Sustained Impact of Real-time Continuous Glucose Monitoring in Adults With Type 1 Diabetes on Insulin Pump Therapy: Results After the 24-Month RESCUE Study

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OBJECTIVE

In recent years, a growing number of people with type 1 diabetes gained access to real-time continuous glucose monitoring (rtCGM). Long-term benefits of rtCGM are unclear because of a lack of large studies of long duration. We evaluated whether real-world rtCGM use up to 24 months offered benefits, particularly in those living with impaired awareness of hypoglycemia (IAH).

RESEARCH DESIGN AND METHODS

This 24-month, prospective, observational cohort study followed 441 adults with insulin pumps receiving full reimbursement for rtCGM. Forty-two percent had IAH. The primary end point was evolution of HbA_{1c}, with secondary end points change in acute hypoglycemia complications, diabetes-related work absenteeism, and quality of life scores. Additionally, we evaluated whether people could achieve glycemic consensus targets during follow-up.

RESULTS

After 24 months, HbA_{1c} remained significantly lower compared with baseline (7.64% [60 mmol/mol] vs. 7.37% [57 mmol/mol], $P < 0.0001$). Sustained benefits were also observed for the score on the hypoglycemia fear survey and hypoglycemia-related acute complications irrespective of hypoglycemia awareness level. People with IAH had the strongest improvement, especially for severe hypoglycemia (862 events in the year before vs. 119 events per 100 patient-years in the 2nd year, $P < 0.0001$). Over 24 months, more people were able to meet hypoglycemia consensus targets at the expense of slightly fewer people achieving hyperglycemia consensus targets. Furthermore, the number of people with HbA_{1c} <7% (<53 mmol/mol) without severe hypoglycemia events more than doubled (11.0% vs. 25.4%, $P < 0.0001$).

CONCLUSIONS

Use of rtCGM led to sustained improvements in hypoglycemia-related glucose control over 24 months. Lower fear of hypoglycemia, fewer acute hypoglycemia-related events, and fewer diabetes-related days off from work were observed, particularly in those with IAH.

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Achieving optimal glycemic control remains a challenge for people living with type 1 diabetes, despite rapid advancements in insulin administration technology and better insulin preparations (1). Therefore, the development of strategies and technological tools to lessen the burden of diabetes management with favorable results on metabolic control and quality of life is a continuous endeavor.

In recent years, more and more people living with diabetes have access to real-time continuous glucose monitoring (rtCGM), which has shown both in randomized controlled and observational trials that it improves glucose control and quality of life in people treated with multiple daily insulin injections (MDI) (2–6) or continuous subcutaneous insulin infusion (CSII) (6–12). However, randomized controlled trials are often of short duration (typically 6 months), making it less clear how much of the observed effects are due to heightened motivation of trial participants. In addition, longer-term observational studies often lack sufficient patient numbers to generalize the outcomes to the broader community of people with type 1 diabetes (6,12).

Since September 2014, rtCGM has been reimbursed in Belgium for people with type 1 diabetes who use CSII and are treated in selected specialized diabetes centers. We previously reported 12-month findings from the Reimbursement Study of Continuous Glucose Monitoring in Belgium (RESCUE) study (13). At the start of rtCGM, the RESCUE population had suboptimal glucose control with a high incidence of acute hypoglycemia-related complications, which was also reflected in lower perceived quality of life compared with a general population with type 1 diabetes (14). We reported that 12-month use of rtCGM led to improved glycemic control and fewer hypoglycemia-related hospitalizations and diabetes-related days off from work, with a significant cost reduction. Our aim in the current analysis was to determine whether the observed benefits could be sustained up to 24 months for the total population, with additional specific attention to people with impaired awareness of hypoglycemia (IAH) because they are at higher risk of severe hypoglycemia (15,16).

RESEARCH DESIGN AND METHODS

Study Design

This multicenter, prospective, observational, cohort study evaluated the impact of nationwide reimbursement of rtCGM systems for adults with type 1 diabetes on CSII therapy. The results from the full 24 months of the study are reported here and consist of the first 12-month period from which the results have been published (13) followed by an additional 12-month extension phase. The study was conducted from September 2014 to March 2019.

The study complied with the Declaration of Helsinki and the International Conference on Harmonization/Good Clinical Practice Guidelines and was approved by the institutional review boards and independent ethics committees of the participating centers. All participants provided informed consent before entering the study.

Study Participants

Originally, a total of 515 adults started in the reimbursement program and were included in the previous analysis (13). Since four centers stopped collecting data after 12 months, only participants of the 13 centers that collected data up to 24 months ($n = 441$) were included in this analysis. Minimum criteria to receive reimbursement were previously reported (13). Basically, the specialized diabetes centers were free to decide to which adults with type 1 diabetes on CSII they would offer rtCGM reimbursement. Every person who entered the reimbursement program between September 2014 and January 2017 was included, without exception, in the study after informed consent.

Outcomes

The primary end point was evolution over time of HbA_{1c} between baseline and 24 months after the start of rtCGM reimbursement. Secondary end points were effect of rtCGM on acute diabetes complications (hypoglycemia and/or ketoacidosis), work absenteeism, quality of life, proportion of participants with HbA_{1c} <7% (<53 mmol/mol), and reasons for discontinuing rtCGM. Additional post hoc analyses examined how many participants reached clinical consensus targets (17) and clinical composite end points (18).

Devices and Education

There was no restriction in the devices participants could use in the reimbursement program. Participants were able to switch between insulin pump and glucose sensor brands or switch to newer versions. This led to a shift from low-glucose threshold suspend systems that were used at the start of the study toward low-glucose predictive suspend systems at the end (Supplementary Table 1).

