Sustained Intensive Treatment and Long-term Effects on HbA_{1c} Reduction (SILVER Study) by CGM in People With Type 1 Diabetes Treated With MDI

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OBJECTIVE

Continuous glucose monitoring (CGM) reduces HbA_{1c} and time spent in hypoglycemia in people with type 1 diabetes (T1D) treated with multiple daily insulin injections (MDI) when evaluated over shorter time periods. It is unclear to what extent CGM improves and helps to maintain glucose control, treatment satisfaction, diabetes distress, hypoglycemic concerns, and overall well-being over longer periods of time.

RESEARCH DESIGN AND METHODS

The GOLD trial was a randomized crossover trial performed over 16 months of CGM treatment in people with T1D treated with MDI. People completing the trial (n = 141) were invited to participate in the current SILVER extension study in which 107 patients continued CGM treatment over 1 year along with the support of a diabetes nurse every 3 months.

RESULTS

The primary end point of the change in HbA_{1c} over 1.0–1.5 years of CGM use compared with previous self-monitoring of blood glucose during GOLD showed a decrease in HbA_{1c} of 0.35% (95% CI 0.19–0.50, P < 0.001). Time spent in hypoglycemia <3.0 mmol/L (54 mg/dL) and <4.0 mmol/L (72 mg/dL) decreased from 2.1% to 0.6% (P < 0.001) and from 5.4% to 2.9% (P < 0.001), respectively. Overall well-being (World Health Organization 5-item well-being index, P = 0.009), treatment satisfaction (Diabetes Treatment Satisfaction Questionnaire, P < 0.001), and hypoglycemic confidence (P < 0.001) increased, while hypoglycemic fear (Hypoglycemia Fear Survey–Worry, P = 0.016) decreased and diabetes distress tended to decrease (Problem Areas in Diabetes Scale, P = 0.06). From randomization and screening in GOLD, HbA_{1c} was lowered by 0.45% (P < 0.001) and 0.68% (P < 0.001) after 2.3 and 2.5 years, respectively.

CONCLUSIONS

The SILVER study supports beneficial long-term effects from CGM on HbA_{1c}, hypoglycemia, treatment satisfaction, well-being, and hypoglycemic confidence in people with T1D managed with MDI.

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Maintaining glycemic levels within recommended targets is essential for reducing the risk of long-term complications in people with type 1 diabetes (T1D) (1,2). A major barrier for lowering mean glucose levels is hypoglycemia (1). Lowering glucose levels requires insulin delivery via insulin pump or multiple daily insulin injections (MDI) (3,4). Continuous glucose monitoring (CGM) or self-monitoring of blood glucose (SMBG) by capillary finger-stick testing are used to guide the patient on insulin dosing and other activities to optimize glucose levels (5,6).

In people using MDI, which is still the most common insulin delivery method worldwide in adults with T1D, CGM has been shown to be more efficient than SMBG in optimizing glucose levels (7,8). However, key clinical trials of CGM only followed patients without blinded treatments for 24–26 weeks. Initially, patients had frequent visits and were without support from diabetes staff for only 3 months (7,8). Since diabetes is a life-long chronic disease, it is important to understand effects of CGM over a longer period of time and with support that is more in line with clinical practice.

The aim of this study was to evaluate the effects of CGM in adults with T1D managed with MDI and guideline-based clinical support over 1 year. Together with the previous GOLD trial, the current SILVER study comprised 2.5 years of follow-up using CGM and SMBG.

RESEARCH DESIGN AND METHODS

Overall Study Design

The SILVER study was a 1-year extension of the GOLD trial. GOLD was a randomized, multicenter crossover trial evaluating the effects of CGM versus SMBG in people with T1D treated with MDI (8).

GOLD Trial

The GOLD trial has previously been described in detail (8–10) and constitutes the first 16 months of follow-up in the current study. People with T1D managed with MDI were randomized in a crossover design to start CGM (Dexcom G4; Dexcom, Inc., San Diego CA) or SMBG for 26 weeks, with a 17-week wash-out period between treatment phases. Adults $\geq$18 years with HbA_{1c} $\geq$7.5% (58 mmol/mol) managed with MDI were included. Other inclusion and exclusion criteria have previously been described (8,9). During a run-in period of up to 6 weeks, participants completed masked CGM for 2 weeks and questionnaires including overall well-being (World Health Organization 5-item well-being index [WHO-5]) (11), treatment satisfaction (Diabetes Treatment Satisfaction Questionnaire [DTSQ]) (12,13), hypoglycemic confidence (Hypoglycemic Confidence Scale [HCS]) (14), fear of hypoglycemia (Hypoglycemia Fear Survey [HFS-II]) (15–17), diabetes-related distress (Problem Areas in Diabetes Scale [PAID]) (18,19), and physical activity (International Physical Activity Questionnaire [IPAQ]) (20). Masked CGM was also performed during the last 2 weeks of the SMBG period and during the wash-out period.

SILVER Study

The SILVER study was an investigator-initiated, open-label, clinical trial following participants over 1 year approved by the ethical committee at the University of Gothenburg, Gothenburg, Sweden. It was carried out at 13 hospitals in Sweden.

