




ORIGINAL ARTICLE

The majority of people with type 1 diabetes and multiple daily insulin injections benefit from using continuous glucose monitoring: An analysis based on the GOLD randomized trial (GOLD-5)

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Abstract

Aim: To identify responders to continuous glucose monitoring (CGM) in relation to reductions in HbA1c and percentage of time spent in hypoglycaemia after initiation of CGM for individuals with type 1 diabetes treated with multiple daily insulin injections.

Materials and Methods: We analysed data from 142 participants in the GOLD randomized clinical trial. We evaluated how many lowered their HbA1c by more than 0.4% (>4.7 mmol/mol) or decreased the time spent in hypoglycaemia over 24 hours by more than 20 or 30 minutes, and which baseline variables were associated with those improvements.

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Results: Lower reduction of HbA1c was associated with greater reduction of hypoglycaemia ($r = -0.52$; $P < .0001$). During CGM, 47% of participants lowered their HbA1c values by more than 0.4% (>4.7 mmol/mol) than with self-measurement of blood glucose, and 47% decreased the time spent in hypoglycaemia by more than 20 minutes over 24 hours. Overall, 78% either reduced their HbA1c by more than 0.4% (>4.7 mmol/mol) or the time spent in hypoglycaemia by more than 20 minutes over 24 hours, but only 14% improved both. Higher HbA1c, a lower percentage of time at less than 3.0 or 3.9 mmol/L, a lower coefficient of variation (CV) and a higher percentage of time above 13.9 mmol/L ($P = .016$) were associated with greater HbA1c reduction during CGM. The variables associated with a greater reduction of time in hypoglycaemia were female sex, greater time with glucose levels at less than 3.0 mmol/L, higher CV, and higher hypoglycaemia confidence as evaluated by a hypoglycaemic confidence questionnaire.

Conclusion: The majority of people with type 1 diabetes managed by multiple daily insulin injections benefit from CGM; some experienced reduced HbA1c while others reduced the time spent in hypoglycaemia. These factors need to be considered by healthcare professionals and decision-makers for reimbursement and diabetes guidelines.

KEYWORDS

clinical trial, CGM, randomized trial, type 1 diabetes

1 | INTRODUCTION

Good glycaemic control is important for reducing the risk of long-term complications in type 1 diabetes, including microvascular and macrovascular complications.^{1–3} It has also been shown to reduce excess risk of mortality.^{4,5} Many people with type 1 diabetes struggle to keep blood glucose at acceptable levels while avoiding periods of hypoglycaemia.¹ Hypoglycaemia, if left untreated, can lead to loss of consciousness, seizures and, in the worst cases, death.⁶ It can also contribute to falls, injuries and motor vehicle accidents. Frequent periods of hypoglycaemia have also been shown to negatively influence quality of life.⁶

The use of continuous glucose monitoring (CGM) has been shown to reduce both HbA1c levels and the rate of hypoglycaemia for patients using multiple daily insulin injections (MDI) and subcutaneous insulin infusion.^{7–9}

It is not fully understood how the effect of CGM in type 1 diabetes varies among CGM users and what factors may be related to successful treatment. Such knowledge is essential for resolving treatment barriers and improving the benefits of CGM use, as well as from a health-economical perspective. Earlier research found that people aged 25 years or older and those with frequent self-measurement of blood glucose (SMBG) used their CGM devices more frequently after 6 months of CGM use than younger people or those who performed less SMBG.¹⁰ It is also of interest to understand whether there are certain patient groups that respond with an overall beneficial effect of

CGM, that is, in both reducing HbA1c and time in hypoglycaemia, whereas others are non-responders. Furthermore, it may be of interest to determine whether the opposite pattern exists, where certain patient groups reduce HbA1c and others benefit with respect to time in hypoglycaemia.

The aim of this study was to identify responders to CGM therapy in relation to reductions in HbA1c and percentage of time in hypoglycaemia after initiation of CGM compared with SMBG among people with type 1 diabetes treated with MDI.

2 | MATERIALS AND METHODS

The GOLD trial (ClinicalTrials.gov number NCT02092051) was approved by the ethics committee at the University of Gothenburg, Gothenburg, Sweden (12 December 2013, diary number 857-13). All participants provided verbal and written informed consent prior to starting the trial.