In the Belgian rtCGM reimbursement program, 5 h of specialized education required for the correct application of rtCGM were provided in the first 4 months of the program followed by an additional 1 h of specialized education per 12 months of follow-up, in addition to standard-of-care diabetes education. Specialized education in the rtCGM reimbursement program taught participants how to use rtCGM, including all aspects of monitoring, as well as how to react to the obtained glycemic values.

Data Collection

Prespecified clinical data were collected from a period of 12 months before until 24 months after the start of the reimbursement program. Information about clinical parameters was collected from clinical files at baseline and 4, 8, 12, and 24 months. HbA_{1c} levels were averaged for prespecified time points: prereimbursement/baseline (before = −12 months until −1 day), 4 months (±2 months), 8 months (±2 months), 12 months (±2 months), and 24 months (±2 months) after start of reimbursement.

Questionnaires (36-Item Short Form Health Survey [19], Problem Areas in Diabetes Short Form [20], and Hypoglycemia Fear Survey [HFS] worry subscale [21]) and standardized diaries (13) were completed at baseline and after 12 and 24 months and scored manually. For patient-reported days off from work, all reasons owing to diabetes were taken into account without differentiating between hypo- and hyperglycemia but excluding consultation appointments with the diabetes team. Patient-reported emergency department admissions and hospitalizations for hypoglycemia (any event) and/or proven ketoacidosis were validated using hospital records in the individual centers.

rtCGM data were collected using the designated diabetes management software from the various manufacturers. Data for the following time points were extracted and averaged: data from entry in the reimbursement program (2 weeks = week 0 until week 2), 4 months

(±2 months), 8 months (±2 months), 12 months (±2 months), and 24 months (±2 months) after start of reimbursement. An overview of data completeness is available in Supplementary Table 2.

Statistical Analysis

For data analysis, the full analysis set was used, which comprised all patients who were registered as receiving reimbursement for rtCGM in 1 of the 13 centers. In total, 441 adults were included in the analysis, which gave, even with the observed drop-out rate, enough power (>80%) with a two-sided 5% significance level to detect a mean difference in HbA_{1c} of 0.3% (4 mmol/mol).

Using a linear mixed model, we evaluated HbA_{1c} and quality of life, as a function of time, with a random effect of center to handle the correlation between patients of the same center and an unstructured covariance matrix for the five or three repeated measurements within the same patient. By using a linear mixed model, patients with missing data still contributed to the analyses. For evolution of HbA_{1c}, values at 4, 8, 12, and 24 months were compared with the average value from −12 months until −1 day (before = baseline). For evolution of quality of life, scores on the different questionnaires at 12 and 24 months were compared with the scores at the start of reimbursement. From the multivariable normal distribution implied by the linear mixed model, we derived the relation between baseline HbA_{1c} and changes in HbA_{1c} versus baseline. Taking regression to the mean into account, the obtained correlation is not tested versus 0 but versus the correlation, which is already expected purely on the basis of regression to the mean (22). A logistic regression model with generalized estimating equations was used to evaluate the evolution of proportion of participants who reached target HbA_{1c} (<7% [53 mmol/mol]), who reached clinical consensus targets, who reached composite end points (17,18), with hospitalizations for hypoglycemia or ketoacidosis, with diabetes-related work absenteeism, and with acute hypoglycemic events. Differences in days of diabetes-related work absence, number of hospitalizations for hypoglycemia or ketoacidosis, and acute hypoglycemic events per 100 patient-years were assessed with a negative binomial generalized estimating equation model. Participants who were incapable of working because of disability were excluded.

A Bonferroni-Holm correction was considered for results at 24 months referring to the primary outcome: evolution of HbA_{1c} for the total population. No adjustment was made for multiple testing of secondary end points.

Post hoc, all analyses were repeated for participants with and without IAH. HbA_{1c} evolution was also assessed for groups of baseline HbA_{1c}. The number of participants in these subgroups at baseline and 4, 8, 12, and 24 months is shown in Supplementary Table 3. Differences between the subgroups at different time points were compared using the Mann-Whitney *U* test for continuous data and with the χ^2 test for dichotomous data. Statistical analyses were performed using SPSS for Windows software (IBM Corporation, Armonk, NY).

RESULTS

Patient Characteristics and rtCGM Use

Baseline characteristics of the 441 participants are shown in Supplementary Table 4. In short, the majority was highly educated and had a long history of type 1 diabetes. On average, they had 6 years of CSII experience at baseline, 56% had hypoglycemia as indication to start rtCGM, and 44% had IAH.

Of 441 adults who started rtCGM in 1 of 13 centers, 87.8% (n = 387) and 81.6% (n = 360) had >12 and 24 months of follow-up, respectively. In total, 81 participants (18.4%) stopped using rtCGM (Supplementary Fig. 1). Participants could have multiple reasons for deciding to stop rtCGM. The most frequent reason for discontinuation was related to the system itself, such as alarm fatigue (n = 27 [6%]). Other reasons were local and/or technical problems (n = 20 [5%]), no apparent benefit for patient and/or physician (n = 20 [5%]), and <70% usage of rtCGM (n = 17 [4%]).

Mean percentage of rtCGM wear time was high throughout the 24 months and remained stable, with 87.1 ± 9.6%, 86.6 ± 8.4%, 86.9 ± 9.5%, and 87.1 ± 10.4% at 4, 8, 12, and 24 months, respectively.