Among 141/161 (87.6%) participants who completed the GOLD trial, 138/141 (97.9%) were invited to participate in the SILVER study. Of those, 107 (77.5%) were enrolled and comprised the safety population. All enrolled participants gave verbal and written informed consent. Exclusion criteria were *1*) planned pregnancy for the study duration or pregnancy during the last 6 months; *2*) required continuous use of paracetamol (because paracetamol can interact with CGM-measurements by DexComG4); *3*) history of allergic reaction to any of the CGM materials or adhesives in contact with the skin, chlorhexidine, or alcoholic antiseptic solution; *4*) severe cognitive dysfunction or other disease as judged by the investigator to be unsuitable for inclusion; *5*) abnormal skin at the anticipated glucose sensor attachment sites; and *6*) other investigator-determined criteria making patients unsuitable for participation.

All participants received CGM (Dexcom G4 or G5). Clinical visits to a diabetes nurse occurred at weeks 13, 26, 39, and 52. If it was clinically indicated due to very high HbA_{1c} in accordance with guidelines, an extra visit at 6 weeks could be scheduled. At each visit, CGM and SMBG data were downloaded; HbA_{1c} was measured; and 10 guidelines for glucose control optimization during CGM use were discussed (9). These included advice for the adjustment of insulin doses based on CGM curves and recommendations for what glucose level the alarms could be set at in the CGM system warning for low and high glucose levels. Severe hypoglycemia was defined as unconsciousness or the need for assistance to resolve the event. At weeks 26 and 52, participants completed the same questionnaires that were administered during the GOLD trial.

Laboratory tests were analyzed at the same central laboratory as used in the GOLD trial (Karolinska University Hospital, Stockholm, Sweden). HbA_{1c} levels were reported in mmol/mol and converted to percent according to the NGSP standard for dual reporting (21). Gothia Forum (Gothenburg, Sweden) performed trial monitoring.

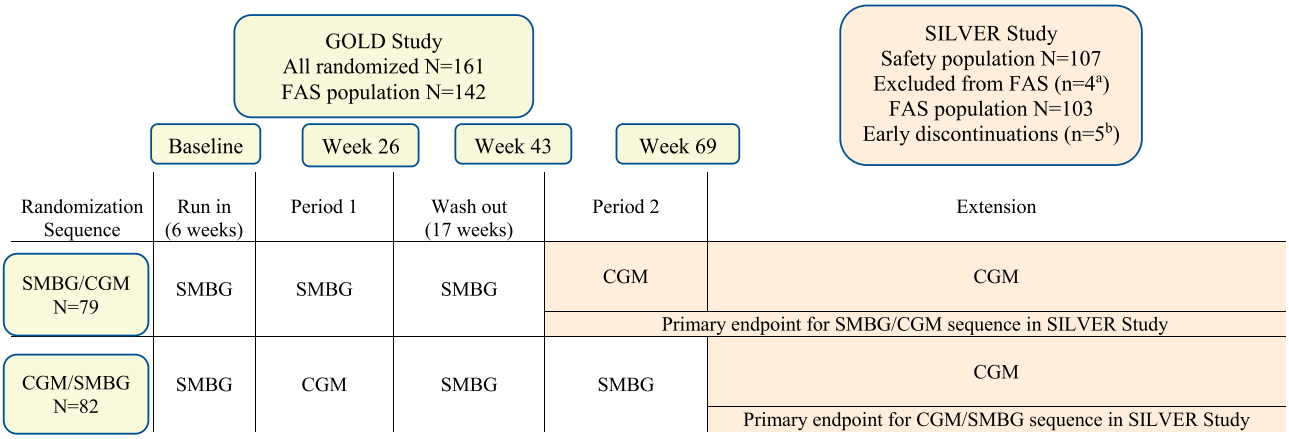
Primary and Secondary End Points

The primary end point was change between HbA_{1c} at the end of the SMBG period in the GOLD study (before long-term CGM use) and at the end of the SILVER study (Fig. 1). For the SMBG/CGM sequence in GOLD, comparisons were performed between HbA_{1c} at the start of CGM in GOLD and at the end of SILVER. For the CGM/SMBG sequence, comparisons were performed between HbA_{1c} at the end of GOLD and at the end of SILVER (Fig. 1).

Secondary end points were evaluated over the same time period as for HbA_{1c} and were hierarchically tested in the following order: *1*) time in hypoglycemia ($<$3.0 mmol/L [54 mg/dL]); *2*) time in hypoglycemia ($<$4.0 mmol/L [72 mg/dL]); and *3*) time in range (TIR) (4–10 mmol/L [72–180 mg/dL]). All end points were even analyzed between the start of GOLD and end of SILVER.

Exploratory End Points

The following variables based on CGM data were analyzed over the same time period as the primary and secondary end points described above: mean glucose level, mean amplitude of glycemic excursions (MAGE), SD, time in hyperglycemia ($>$10 mmol/L [180 mg/dL] and $>$13.9 mmol/L [252 mg/dL]), and time with glucose levels 5.5–10 mmol/L (99–180 mg/dL). All end points were even analyzed between the start of GOLD and the end of SILVER together with the six patient-reported outcomes (WHO-5, DTSQ, HFS-II, HCS, PAID, and IPAQ). We also evaluated whether the HbA_{1c} effect



[a] Lost to follow-up (n=1), pregnancy or intentions of becoming pregnant (n=1), non-compliance with study procedure (n=1), stress-related issues (n=1).
[b] Lost to follow-up (n=1), non-compliance with study procedures (n=3) and withdrawn consent (n=1).

