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

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OBJECTIVE

In 2016, nationwide reimbursement of intermittently scanned continuous glucose monitoring (isCGM) for people living with type 1 diabetes treated in specialist diabetes centers was introduced in Belgium. We undertook a 12-month prospective observational multicenter real-world study to investigate impact of isCGM on quality of life and glycemic control.

RESEARCH DESIGN AND METHODS

Between July 2016 and July 2018, 1,913 adults with type 1 diabetes were consecutively recruited in three specialist diabetes centers. Demographic, metabolic, and quality of life data were collected at baseline, 6 months, and 12 months of standardized clinical follow-up. The primary end point was evolution of quality of life from baseline to 12 months. Secondary outcome measures were, among others, change in HbA_{1c}, time spent in different glycemic ranges, occurrence of acute diabetes complications, and work absenteeism.

RESULTS

General and diabetes-specific quality of life was high at baseline and remained stable, whereas treatment satisfaction improved ($P < 0.0001$). Admissions for severe hypoglycemia and/or ketoacidosis were rare in the year before study ($n = 63$ out of 1,913; 3.3%), but decreased further to 2.2% ($n = 37$ out of 1,711; $P = 0.031$). During the study, fewer people reported severe hypoglycemic events ($n = 280$ out of 1,913 [14.6%] vs. $n = 134$ out of 1,711 [7.8%]; $P < 0.0001$) or hypoglycemic comas ($n = 52$ out of 1,913 [2.7%] vs. $n = 18$ out of 1,711 [1.1%]; $P = 0.001$) while maintaining HbA_{1c} levels. Fewer people were absent from work ($n = 111$ out of 1,913 [5.8%] vs. $n = 49$ out of 1,711 [2.9%]; $P < 0.0001$). Time spent in hypoglycemia significantly decreased in parallel with less time in range and more time in hyperglycemia. Eleven percent ($n = 210$) of participants experienced skin reactions, leading to stopping of isCGM in 22 participants (1%).

CONCLUSIONS

Nationwide unrestricted reimbursement of isCGM in people with type 1 diabetes treated in specialist diabetes centers results in higher treatment satisfaction, less severe hypoglycemia, and less work absenteeism, while maintaining quality of life and HbA_{1c}.

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Achieving optimal glycemic control while avoiding hypoglycemia (1) remains a challenge for people living with type 1 diabetes (2) despite rapid advancements in insulin administration technology and better insulin preparations. Successful intensive insulin treatment requires close self-monitoring of blood glucose. Measurement of blood glucose is especially important before main meals because prandial insulin dose will vary with blood glucose level, planned carbohydrate consumption, and other factors (e.g., exercise and alcohol consumption). Since the introduction of continuous glucose monitoring (CGM), the daily burden of multiple daily finger-stick tests and the need to constantly carry a blood glucose meter, test strips, lancets, and blood glucose logbooks have been reduced. Moreover, favorable results on hypoglycemia risk, quality of life, and hospitalization rate have been reported (3–6). However, widespread use of CGM has been hampered by high costs and lack of reimbursement (7), relatively short sensor lifetime, and need for daily calibration (8).

From 2014 onwards, intermittently scanned CGM (isCGM) (FreeStyle Libre; Abbott Diabetes Care, Witney, U.K.) was introduced onto the market. This device differs from CGM by the need for active "scanning" of the sensor, absence of alarms for hypo- and hyperglycemia in the first version, no need for calibration, and a sensor life span of 14 days (9). Results from two randomized controlled trials indicated that using isCGM reduces time spent in the hypoglycemic glucose range, without changing HbA_{1c}, in people living with well-controlled type 1 and type 2 diabetes on intensive insulin therapy (10–12). Some small observational studies describe improved glucose control, reduced hypoglycemia, and improved quality of life in adults (13–15) as well as in the pediatric age group (16–18). Recently, an observational study in 900 people with type 1 diabetes who received isCGM funded by the U.K. National Health Service showed significant decrease in HbA_{1c} (19). Despite the findings of these studies, it remains unclear whether use of isCGM has a benefit in a large unselected population in real-world settings.

In this study, the impact of isCGM on quality of life, diabetes control, and acute complication risk in an unselected real-world cohort of adults living with type 1 diabetes followed by multidisciplinary teams in specialized diabetes centers over a period of 12 months was analyzed.

RESEARCH DESIGN AND METHODS

Study Design and Participants

Adults with diabetes (type 1, type 2, and secondary forms of diabetes) were consecutively recruited between July 2016 and July 2018 for this multicenter, prospective, observational real-world cohort study (Flash Glucose Monitoring Study for Diabetes [FUTURE]; ClinicalTrials.gov NCT02898714). Recruitment took place at University Hospitals Leuven, University Hospital Antwerp, and OLV Hospital Aalst in Belgium (Supplementary Table 1). All of the people who planned to start isCGM were proposed to participate and included in the study after signed informed consent. For the current analysis, only data of people with type 1 diabetes for >3 months were used.

Data were collected during standardized clinical follow-up and from validated questionnaires that were presented to the participants at defined time points.

