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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

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IMPORTANCE The majority of individuals with type 1 diabetes do not meet recommended glycemic targets.

OBJECTIVE To evaluate the effects of continuous glucose monitoring in adults with type 1 diabetes treated with multiple daily insulin injections.

DESIGN, SETTING, AND PARTICIPANTS Open-label crossover randomized clinical trial conducted in 15 diabetes outpatient clinics in Sweden between February 24, 2014, and June 1, 2016 that included 161 individuals with type 1 diabetes and hemoglobin A_{1c} (HbA_{1c}) of at least 7.5% (58 mmol/mol) treated with multiple daily insulin injections.

INTERVENTIONS Participants were randomized to receive treatment using a continuous glucose monitoring system or conventional treatment for 26 weeks, separated by a washout period of 17 weeks.

MAIN OUTCOMES AND MEASURES Difference in HbA_{1c} between weeks 26 and 69 for the 2 treatments. Adverse events including severe hypoglycemia were also studied.

RESULTS Among 161 randomized participants, mean age was 43.7 years, 45.3% were women, and mean HbA_{1c} was 8.6% (70 mmol/mol). A total of 142 participants had follow-up data in both treatment periods. Mean HbA_{1c} was 7.92% (63 mmol/mol) during continuous glucose monitoring use and 8.35% (68 mmol/mol) during conventional treatment (mean difference, −0.43% [95% CI, −0.57% to −0.29%] or −4.7 [−6.3 to −3.1 mmol/mol]; $P < .001$). Of 19 secondary end points comprising psychosocial and various glycemic measures, 6 met the hierarchical testing criteria of statistical significance, favoring continuous glucose monitoring compared with conventional treatment. Five patients in the conventional treatment group and 1 patient in the continuous glucose monitoring group had severe hypoglycemia. During washout when patients used conventional therapy, 7 patients had severe hypoglycemia.

CONCLUSIONS AND RELEVANCE Among patients with inadequately controlled type 1 diabetes treated with multiple daily insulin injections, the use of continuous glucose monitoring compared with conventional treatment for 26 weeks resulted in lower HbA_{1c}. Further research is needed to assess clinical outcomes and longer-term adverse effects.

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Intensive insulin therapy resulting in good glycemic control has been shown to prevent and reduce the progression of diabetes-related complications in patients with type 1 diabetes.[1] Today, intensive glycemic control is generally achieved through multiple daily insulin injections or continuous subcutaneous insulin infusions through an insulin pump.[2] Regular self-measured capillary blood glucose values have been crucial to optimal insulin dosing for good glycemic control.[3-5]

In recent years, continuous glucose monitoring (CGM) has become an option for optimal insulin dosing and other activities.[6] The advantages of CGM include providing continuous feedback on estimated glucose values and illustrating glucose trends. CGM systems include a subcutaneous sensor with a transmitter attached and continuous reporting of glucose levels and trends to the patient by a handheld monitor.

Data from clinical trials of CGM have been mixed regarding its effect on glycemic control.[7] Such trials have, for example, consisted only of patients with the following characteristics: (1) continuous subcutaneous insulin infusions; (2) initiated CGM and continuous subcutaneous insulin infusions simultaneously; or (3) included patients with both multiple daily insulin injections and continuous subcutaneous insulin infusions.[7-10] Post hoc findings have also been mixed, in that glycemic control appears to differ when CGM is combined with either multiple daily insulin injections or continuous subcutaneous insulin infusions.[8-10] Although the majority of adults with type 1 diabetes in the United States and Europe are treated with multiple daily insulin injections, to our knowledge, clinical trials evaluating CGM vs conventional therapy in persons treated with multiple daily insulin injections have not been performed.

The aim of this study was to analyze the effect of CGM on glycemic control, hypoglycemia, well-being, and glycemic variability in individuals with type 1 diabetes treated with multiple daily insulin injections.

Key Points

Question Does continuous glucose monitoring improve glycemic control in adults with type 1 diabetes treated with multiple daily insulin injections?

Findings In this randomized clinical trial of 161 adults with type 1 diabetes, glycemic control was improved during continuous glucose monitoring compared with conventional treatment (hemoglobin [HbA_{1c}] of 7.92% vs 8.35% [63 vs 68 mmol/mol]). The mean difference in HbA_{1c} was 0.43% (4.7 mmol/mol).

Meaning Continuous glucose monitoring may result in better glycemic control compared with conventional treatment, but further research is needed to assess clinical outcomes and longer-term adverse effects.

Methods

The GOLD trial was approved by the ethics committee at the University of Gothenburg, Gothenburg, Sweden. All participants provided verbal and written informed consent (trial protocol in Supplement 1).

The study was an investigator-initiated randomized, open-label, clinical trial with a crossover design conducted at 15 sites in Sweden. The study took place from February 24, 2014, to June 1, 2016. After a run-in period of up to 6 weeks, patients were randomized to receive CGM or conventional treatment for 26 weeks with a 17-week washout between treatment periods (**Figure 1**).