Evolution of HbA_{1c}

For the total population, HbA_{1c} was significantly lower at 24 months (7.37% [95% CI 7.19–7.55] [57 mmol/mol (55–59)]) compared with baseline (7.64% [7.46–7.82] [60 mmol/mol (58–62)], P < 0.0001), and was stable compared with 12 months (7.34% [7.16–7.52] [57 mmol/mol (55–59)], P = 0.316) (Fig. 1*A*). A stronger decrease in HbA_{1c} was observed in participants with higher baseline HbA_{1c}, although this correlation never exceeded the regression to the mean effect (Fig. 1*B*). There was no difference in evolution of HbA_{1c} for participants with and without IAH (Fig. 1*C*).

Change in Acute Diabetes Complications and Work Absenteeism

The prevalence of acute diabetes complications was lower throughout the study than in the year before. This was already apparent in the 1st year, but was confirmed in the 2nd year. The largest benefit was seen for hypoglycemia-related events for which we gathered data on different levels, from hospitalizations for any hypoglycemic event to receiving glucagon. In some cases, this may have led to a simultaneous decrease in diabetes-related work absenteeism (Table 1).

The decline in hypoglycemia-related events was seen in participants with and without IAH, but those with IAH had higher baseline prevalence and a larger proportion of reduction at follow-up than those with normal hypoglycemia awareness (Fig. 2). Participants with IAH missed, on average, 709 days of work per 100 patient-years in the year before the study, which dropped significantly to 107 days after 24 months (P < 0.0001). For those with normal awareness, this reduced to a lesser extent from 264 days in the year before to 66 days per 100 patient-years at 24 months (P = 0.048).

Change in Quality of Life

For the total population, previously observed improvements in general quality of life, as measured by the 36-Item Short Form Health Survey, were sustained throughout the 24-month study. Problem Areas in Diabetes Short Form scores overall decreased by −1.3 points (95% CI −1.7 to −0.9, P < 0.0001), and the worry subscale of HFS was also lower through 24 months of follow-up (18.3 [16.7–19.9] at baseline vs. 14.1 [12.5–15.7] after 24 months, P < 0.0001) (Supplementary Table 5).

Both those with and those without IAH showed improvement in quality of life scores. However, improvement in