Outcomes

The primary end point was defined as evolution over time of quality of life between baseline and 12 months after start of isCGM. Secondary outcome measures were change in acute diabetes complications (hypoglycemia and/or ketoacidosis), work absenteeism, HbA_{1c}, and percentage of time in different glycemic ranges: level 2 hypoglycemia (<54 mg/dL [<3.0 mmol/L]), level 1 hypoglycemia (<70 mg/dL [<3.9 mmol/L] and ≥54 mg/dL [≥3.0 mmol/L]), in range (70–180 mg/dL [3.9–10.0 mg/dL]), level 1 hyperglycemia (>180 mg/dL [>10.0 mmol/L] and ≤250 mg/dL [≤13.9 mmol/L]), and level 2 hyperglycemia (>250 mg/dL [>13.9 mmol/L]) (20–22). Other secondary outcomes were changes in proportion of participants with HbA_{1c} <7% (<53 mmol/mol), total daily insulin dose, body weight, reasons to discontinue isCGM, and monitoring complaints.

Device and Diabetes Management

In Belgium, people with type 1 diabetes treated for their diabetes in specialist centers by multidisciplinary teams led by endocrinologists are free to choose which reimbursed device they use for diabetes management. On 1 July 2016, the first version of the FreeStyle Libre flash glucose monitoring system (Abbott Diabetes Care) became fully reimbursed for adults with type 1 diabetes in Belgium. If they chose to switch to isCGM, people were trained individually or in groups for 2 to 3 h by experienced diabetes educator nurses, as was organized by every individual diabetes center as part of the standard of care (for details on training, see Supplementary Table 2). After the training session, the device was immediately unblinded. They received instructions to scan frequently (at least four times daily), to adapt insulin dose based on the actual value, and to take associated trend arrows into account. During every standardized multidisciplinary diabetes consultation, isCGM data were uploaded, and relevant reports were generated using the designated software. These reports were thoroughly reviewed together with the multidisciplinary team, and, if necessary, treatment adaptations were proposed.

Data Collection

Prespecified clinical data were collected from the electronic medical databases from 12 months before until 12 months after start of isCGM.

For the primary end point, different questionnaires were presented to participants at baseline, 6 months, and 12 months. All questionnaires (SF-36 [23]; Problem Areas in Diabetes, short form [PAID-SF] [24]; Hypoglycemia Fear Survey [HFS]–Worry [25]; and Diabetes Treatment Satisfaction Questionnaire [DTSQ], status and change [26,27]) were validated in both Belgian languages (Dutch and French) and English and presented to participants in their mother tongue or the language they understood best.

At baseline, participants were asked to report on how many diabetes-related events they experienced in the previous 6 months. After 6 and 12 months, diabetes-related events were gathered from the previous 6 months (Supplementary Table 3). Patient-reported medical interventions, emergency room admissions, and hospitalizations for (symptoms of) acute diabetes complications (hypoglycemia/ketoacidosis/ketosis) were validated using hospital records. Hospitalizations for ketoacidosis at diagnosis of type 1 diabetes were excluded. After 6 and 12 months, participants were asked how satisfied they were

with the new device on a 10-point Likert scale ranging from 0 ("not at all satisfied") to 10 ("very satisfied, could not be better"), and they could indicate if they found isCGM less convenient, similar, or more convenient than finger-stick testing. Additionally, comments on the use of isCGM were gathered and grouped for qualitative research purposes.

isCGM data were collected using the designated diabetes management software (FreeStyle Libre software version 1.0 and LibreView). Data for the following time points were extracted and averaged: 2 weeks (week 0 until week 2), 6 months (month 5 until month 6), and 12 months (month 11 until month 12).

Ethics

The protocol was approved by the coordinating institutional review board (Ethics Committee, University Hospitals Leuven, Leuven, Belgium) after obtaining advice from the two local ethical committees. The study was executed in line with Good Clinical Practice guidelines of the Declaration of Helsinki in its latest form.

Study Size

Beforehand, we estimated that ~70% (n = 1,850) of people with type 1 diabetes would be willing to use isCGM. Every person was informed of the study and, after giving informed consent, included in the analysis. No formal sample size calculation was performed a priori. However, with the anticipated accrual rate for the primary end point, effect on quality of life, there was enough power (>90%) with a two-sided 5% significance level to detect a mean difference of 5 with an SD of 20 for the SF-36 subscales, a mean difference of 1 point on the PAID-SF scale with an SD of 5, a mean difference of 3 points on the HFS-Worry scale assuming an SD of 10 points, and a mean difference of 2 on the DTSQ status satisfaction scale with an SD of 4 points. Note that the power level is even safeguarded under a conservative scenario of a low (or zero) correlation between time points.

Statistical Analysis

Post hoc, the total population was grouped based on clinically relevant parameters for subgroup analyses: tertiles of scan frequency at 12 months (≤6 times/day, 7–10 times/day, and >10 times/day) and clinically relevant subgroups of baseline HbA_{1c} (<7.0%, 7.0–7.9%, 8.0–9.9%, and ≥10.0% [<53 mmol/mol, 53–63 mmol/mol, 64–85 mmol/mol, and ≥86 mmol/mol, respectively]). The number of people in different subgroups at baseline, 6 months, and 12 months is shown in Supplementary Table 4.