Screening

Individuals aged 18 years or older with hemoglobin A_{1c} (HbA_{1c}) of at least 7.5% (58 mmol/mol) treated with multiple daily insulin injections were included. Patients were required to have a fasting C-peptide level of less than 0.91 ng/mL (to convert to nmol/L, multiply by 0.331) and diabetes duration of greater than 1 year. Race and ethnicity were classified by the investigator or other research staff; if there was any uncertainty, the final decision was made in collaboration with the participant.

Patients treated with insulin pumps were excluded. The study design, including other inclusion and exclusion criteria, have been described elsewhere.[11] All laboratory tests were analyzed at a central laboratory (Research Centre for Laboratory Medicine, Karolinska University Hospital, Stockholm, Sweden). Gothia Forum (Gothenburg, Sweden) performed trial monitoring.

Run-in Period

During a 6-week run in, patients completed masked CGM for 2 weeks and questionnaires regarding the following characteristics: subjective well-being (World Health Organization-5 [WHO-5]),[12] treatment satisfaction (Diabetes Treatment Satisfaction Questionnaire [status version and change version]),[13-15] fear of hypoglycemia (Hypoglycemia Fear Survey),[16-18] hypoglycemic confidence (Hypoglycemia Confidence Questionnaire), and diabetes-related distress (Problem Areas in Diabetes Scale).[19,20] During masked CGM, glucose levels were recorded but were not seen by the patient. After masked CGM, patients were excluded if they either did not believe they would wear the CGM sensor more than 80% of the time or did not perform adequate calibrations during the run in (on average ≥12 of 14 during a 7-day period).

Randomization

Patients were randomized 1:1 into the first treatment period to CGM using the Dexcom G4 PLATINUM stand-alone system or conventional therapy. Randomization was performed by a centralized web-based program stratifying patients by site according to a predefined sequence; random block size varied between 1 + 1 and 2 + 2 (eAppendix in Supplement 2).

Treatment

CGM was compared with conventional therapy using only self-monitoring of blood glucose. Patients were not blinded to treatment. All patients received basic instruction on insulin dosing, such as bolus correction, food choices, and the effect of physical activity on glucose control. A graph was displayed for patients showing the proportion of insulin at time of injection (100%) and the proportion of insulin remaining to give effect at various time points after injection.[21] The patients received general guidelines for interpreting glucose levels and trends obtained by CGM.[11]

During the first week, no alarms were set on the CGM device for low glucose levels except for acute hypoglycemia (<55 mg/dL

[to convert to mmol/L, multiply by 0.0555]). Alarm settings were introduced no later than 2 weeks after randomization. At each visit, patients were encouraged to use CGM information at least every 1 to 2 hours during daytime. In the conventional group, patients were encouraged to measure blood glucose levels according to guidelines (ie, ≥4 times daily). Insulin dosing was based on self-measurement of blood glucose and not CGM values. Assessment of HbA_{1c} was blinded to treatment status. During the 17-week washout period, patients used conventional therapy and masked CGM was performed for 2 weeks.

Clinical Assessments

Patients were assessed at the start of each treatment period and at weeks 2, 4, 13, and 26. HbA_{1c} was measured at all visits in each treatment period except week 2.

Masked CGM was performed 2 weeks before both treatment periods. During conventional therapy, masked CGM was also performed during 2 of the 4 last weeks to evaluate total time in hypoglycemia, euglycemia, hyperglycemia, and glycemic variability. At all visits, CGM and self-measurements of blood glucose data were downloaded and used to assess glucose levels, number of self-measurements of blood glucose, time CGM was in use, and for optimizing glycemic control. To maintain an equal number of visits for both treatment periods, the study did not permit extra patient visits for improving glycemic control.