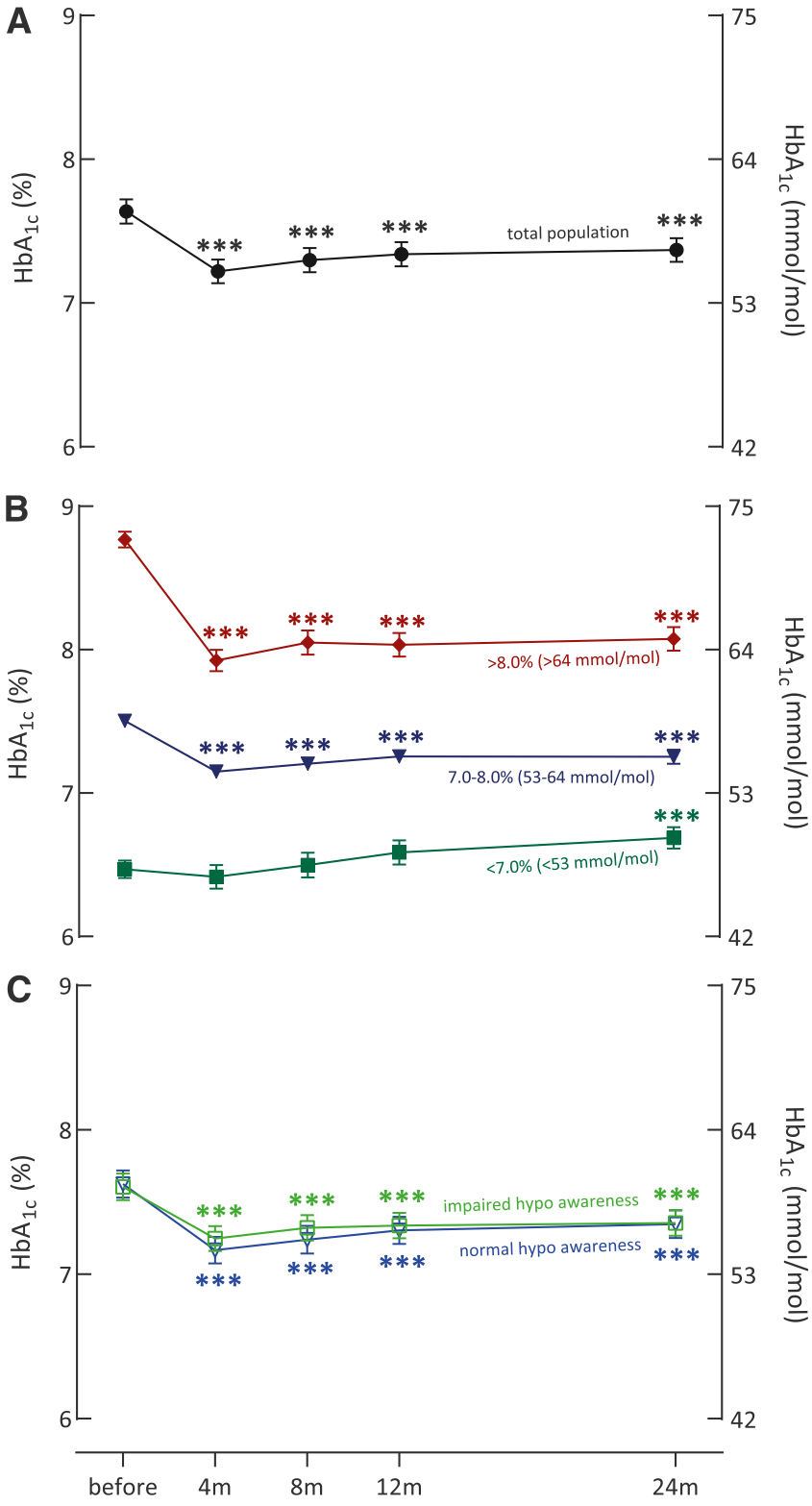

Figure 1—Evolution of HbA_{1c}. Data points represent least squares mean (SE) of HbA_{1c} measurements per time point for the total population (*A*), as a function of baseline HbA_{1c} (*B*), and as a function of degree of awareness of hypoglycemia (*C*). In panel *B*, the correlation between baseline HbA_{1c} and the change in HbA_{1c} did not exceed the regression to the mean effect. ***$P < 0.001$, for the comparisons vs. baseline HbA_{1c}. HbA_{1c} follow-up *P* values are still significantly different from baseline after Bonferroni-Holm correction. m, months.

participants with IAH tended to be higher partly because of the lower perceived quality of life at baseline. This is particularly evident for the HFS worry subscale, for which they had worse baseline scores (20.7 ± 10.8 vs. 16.2 ± 9.5 for IAH vs. non-IAH, respectively, $P < 0.0001$) and were able to bring them closer to the level of those without IAH during follow-up (Supplementary Table 5).

Meeting Glycemic Targets

Because of the observational real-world study design, no blinded glucose measuring period was available. Therefore, we report on the percentage of participants who reached the clinical consensus targets as measured by rtCGM from the first 2 weeks until 24 months onward. For HbA_{1c} targets, data were available up to 1 year before start.

Compared with the year before rtCGM reimbursement, more participants were able to obtain HbA_{1c} below the target level of 7% (53 mmol/mol) (Table 2). More participants could attain the targets of time spent <70 mg/dL (<3.9 mmol/L) and <54 mg/dL (<3.0 mmol/L) after 24 months (Table 2). Of those who did not reach these hypoglycemia consensus targets in the first 2 weeks, 53.8% and 48.4% did reach the targets for time <54 mg/dL (<3.0 mmol/L) and <70 mg/dL (<3.9 mmol/L) after 24 months, respectively.

The proportion of participants who reached consensus targets of time in range (TIR) and time >250 mg/dL (>13.9 mmol/L) did not significantly change with even a trend toward a small reduction during follow-up. However, a significant reduction was observed in the number of participants who spent <25% of time >180 mg/dL (>10.0 mmol/L) (Table 2).

The number of participants who reached the combined end points of HbA_{1c} <7% (<53 mmol/mol) with <1% of time spent <54 mg/dL (<3.0 mmol/L) and HbA_{1c} <7% (<53 mmol/mol) without severe hypoglycemic episodes more than doubled during the study. This was not observed for the combined end points with TIR (Table 2).

Both participants with and participants without IAH benefited from rtCGM, with increased proportions in both groups achieving the predefined targets for hypoglycemia throughout 24 months of follow-up. While there were no differences within or between groups for

Table 1—Diabetes-related acute complications and work absenteeism for the total population

	Year before	0–12 months	*P* value*	12–24 months	*P* value*
Participants with					
Hospitalizations because of hypoglycemia and/or ketoacidosis	65 (14.7)	13 (3.4)	<0.0001	11 (3.1)	<0.0001
Hospitalizations because of hypoglycemia	50 (11.3)	11 (2.8)	<0.0001	7 (1.9)	<0.0001
Hospitalizations because of ketoacidosis	18 (4.1)	3 (0.8)	0.002	5 (1.4)	0.007
Work absenteeism	107 (24.3)	38 (9.8)	<0.0001	24 (6.7)	<0.0001
Help from third parties because of hypoglycemia	183 (41.5)	56 (14.5)	<0.0001	46 (12.8)	<0.0001
Hypoglycemic comas	76 (17.2)	21 (5.4)	<0.0001	13 (3.6)	<0.0001
Hypoglycemia with seizure	33 (7.5)	9 (2.3)	<0.0001	8 (2.2)	<0.0001
Needing glucagon	88 (20.0)	18 (4.7)	<0.0001	14 (3.9)	<0.0001
Needing help from ambulance because of hypoglycemia	67 (15.2)	13 (3.4)	<0.0001	7 (1.9)	<0.0001
Number of events per 100 patient-years of					
Hospitalizations because of hypoglycemia and/or ketoacidosis	22.2	3.9	<0.0001	3.9	<0.0001
Hospitalizations because of hypoglycemia	17.7	2.8	<0.0001	1.9	<0.0001
Hospitalizations because of ketoacidosis	4.5	1.0	0.006	1.9	0.019
Help from third parties because of hypoglycemia	488.7	66.4	<0.0001	77.5	<0.0001
Hypoglycemic comas	74.4	15.8	<0.0001	10.8	<0.0001
Hypoglycemia with seizure	22.9	6.7	0.002	7.2	0.026
Needing glucagon	65.3	20.9	<0.0001	15.6	<0.0001
Needing help from ambulance because of hypoglycemia	24.9	3.6	<0.0001	2.5	<0.0001
Number of days per 100 patient-years of					
Work absenteeism	456.3	240.3	0.011	84.4	0.003

Data are *n* (%) or *n*. Patient-reported hospital admissions were validated by clinicians. **P* value for change vs. baseline.

targets of TIR and hyperglycemia, more participants with normal awareness reached consensus targets for hypoglycemia than those with IAH (Supplementary Table 6).