Figure 1—A schematic picture of the study design for GOLD/SILVER showing when the primary and secondary end points were evaluated.

was sustained when HbA_{1c} levels were compared at the end of the CGM period in GOLD versus the levels at the end of SILVER.

Statistics

Power calculations showed that including 129 individuals to detect a difference in HbA_{1c} of 0.3% with an assumed SD of 1.1% would be required to achieve 87% power. Including 97 individuals assuming a SD of 1.0% for HbA_{1c} and detecting the same effect on HbA_{1c} would achieve 83% power.

Continuous variables and their changes were described as mean (SD), median (range), and 95% CI based on either normal distribution or by using the inversion of Fisher's nonparametric permutation test for nonnormally distributed variables, as applicable, and categorical variables as number and percentage.

The change in variables before the start of CGM until the end of the study was tested using paired *t* test for normally distributed continuous variables, Fisher's nonparametric permutation test for paired data with nonnormally distributed continuous variables, and the sign test for changes in ordered categorical and dichotomous variables.

The primary and secondary analyses were performed on the full analysis set (FAS) population using patients with available data, i.e., missing data were not imputed. The theory of fixed sequential testing was applied for the primary and secondary analyses. The total test mass of 0.05 was transferred to the next-in-order variable in the case of achieved significance, and all significant results were considered confirmative. The first nonsignificant result in the testing procedure led to cessation of further statistical testing (22).

All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC). All statistical tests were two-tailed and conducted at 0.05 significance level.

Post Hoc Analyses

Primary analysis was performed *1*) on population excluding patients not requiring additional visits, *2*) on a subgroup of patients with >70% compliance measured by CGM wear time, *3*) on a subgroup of patients with >80% compliance, and *4*) divided by the randomized sequence in the GOLD trial. The association between the change in HbA_{1c} during the SILVER study and the following variables was performed using the Spearman correlation: number of visits performed and percent compliance. Achieved target levels of ≤52 mmol/mol (≤6.9%) and TIR 4–10 mmol/L (72–180 mg/dL) were obtained.

Data and Resource Availability

Data can be accessed after a written research proposal and support from investigators and upon request and after legal procedures have taken place for making a data transfer possible.

RESULTS

Figure 1 shows a schematic of the participants questioned for participation, those who were included, and those who discontinued in the SILVER study. In total, 107 people were enrolled and followed for a median of 1.2 years (range 1.0–1.5 years) in the study between December 22, 2014, and June 1, 2017. On average, the participants had five visits with a median interval of 92 days (91–94 days) between visits. There were 20 (18.7%) participants who required additional visits. The median number of both planned and additionally performed visits was 5 (1–8). CGM data used for analyses as a measure of compliance was 71.4% (14.6–97.8%). The FAS population consisted of all enrolled people with at least one follow-up measurement and included 103/107 (96.3%) participants.

Patient Characteristics

Baseline characteristics are shown in Table 1 for participants enrolled in SILVER as well as those who completed GOLD but declined to participate in SILVER. Mean age of participants enrolled in SILVER was 45.7 years (12.7 years); mean HbA_{1c} was 8.39% (68.2 mmol/mol); 41 (38.3%) were women; and mean diabetes duration was 24.6 years (11.9 years). Females and people with shorter diabetes duration more often declined participation.

Effects over 1.0–1.5 Years CGM Treatment

Effects when treatment shifted from SMBG during the GOLD trial until the end of long-term CGM in the SILVER study are shown in Table 2. For the primary end

Table 1—Baseline characteristics

Variable	Agreed to continue and included in FAS population (n = 107)	Declined to continue SILVER study (n = 31)	P value
Age, years			0.12
Mean (SD)	45.7 (12.7)	41.6 (12.5)	
Median (min; max)	44 (19; 77)	45 (20; 65)	
n	107	31	
Sex, *n* (%)			
Male	66 (61.7)	12 (38.7)	
Female	41 (38.3)	19 (61.3)	0.039
Race, *n* (%)			
Black	1 (0.9)	0 (0.0)	
White (Caucasian, including Middle East and North Africa)	106 (99.1)	31 (100.0)	1.00
Ethnicity, *n* (%)			
Not Hispanic or Latino	107 (100.0)	31 (100.0)	1.00
Smoking, *n* (%)			
Current	8 (7.5)	9 (29.0)	
Previous	28 (26.2)	3 (9.7)	
Never	71 (66.4)	19 (61.3)	0.065
Years from diabetes onset to inclusion			0.0094
Mean (SD)	24.6 (11.9)	18.3 (11.3)	
Median (min; max)	25.2 (4.4; 58)	18.6 (1.4; 47.3)	
n	107	31	
GOLD baseline			
HbA_{1c} (mmol/mol)			0.96
Mean (SD)	71.8 (9.0)	71.6 (10.0)	
Median (min; max)	70 (58; 104)	70 (58; 98)	
n	107	31	
HbA_{1c} (%)			0.96
Mean (SD)	8.72 (0.82)	8.71 (0.91)	
Median (min; max)	8.56 (7.46; 11.67)	8.56 (7.46; 11.12)	
n	107	31	
SILVER baseline			
HbA_{1c} (mmol/mol)			0.57
Mean (SD)	68.2 (10.0)	69.4 (11.4)	
Median (min; max)	68 (48; 117)	68 (51; 96)	
n	107	30	
HbA_{1c} (%)			0.57
Mean (SD)	8.39 (0.92)	8.50 (1.04)	
Median (min; max)	8.38 (6.55; 12.86)	8.38 (6.82; 10.94)	
n	107	30	