We used a linear mixed model to evaluate SF-36, PAID-SF, HFS-Worry, DTSQ status, HbA_{1c}, time in different glycemic ranges, insulin dose per day, body weight, and BMI with a random effect of center to handle correlation between participants of the same center and an unstructured covariance matrix for three repeated measurements within the same patient. By using a linear mixed model, case subjects with missing data still contributed to the analyses (see Supplementary Table 5 for number of missing case subjects per outcome). From the multivariate normal distribution implied by the linear mixed model, we derived the relation (r) 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 zero but versus the correlation, which is already expected purely based on regression to the mean (28). Scores on the DTSQ change questionnaire were compared with zero with a one-sample t test. To analyze the relationship between scan frequency and HbA_{1c}, a linear regression analysis was carried out after transforming scan frequency on a $\log_2$ scale, due to a better fit of the linear model. To evaluate the evolution of a proportion of participants (who reached target HbA_{1c} [<7% (<53 mmol/mol)], with work absenteeism, needing help from third parties due to hypoglycemia, having hypoglycemic comas, and with admissions due to hypoglycemia/ketoacidosis), a logistic regression model was used with generalized estimating equations. Differences in days of work absenteeism, number of times help from third parties was needed, number of hypoglycemic comas, and number of days of hospitalizations for hypoglycemia/ketoacidosis per 100 patient-years were assessed with a negative binomial generalized estimating equation model. Differences in baseline characteristics between different scan frequency groups were analyzed using one-way ANOVA.

A Bonferroni-Holm correction was considered for results at 12 months from all 16 scales referring to the primary outcomes (8 subscales of SF-36, PAID-SF, HFS-Worry, 3 subscales of DTSQ status, and 3 subscales of DTSQ change). No adjustment was made for multiple testing of secondary end points.

Statistical analyses were performed with SPSS software for Windows (SPSS Statistics version 25; IBM, Armonk, NY) or SAS software for Windows (version 9.4; SAS Institute Inc., Cary, NC). Data are shown as mean ± SD or least-squares mean (95% CI), unless otherwise stated.

RESULTS

Patient Characteristics

Between July 2016 and July 2018, 1,913 people living with type 1 diabetes for >3 months were included. Up until April 2019, 1,711 (89%) participants had ≥12 months follow-up, 47 (3%) had <12 months follow-up, and 155 (8%) participants stopped participating (Supplementary Fig. 1). There were three reasons for stopping: stopped using isCGM (n = 114 out of 155; 74%), lost to follow-up (n = 30 out of 155; 19%), or death during the study period (n = 11 out of 155; 7%). Participants stopped using isCGM mainly due to skin reactions (n = 22 out of 114; 19%), low confidence in sensor values (n = 19 out of 114; 17%), and frequent sensor loss (n = 19 out of 114; 17%).

Participants represent an average population with type 1 diabetes (Supplementary Table 6): a majority were male (n = 1,031; 54%), with a BMI of 25.5 ± 4.2 kg/m^2, a long history of type 1 diabetes (22.8 ± 13.7 years), mostly on multiple daily injections (n = 1,472; 78%), with impaired awareness of hypoglycemia in a minority of cases (n = 301; 16%) and suboptimal mean baseline HbA_{1c} of 7.8 ± 1.2% (62 ± 12 mmol/mol).

Change in Quality of Life

Overall, quality of life was high at baseline. Scores on the SF-36, PAID-SF, and HFS-Worry were overall stable (Table 1). DTSQ status satisfaction significantly increased from baseline to 12 months (28.0 [95% CI 26.1; 29.9] vs. 30.4 [28.9; 32.6]; P < 0.0001), with DTSQ change satisfaction significantly higher than zero (Table 1). Perceived frequency of hyper- and hypoglycemia was higher, which indicates increased awareness of hyper- and hypoglycemia when using isCGM (Table 1). Overall, participants self-reported that they were very satisfied with the device

Table 1—Quality of life scores before and after initiation of isCGM

	Baseline	6 months	*P* value*	12 months	*P* value*
SF-36					
Physical functioning	80.2 (76.7; 83.7)	80.0 (76.7; 83.3)	0.575	79.8 (76.6; 83.1)	0.377
Role-physical	71.6 (67.8; 76.3)	72.7 (69.1; 76.3)	0.041	72.5 (68.8; 76.1)	0.123
Bodily pain	73.7 (71.5; 75.9)	72.6 (70.5; 74.6)	0.012	72.9 (70.8; 75.0)	0.086
General health	58.6 (56.3; 60.8)	57.6 (55.5; 59.8)	0.012	56.8 (54.7; 58.9)	<0.0001†
Vitality	61.3 (58.0; 64.5)	60.9 (57.8; 64.0)	0.391	60.2 (57.2; 63.3)	0.015
Social functioning	79.1 (75.4; 82.7)	79.0 (75.6; 82.5)	0.984	78.6 (75.2; 82.1)	0.428
Role-emotional	77.1 (72.4; 81.9)	77.8 (73.1; 82.4)	0.324	77.1 (72.5; 81.7)	0.999
Mental health	69.8 (67.2; 72.4)	69.3 (66.8; 71.8)	0.157	69.0 (66.5; 71.5)	0.042
PAID-SF	5.0 (4.5; 5.6)	5.0 (4.5; 5.6)	0.956	5.1 (4.5; 5.6)	0.898
HFS-Worry	18.1 (15.7; 20.6)	17.9 (15.6; 20.2)	0.340	17.8 (15.5; 20.1)	0.121
DTSQ status					
Satisfaction	28.0 (26.1; 29.9)	30.7 (28.9; 32.6)	<0.0001†	30.4 (28.5; 32.2)	<0.0001†
Perceived frequency of hyperglycemia	3.9 (3.7; 4.1)	3.8 (3.6; 4.0)	0.148	3.8 (3.6; 4.0)	0.179
Perceived frequency of hypoglycemia	3.0 (2.7; 3.3)	3.4 (3.1; 3.7)	<0.0001†	3.4 (3.1; 3.6)	<0.0001†
DTSQ change					
Satisfaction	NA	13.4 (13.2; 13.7)	<0.0001†	13.3 (13.0; 13.5)	<0.0001†
Perceived frequency of hyperglycemia	NA	1.0 (0.9; 1.1)	<0.0001†	0.9 (0.8; 1.0)	<0.0001†
Perceived frequency of hypoglycemia	NA	0.9 (0.8; 1.0)	<0.0001†	0.8 (0.7; 0.9)	<0.0001†