CONCLUSIONS

This study tried to provide more insight into how people with type 1 diabetes use advanced technology to manage their diabetes and how this influences daily life in the long run. To our knowledge, the RESCUE study is the largest and one of the longest prospective real-world cohort studies to assess clinical and patient-reported outcome measures after initiation of rtCGM reimbursement in the long term. As reported here, rtCGM use by adults with type 1 diabetes on CSII therapy followed in 13 specialized centers was associated with 24 months of sustained improvements in HbA_{1c}; quality of life, especially for fear of hypoglycemia; and acute hypoglycemic events.

Although the clinical benefits of rtCGM have been demonstrated in numerous randomized controlled trials (2–5,7–9), the trials often lacked sufficient length to inform us about the long-term sustainability and clinical impact of rtCGM use. Moreover, stringent inclusion and exclusion criteria often preclude high-risk populations from participation. Therefore, real-world evidence is needed to evaluate the long-term effectiveness of already-approved technology (23,24). To our knowledge, RESCUE is the largest prospective real-world study where adults with type 1 diabetes were followed for 2 years while using rtCGM, which allowed us to distinguish study effects from sustained benefits. Only two other prospective observational studies were of longer duration. First, the prospective Comparison of Sensor-Augmented Insulin Regimens (COMISAIR) study followed 94 people divided into four groups (rtCGM + CSII, rtCGM + MDI, capillary tests + CSII, and capillary tests + MDI) and lasted 3 years (6). The investigators showed that rtCGM combined with CSII or MDI were equally superior to capillary finger stick tests with CSII or MDI regarding HbA_{1c} and time spent in hypoglycemia. Second, a study by Gómez et al. (12) prospectively followed 111 adults with type 1 diabetes starting sensor-augmented pump therapy because of hypoglycemia. Mean follow-up time was 47 months, with only 50 patients followed for >40 months. This poorly controlled population could achieve an HbA_{1c} reduction of −1.7% (−19 mmol/mol) together with a reduction in severe hypoglycemic events. In addition to these studies, our study provided an association between rtCGM use in a large population and the long-term sustainability of its benefits regarding clinical and patient-reported outcome measures within the context of real-world diabetes self-management and sufficient diabetes education (25).

Because the diverse risks of recurrent and severe hypoglycemia have been identified in the literature (26), it is important that hypoglycemia is prevented through the use of rtCGM. In the unique Belgian rtCGM reimbursement system (13), the diabetes teams, independently of each other or of predefined criteria, selected a population with a high prevalence of hypoglycemia-related acute complications, which is now included as a main indication for rtCGM reimbursement by other countries (27) and is acknowledged by the international community as one of the most important factors contributing to why people should use continuous glucose sensors (18). Our results show that the number of clinically severe hypoglycemic events can be markedly reduced by use of rtCGM. Importantly, the improvement in HbA_{1c} indicates that hypoglycemia reduction was not achieved at the expense of a deterioration of overall glycemic control. Together with findings from other studies addressing the use of rtCGM in adults prone to