For comparison between groups, the Fisher Exact test (lowest one-sided P value multiplied by 2) was used for dichotomous variables and the Mantel-Haenszel χ^2 test was used for ordered categorical variables and the Fisher nonparametric Permutation Test was used for continuous variables.

point, HbA_{1c} decreased over 1.0–1.5 years CGM use compared with the previous SMBG by 0.35% (3.8 mmol/mol) (95% CI 0.19–0.50% [95% CI 2.0–5.5 mmol/mol], $P < 0.001$), from 8.34% (67.6 mmol/mol) to 7.96% (63.5 mmol/mol). HbA_{1c} levels are shown in Fig. 1 over 2.5 years from screening in the GOLD trial, randomization in GOLD, different treatment phases in GOLD, and throughout the SILVER study. HbA_{1c} levels were sustained when levels at the end of GOLD were compared among patients treated with CGM and the end of the SILVER 1-year extension phase 7.93% (63.1 mmol/mol) vs. 7.96% (63.5 mmol/mol, $P = 0.40$).

The first secondary end point, i.e., the change in time spent in hypoglycemia (<3.0 mmol/L) when the previous SMBG was compared with long-term CGM treatment over 1.0–1.5 years, showed a reduction in percent of time spent in hypoglycemia per 24-h period of 2.1% vs. 0.6% (change −1.4%, 95% CI −1.9 to −0.9%, $P < 0.001$). The other two predefined secondary end points for hierarchical testing, evaluated over the same period, were both significant in favor of long-term CGM compared with earlier SMBG. The proportion of time spent in hypoglycemia per 24-h period (<4.0 mmol/L) decreased from 5.4 to 2.9%, (change −2.3%, 95% CI −3.2 to −1.5%, $P < 0.001$), time spent in range (4–10 mmol/L) increased by 8.6% (95% CI 5.1–12.0%), from 43.0 to 51.0%. Exploratory end points evaluated over the same time period were also improved by CGM, including time spent in glucose levels 5.5–10 mmol/L and time spent in high glucose levels (>10 mmol/L and >13.9 mmol/L) as well as glycemic variability estimated by SD and MAGE (Table 2).

Overall well-being (WHO-5, $P = 0.009$), treatment satisfaction (DTSQ, $P < 0.001$), and hypoglycemic confidence ($P < 0.001$) increased; while hypoglycemic fear (HFS-Worry, $P = 0.016$) decreased, and diabetes-related emotional distress tended to decrease (PAID, $P = 0.06$) during long-term CGM compared with earlier SMBG (Table 2).

Evaluations Over 2.5 Years

Compared with the start of the GOLD trial, HbA_{1c} levels and the end of the SILVER study decreased by 0.45% (4.9 mmol/mol) (95% CI 0.27–0.62% [95% CI 3.0–6.8 mmol/mol]) (Supplementary Table 1). During the same time period, the percent of time spent in hypoglycemia per 24-h period (<3.0 mmol/L) decreased from 2.12 to 0.60% ($P < 0.001$). Time spent in hypoglycemia per 24-h period (<4.0 mmol/L) decreased from 5.53 to 2.86% ($P < 0.001$). Other glycemic metrics were also improved in favor of long-term CGM compared with the start of GOLD (Supplementary Table 1). Overall well-being, assessed by the WHO-5 ($P < 0.001$), and treatment satisfaction estimated by DTSQ ($P < 0.001$) improved over the same time period (Supplementary Table 1). Moreover, confidence in one's ability to address or avoid problems related to hypoglycemia, assessed by the HCS, increased over 2.5 years ($P < 0.001$) while worries about hypoglycemia, assessed by the HFS-Worry subscale, decreased over the same time period ($P = 0.009$). Diabetes-related emotional distress, assessed by the PAID questionnaire also decreased ($P = 0.006$) (Supplementary Table 1). Compared with levels at screening in the GOLD trial and after long-term CGM use at the end of SILVER, HbA_{1c} had decreased from 8.69% (68.8 mmol/mol)

Table 2—Results of comparisons from SMBG period in GOLD (start of SILVER) to end of SILVER for primary (primary analysis), secondary (secondary analyses), and exploratory (exploratory analyses) variables