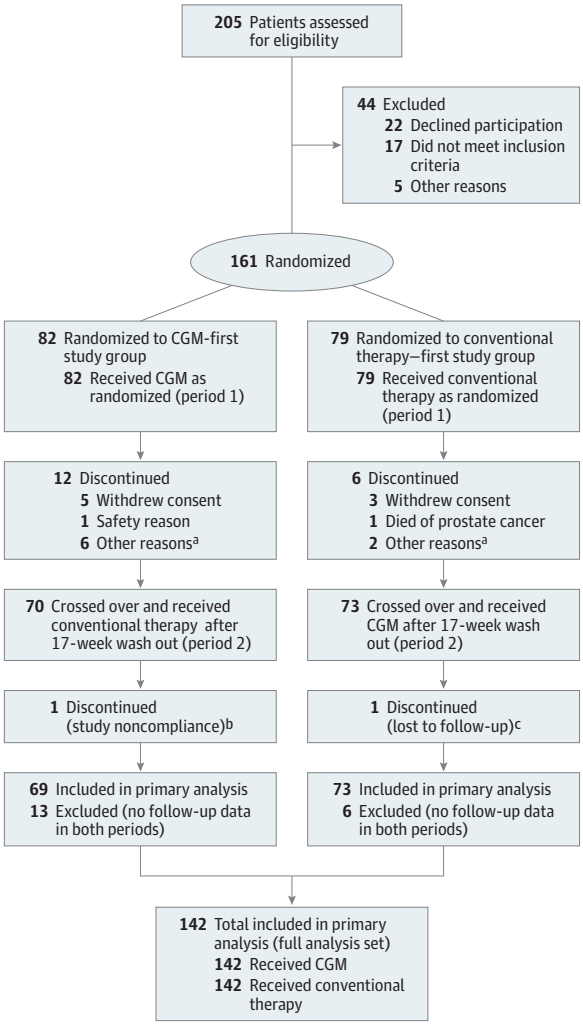
End Points

The primary end point was the difference in HbA_{1c} between CGM and conventional therapy at weeks 26 and 69. Secondary end points included mean amplitude glycemic excursions[22]; the standard deviation of glucose levels; and the amount of time in hypoglycemia, hyperglycemia, and euglycemia during CGM use. Other end points included the following questionnaire results: Diabetes Treatment Satisfaction status (minimum score, 0; maximum, 36; higher value indicates better satisfaction) and change in satisfaction (minimum, −18; maximum, 18; higher value indicates better change in satisfaction), WHO-5 Well-Being Index (minimum, 0; maximum, 100, higher value indicates better well-being), Hypoglycemic Fear Behavior Scale (minimum, 0; maximum, 4; higher value indicates greater fear) and Hypoglycemic Fear Worry Scale (minimum, 0; maximum, 4; higher value indicates greater fear), and the Problem Areas In Diabetes scale (minimum, 0; maximum, 100; higher value indicates greater problems). Other end points were the number of self-measurements of blood glucose and rate of severe hypoglycemia, defined as unconsciousness from hypoglycemia or requiring assistance from another person. All end points were described in the original protocol submitted to the ethical committee before study start (Supplement 1). At study start, the protocol was amended to substitute number of self-measurements of blood glucose as an end point for total insulin dose, and the Hypoglycemia Confidence Questionnaire was added.

Statistics

The reduction 0.3% (3 mmol/mol) in HbA_{1c} is generally considered a clinically meaningful reduction to reduce diabetic long-term complications.[23,24] The study was powered to detect a difference of 0.3% (3 mmol/mol) in HbA_{1c} between weeks 26 and 69 at 90% power and assuming a standard deviation of 1.1%, which required 144 participants. Assuming a dropout rate of 10%, 160 individuals were required for enrollment. No interim analysis was performed.

Figure 1. Screening, Randomization, and Analysis for Continuous Glucose Monitoring and Conventional Treatment Groups



CGM indicates continuous glucose monitoring.

[a] Other reasons for the CGM-first group were dermatological reaction (1), preference to continuing use of CGM (2), preference to switch to insulin pump (1), paracetamol (acetaminophen) use for shoulder pain (1), and unwillingness to proceed (1); for the conventional therapy–first group, other reasons were lack of time (1) and patient request (1).

[b] Patient had no follow-up data reported during period 2 of the study.

[c] Follow-up data maintained during period 2 of the study.

The full analysis set consisted of all randomized patients who had at least 1 follow-up measurement in each treatment period. The safety analysis consisted of all randomized patients who received treatment (CGM or conventional therapy) at any time with patients assigned to treatment administered but not randomized treatment.

The primary efficacy analysis was the difference in HbA_{1c} at weeks 26 and 69 between CGM and conventional therapy

for the full analysis set, with adjustment for treatment period and patient effects using procedure for generalized linear models in SAS software, with sequence, patient (sequence), period, and treatment as class variables.

The last observation carried forward principle was applied for any missing efficacy measurements from the last weeks of each treatment period. Last observation carried forward was not applied to measurements at the first visit in each treatment period. A post hoc sensitivity analysis of primary outcome was performed by multiple imputation with 50 study samplings on all patients randomized by using demographics, baseline characteristics, baseline comorbidities, and HbA_{1c} values at run in and randomization as imputation variables. A second post hoc sensitivity analysis investigating the effect of the site and interaction between site and treatment modeled as fixed effects on the primary outcome was performed.

Secondary efficacy analyses of normally distributed variables were also adjusted for treatment period and patient effects on the full analysis set. For other secondary efficacy variables, the Fisher nonparametric 2-sample permutation test was used to test between treatment sequences on period changes (except for analysis of the occurrence of severe hypoglycemic events in which the treatment groups were handled as 2 independent samples and tested using the Fisher exact test).

The theory of sequential multiple test procedures was applied for the primary and secondary confirmatory analyses. If a 2-sided test gave a significant result at the .05 significance level, the total test mass of .05 was transferred to the next variable in the test sequence until a nonsignificant result was achieved. All these significant tests were then considered confirmatory. All other end points are considered descriptive and are presented in eTable 3 (in Supplement 2).

Calculations were performed using SAS statistical software version 9.4.