Data are least-squares mean (95% CI). NA, not applicable. **P* value for the change vs. baseline, except for DTSQ change, in which *P* value is for the change vs. zero. †Significant after Bonferroni-Holm correction.

(8.4 ± 1.4 on a scale of 10 at 6 and 12 months), and they agreed almost unanimously that isCGM was more convenient than finger-stick tests ($n = 1,384$ out of 1,463 [94.6%] and $n = 1,312$ out of 1,379 [95.1%] after 6 and 12 months, respectively).

Evolution of SF-36, PAID-SF, HFS-Worry, DTSQ status, and DTSQ change was not different for subgroups of scan frequency and baseline HbA_{1c} level (data not shown).

Change in Acute Diabetes Complications and Work Absenteeism

The number of participants admitted to the emergency room or hospital because of hypoglycemia and/or ketoacidosis decreased from 3.3% ($n = 63$ out of 1,913) in the previous year to 2.2% ($n = 37$ out of 1,711; $P = 0.031$) during the study, together with a decrease in hospitalization days (Table 2). Fewer people reported severe hypoglycemic events with help from third parties ($P < 0.0001$), hypoglycemic comas ($P = 0.001$), and diabetes-related work absenteeism ($P < 0.0001$) (Table 2).

Change in HbA_{1c}

For the total population, HbA_{1c} was slightly lower at 6 months (7.7% [95% CI 7.4; 8.0] [61 (57; 64) mmol/mol]) compared with baseline (7.8% [7.5; 8.1] [62 (58; 65) mmol/mol]; $P < 0.0001$), with a return to the baseline value after 12 months (7.8% [7.5; 8.1] [62 (58; 65) mmol/mol]; $P = 0.287$) (Fig. 1*A*). The proportion of participants who achieved HbA_{1c} <7% (<53 mmol/mol) decreased from 20.8% ($n = 397$ out of 1,913) to 18.3% ($n = 302$ out of 1,651) at 12 months ($P = 0.010$).

All scan frequency groups followed the same evolution as the total population (Fig. 1*B*). 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*C*).

The highest scan frequency group had the lowest baseline HbA_{1c} (7.6 ± 1.0% [58 ± 5.0 mmol/mol] vs. 8.2 ± 1.3% [66 ± 5.3 mmol/mol] for the group scanning ≤6 times/day, $P < 0.0001$; vs. 7.7 ± 1.0% [61 ± 5.0 mmol/mol] for the group scanning 7–10 times/day, $P = 0.015$).

HbA_{1c} weakly correlated with scan frequency at 6 months ($r = -0.308$, $R^2 = 0.095$, $P < 0.0001$) and 12 months ($r = -0.344$, $R^2 = 0.119$, $P < 0.0001$). The correlation and goodness of fit of the change in HbA_{1c} versus scan frequency was very low ($r = -0.064$, $R^2 = 0.004$, $P = 0.011$ at 6 months; $r = -0.076$, $R^2 = 0.006$, $P = 0.003$ at 12 months), and 95% prediction intervals were wide (Fig. 2).

Evolution of Time in Different Glycemic Ranges

For the total population, percentage of time in level 1 and level 2 hypoglycemia changed from 5.1% (4.3; 6.0) and 4.0% (2.6; 5.3) in the first 2 weeks to 4.5% (3.6; 5.4) and 3.5% (2.1; 5.0) at 6 months ($P < 0.0001$) and 4.5% (3.6; 5.3) and 3.5% (2.1; 4.9) at 12 months ($P < 0.0001$), respectively. Time in range slightly decreased from 2 weeks to 12 months (mean change −0.9% [−1.5; −0.3] from 2 weeks to 12 months; $P = 0.004$). Time in level 1 hyperglycemia slightly increased from 22.3% (20.7; 23.9) in the first 2 weeks to 23.6% (22.0; 25.2) at 6 months and 24.2% (22.6; 25.7) at 12 months ($P < 0.0001$ for both time points), and time in level 2 hyperglycemia did not change from 2 weeks to 12 months (Supplementary Fig. 2).

The decrease of time in level 1 and level 2 hypoglycemia was independent of number of scans per day. However, evolution of time in range was dependent on scan frequency. Those who scanned the sensor ≤6 times/day showed a decrease of −3.4% (−4.5; −2.2) from 2 weeks to 12 months ($P < 0.0001$), those with scan frequency of 7–10 times/day remained stable, and in those who scanned >10 times/day time in range increased 1.3% (0.2; 2.4) from 2 weeks to 12 months ($P = 0.018$). Time in level 1 hyperglycemia increased in all scan frequency groups, while time in level 2 hyperglycemia only increased in the lowest scan frequency tertile (Supplementary Fig. 2).