This was an investigator-initiated, open-label, randomized clinical trial with a cross-over design conducted in Sweden from February 2014 to June 2016. The trial started with an up to 6-week run-in period before participants were randomized to either CGM-guided treatment, using real-time CGM, or to treatment guided by SMBG for 26 weeks. After the initial 26 weeks of treatment, a 17-week wash-out period followed before the treatments were switched.

2.1 | Participants

To be included in the study, participants had to be aged 18 years or older, have an HbA1c of 7.5% or higher (≥ 58 mmol/mol) and be treated with MDI. Fasting C-peptide levels had to be less than 0.91 ng/mL and diabetes duration longer than 1 year. No participants treated with insulin pumps were included. The study design, including other inclusion and exclusion criteria, has been described in detail elsewhere.^{9,11}

2.2 | Run-in period and randomization

During a 6-week run-in phase, participants completed masked CGM for 2 weeks and answered questionnaires on well-being, treatment satisfaction, diabetes distress, hypoglycaemic fear and confidence. During masked CGM, glucose levels were recorded but not seen by participants. After masked CGM, participants were excluded if they either did not believe they would wear the CGM more than 80% of the time or did not perform adequate calibrations during run-in (on average, at least 12 of 14 during a 7-day period).

Participants were randomized 1:1 into the first treatment phase, stratified by site, to CGM using the Dexcom G4 PLATINUM (San Diego, CA, USA), real-time, stand-alone system or SMBG.

2.3 | Treatment

All participants received basic instruction on insulin dosing, such as bolus correction, food choices and the effect of physical activity on glucose control. A graph was used to explain the effect of active insulin in the body.¹² The participants received guidelines for interpreting glucose levels and trends obtained by the CGM system.⁹

During the first week, no alarms were set on the CGM device for low glucose levels except for acute hypoglycaemia (<55 mg/dL; <3.1 mmol/L). Alarm settings were introduced no later than 2 weeks after randomization; all the alarm settings were individualized. At each visit, participants were encouraged to use CGM information at least every 1-2 hours during daytime. During the SMBG period, participants were encouraged to measure blood glucose levels according to the guidelines (i.e. at least four times daily). During both periods, participants were instructed to adjust insulin doses based on SMBG and not CGM values. For the SMBG measurement, participants used their own glucose meters, which came from various manufacturers. During the 17-week wash-out period, participants used SMBG and masked CGM was performed during the last 2 weeks.

2.4 | Clinical assessments

Participants were assessed at the start of each treatment phase and at weeks 2, 4, 13 and 26. HbA1c was measured at all visits in each treatment phase except for week 2.

Masked CGM was performed 2 weeks before both treatment phases. During SMBG, masked CGM was also performed during 2 of the last 4 weeks to evaluate total time in hypoglycaemia, euglycaemia, hyperglycaemia and glycaemic variability. At all visits, CGM and SMBG data were downloaded and used for optimizing glycaemic control. Participants were not allowed to have any extra visits for improving glycaemic control to ensure the number of visits were equal in both treatment groups.

2.5 | Endpoints and procedures

For analyses of time in hypoglycaemia, we used both 70 mg/dL (3.9 mmol/L) and 54 mg/dL (3.0 mmol/L) as glucose cut-offs. HbA1c was analysed at a central laboratory (Karolinska University Hospital) and measured according to the International Federation of Clinical Chemistry method. All values were converted to percentages according to the National Glycosylation Standard Program for dual reporting.¹³ Patients with a reduction in HbA1c of more than 0.4% (4.7 mmol/mol) between treatments were considered to be HbA1c responders. A reduction of 0.4% HbA1c is generally regarded as a clinically significant improvement for reducing the risks of complications. Those achieving a reduction in time in hypoglycaemia over 24 hours of longer than 20 or 30 minutes between treatments were considered to be hypoglycaemia responders. For time in range (TIR), an improvement of greater than 5% was used for responders.¹⁴

We evaluated the proportion of patients obtaining:

1. Only HbA1c reduction.
2. Only TIR improvement.
3. Only reduction of time in hypoglycaemia.
4. Either HbA1c reduction or reduction of time in hypoglycaemia.
5. Either TIR improvement or reduction of time in hypoglycaemia.
6. Both HbA1c reduction and reduction of time in hypoglycaemia.
7. Both TIR improvement and reduction of time in hypoglycaemia.
8. No effect on either reducing HbA1c or time in hypoglycaemia.

