-effects model. P values <0.05 were considered statistically

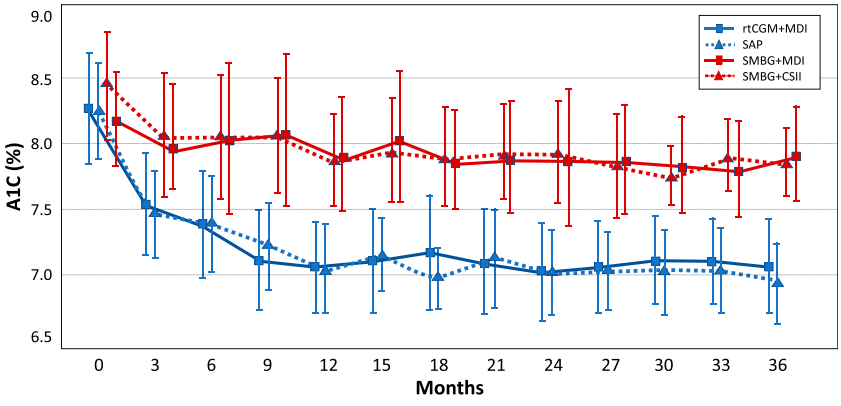

Figure 1—Change in A1C from baseline by study group. SAP, sensor-augmented pump.

Table 2—Significance of A1C change over 36 months

	Month 3	Month 6	Month 9	Month 12	Month 15	Month 18	Month 21	Month 24	Month 27	Month 30	Month 33	Month 36
rtCGM+MDI	0.0017	0.0006	<0.0001	<0.0001	<0.0001	0.0003	<0.0001	<0.0001	0.0001	0.0004	0.0006	0.0002
rtCGM+CSII	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.0001	<0.0001
SMBG+MDI	1.0000	1.0000	1.0000	0.3914	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
SMBG+CSII	1.0000	1.0000	1.0000	0.0183	0.1778	1.0000	0.9125	0.9740	0.7677	0.2954	1.0000	0.3574

significant. Analyses were conducted using the R statistical package, version 3.1.1. Data are expressed as mean ± SD values.

RESULTS

Baseline Characteristics and Adherence

A total of 94 participants were enrolled in the study; 88 completed all study visits. Among the six participants who discontinued the study, two SMBG+CSII participants and one rtCGM+CSII participant withdrew for personal reasons, one SMBG+CSII participant decided to initiate rtCGM after 1 year, one rtCGM+MDI participant initiated rtCGM+CSII, and one SMBG+MDI participant died due to breast cancer. Baseline characteristics were similar in the four study groups (Table 1).

All SAIR participants wore their sensors >70% of the time. No significant changes in total insulin dose or body weight were observed in any of the study groups.

Primary and Secondary End Points

Change in A1C

At 3 years, the rtCGM+MDI and rtCGM+CSII groups had significantly lower A1C (7.0% [53 mmol/mol], $P = 0.0002$, and 6.9% [52 mmol/mol], $P < 0.0001$, respectively), compared with the SMBG+MDI and SMBG+CSII groups (8.0% [64 mmol/mol], $P = 1.000$, and 7.7% [61 mmol/mol], $P = 0.3574$, respectively). No significant differences in A1C between the rtCGM+MDI and rtCGM+CSII groups ($P = 0.61$) or SMBG+MDI and SMBG+CSII ($P = 0.69$) were observed.

Significant reductions in A1C were seen in the rtCGM+MDI and rtCGM+CSII groups at all follow-up visits throughout the 3-year study period (Fig. 1 and Table 2). Significant A1C reductions were seen in the SMBG+CSII group only at month 12 ($P = 0.0183$); no significant reductions were seen in the SMBG+MDI group. Supplementary Table 1 presents A1C changes in each study group at all study visits.

Forty-eight percent ($n = 23$) of SAIR participants achieved <7.0% A1C at 3 years (rtCGM+MDI, 43% [$n = 9$]; rtCGM+CSII, 56% [$n = 14$]) compared with 9% ($n = 2$) of SMBG+CSII and 16% ($n = 3$) of SMBG+MDI participants.

Between-group comparisons of A1C changes showed significant differences between the SAIR and SMBG groups at 3 years, favoring use of rtCGM (Table 3). No significant differences between the SAIR subgroups or SMBG subgroups were observed.

Significant differences between the rtCGM+MDI group and SMBG groups were observed beginning at month 6, whereas the differences between the rtCGM+CSII group and SMBG groups were observed beginning at month 3.