People with the lowest baseline HbA_{1c} (<7% [<53 mmol/mol]) had the highest

Table 2—Diabetes-related acute complications and work absenteeism before and after initiation of isCGM

	Baseline	6 months	*P* value§	12 months	*P* value§
People with					
Hospitalizations due to hypoglycemia and/or ketoacidosis*†	63 (3.3)	—	—	37 (2.2)	0.031‖
Hospitalizations due to hypoglycemia†	36 (1.9)	—	—	21 (1.2)	0.104
Hospitalizations due to ketoacidosis*†	27 (1.4)	—	—	17 (1.0)	0.242
Help from third parties due to hypoglycemia‡	280 (14.6)	153 (8.4)	<0.0001‖	134 (7.8)	<0.0001‖
Hypoglycemic comas‡	52 (2.7)	16 (0.9)	<0.0001‖	18 (1.1)	0.001‖
Work absenteeism‡	111 (5.8)	59 (3.2)	<0.0001‖	49 (2.9)	<0.0001‖
Number per 100 patient-years of					
Help from third parties due to hypoglycemia‡	97.2	63.9	0.024‖	64.6	0.022‖
Hypoglycemic comas‡	11.2	2.6	<0.0001‖	4.3	0.017‖
Days per 100 patient-years of					
Hospitalizations due to hypoglycemia and/or ketoacidosis*†	9.3	—	—	6.6	0.021‖
Hospitalizations due to hypoglycemia†	2.5	—	—	1.8	0.129
Hospitalizations due to ketoacidosis*†	6.8	—	—	4.8	0.078
Work absenteeism‡	109.5	49.3	0.038‖	53.5	0.058

Data are *n* (% of total population) or *n*. Patient-reported hospital admissions were validated by clinicians. *Hospitalizations for ketoacidosis at diagnosis of type 1 diabetes were excluded. †Numbers represent period of 12 months before start and 12 months' follow-up. ‡Numbers represent period of 6 months before each time point. §*P* value for the change vs. baseline. ‖$P < 0.05$.

decrease in time in level 1 and level 2 hypoglycemia. Time in range decreased in people with high baseline HbA_{1c}. Time in level 1 hyperglycemia increased in all HbA_{1c} subgroups, except for the highest baseline HbA_{1c}, while for time in level 2 hyperglycemia, the opposite was observed (Supplementary Fig. 2).

Change in Insulin Dose and Body Weight

Over the study period, total daily insulin dose changed by −0.022 (−0.027; −0.016) units per kilogram body weight ($P < 0.0001$). The largest decrease was observed in bolus insulin (−0.014 [−0.018; −0.009] units per kilogram body weight; $P < 0.0001$), with a smaller decrease in basal insulin (−0.008 [−0.011; −0.005] units per kilogram body weight; $P < 0.0001$). Body weight and BMI slightly increased by 0.7 (0.5; 0.9) kg and 0.3 (0.2; 0.3) kg/m^2 during 12 months, respectively ($P < 0.0001$ for both).

Self-Reported Adverse Events and Complaints With isCGM

Although users were very satisfied with the system, 64% ($n = 1,218$ out of 1,913) of participants reported 3,081 negative user experiences with the device in total. Comments were mainly regarding the frequent sensor loss ($n = 616$ out of 1,913 [32%]; 52% of comments) and accuracy ($n = 540$ out of 1,913 [28%]; 42% of comments). Other comments were on technical issues ($n = 273$ out of 1,913 [14%]; 21% of comments), wearing comfort and pain ($n = 253$ out of 1,913 [13%]; 18% of comments), skin irritation or allergy ($n = 210$ out of 1,913 [11%]; 14% of comments), and visibility on the upper arm ($n = 189$ out of 1,913 [10%]; 12% of comments). Irritation or allergy was mentioned by 128 out of 210 participants from the first half of the first year and by 82 out of 210 participants from the second half of the first year onward.

CONCLUSIONS

Results from our observational real-world cohort study show that nationwide reimbursement of isCGM in adults living with type 1 diabetes treated in specialist diabetes centers resulted in higher treatment satisfaction and less severe hypoglycemia while maintaining HbA_{1c}. General and diabetes-related quality of life, which were already high at baseline, remained stable.

Since July 2016, isCGM is fully reimbursed for adults with type 1 diabetes in Belgium. Since then, every person with diabetes who started isCGM in three centers was asked to participate in the study, and only 8% declined. This makes the FUTURE study the largest real-life observational study to date investigating effectiveness of isCGM under everyday conditions in a general population with type 1 diabetes. In randomized controlled trials, stringent inclusion and exclusion criteria introduce selection bias, as investigators may only select those participants who are likely to benefit from study participation (29). Also, in real-world studies, bias can be introduced if only people with defined criteria receive reimbursement (19) or when only those who are motivated and willing to pay for the device participate (14). The population studied reflects the overall population with type 1 diabetes in Belgium, as shown by our nationwide ongoing quality survey (30). This survey has shown over the last 20 years a high quality of care for people living with type 1 diabetes in our system, in which >95% are followed by multidisciplinary teams in specialist diabetes centers.