Results

Patient Characteristics

The numbers of patients screened, randomized, and not completing the study are shown in Figure 1. There were 161 patients randomized between February and December 2014. The mean age was 43.7 years, 45.3% were women, and mean HbA_{1c} was 8.6% (70 mmol/mol). Of the 161 randomized patients, 142 (88.0%) had follow-up data during both treatment periods in the full analysis set population. Characteristics of patients in the full analysis set population by treatment sequence are shown in **Table 1**. The mean (SD) age was 44.6 (12.7) years, and 56.3% were men. Mean HbA_{1c} was 8.7% (SD, 0.8%) (72 mmol/mol), and mean diabetes duration was 22.2 (11.8) years. Data from the run-in visit are provided in **Table 2**. For the primary efficacy outcome HbA_{1c}, full analysis set population, the LOCF imputation was done for 2 (2.9%) patients at the end of CGM therapy and 3 (4.1%) at the end of conventional therapy.

Glycemic Outcomes

Results of prespecified analyses of the primary and secondary end points are shown in **Table 3**. For the primary efficacy analysis, mean (SD) HbA_{1c} during CGM use was 7.92% (0.8%) (63 mmol/mol) and during conventional treatment was 8.35% (0.9%) (68 mmol/mol) (mean difference, −0.43% [95% CI, −0.57% to −0.29%] or −4.7 mmol/mol [95% CI, −6.27 to −3.13 mmol/mol]); $P < .001$). HbA_{1c} was lower in CGM-treated patients during the first and second treatment periods, whereas levels were similar at the beginning of both periods (**Figure 2**). The standard deviation of blood glucose estimated by CGM and compared with masked CGM during conventional treatment was lower during CGM use than conventional therapy (68.49 vs 77.23 mg/dL; $P < .001$) as was the case for mean amplitude of glycemic excursions (Table 3).

Well-being, Treatment Satisfaction, Diabetes Distress, and Hypoglycemic Fear and Confidence

Results of prespecified analyses of patient-reported outcomes of well-being and diabetes treatment satisfaction are shown in Table 3. Overall well-being, estimated with the WHO-5 questionnaire, improved during CGM use (66.1 vs 62.7; $P = .02$). Treatment satisfaction was higher during CGM use as measured by the Diabetes Treatment Satisfaction Questionnaire status version (30.21 vs 26.62; $P < .001$) and also for the change version (13.20 vs 5.97; $P < .001$). The Hypoglycemia Confidence Questionnaire scale showed less hypoglycemia fear in favor of CGM (3.40 vs 3.27; $P < .001$)(Table 3). Using the theory of sequential tests, the analysis of the primary variable (HbA_{1c}) and the secondary variables (mean glucose levels, mean amplitude of glycemic excursions, standard deviation of glucose levels, Diabetes Treatment Satisfaction Questionnaire status and change versions, and WHO-5 Well-Being Index) were considered confirmatory. Other secondary end points were not tested, and descriptive data for these variables are shown in eTable 3 (in Supplement 2).

Treatment Adherence

Overall mean time of CGM use, estimated by the proportion of CGM data downloaded in relation to follow-up time, was 87.8% during CGM treatment periods. CGM use ranged between 86.5% and 91.9% during various study visits (eTable 1 in Supplement 2). HbA_{1c} was reduced by 0.46% (0.31%-0.61%) in patients using the CGM sensor more than 70% of the time, and there was no significant difference in HbA_{1c} for those using the CGM sensor for less than 70% of the time.

Self-measurement of Blood Glucose

Patients performed a mean (SD) of 2.75 (1.39) self-measurements of blood glucose during CGM therapy and 3.66 (2.30) during conventional therapy.

Patients Not Included in the Full Analysis Set Population

There were 19 patients (11.8%) excluded from the full analysis set population (Figure 1) for lack of follow-up data in the second treatment period. Patient characteristics are shown in eTable 2 in Supplement 2). These patients were younger (37.2 vs 44.6 years; $P = .02$), had higher HbA_{1c} (9.4% vs 8.5%; $P < .001$), and had a history with more severe hypoglycemia events both during the last year (0.37 vs 0.07; $P = .01$) and the past 5 years (1.79 vs 0.60; $P = .04$) compared with individuals in the full analysis set population. In the first treatment period, 16 of these 19 patients had

follow-up data of the primary effect variable HbA_{1c}. Of these, patients treated with CGM (n = 11) had reduced HbA_{1c} from randomization to follow-up—from 9.4% to 8.4% (reduction, 1.0%)—whereas patients with conventional therapy had increased HbA_{1c} from 9.9% to 10.0% (increase, 0.1%).

Hypoglycemia

During CGM use, the mean (SD) percentage of time patients were in a hypoglycemic range (<70 mg/dL) was 2.79% (2.97%) and 4.79% (4.03%) during conventional therapy and for glucose levels of less than 54 mg/dL, the percentage of time was 0.79% (1.23%) during CGM use and 1.89% (2.12%) during conventional therapy. There were 5 events of severe hypoglycemia during conventional treatment (event rate, 0.19 per 1000 patient-years) and 1 event occurred during CGM therapy (event rate, 0.04 per 1000 patient-years). There were 7 severe hypoglycemia events during the washout period when patients were undergoing conventional therapy (event rate, 0.41 per 1000 patient-years).