Average Sensor Glucose

Significant differences in improvements in average sensor glucose were seen in the rtCGM+MDI and rtCGM+CSII groups but not in the SMBG+CSII or SMBG+MDI groups (Table 3). No significant between-group differences within the SAIR or SMBG subgroups were observed.

Glycemic Variability

Significant differences in glycemic variability were observed between rtCGM+MDI versus SMBG+MDI, rtCGM+CSII versus SMBG+MDI, and SMBG+CSII versus SMBG+MDI (Table 3). No significant differences were seen between rtCGM+MDI and rtCGM+CSII. Significant improvements in time in range and time spent in hypoglycemia were observed at 3 years in the rtCGM+MDI, rtCGM+CSII, and SMBG+CSII groups but not the SMBG+MDI group (Fig. 2).

Time in Range

Improvements in time in range (70–180 mg/dL [3.9–10.0 mmol/L]) among SAIR subgroups were significantly greater than observed in the SMBG subgroups: rtCGM+MDI versus SMBG+MDI, 14.21% (95% CI 6.45 to −22, $P = 0.0007$); rtCGM+MDI versus SMBG+CSII, 11.13% (95% CI 4.46–17.81, $P = 0.0016$); rtCGM+CSII versus SMBG+MDI, 17.58% (95% CI 10.9–24.27, $P < 0.0001$); and rtCGM+CSII versus SMBG+CSII, 14.5% (95% CI 8.82–20.19, $P < 0.0001$). No differences were seen between the rtCGM+MDI and rtCGM+CSII groups. Significant reductions in percentage of time below range (<70 mg/dL [<3.9 mmol/L]) were seen in the rtCGM+MDI ($P = 0.0387$) and rtCGM+CSII ($P = 0.0235$) groups but not the SMBG+CSII (0.4847) or SMBG+MDI ($P = 1.000$) groups (Fig. 2).

Insulin Boluses

At study end, the average number of boluses per day was lower in both SMBG groups in comparison with the rtCGM groups (6.9 ± 1.9 vs. 4.5 ± 1.1, $P < 0.0001$). A higher frequency of boluses was seen in participants with SMBG+CSII versus the self-reported boluses in the SMBG+MDI group (4.9 ± 1.2 vs. 4.1 ± 0.8, $P = 0.02$). No significant difference between rtCGM+CSII and rtCGM+MDI was observed (7.1 ± 1.9 vs. 6.6 ± 1.9, $P = 0.4$) (Supplementary Table 2).

rtCGM Use

Mean percentage use of rtCGM in the SAIR groups was high throughout the study period, with slight but notable increases from year 1 (rtCGM+MDI, 85.7 ± 9%; rtCGM+CSII, 86.7 ± 10%) to year 3 (rtCGM+MDI, 88.0 ± 8%; rtCGM+CSII, 87.0 ± 8%). No significant differences between the subgroups were observed (Supplementary Table 2).

SMBG Use

The average frequency of fingerstick tests performed per day was lower in the SAIR group compared with the SMBG group (3.0 ± 0.9 vs. 3.8 ± 1.2, $P = 0.001$). It is important to note that the rtCGM devices required twice daily calibration with fingerstick testing. Within the SAIR group, daily SMBG frequency

was significantly lower among Dexcom G4 sensor users ($n = 32$) compared with Medtronic Enlite sensor users ($n = 14$): 2.7 ± 0.6 vs. 3.9 ± 0.8, $P < 0.001$ (Supplementary Table 2).

Adverse Events

Seven severe episodes of hypoglycemia were reported during the 3-year study period: two within the SMBG+CSII group, three in the SMBG+MDI group, one within the rtCGM+CSII group (which occurred when the participant was not wearing the sensor), and one within the rtCGM+MDI group. Three episodes of ketoacidosis occurred: one in the SMBG+CSII group, one in the SMBG+MDI group, and one in the rtCGM+CSII group; all cases were adjudicated. Four allergic reactions to sensor wear occurred but did not result in study discontinuation. No infections requiring assistance were reported during the 3-year study period.

CONCLUSIONS

To our knowledge, this is the first prospective, real-world, 3-year study to simultaneously compare four different treatment strategies based on different combinations of glucose monitoring systems and insulin delivery methods. As reported here, use of rtCGM among adults with T1D treated with MDI or CSII therapy was associated with 3 years of sustained improvements from baseline in A1C, glycemic variability, and time in range, with significantly greater reductions in time spent below range (<70 mg/dL [<3.9 mmol/L]); both time in range and time below range are now emerging as important metrics of glycemic control. Importantly, we observed comparable improvements in both the rtCGM+CSII and rtCGM+MDI groups, suggesting equivalent efficacy regardless of the insulin delivery method used.