Additionally, pairwise correlations for reduction in HbA1c, reduction in hypoglycaemia and improvement of TIR using continuous variables, instead of categorization as responders/non-responders, were also studied. All analyses performed on TIR were post hoc analyses.

The following baseline variables were evaluated separately as potential predictors for difference in HbA1c and difference in percentage of time in hypoglycaemia between treatments: age; sex; HbA1c at baseline; glycaemic variation measured by standard deviation (SD) of glucose levels and coefficient of variation (CV); percentage of time with glucose levels lower than 70 mg/dL (>3.9 mmol/L), and lower than 53 mg/dL (>3.0 mmol/L) and greater than 250 mg/dL (>13.9 mmol/L); the average number of hypoglycaemias experienced per week during the last 2 months at inclusion; the number of severe hypoglycaemias in the last year and the last 5 years; the hypoglycaemic confidence questionnaire total score, the frequency of SMBG, diabetes duration and c-peptide. The last HbA1c value and

2-week registration of time in hypoglycaemia during each treatment period were used in correspondence with earlier analyses.⁹

2.6 | Statistics

Descriptively, skewed continuous variables were described by mean, SD, median and range and normally distributed by mean and SD or 95% confidence intervals (CI). For categorical variables, numbers and percentages were given.

The cross-over design was taken into account when analysing the impact of selected baseline variables on the effect of CGM compared with SMBG. The effect on HbA1c at the end of the two treatments was analysed using general linear models with randomized sequence, subject within sequence, period, treatment, selected baseline characteristics and the interaction between the baseline variable and the treatment as fixed effects. *P*-value for interaction indicated whether a baseline characteristic had a significant impact on the treatment effect. The effect size shown by the mean difference and 95% CI in HbA1c between the treatments was described for the 25th, 50th and 75th percentile of the baseline variable, or the available categories.

The effect on percentage of time in hypoglycaemia was analysed using fractional response models, with binomial distribution and log-link function, specifying randomized sequence, period, treatment, baseline characteristics and interaction between the baseline variable and the treatment as fixed effects. Within-subject effect was modelled as random residual effect. The effect size shown by the relative risk (RR) and 95% CI in percentage of time in hypoglycaemia between the treatments was described for the 25th, 50th and 75th percentile of the baseline variable, or the available categories.

Interaction analyses adjusted for interaction with treatment and the respective baseline values of the studied outcomes were performed post hoc.

Spearman correlation was applied when analysing the relationship between differences in HbA1c and percentage of time in hypoglycaemia for CGM versus SMBG. Analysis was performed on all patients with data from at least one follow-up visit for both the CGM and SMBG periods (full analysis set [FAS]).

All tests were two-tailed and conducted at .05 significance level. All analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

3 | RESULTS

3.1 | Baseline characteristics

There were 161 participants randomized, of whom 142 (88.2%) had follow-up data for both the CGM and SMBG phases and thus were included in the FAS population. The baseline characteristics of the FAS population per treatment sequence are shown in Table S1. The mean (SD) age was 44.6 (12.7) years and 43.7% were women. Mean