Adverse Events

In total, there were 77 patients with 137 adverse events during CGM and 67 patients with 122 adverse events during conventional therapy (eTable 4 in Supplement 2). There were no obvious numerical differences for any adverse event between the treatments. One patient in the CGM group discontinued use because of an allergic reaction to the sensor. There were 7 patients with a total of 9 serious adverse events during CGM treatment and 3 patients with total of 9 serious adverse events during conventional treatment (eTable 5 in Supplement 2). Ketoacidosis was not reported during the study.

Sensitivity Analyses of the Primary Outcome HbA_{1c}

In a sensitivity analysis (performed by using multiple imputation) of the primary outcome, including all participants in the trial (n = 161), the effect on HbA_{1c} by CGM was 0.39% (95% CI, 0.24%-0.55% [$P < .001$]). The second sensitivity analysis of primary outcome (adjusted for the site effect and interaction between site and treatment) showed an HbA_{1c} reduction of 0.43% (95% CI, 0.22%-0.64% [$P < .001$]) for CGM use vs conventional therapy. The interaction between site and treatment term was not significant ($P = .84$).

Post hoc Analysis

The weight at the end of conventional therapy was 82.5 kg and for CGM therapy was 83.1 kg (mean difference, 0.63 [$P = .01$]) and total daily insulin dose was 57.8 U (0.69 units/kg) at the end of conventional therapy and 56.5 U (0.67 units/kg) for CGM therapy (mean difference for total dose in U/kg, −0.02 [$P = .01$]).

Discussion

In this crossover study of persons with type 1 diabetes treated with multiple daily insulin injections, CGM was associated with a mean HbA_{1c} level that was 0.43% (4.7 mmol/mol) less than conventional treatment. Moreover, glycemic variability was reduced by CGM. Subjective well-being and treatment satisfaction were greater during CGM than conventional therapy.

Table 1. Clinical Characteristics of the Full Analysis Set Population at Baseline and Randomization[a]

Variable	CGM First (n = 69)	Conventional Therapy First (n = 73)
Demographic and Clinical Data		
Age at inclusion visit, mean (SD), y	46.7 (13.0)	42.6 (12.2)
Sex, No. (%)		
Men	37 (53.6)	43 (58.9)
Women	32 (46.4)	30 (41.1)
Race, No. (%)		
Black	0	1 (1.4)
White (including Middle East and North Africa)	69 (100.0)	72 (98.6)
Hispanic ethnicity	0	0
Weight at randomization visit, mean (SD), kg	81.3 (14.7)	83.0 (17.1)
Body mass index at randomization visit, mean (SD)	27.0 (4.1)	27.2 (4.8)
HbA_{1c} (NGSP) at inclusion visit, mean (SD), %	8.71 (0.8)	8.70 (0.9)
HbA_{1c} (NGSP) at randomization visit, mean (SD), %	8.49 (0.9)	8.45 (0.9)
Time from diabetes onset to inclusion visit, mean (SD), y	23.4 (11.9)	21.0 (11.7)
Smoking at inclusion visit, No. (%)		
Current	7 (10.1)	10 (13.7)
Previous	17 (24.6)	15 (20.5)
Never	45 (65.2)	48 (65.8)
Treatment Use at Randomization Visit		
Base insulin type, No. (%)		
Insulatard (NPH insulin)	2 (2.9)	1 (1.4)
Glargine	55 (79.7)	57 (78.1)
Detemir	8 (11.6)	12 (16.4)
Degludec	4 (5.8)	3 (4.1)
Meal insulin type, No. (%)		
Lispro	28 (40.6)	25 (34.2)
Aspart	35 (50.7)	45 (61.6)
Glulisine	4 (5.8)	3 (4.1)
Insulin regular human	2 (2.9)	0 (0.0)
Total daily meal insulin dose, mean (SD), U	26.8 (14.1)	28.2 (12.7)
Total daily base insulin dose, mean (SD), U	29.6 (11.9)	30.9 (15.5)
Total daily insulin dose, U		
Mean (SD)	56.4 (21.6)	59.1 (24.7)
No. of insulin injections, mean (SD), per d	4.90 (1.06)	4.75 (0.86)
Median (range)	5.00 (1.00-7.00)	5.00 (2.00-8.00)
No. of insulin injections (categories), No. (%), per d		
<3	2 (2.9)	1 (1.4)
≥3	67 (97.1)	72 (98.6)
Metformin used, No. (%)	2 (2.9)	0
Other glucose-lowering medication, No. (%)	0	0

Abbreviations: CGM, continuous glucose monitoring; HbA_{1c}, hemoglobin A_{1c}; NGSP, National Glycohemoglobin Standardization Program.