To our knowledge, this is the first study in which quality of life was prospectively evaluated as the primary end point in a large real-world population with type 1 diabetes on isCGM using validated questionnaires. As observed in other studies (10), device acceptance was high, as seen by improvement in overall diabetes treatment satisfaction scores and unambiguous scores on system utilization. Similar to findings from randomized controlled trials on isCGM use (10,11), no effects on aspects of general quality of life, emotional distress due to diabetes, and patient-reported fear of hypoglycemia were seen. Absence of improvement in general and diabetes-specific quality of life can be explained by the high perceived health status at baseline, which is in line with a European study in adults on insulin pump therapy or multiple daily injections (31).

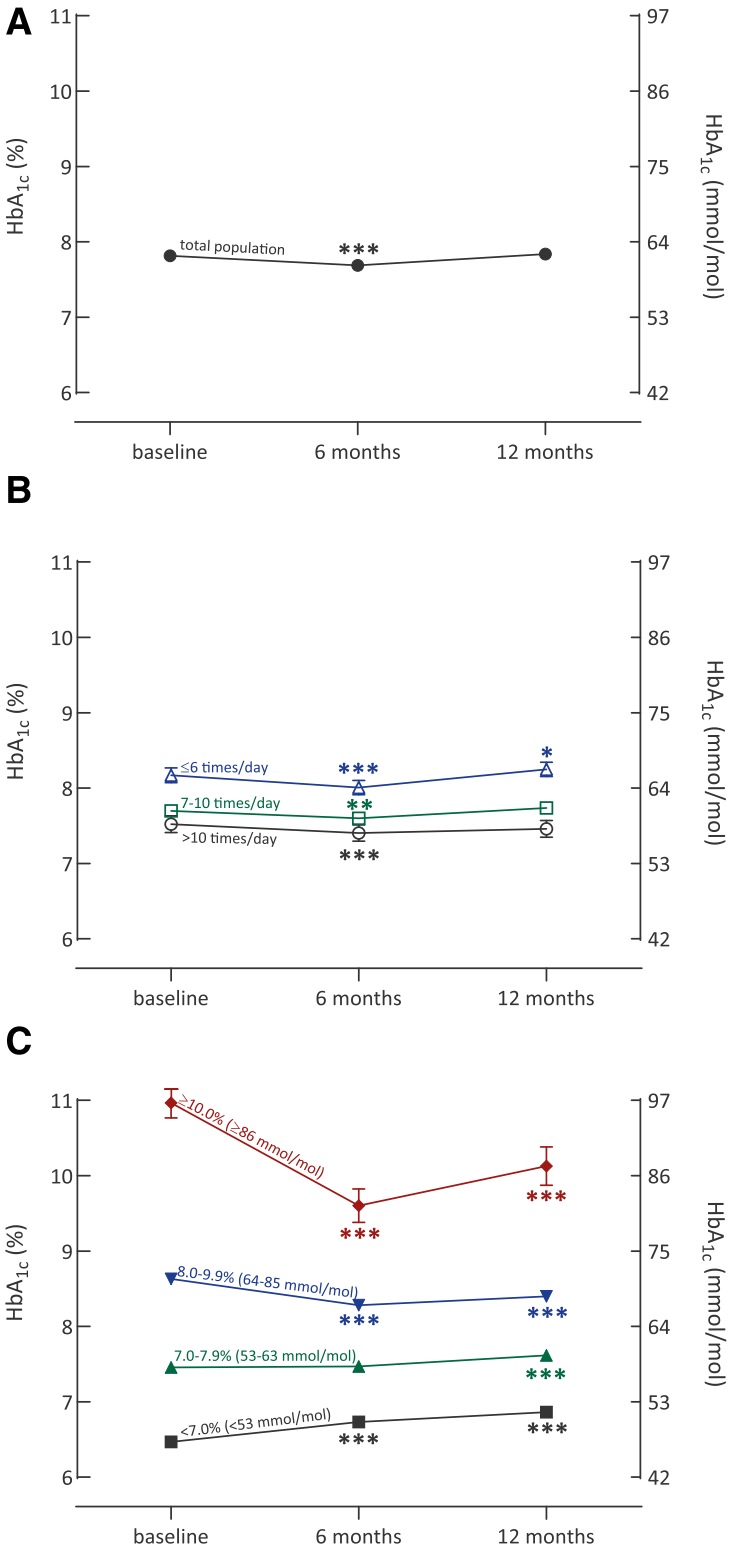

Figure 1—HbA_{1c} from baseline to 12 months after initiation of isCGM for the total population, different scan frequency groups, and groups based on baseline HbA_{1c}. Data points represent least-squares mean (SE) of HbA_{1c} measurements per time point for the total population (*A*), as a function of scan frequency at 12 months (*B*), and as a function of baseline HbA_{1c} (*C*). $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ for the comparisons vs. baseline HbA_{1c}. In *C*, the correlation between baseline HbA_{1c} and the change in HbA_{1c} did not exceed the regression-to-the-mean effect.

An important observed advantage of introducing isCGM in this unselected patient population is a significant reduction of self-reported severe hypoglycemia and hypoglycemic comas. Probably related, people with work absenteeism also significantly decreased, representing an important advantage on both an individual and societal level. These findings indicate that with isCGM, people might be able to intervene earlier on upcoming lows and thus prevent life-threatening situations. As was reported for CGM (3), diabetes-related hospital admissions decreased in the first 12 months compared with the year before. Taking into account a mean Belgian cost of €4,733 per hospitalization for hypoglycemia or ketoacidosis (3), the Belgian health care provider could save €151,456 of direct costs in the first year of isCGM reimbursement. However, the magnitude is much lower, which could be explained by low baseline incidence of diabetes-related admissions in the current cohort (3.3%) compared with the high incidence (16%) in the CGM trial, in which people were mainly selected on the basis of problematic hypoglycemia (3).