Although similar improvements in glycemic control have been shown in previous RCTs (7–13), our findings demonstrate the long-term sustainability of rtCGM use, its clinical benefits, and its implications regarding medication adherence within the context of real-world diabetes self-management. The consistently high percentage of time that participants wore their sensors during the 3-year study period suggests that rtCGM was perceived to be a valuable tool in

Table 3—Between-group differences in A1C, average sensor glucose, and glycemic variability (SD) at 3 years

Study groups	A1C, % (mmol/mol)			Average sensor glucose, mg/dL (mmol/L)			Glycemic variability, mg/dL (mmol/L)		
	Difference	95% CI	*P* value	Difference	95% CI	*P* value	Difference	95% CI	*P* value
rtCGM+MDI vs. SMBG+MDI	−0.87 (−9.5)	−1.38 to −0.35 (−15.2 to −3.8)	0.0016	−27.0 (−1.51)	−42.3 to 12.24 (−2.35 to −0.68)	0.0007	−12.24 (−0.68)	−18.36 to 5.94 (−1.02 to −0.33)	0.0003
rtCGM+MDI vs. SMBG+CSII	−0.78 (−8.5)	−1.23 to −0.33 (−13.4 to −3.6)	0.0011	−21.1 (−1.17)	−32.76 to 9.18 (−1.82 to −0.51)	0.0009	−4.5 (−0.25)	−10.62 to 1.44 (−0.59 to −0.08)	0.14
rtCGM+MDI vs. rtCGM+CSII	0.12 (1.3)	−0.35 to 0.59 (−3.8 to 6.4)	0.61	1.98 (0.11)	−10.44 to 14.4 (−0.58 to 0.8)	0.75	−0.18 (−0.01)	−6.3 to 5.76 (−0.35 to 0.32)	0.95
rtCGM+CSII vs. SMBG+MDI	−0.99 (−10.8)	−1.45 to −0.52 (−15.8 to −5.7)	<0.0001	−29.2 (−1.62)	−42.66 to −15.84 (−2.37 to −0.88)	<0.0001	−12.06 (−0.67)	−18.54 to 5.58 (−1.03 to 0.31)	0.0006
rtCGM+CSII vs. SMBG+CSII	−0.9 (−9.8)	−1.3 to −0.5 (−14.2 to −5.5)	<0.0001	−23.0 (−1.28)	−33.48 to −12.6 (−1.86 to −0.7)	<0.0001	−4.32 (−0.24)	−10.62 to 1.98 (−0.59 to −0.11)	0.17
SMBG+CSII vs. SMBG+MDI	−0.09 (−1.0)	−0.52 to 0.35 (−5.7 to 3.8)	0.69	−6.2 (−0.35)	−19.08 to 6.66 (−1.06 to 0.37)	0.33	−7.56 (−0.42)	−14.04 to 1.26 (−0.78 to −0.07)	0.02

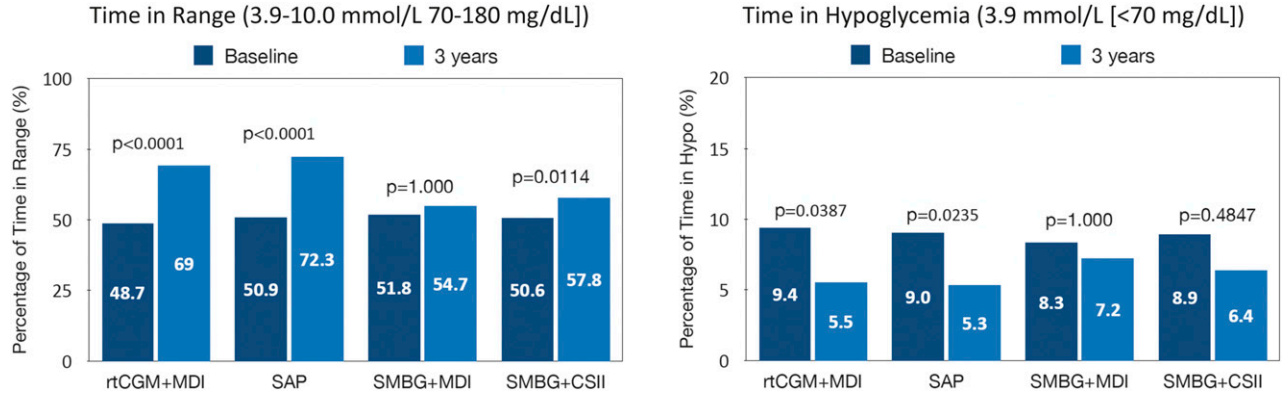

Figure 2—Changes in percentage of time in range and time in hypoglycemia. SAP, sensor-augmented pump.