[a] Categorical variables are reported as No. (%), continuous variables as mean (SD), and not normally distributed continuous variables are reported as mean (SD), median (range).

Table 2. Clinical and Questionnaire Data at Run-in Visit[a]

Variable	CGM First (n = 69)	Conventional Therapy First (n = 73)
Glucose Data		
Glucose level, mean (SD), mg/dL[b]	193.7 (31.4)	194.5 (31.3)
Mean amplitude glycemic excursions, mean (SD), mg/dL[c]	183.5 (31.8)	180.3 (29.1)
Glucose levels, mg/dL, mean (SD)[b]	80.1 (13.2)	77.5 (12.7)
Percent of time with low glucose levels <54 mg/dL[b]		
Mean (SD)	2.31 (2.39)	2.06 (2.42)
Median (range)	1.75 (0.00-10.02)	1.11 (0.00-12.33)
Percent of time with low glucose levels <70 mg/dL[b]		
Mean (SD)	5.52 (4.33)	5.12 (4.24)
Median (range)	4.89 (0.00-16.12)	4.32 (0.09-19.97)
Percent of time with high glucose levels >180 mg/dL, mean (SD)[b]	45.4 (14.3)	49.8 (13.4)
Percent of time with high glucose levels above 250 mg/dL, mean (SD)[b]	22.1 (11.6)	23.0 (11.3)
Percent of time with euglycemic levels 99-180 mg/dL, mean (SD)[b]	29.8 (11.1)	31.2 (13.3)
Percent of time with euglycemic levels 70-180 mg/dL, mean (SD)[b]	37.9 (14.6)	39.5 (16.6)
Medical history at inclusion visit, No. (%)		
Previous laser photocoagulation of the retina	14 (20.3)	14 (19.2)
Previous myocardial infarction	3 (4.3)	0
Previous stroke	1 (1.4)	1 (1.4)
Previous bypass graft	1 (1.4)	0
Previous PCI	2 (2.9)	0
Previous amputation	0	1 (1.4)
Previous diabetic foot (or leg) ulcer	1 (1.4)	5 (6.8)
Current diabetic foot (or leg) ulcer	0	3 (4.1)
No. of hypoglycemia events/wk during the last 2 months at inclusion visit[c]		
Mean (SD)	1.90 (1.48)	2.36 (2.23)
Median (range)	1.75 (0.00-7.00)	2.00 (0.00-12.00)
No. of patients	66	68
No. of severe hypoglycemia events during the past year[d]		
Mean (SD)	0.101 (0.425)	0.042 (0.262)
Median (range)	0.0 (0.0-3.0)	0.0 (0.0-2.0)
No. of patients	69	72
No. of severe hypoglycemia events in past 5 y[d]		
Mean (SD)	0.884 (3.042)	0.319 (0.709)
Median (range)	0.0 (0.0-20.0)	0.0 (0.0-4.0)
Questionnaires		
DTSQ total scale		
Mean (SD)	25.8 (6.1)	24.6 (5.8)
Median (range)	27.0 (4.0-36.0)	25.0 (5.0-36.0)
No. of patients	68	73
WHO-5 Well-Being Index		
Mean (SD)	62.8 (16.6)	57.3 (18.0)
Median (range)	68.0 (12.0-92.0)	64.0 (20.0-100.0)
No. of patients	68	73
SWE-HFS Behavior/Avoidance		
Mean (SD)	1.99 (0.58)	1.85 (0.58)
Median (range)	2.00 (1.00-3.70)	1.80 (0.60-3.30)
No. of patients	68	73
SWE-HFS Worry		
Mean (SD)	0.808 (0.740)	0.880 (0.609)
Median (range)	0.6 (0.0-3.6)	0.8 (0.0-2.8)
No. of patients	68	72
SWE-PAID-20 total scale		
Mean (SD)	24.4 (17.6)	26.8 (16.8)
Median (range)	21.9 (0.0-83.8)	23.8 (2.5-72.5)
No. of patients	68	73
HCQ total scale		
Mean (SD)	3.25 (0.47)	3.22 (0.48)
Median (range)	3.22 (2.13-4.00)	3.28 (2.11-4.00)
No. of patients	67	70

Abbreviations: CGM, continuous glucose monitoring; DTSQ, the Diabetes Treatment Satisfaction Questionnaire; HbA_{1c}, hemoglobin A_{1c}; HCQ, Hypoglycemic Confidence Questionnaire; NPH, negative pH; PCI, percutaneous coronary intervention; SWE-HFS, Swedish Hypoglycemic Fear Scale; SWE-PAID-20, Swedish Problem Areas in Diabetes-20 scale; WHO-5, World Health Organization-5.

SI conversion factor: To convert glucose to mmol/L, multiply values by 0.0555.

[a] Categorical variables are reported as No. (%), continuous variables as mean (SD), and not normally distributed continuous variables are reported as mean (SD), median (range).

[b] Number of patients in the CGM-first group was 63; number in the conventional therapy–first group was 69.

[c] Subjective estimation not based on blood glucose values.