HbA_{1c} in this unselected population was suboptimal at baseline and comparable to what is reported for the Belgian population with type 1 diabetes (30). Still, overall glycemic control is better than what has been reported in other real-world studies in other regions (19). For the entire study group, HbA_{1c} levels were maintained, while subgroups with high HbA_{1c} (≥8.0% [≥64 mmol/mol]) showed a decrease, although results should be interpreted with caution because a regression-to-the-mean effect could not be excluded. Absence of HbA_{1c} improvement in the entire study group might be related to a more defensive attitude toward hypoglycemic events (e.g., more snacking and lower insulin dose) following higher perceived prevalence of hypoglycemia, as indicated by the DTSQ status and change perceived frequency of hypoglycemia subscale. This altered attitude resulted in a continuous reduction of time in hypoglycemia of ~16 min/day. In addition, it has been reported that both pressure-induced sensor attenuation and lower accuracy in hypoglycemic ranges can cause false low measurements (32,33) and thus hyperglycemia due to unnecessary carbohydrate intake and/or insulin dose reduction. Also, lower scan

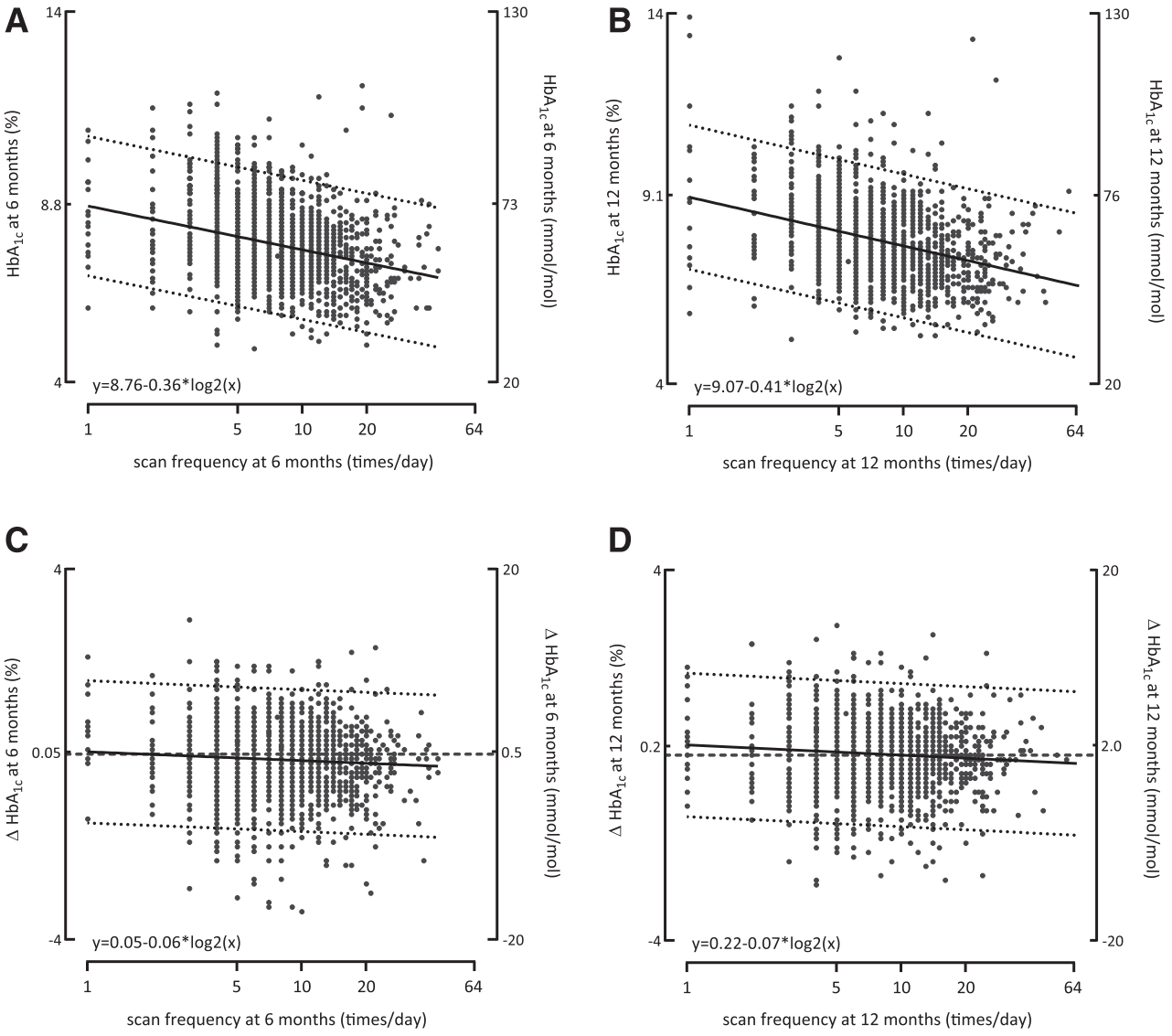

Figure 2—Relationship between scan frequency and HbA_{1c}. Mean scan frequency per day over the preceding 4 weeks is plotted on a log2 scale against its concurrent HbA_{1c} value at 6 (*A*) and 12 months (*B*) or against the change in HbA_{1c} from baseline to 6 (*C*) and 12 months (*D*). The change in HbA_{1c} is defined as HbA_{1c} at follow-up (6 or 12 months) − HbA_{1c} at baseline. Negative values indicate a reduced HbA_{1c}, whereas positive values indicate an increase in HbA_{1c}. Black solid lines represent the linear regression line with function y = a − b * log2(x) (for HbA_{1c} in %) as stated in the figures. The fine black dotted lines represent the 95% prediction interval of the regression line. The thicker dashed lines in *C* and *D* represent a change in HbA_{1c} of zero. The tick mark on the *y*-axis denotes the intercept of the regression line.

frequency (mean 9.7 times/day) in our study compared with 13.2–17.8 times/day in other trials (10,12,34) might explain the absence of HbA_{1c} improvement because previous data showed an inverse correlation between scan frequency and HbA_{1c} (34). We could not reproduce this correlation as illustrated by low correlation between HbA_{1c} change and scan frequency and absence of HbA_{1c} decrease in people scanning >10 times/day. People with high scan frequency already had good glycemic control at baseline and were able to retain it in contrast to the low scan frequency group, in whom opposite findings were noted. This was also reported by a JDRF CGM Study Group, who identified the frequency of finger-stick tests before CGM initiation as an independent factor for successful use of the device (35). Both observations suggest that baseline motivation and behavior play a bigger role than scan frequency per se.

The reduction in hypoglycemia did not result in more time in range after 12 months but led to more time spent in level 1 hyperglycemia (28 min/day) compared with the first 2 weeks of isCGM use. Because data are lacking to compare 12-month data with time in hyperglycemia before the first use of isCGM, it cannot be excluded that the greatest benefit already happened within the first 2 weeks, as was seen in the IMPACT trial (10). Nevertheless, with isCGM, 83% of those studied could not achieve the new recommendation of <25% of time >180 mg/dL (10 mmol/L) (22). Data are emerging about the possible negative impact of hyperglycemia on cognitive function in both those with type 2 diabetes (36) and children and adolescents with type 1 diabetes (37). Therefore, continued efforts are needed to improve education