	Baseline (after conventional therapy in GOLD study)	End of SILVER study	Change from baseline to end of study	*P* value within group
Primary analysis (confirmatory test)				
HbA_{1c} (mmol/mol)				<0.0001
Mean (SD)	67.6 (8.9)	63.5 (8.6)	−3.77 (8.62)	
Median (min; max)	68 (48; 91)	63 (46; 88)	−3 (−25; 19)	
95% CI for mean	(65.8–69.3)	(61.7–65.2)	(−5.51 to −2.04)	
n	103	97	97	
HbA_{1c} (%)				<0.0001
Mean (SD)	8.34 (0.82)	7.96 (0.79)	−0.345 (0.789)	
Median (min; max)	8.38 (6.55; 10.48)	7.92 (6.36; 10.21)	−0.275 (−2.288; 1.739)	
95% CI for mean	(8.18–8.50)	(7.80–8.12)	(−0.504 to −0.186)	
n	103	97	97	
Secondary analyses (confirmatory test)				
Percent of time with glucose levels <3.0 mmol/L				0.0002
Mean (SD)	2.08 (2.48)	0.597 (0.949)	−1.41 (2.11)	
Median (min; max)	1.06 (0; 11.84)	0.246 (0; 4.936)	−0.69 (−8.31; 2.04)	
95% CI for mean	(1.57–2.59)	(0.402–0.792)	(−1.87 to −0.94)	
n	92	93	85	
Percent of time with glucose levels <4.0 mmol/L				0.0002
Mean (SD)	5.43 (5.03)	2.86 (2.77)	−2.33 (4.00)	
Median (min; max)	3.99 (0.05; 26.97)	1.92 (0; 14.15)	−1.54 (−16; 4.64)	
95% CI for mean	(4.40–6.47)	(2.29–3.44)	(−3.20 to −1.47)	
n	92	93	85	
Percent of time with glucose levels 4–10 mmol/L				<0.0001
Mean (SD)	43.0 (11.6)	51.0 (16.2)	8.62 (15.96)	
Median (min; max)	42 (12.6; 65.7)	53.1 (10.2; 86.7)	8.43 (−30.95; 47.35)	
95% CI for mean	(40.5–45.3)	(47.7–54.3)	(5.12–12.00)	
n	92	93	85	
Exploratory analyses				
Mean of glucose levels from CGM (mmol/L)				0.016
Mean (SD)	10.7 (1.9)	10.1 (1.8)	−0.53 (2.05)	
Median (min; max)	10.8 (5.1; 15.8)	9.8 (7.1; 16.2)	−0.70 (−5.72; 5.66)	
n	99	92	91	
MAGE for glucose levels from CGM (mmol/L)				<0.0001
Mean (SD)	10.0 (1.7)	7.74 (1.56)	−2.26 (1.92)	
Median (min; max)	10.1 (6.5; 14.9)	7.31 (5.06; 12.01)	−2.13 (−6.03; 2.36)	
n	95	91	87	
SD for glucose levels from CGM (mmol/L)				<0.0001
Mean (SD)	4.20 (0.88)	3.59 (0.71)	−0.62 (0.86)	
Median (min; max)	4.22 (1.48; 6.26)	3.6 (2.12; 5.26)	−0.7 (−2.41; 2.15)	
n	99	92	91	
Percent of time with glucose levels >10.0 mmol/L				0.014
Mean (SD)	51.6 (17.9)	45.7 (17.5)	−5.12 (19.28)	
Median (min; max)	51.8 (0; 100)	43.5 (8.7; 89.5)	−8.33 (−55.42; 40.86)	
n	99	90	89	
Percent of time with glucose levels >13.9 mmol/L				0.0002
Mean (SD)	24.4 (14.4)	17.4 (15.4)	−6.29 (15.32)	
Median (min; max)	21.7 (0; 70.7)	11.9 (0; 68.7)	−6.11 (−52.98; 47.2)	
n	99	90	89	
Percent of time with glucose levels 5.5–10.0 mmol/L				<0.0001
Mean (SD)	33.9 (10.2)	42.6 (13.3)	7.93 (12.82)	
Median (min; max)	34.6 (0; 52.2)	45.2 (9.3; 65.3)	8.19 (−23.21; 46.71)	
n	99	90	89	
Treatment Satisfaction scale total (DTSQs)				<0.0001
Mean (SD)	26.0 (6.2)	31.2 (3.8)	5.21 (6.19)	
Median (min; max)	27 (6; 36)	32 (21; 36)	4 (−8; 24)	
n	99	91	87	
WHO-5 well-being index				0.0088
Mean (SD)	61.0 (16.9)	66.2 (16.1)	4.66 (16.60)	