[d] Severe hypoglycemic events are defined as unconsciousness due to hypoglycemia or need of assistance from another person to resolve the hypoglycemia.

The population evaluated in the current study differs to a great extent from earlier clinical trials of CGM.[7-10,25,26] The current study aimed to include a more general population of persons with type 1 diabetes. In contrast to earlier trials, the current study had no upper limit of HbA_{1c} for inclusion, which includes the group of patients with the greatest excess mortality[27,28] and the highest risk of diabetic complications since an exponential relationship exists between higher HbA_{1c} levels and diabetic complications.[23] Hence, finding treatment options for reducing HbA_{1c} in these patients is of great concern. Baseline HbA_{1c} was also high (8.7%) in the current population, and not only was mean HbA_{1c} reduced but fewer patients also had very high HbA_{1c} levels during CGM therapy.

Table 3. Primary and Secondary End Points

	CGM, Mean (95% CI)	Conventional Therapy, Mean (95% CI)	Least Square Means or Mean for Difference: CGM−Conventional Treatment (95% CI)[a]	*P* Value
Primary end point				
HbA_{1c}, %[b]	7.92 (7.79 to 8.05)	8.35 (8.19 to 8.51)	−0.43 (−0.57 to −0.29)	<.001
HbA_{1c}, mmol/mol	63 (61.6 to 64.5)	68 (66.0 to 69.4)	−4.7 (−6.27 to −3.13)	
No. of patients	142	142		
Secondary end points (sequential testing performed)[c]				
Mean glucose level, mg/dL[d]	186.93 (181.66 to 192.20)	193.68 (188.31 to 199.04)	−6.61 (−12.01 to −1.20)	.02
No. of patients	133	133		
Mean amplitude glycemic excursions, mg/dL[d]	161.93 (156.94 to 166.91)	180.96 (175.72 to 186.20)	−19.36 (−24.26 to −14.46)	<.001
No. of patients	123	127		
SD of glucose levels, mg/dL[d]	68.49 (66.36 to 70.63)	77.23 (74.96 to 79.50)	−8.69 (−10.76 to −6.61)	<.001
No. of patients	133	133		
DTSQ status version, scale total	30.21 (29.47 to 30.96)	26.62 (25.61 to 27.64)	3.43 (2.31 to 4.54)	<.001
No. of patients	136	137	131	
DTSQ change version, scale total[e]	13.20 (12.13 to 14.28)	5.97 (3.64 to 8.30)	3.76 (1.70 to 5.82)	<.001
No. of patients	69	67	136	
WHO-5 Well-Being Index	66.13 (62.94 to 69.32)	62.74 (60.18 to 65.31)	3.54 (0.61 to 6.48)	.02
No. of patients	139	140		
Hypoglycemic Fear Scale Behavior/Avoidance	1.93 (1.83 to 2.03)	1.91 (1.81 to 2.00)	0.03 (−0.05 to 0.10)	.45
No. of patients	140	140		
HCQ, scale total[f]	3.40 (3.32 to 3.47)	3.27 (3.18 to 3.35)	0.12 (0.05 to 0.19)	<.001
No. of patients	137	137	135	
Follow-up time, d	182 (180 to 187)	182 (175 to 187)		
No. of patients	142	142		

Abbreviations: CGM, continuous glucose monitoring; DTSQ, the Diabetes Treatment Satisfaction Questionnaire; HCQ, Hypoglycemic Confidence Questionnaire; WHO-5, World Health Organization-5.

[a] Least-square means (95% CIs) and *P* value were calculated using SAS procedure PROC GLM with sequence, patient (sequence), treatment period, and treatment as class variables (calculated only for normally distributed variables). For other variables in which nonparametric tests were performed, values are reported as mean (95% CI).

[b] Values are reported as last observation carried forward with HbA_{1c} measurement standardized by the National Glycohemoglobin Standardization Program.

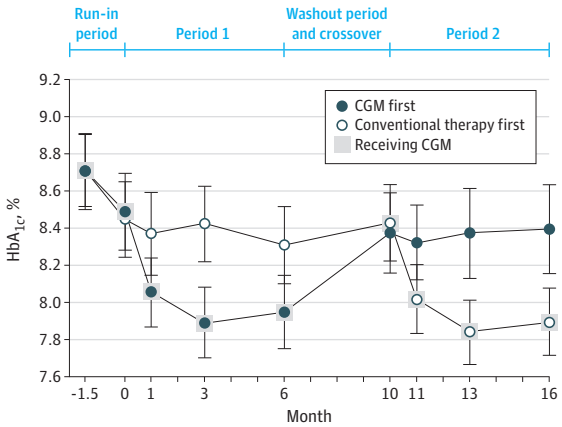
[c] Other prespecified secondary end points and descriptive data (eTable 3 in Supplement 2) were not tested due to the rule of sequential testing (hypoglycemic fear scale-worry, problem areas in diabetes scale, percent of time with high and euglycemic levels, number and percent of patients reducing their HbA_{1c} by 0.5% and by 1%).