their self-management regimens, and it may also explain the significant increase in the number of daily boluses observed in the SAIR groups; no changes in daily bolusing were seen in the SMBG groups. Additionally this persistence in CGM use correlates with the increased number of participants getting to the goal, suggesting the perceived value translated into improved clinical outcomes.

From a clinical perspective, the glycemic improvements observed among rtCGM users will likely lead to significant reductions in long-term complications (21). However, our findings also have important implications for payers. As reported by Gilmer et al. (22), a 1.0% reduction in A1C from 8.0% to 7.0% is associated with ~$820 in savings over 3 years in adults with diabetes but without heart disease and hypertension; the savings are even greater when one or both of these comorbidities are present.

In addition to the long duration of assessment, another strength is the use of a real-world study design. Although the efficacy and clinical utility of rtCGM have been demonstrated in numerous RCTs (7–13), they do not necessarily reflect the behaviors and clinical responses of participants in real life because RCTs strictly control the setting and delivery of interventions to minimize the effect of external factors on outcomes (16–18). Nor do they inform us about the long-term sustainability and clinical impact of rtCGM use beyond the defined study durations. In our study, we allowed participants to choose the insulin/monitoring option that met their individual needs, which reflects real-life decision-making in most clinical practices.

Additionally, an increasing number of payers and regulatory agencies are recognizing the inherent limitations of RCTs in providing real-world evidence (RWE) about the efficacy of medications and use of medical devices in clinical practice. As such, they are now focusing on RWE to inform their decisions. For example, both the U.S. Food and Drug Administration and European Medicines Agency are asking manufacturers to provide RWE in combination with RCT findings when evaluating both the short- and long-term safety and effectiveness of new drug and medical device submissions, particularly in the assessment of medical devices in real-world clinical practice (23–26).

The study has notable limitations. Because this was a nonrandomized study, it is possible that there were some unmeasured factors that could impact our findings. For example, it is possible that the more motivated study participants may have selected to use rtCGM. Although one would expect motivated participants to achieve greater improvements than participants who are less motivated, we observed no significant between-group differences in motivation. Because all subjects were willing to participate in a "Dose Adjustment for Normal Eating (DAFNE)-like" 4-day training program, motivation likely only had a minor impact on results, if any. Moreover, if we had not allowed participants to choose the regimens that met their individual needs and preferences, we would have likely seen a much higher discontinuation rate, which would have resulted in a gradual loss in our ability to describe differences between study groups. Another potential limitation is that different types of insulin pumps and rtCGM systems were used in this study. However, as reported, changes in A1C between the study subgroups were comparable, which suggests that device differences did not impact our findings. Additionally, with the exception of patients with insulin pumps (CGM+CSII and SMBG+CSII groups), all bolusing data gathered from the other study groups were self-reported. Although it is possible that participants may have overreported their bolusing frequency, given the higher number of boluses within the rtCGM groups, which appear to correlate with better glycemic outcomes versus SMBG groups, we believe the impact of overreporting was minimal.

Importantly, our findings demonstrate that the use of rtCGM with MDI can be considered an equivalent but more cost-effective treatment alternative to sensor-augmented insulin pumps for many individuals with T1D. For example, in a recent analysis of the Multiple Daily Injections and Continuous Glucose Monitoring in Diabetes (DIAMOND) trial (8), Skandari and colleagues (27) found that among rtCGM+CSII participants, the total per-person 28-week costs were $8,272 vs. $5,623 among rtCGM+MDI users; the difference was primarily attributed to CSII use. The increasing focus on reducing costs while improving outcomes may impact reimbursement decisions regarding current and future sensor-augmented insulin pump systems.

In conclusion, in individuals with T1D with suboptimal glycemic control, use of rtCGM was superior to SMBG in reducing A1C, hypoglycemia, and the other end points regardless of the insulin delivery method used; both methods provided comparable glycemic benefits. Our findings may provide guidance to clinicians

when discussing treatment/monitoring options with their participants.

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