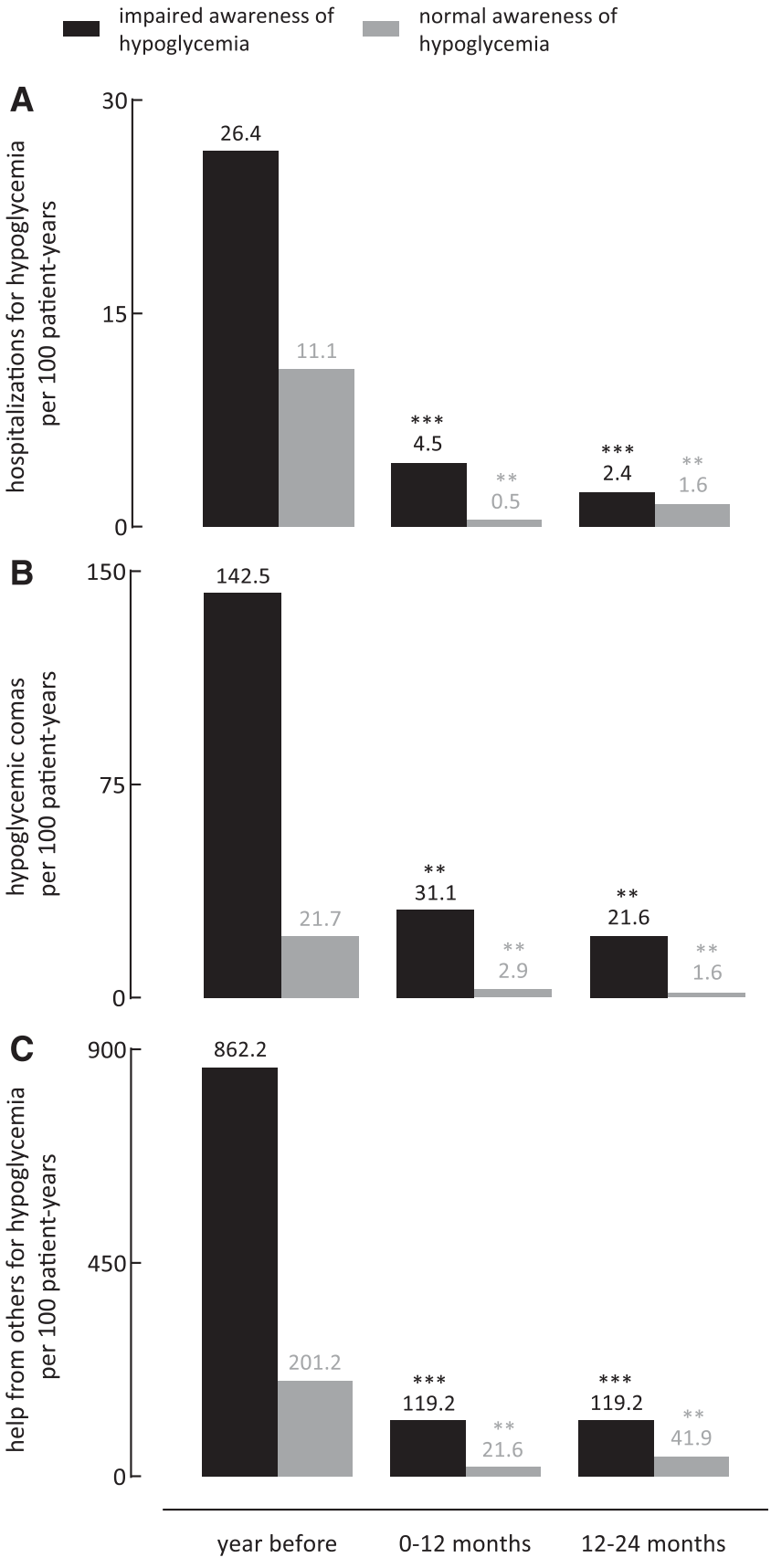

Figure 2—Hypoglycemia-related acute complications for participants with and without IAH. Data points represent number of events per 100 patient-years of hypoglycemia-related hospitalizations (*A*), hypoglycemic comas (*B*), and help from third parties because of hypoglycemia (*C*). $^{**}P < 0.01$, $^{***}P < 0.001$ vs. baseline.

hypoglycemia, this indicates that rtCGM can effectively address problematic hypoglycemia in people treated by MDI as well as by CSII (4,7,9,12).

In the RESCUE population, 44% of participants had IAH in varying degrees. This is two to three times more than what has been described in the type 1 diabetes community (14,16). It was apparent from frequencies of hypoglycemia-related hospitalizations and severe hypoglycemic events that participants with IAH had a higher risk of developing such acute complications, something that has already been described previously by others (16,28,29). Previous studies have not found evidence that the use of rtCGM could improve hypoglycemia awareness (4,7). One study suggested that improvement in IAH can be achieved through structured education and frequent contact irrespective of the treatment modality or use of rtCGM (30). The effect of this structured education could even be maintained when people return to standard care, switch from CSII to MDI or vice versa, and do not wear their sensor for a sufficient amount of time (31). Therefore, the best option to effectively manage people with IAH is to implement a combination of rtCGM (with or without CSII per preference) and structured education with frequent follow-up contacts (32).

Our study reports on the proportion of people treated by rtCGM and CSII achieving the consensus targets for glycemic control (17) in real life. rtCGM and sensor-augmented pumps focus primarily on hypoglycemia avoidance, which helped in reaching the consensus targets for hypoglycemia in ~70% of the RESCUE population. Of note, our population gradually transitioned to devices with more advanced algorithms as they were introduced into the market during the duration of the study, which could have led to some being able to further prevent hypoglycemia. On the other hand, reaching targets for TIR and hyperglycemia proved to be more difficult, with barely 30% achieving the recommended levels. We even observed a small trend toward fewer participants achieving targets for TIR and hyperglycemia, an observation that has been previously described in studies with sensor-augmented pumps with the low-glucose predictive suspend feature (33,34). A possible reason for this finding may be attributed to how the

Table 2—Participants meeting glycemic targets in the total population

	Baseline	4 months	8 months	12 months	24 months	*P* value†
Clinical consensus targets						
HbA_{1c} <7% (<53 mmol/mol)	96 (21.9)	153 (37.1)	132 (35.7)	119 (31.8)	115 (32.8)	<0.0001
<1% of time spent <54 mg/dL (<3.0 mmol/L)*	186 (60.6)	238 (63.8)	213 (71.2)	222 (63.4)	214 (72.1)	0.001
<4% of time spent <70 mg/dL (<3.9 mmol/L)*	169 (55.0)	219 (58.7)	194 (65.1)	213 (61.0)	198 (66.2)	<0.0001
>70% of TIR*	94 (30.6)	103 (27.6)	81 (27.2)	84 (24.1)	76 (25.4)	0.099
<25% of time spent >180 mg/dL (>10.0 mmol/L)*	102 (33.2)	104 (27.9)	80 (26.8)	91 (26.1)	74 (24.7)	0.025
<5% of time spent >250 mg/dL (>13.9 mmol/L)*	108 (35.2)	112 (30.0)	83 (27.9)	105 (30.1)	83 (28.0)	0.111
Composite end points						
HbA_{1c} <7% (<53 mmol/mol) and <1% of time spent <54 mg/dL (<3.0 mmol/L)*	38 (9.4)	73 (18.6)	57 (17.0)	59 (16.1)	65 (19.5)	<0.0001
HbA_{1c} <7% (<53 mmol/mol) and no severe hypoglycemia	48 (11.0)	NA	NA	105 (28.5)	87 (25.4)	<0.0001
>70% TIR and <1% of time spent <54 mg/dL (<3.0 mmol/L)*	61 (19.9)	64 (17.2)	57 (19.1)	55 (15.7)	54 (18.1)	0.209
>70% TIR and no severe hypoglycemia*	54 (14.8)	NA	NA	64 (18.4)	60 (19.6)	0.214

Data are *n* (%). Percentage is based on the people who had data at that time point for those variables (different from the total population). NA, not applicable; TIR = 70–180 mg/dL (3.9–10.0 mmol/mol). *Baseline for this variable is the first 2 weeks after start. †*P* value for the evolution over the follow-up period.

patient manages a predictive insulin pump suspension, namely the consumption of carbohydrates in addition to insulin suspension to correct for a future hypoglycemic episode (34).