about the use of isCGM focusing on increasing time in range while decreasing both time in hyper- and hypoglycemia.

The most frequent reported problems with the device comprised early loss of sensors and low confidence in reported sensor values triggered by well-known lower accuracy during the first 24 h after sensor insertion (38), in low glucose ranges (33), and when glucose is rapidly changing (39). It remains important to advise people to measure capillary glucose when they do not trust sensor values. Another important issue was the development of irritation or allergy against the sensor's adhesive patch in 11% of participants, leading 1% of the total study population to stop using the device completely. Recently, two causative allergens in the adhesive sensor patch have been identified, namely isobornyl acrylate and *N*,*N*-dimethylacrylamide (40,41). The observation that skin reactions could appear early as well as later in the first year seems to indicate that, cumulatively, >11% of people will suffer some kind of skin reaction while using the device. This is in line with the scarce literature on the prevalence of isCGM-related skin allergy, in which 3–5% of isCGM users develop sensor-related allergic reactions, leading ~1% of these users to stop isCGM (10,42). Development of hypoallergic adhesives is therefore needed to avoid dropout from sensor technology, certainly because cross-reactivity with adhesives used in other sensors might be an issue (42).

Our study has limitations, like the fact that severe hypoglycemic events prior to initiation could only be recorded by recall. However, all hospitalizations for hypoglycemia and ketoacidosis were validated using the hospital records of the participants. The most important limitation lies in the interpretation of evolution in time in ranges, as no baseline blinded measuring period was introduced in this real-world study. Thus, participants were unblinded from the very beginning, therefore leading most probably to altered behaviors already in the first days after initiation of isCGM, with insulin dose adaptations and carbohydrate intake. Hence, our comparison between 2 weeks after start and later moments most probably underestimates the real impact of isCGM introduction on time in ranges. It is also not known if our three multidisciplinary teams are representative of other teams across the country. However, because care for people with type 1 diabetes is centrally organized in Belgium via a system of diabetes conventions, we believe that current results are most likely generalizable to other specialized diabetes centers in the country.

In conclusion, broad introduction of isCGM in a population of adults living with type 1 diabetes treated by multidisciplinary teams in specialist diabetes centers increases treatment satisfaction while maintaining general and diabetes-specific quality of life and HbA_{1c}. It is associated with fewer people being absent from work, fewer hospitalizations for ketoacidosis and hypoglycemia, and less severe hypoglycemia. This observation, combined with the fact that participants rated the system as much more convenient than classical finger-sticking, shows that isCGM can be successfully implemented with clinically relevant benefits.

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Author Contributions. S.C. designed the study, collected and analyzed the data, performed statistical analyses, wrote the manuscript, and made figures and tables. C.D.B., L.V.H., B.B., and F.N. collected and discussed the data and edited the manuscript. S.F. performed statistical analyses and edited the manuscript. C.M. and P.G. designed the study, collected and discussed the data, and wrote the manuscript. S.C. and P.G. are the guarantors of this work and, as such, had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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