Continued on p. 146

Table 2—Continued

	Baseline (after conventional therapy in GOLD study)	End of SILVER study	Change from baseline to end of study	*P* value within group
Median (min; max)	64 (12; 100)	68 (16; 100)	8 (−48; 44)	
n	102	91	91	
Swe-HFS behavior/avoidance				0.073
Mean (SD)	1.91 (0.61)	1.84 (0.60)	−0.07 (0.39)	
Median (min; max)	1.9 (0.6; 4)	1.9 (0.3; 3.5)	−0.1 (−1; 0.86)	
n	103	91	91	
Swe-HFS–Worry				0.016
Mean (SD)	0.88 (0.77)	0.78 (0.65)	−0.12 (0.47)	
Median (min; max)	0.77 (0; 3.69)	0.61 (0; 3.38)	−0.08 (−1.78; 1.08)	
n	101	91	89	
PAID (Swe-PAID-20) scale				0.063
Mean (SD)	25.3 (18.6)	22.4 (16.0)	−2.24 (11.34)	
Median (min; max)	21.3 (0; 78.8)	19.7 (0; 71.1)	−1.25 (−41.25; 27.5)	
n	103	91	91	
IPAQ categorical score, *n* (%)				
Inactive	64 (62.1)	63 (69.2)	Decrease: 17 (18.7)	0.18
Minimally active	6 (5.8)	3 (3.3)	Equal: 64 (70.3)	
HEPA active	33 (32.0)	25 (27.5)	Increase: 10 (11.0)	
HCS total score				<0.0001
Mean (SD)	3.23 (0.54)	3.45 (0.43)	0.24 (0.48)	
Median (min; max)	3.22 (1.22; 4)	3.56 (2.22; 4)	0.11 (−0.78; 2.33)	
n	98	89	86	

For not normally distributed variables the 95% CI for the mean was estimated by using the inversion of Fisher nonparametric permutation test. For comparison within groups paired Student *t* test was used for normally distributed variables and Fisher nonparametric permutation test for matched pairs for not normally distributed variables. HEPA, health-enhancing physical activity; Swe, Swedish version.

to 7.96% (63.5 mmol/mol), or by 0.68% (7.4 mmol/mol) (95% CI 0.50–0.85% [95% CI 5.5–9.3 mmol/mol]) (Fig. 2).

Safety Parameters and Adverse Events

There were four patients (five events) with reported severe hypoglycemia (Supplementary Table 2). One patient who used Dexcom G5 and used a telephone as a receiver had turned off all telephone sounds and did not receive any low glucose level alarms, including one for an acute low level. No patient had diabetic ketoacidosis. There were no adverse events observed, which was judged to be likely and unexpectedly related to CGM use. One patient had skin reactions related to the CGM device. All adverse events and serious adverse events are presented in Supplementary Tables 2 and 3.

Reasons for Not Participating

Commonly reported reasons for not having the possibility to participate in the SILVER trial were possible interest to test another glucose-monitoring system during the next year, possibly changing insulin delivery to insulin pump, lack of time to participate in further trial-related activities, or relocation to another geographic region.

Post Hoc Analyses

Mean change in HbA_{1c} during the SILVER study performed on the population excluding 20 patients requiring at least one additional visit was −0.33% (−3.64 mmol/mol) (95% CI −0.51 to −0.15% [95% CI −5.60 to −1.68 mmol/mol], $P <$ 0.001). In a subgroup of patients with >70% compliance the change in mean HbA_{1c} was −0.32% (−3.46 mmol/mol) (95% CI −0.54 to −0.09% [95% CI −5.93 to −1.00 mmol/mol], $P = 0.007$), and in those with >80% compliance, it was −0.37% (−4.09 mmol/mol) (95% CI −0.62 to −0.12% [95% CI −6.80 to −1.37 mmol/mol], $P = 0.004$). The mean change in HbA_{1c} in the randomized sequence group CGM/SMBG in GOLD trial during 1 year follow-up in SILVER was −0.24% (−2.59 mmol/mol) (95% CI −0.41 to −0.06% [95% CI −4.51 to −0.68 mmol/mol], $P = 0.009$), and in the SMBG/CGM sequence during 1.5-year follow-up in SILVER, it was −0.43% (−4.75 mmol/mol) (95% CI −0.69 to −0.18% [95% CI −7.54 to −1.97 mmol/mol], $P =$ 0.001). The mean difference between the sequences was 0.20% (2.16 mmol/mol) (95% CI −0.11 to 0.50% [95% CI −1.18 to 5.51 mmol/mol], $P = 0.20$). The association between the change in HbA_{1c} and the number of visits was $r_s = 0.03$ ($P = 0.78$), and the association between the change in HbA_{1c} and compliance was $r_s = 0.01$ ($P = 0.93$). Target level of HbA_{1c} ≤6.9% (≤52 mmol/mol) was achieved in 10 (10.3%) of patients, and the target for TIR 4–10 mmol/L (72–180 mg/dL) for glucose levels was achieved in 7 (7.5%) of patients.

CONCLUSIONS

Principal Findings

When comparing with SMBG during the more intensive GOLD trial, HbA_{1c} was 0.35% (3.8 mmol/mol) lower at the end of the current extension study (SILVER) when participants used CGM over 1–1.5 years and with less intensive clinical support. Time with very low glucose levels (<3.0 mmol/L [54 mg/dL]) was reduced by ∼70%, from 2.1 to 0.6% per 24 h. Time in hypoglycemia (<4.0 mmol/L [72 mg/dL]) per 24 h decreased by ∼45% during long-term CGM use compared with earlier SMBG, and TIR (4–10 mmol/L [72–180 mg/dL]) increased by 9%. Glycemic variability decreased. Overall well-being, treatment satisfaction, and hypoglycemic confidence improved over the same time period; while hypoglycemic fear decreased, and diabetes distress tended to decrease. Compared with levels at inclusion in GOLD when all patients had SMBG,