We incorporated quality-of-life questionnaires, which are powerful tools to inform other patients, clinicians, and policymakers (35). Management of type 1 diabetes is a daily task with a considerable burden on quality of daily living. An important driver of this burden is hypoglycemia because it can have a negative impact on relationships, sleep quality, employment, and body image as a result of heightened levels of stress and anxiety (36). We provide further evidence that hypoglycemia has debilitating effects on quality of life, as shown by the overall lower perceived health status at baseline of participants with IAH. Nevertheless, the use of technology that helps to identify and prevent hypoglycemia, in this case rtCGM, has proven to be a vital component to normalize daily life for these people, which has also been demonstrated in previous studies (2,4,7,9,11,31).

This study has limitations. First, the RESCUE study originally was a collaboration among 17 centers with a total of 515 participants. However, contribution of data was voluntary, and four centers found the workload too high to keep collecting the data, which contributed to the total drop-out rate of 30%. Therefore, for the complete analysis up to 24 months, we only used data of the 13 centers that contributed until the end of the study. Second, since RESCUE was a nonrandomized observational trial, it is possible that factors other than rtCGM use could affect the studied outcome measures. For example, it is possible that diabetes education that was provided when starting rtCGM sparked the motivation of participants to get their diabetes back on track, apart from rtCGM use. However, this peak in motivation is known to fade after some time (37). Nevertheless, we observed a sustained benefit even after 2 years, which contributes to the rationale that rtCGM instigates altered behavior. Finally, because of the real-world design, a variety of sensor-insulin pump combinations with different suspend features and levels of accuracy were used. This has to be taken into account, in particular when interpreting the hypoglycemia outcomes.

In conclusion, rtCGM led to improvements in hypoglycemia-related glucose control over 24 months in people with type 1 diabetes on an insulin pump. The sustained higher prevalence of people achieving the consensus targets for hypoglycemia, with fewer hypoglycemia-related acute episodes and diabetes-related days off from work, could have been an important factor in the improvement of quality of life, especially fear of hypoglycemia.