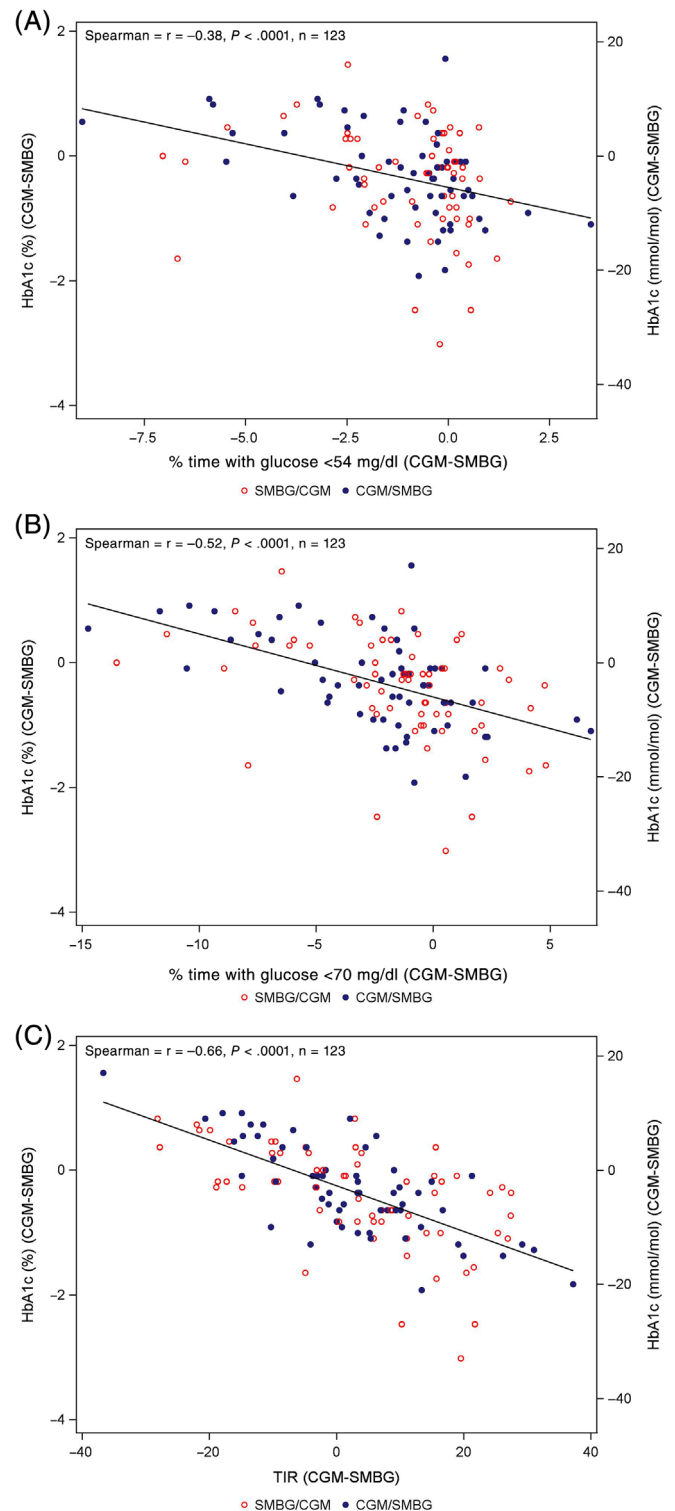


FIGURE 1 A, People with greater reduction in HbA1c had less reduction of time in hypoglycaemia <3 mmol/L (<54 mg/dL), negative correlation $P < .0001$. B, People with greater reduction in HbA1c had less reduction of time in hypoglycaemia <3.9 mmol/L (<70 mg/dL), negative correlation $P < .0001$. C, People with greater reduction in HbA1c had increased improvement of TIR, negative correlation $P < .0001$

(SD) HbA1c at run-in was 8.7% (0.84%) (72 [9.1] mmol/mol) and mean (SD) diabetes duration was 22.2 (11.8) years.

3.2 | Relationship between reduction in HbA1c, reduction of time in hypoglycaemia and improvement in TIR

When evaluating the pairwise relationship of treatment differences in HbA1c, time in hypoglycaemia and TIR, we found a significant

relationship between all of these metrics. With a greater reduction of HbA1c during CGM there was less reduction of time in hypoglycaemia, both with respect to glucose values below 3.0 mmol/L (<54 mg/dL) and 3.9 mmol/L (<70 mg/dL) (Figure 1A,B). The correlation coefficients between change in HbA1c and change in time in hypoglycaemia for blood glucose less than 3.9 mmol/L (<70 mg/dL)