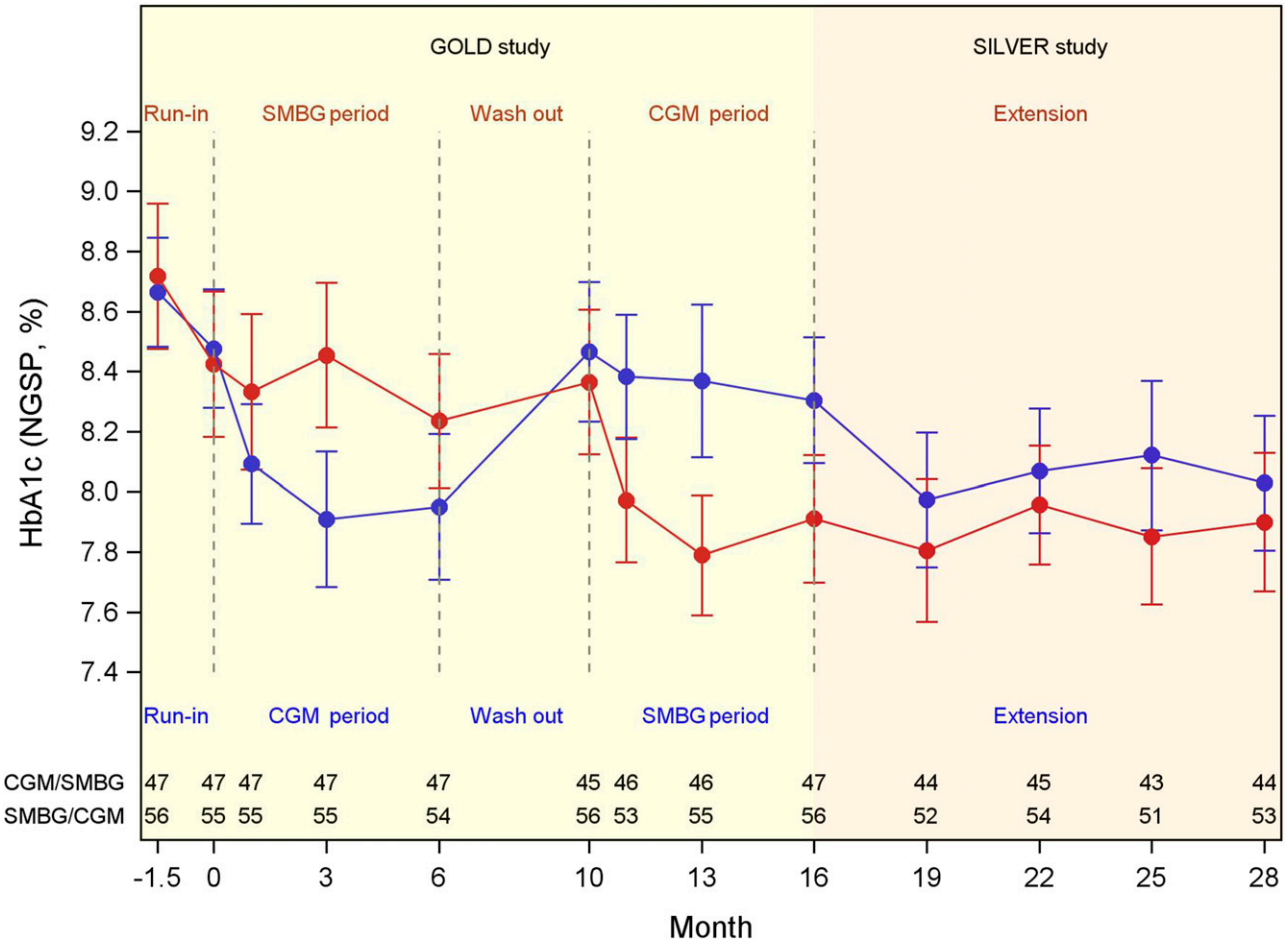


Figure 2—HbA_{1c} levels from the run-in period in the GOLD trial to the end of the SILVER study divided into randomized treatment sequences in the GOLD trial for the CGM/SMBG sequence (blue lines and dots) and the SMBG/CGM sequence (red lines and dots). The numbers at the bottom of the figure represent the number of patients with available HbA_{1c} measurements.

HbA_{1c} was 0.68% (7.4 mmol/mol) lower after 2.5 years at the end of SILVER.

Earlier Studies in the Field

A few randomized trials have compared CGM to SMBG in people with T1D (7,8,23), although the follow-up was generally shorter (up to 26 weeks) and the periods for patients managing the CGM/SMBG without clinical visits were also shorter. It is well known that novel treatments often have greater HbA_{1c}-reducing effects initially that decrease over time, possibly due to less engagement by both patients and health professionals (24). Therefore, it is of particular concern to obtain long-term data on glucose-lowering treatments in people with T1D, especially since glucose monitoring interventions have not been possible to evaluate during blinded conditions. A recent nonrandomized study including relatively few people with T1D managed with MDI ($n = 22$) indicated that long-term beneficial effects of CGM exist over 3 years (25).