[d] Data were measured by CGM during 2 weeks.

[e] Data for the DTSQ change version is collected only at the end of period 2. For the CGM therapy column, it is showing the change in satisfaction from conventional therapy to CGM therapy, and for conventional therapy column, it is showing the change from CGM therapy to conventional therapy.

[f] End point defined as exploratory in the trial protocol.

Figure 2. HbA_{1c} Values at Inclusion, Randomization, and During the 2 Different Periods of Treatment



No. of patients

CGM first	69	69	69	69	69	66	67	68	69
Conventional therapy first	73	72	71	73	73	73	70	73	73

Hemoglobin A1c (HbA_{1c}) was measured according to the National Glycohemoglobin Standardization Program (NGSP). Data markers and error bars indicate mean (95% CIs). Data were plotted using the last-observation-carried-forward approach.

Also in contrast to earlier CGM-studies,[7-10,25,26] the current trial had no limit on the number of self-measurement of blood glucose patients were required to perform for inclusion. Patients who do not perform self-measurement of blood glucose regularly have higher HbA_{1c} levels.[4] Despite the availability of free glucose meters and test strips in Sweden, less than 50% of patients perform self-measurement of blood glucose according to guidelines (>4 times/d). Hence, evaluating alternative glucose monitoring strategies for these patients is also important. In the present study, patients performed self-measurement of blood glucose less during CGM than conventional therapy (2.7 vs 3.7 measurements/d).

When used in connection with an insulin pump, CGM may ease adjusting insulin doses with respect to observed CGM patterns.[2] Certain processes in the pump can also be guided by CGM information, such as halting the insulin infusion during a rapid decline in glucose.[26] Conversely, most adults with type 1 diabetes are treated with multiple daily insulin injections.[29] Therefore, novel complementary treatment strategies are needed on a broad level. In the intervention/control sequence, HbA_{1c} reverted back to prestudy levels during the washout period (Figure 2), indicating that there was no carry-over effect. In accordance with earlier findings,[9] these results also suggest that the effectiveness of CGM depends on uninterrupted use during multiple daily insulin injections treatment. Our study increases knowledge in the field of type 1 diabetes in reporting that CGM may be a beneficial option for multiple daily insulin injections-treated patients with respect to HbA_{1c} levels.

A novel feature of this trial is a more comprehensive investigation of psychosocial variables, which are now recognized as a high priority in clinical diabetes guidelines.[30] To our knowledge, this trial is the first to demonstrate a significant improvement in subjective well-being and treatment satisfaction in adults using CGM in comparison with conventional therapy. The positive effect on well-being is consistent with previous studies that have shown a significant effect due to CGM on the physical component subscale of the SF-36 (Short Form Health Survey).[10,31] In total, these psychosocial benefits may be at least partially due to the significant HbA_{1C} improvement,[32] as well as to the reduction in time spent in hypoglycemia. Indeed, less time in hypoglycemia is known to be associated with better quality of life[33,34] and a lower risk of severe hypoglycemia.[35,36] Furthermore, hypoglycemic confidence improved during CGM therapy, but it should be interpreted with greater caution since this was an exploratory end point. Of note from a safety perspective, there were numerically more severe hypoglycemic episodes (5 vs 1) during conventional compared with CGM therapy. In addition, 7 severe hypoglycemia events occurred during the washout period of 4 months when patients used conventional therapy.

This study had a number of limitations. First, 19 patients (approximately 12.0%) had no follow-up data in the second treatment period and were not included in the primary analysis. Generally, in a parallel-group study, this can lead to an imbalance between groups. However, in the current study, patients served as their own controls and thus no such problem existed. It has therefore been proposed that the full analysis set population should be used in crossover studies as the main analysis.[37] In addition, with the crossover design, it can be determined whether results are going in the same direction during the first treatment period from a parallel design perspective. Sixteen of the 19 patients who had no follow-up data in the second treatment period had HbA_{1c} data during the first follow-up period. Among these patients, those with CGM had a 1.0% decrease in HbA_{1c}, whereas those with conventional therapy had an increase of 0.1%. There were more patients treated with CGM than conventional therapy who discontinued treatment during the first treatment period. This was due to patients wanting to continue CGM and therefore not completing the study while receiving conventional therapy in the second period and also due to patients experiencing device-related problems (Figure 1).

A second limitation is that the study could not be blinded and hence patients were aware of the intervention. It cannot be excluded that this, to some extent, could have influenced the treatment effect. Although the current reduction in HbA_{1c} may be clinically important, other treatment alternatives are needed for persons with type 1 diabetes to obtain good glycemic control on a broad level. In addition, the current results are restricted to patients with HbA_{1c} of at least 7.5%.

Conclusions

Among patients with inadequately controlled type 1 diabetes treated with multiple daily insulin injections, the use of CGM compared with conventional treatment for 26 weeks resulted in lower HbA_{1c}. Further research is needed to assess clinical outcomes and longer-term adverse effects.

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Author Contributions: Dr Lind had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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