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References

1. Foster NC, Beck RW, Miller KM, et al. State of type 1 diabetes management and outcomes from the T1D Exchange in 2016-2018. Diabetes Technol Ther 2019;21:66–72
2. Lind M, Polonsky W, Hirsch IB, et al. Continuous glucose monitoring vs conventional therapy for glycemic control in adults with type 1 diabetes treated with multiple daily insulin injections: the GOLD randomized clinical trial. JAMA 2017;317:379–387
3. Beck RW, Riddlesworth T, Ruedy K, et al.; DIAMOND Study Group. Effect of continuous glucose monitoring on glycemic control in adults with type 1 diabetes using insulin injections: the DIAMOND randomized clinical trial. JAMA 2017;317:371–378
4. Heinemann L, Freckmann G, Ehrmann D, et al. Real-time continuous glucose monitoring in adults with type 1 diabetes and impaired hypoglycaemia awareness or severe hypoglycaemia treated with multiple daily insulin injections (HypoDE): a multicentre, randomised controlled trial. Lancet 2018;391:1367–1377
5. Polonsky WH, Hessler D, Ruedy KJ, Beck RW; DIAMOND Study Group. The impact of continuous glucose monitoring on markers of quality of life in adults with type 1 diabetes: further findings from the DIAMOND randomized clinical trial. Diabetes Care 2017;40:736–741
6. Šoupal J, Petruželková L, Grunberger G, et al. 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. Diabetes Care 2020;43:37–43
7. van Beers CAJ, DeVries JH, Kleijer SJ, et al. Continuous glucose monitoring for patients with type 1 diabetes and impaired awareness of hypoglycaemia (IN CONTROL): a randomised, open-label, crossover trial. Lancet Diabetes Endocrinol 2016;4:893–902
8. Battelino T, Conget I, Olsen B, et al.; SWITCH Study Group. The use and efficacy of continuous glucose monitoring in type 1 diabetes treated with insulin pump therapy: a randomised controlled trial. Diabetologia 2012;55:3155–3162
9. Bosi E, Choudhary P, de Valk HW, et al.; SMILE Study Group. Efficacy and safety of suspend-before-low insulin pump technology in hypoglycaemia-prone adults with type 1 diabetes (SMILE): an open-label randomised controlled trial. Lancet Diabetes Endocrinol 2019;7:462–472
10. Gómez AM, Henao DC, Imitola A, et al. Efficacy and safety of sensor-augmented pump therapy (SAPT) with predictive low-glucose management in patients diagnosed with type 1 diabetes mellitus previously treated with SAPT and low glucose suspend. Endocrinol Diabetes Nutr 2018;65:451–457
11. Nørgaard K, Scaramuzza A, Bratina N, et al.; Interpret Study Group. Routine sensor-augmented pump therapy in type 1 diabetes: the INTERPRET study. Diabetes Technol Ther 2013;15:273–280
12. Gómez AM, Marín Carrillo LF, Muñoz Velandia OM, et al. Long-term efficacy and safety of sensor augmented insulin pump therapy with low-glucose suspend feature in patients with type 1 diabetes. Diabetes Technol Ther 2017;19:109–114
13. Charleer S, Mathieu C, Nobels F, et al.; RESCUE Trial Investigators. Effect of continuous glucose monitoring on glycemic control, acute admissions, and quality of life: a real-world study. J Clin Endocrinol Metab 2018;103:1224–1232
14. Charleer S, De Block C, Van Huffel L, et al. Quality of life and glucose control after 1 year of nationwide reimbursement of intermittently scanned continuous glucose monitoring in adults living with type 1 diabetes (FUTURE): a prospective observational real-world cohort study. Diabetes Care 2020;43:389–397
15. Choudhary P, Geddes J, Freeman JV, Emery CJ, Heller SR, Frier BM. Frequency of biochemical hypoglycaemia in adults with Type 1 diabetes with and without impaired awareness of hypoglycaemia: no identifiable differences using continuous glucose monitoring. Diabet Med 2010;27:666–672
16. Geddes J, Schopman JE, Zammitt NN, Frier BM. Prevalence of impaired awareness of hypoglycaemia in adults with Type 1 diabetes. Diabet Med 2008;25:501–504
17. Battelino T, Danne T, Bergenstal RM, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. Diabetes Care 2019;42:1593–1603
18. Danne T, Nimri R, Battelino T, et al. International consensus on use of continuous glucose monitoring. Diabetes Care 2017;40:1631–1640
19. Ware JE. *SF-36 Health Survey: Manual and Interpretation Guide*. Boston, MA, The Health Institute, New England Medical Center, 1993
20. McGuire BE, Morrison TG, Hermanns N, et al. Short-form measures of diabetes-related emotional distress: the Problem Areas in Diabetes Scale (PAID)-5 and PAID-1. Diabetologia 2010;53:66–69
21. Gonder-Frederick LA, Schmidt KM, Vajda KA, et al. Psychometric properties of the hypoglycemia fear survey-ii for adults with type 1 diabetes. Diabetes Care 2011;34:801–806
22. Tu Y-K, Baelum V, Gilthorpe MS. The relationship between baseline value and its change: problems in categorization and the proposal of a new method. Eur J Oral Sci 2005;113:279–288
23. Resnic FS, Matheny ME. Medical devices in the real world. N Engl J Med 2018;378:595–597
24. Klonoff DC, Gutierrez A, Fleming A, Kerr D. Real-world evidence should be used in regulatory decisions about new pharmaceutical and medical device products for diabetes. J Diabetes Sci Technol 2019;13:995–1000
25. De Ridder F, den Brinker M, De Block C. The road from intermittently scanned glucose monitoring to hybrid closed-loop systems: part A. Keys to success: subject profiles, choice of systems, education. Ther Adv Endocrinol Metab 2019;10:2042018819865399
26. International Hypoglycaemia Study Group. Hypoglycaemia, cardiovascular disease, and mortality in diabetes: epidemiology, pathogenesis, and management. Lancet Diabetes Endocrinol 2019;7:385–396
27. Graham C. Continuous glucose monitoring and global reimbursement: an update. Diabetes Technol Ther 2017;19:S60–S66
28. White NH, Skor DA, Cryer PE, Levandoski LA, Bier DM, Santiago JV. Identification of type I diabetic patients at increased risk for hypoglycemia during intensive therapy. N Engl J Med 1983;308:485–491
29. Gubitosi-Klug RA, Braffett BH, White NH, et al.; Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Research Group. Risk of severe hypoglycemia in type 1 diabetes over 30 years of follow-up in the DCCT/EDIC study. Diabetes Care 2017;40:1010–1016
30. Little SA, Leelarathna L, Walkinshaw E, et al. Recovery of hypoglycemia awareness in long-standing type 1 diabetes: a multicenter 2 × 2 factorial randomized controlled trial comparing insulin pump with multiple daily injections and continuous with conventional glucose self-monitoring (HypoCOMPaSS). Diabetes Care 2014;37:2114–2122
31. Little SA, Speight J, Leelarathna L, et al. Sustained reduction in severe hypoglycemia in adults with type 1 diabetes complicated by impaired awareness of hypoglycemia: two-year follow-up in the HypoCOMPaSS randomized clinical trial. Diabetes Care 2018;41:1600–1607
32. Yeoh E, Choudhary P, Nwokolo M, Ayis S, Amiel SA. Interventions that restore awareness of hypoglycemia in adults with type 1 diabetes: a systematic review and meta-analysis. Diabetes Care 2015;38:1592–1609
33. Battelino T, Nimri R, Dovc K, Phillip M, Bratina N. Prevention of hypoglycemia with predictive low glucose insulin suspension in children with type 1 diabetes: a randomized controlled trial. Diabetes Care 2017;40:764–770
34. Biester T, Kordonouri O, Holder M, et al. "Let the algorithm do the work": reduction of hypoglycemia using sensor-augmented pump therapy with predictive insulin suspension (SmartGuard) in pediatric type 1 diabetes patients. Diabetes Technol Ther 2017;19:173–182
35. Deshpande PR, Rajan S, Sudeepthi BL, Abdul Nazir CP. Patient-reported outcomes: a new era in clinical research. Perspect Clin Res 2011;2:137–144
36. Frier BM. How hypoglycaemia can affect the life of a person with diabetes. Diabetes Metab Res Rev 2008;24:87–92
37. Heller SR, Gianfrancesco C, Taylor C, Elliott J. What are the characteristics of the best type 1 diabetes patient education programmes (from diagnosis to long-term care), do they improve outcomes and what is required to make them more effective? Diabet Med 2020;37:545–554