Explanations and Interpretations

The fact that overall glycemic metrics improved during a 1.0- to 1.5-year CGM extension phase, during which patients had only brief clinical consultations every third month, compared with SMBG in a more intensive previous study, support the long-term beneficial effects of CGM. HbA_{1c} levels were sustained among patients treated with CGM when compared at the end of the GOLD trial and the end of the SILVER 1-year extension phase 7.93% (63.1 mmol/mol) vs. 7.96% (63.5 mmol/mol, $P = 0.40$). These findings support the suggestion that CGM has an independent and sustained effect over time in lowering HbA_{1c} and improving other glycemic metrics not related to support from health professionals or improved motivation by patients during shorter clinical trials.

Several factors likely explain why CGM has an independent beneficial effect on glycemic metrics in people with T1D managed with MDI. First, CGM offers the individual real-time guidance regarding current glucose level and its direction, which likely contributes to more effective decisions when dosing insulin. Second, for many people, CGM may improve their understanding of how glucose levels react to different types of diet, physical exercise, and insulin dosing, thereby acting as a pedagogic tool. In addition, CGM can, in contrast to SMBG, provide alarms for low glucose levels, which may be of critical value, since hypoglycemia as well as concerns about hypoglycemia are often a major barrier for glucose-lowering treatment in T1D.

Implications

In many developed countries, SMBG remains the most common methods for glucose monitoring for people with T1D.

One reason has been the lack of long-term clinical trials of CGM confirming important clinical effects since it is a relatively costly treatment. Data are also lacking on the extent to which CGM influences long-term diabetes complications such as retinopathy, nephropathy, cardiovascular disease and mortality. However, it does not seem likely that such randomized trials will be performed as it may be unethical to withhold CGM from patients in a control group over the course of several years. Hence, long-term studies, such as the current SILVER trial, are most essential for understanding effects on risk factors. Besides the HbA_{1c}-lowering effect known to be related to complications, it is essential to notice that time in hypoglycemia (<3.0 mmol/L [54 mg/dL]), during which cognitive impairment appears, was dramatically reduced by ~70% by CGM. It is essential to see the full picture of CGM for understanding effects that also include less glycemic variability and reduction of very high glucose levels (1,2,26–28).

The fact that CGM in the SILVER study, as well as in the GOLD trial, positively influenced overall well-being, treatment satisfaction, and hypoglycemic concerns (enhancing confidence and reducing worries) for people with T1D, is of great importance. Greater confidence in one's own ability to address or avoid hypoglycemia as well as an enhanced sense of satisfaction with one's treatment can lead to closer and more prolonged engagement with the treatment regimen, due to fewer frustrations, less inconvenience, and a greater sense of safety. T1D must be managed continuously, and diabetes burnout is common among both people with T1D and their loved ones (29–31). Hence, any support that can simplify daily diabetes self-care and help these people to feel safer is beneficial. Although CGM reduces time in hypoglycemia, there were five events of severe hypoglycemia in four patients during the current study in whom three patients wore an active CGM system during the time of the event. Overall, patients used CGM 71% of the time. These results imply that CGM is not completely successful in terms of preventing severe hypoglycemia and that it is essential to wear the system regularly. Moreover, although CGM improved both HbA_{1c} and TIR, it is essential to notice that most participants did not reach targets for HbA_{1c} or TIR. These findings indicate that extended support likely needs to be developed for patients treated with MDI and certain patient groups may benefit to switch to advanced technology systems, including insulin pumps, integrated systems, or hybrid systems (32,33).

Strengths and Limitations

Strengths of the current study include that CGM use with support intensity similar to that recommended in clinical practice could be compared within people having both previous SMBG and CGM during a more intensive study. Limitations include that there was no parallel control group with SMBG treatment in the extension long-term phase. However, it is unlikely that other external factors influenced estimated variables over that time period since the same study sites, central laboratory, and methods for collecting glucose data and self-reported questionnaires were used as in the original GOLD trial. Another limitation was that ~20% of patients declined participation, for reasons including request to switch type of glucose-monitoring system (CGM or flash glucose monitoring) or switch to pump-based treatment, lack of time to participate in further trial-related activities, or relocation to another geographic region. Moreover, it should be noticed that the 2.5-year comparisons should be interpreted with somewhat greater caution since comparisons at the end of the SILVER trial were performed up to before randomization of GOLD, i.e., when patients did not have as intensive support. However, patients were involved in study-related procedures during the run-in period of GOLD, including masked CGM, filling in questionnaires, and repeated contacts with the research unit. Further, although guidelines generally recommend clinical contacts every third month for patients with poor glycemic control as was the case in the current SILVER trial, it is noteworthy that in clinical practice, many clinics cannot offer such regular visits (34). Information of sensor operations or problems with data transmission from the CGM sensor was not available in the current study.

The SILVER study supports long-term beneficial effects of CGM on HbA_{1c}, time spent in hypoglycemia, time spent in range, glucose variability, and improvements in patient experience in managing T1D. These data are important for patients, caregivers, and decision makers in terms of making CGM treatment more widespread among people with T1D.

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