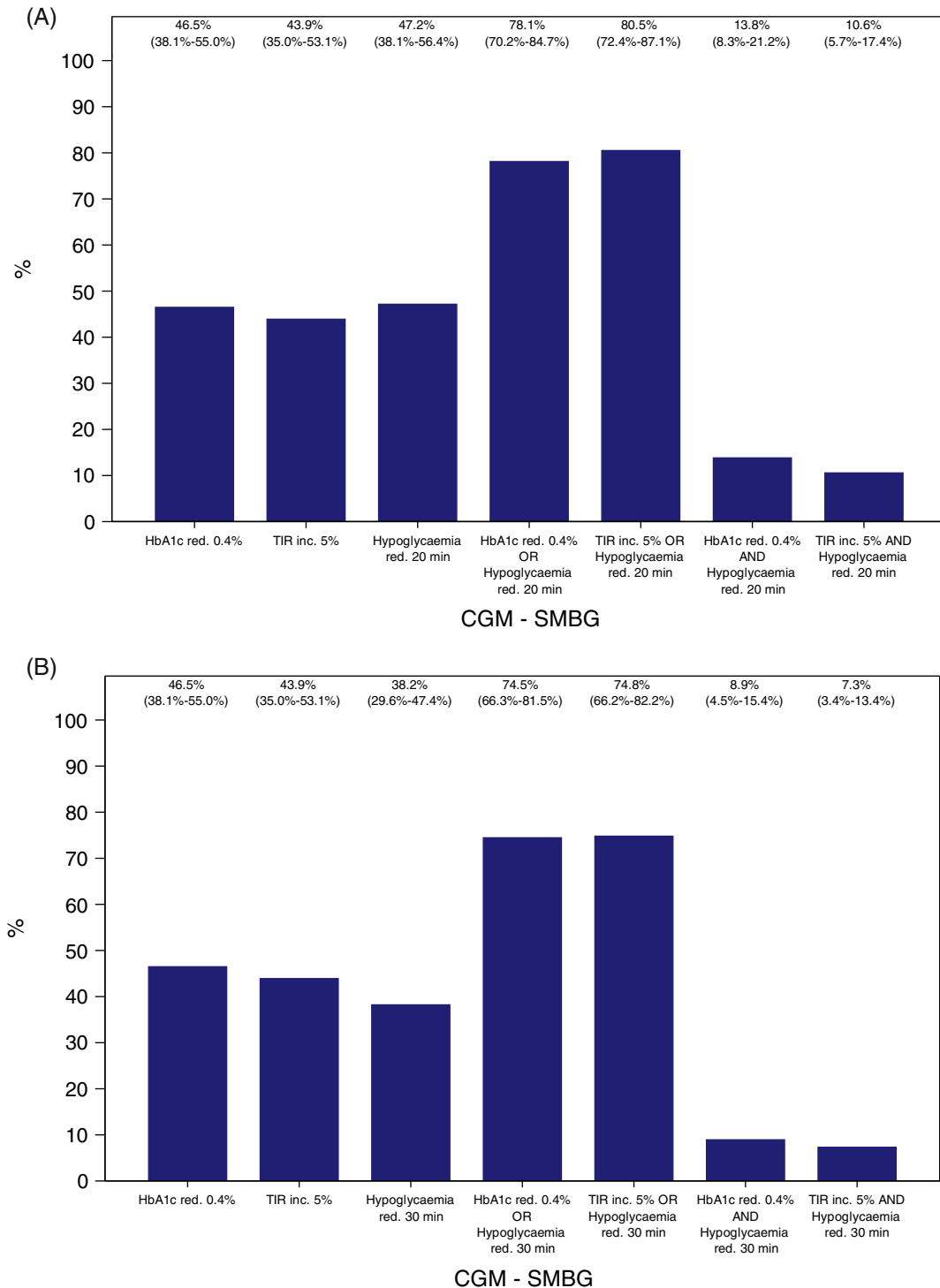


FIGURE 2 A, Proportion of people who improved their HbA1c by at least 0.4%, TIR > 5% and/or decreased their time in hypoglycaemia by 20 minutes. B, Proportion of people who improved their HbA1c by at least 0.4%, TIR > 5% and/or decreased their time in hypoglycaemia by 30 minutes

TABLE 1 Interaction between treatment and selected baseline variables on HbA1c (LOCF) (% and mmol/mol) (full analysis set population)

Baseline variable	Baseline variable value	HbA1c (LOCF, %) LSM (95% CI) ^a for difference CGM-SMBG	HbA1c (LOCF, mmol/mol) LSM (95% CI) ^a for difference CGM-SMBG	P-value for interaction between study group and baseline variable	Adjusted ^b P-value for interaction between study group and baseline variable
Age at inclusion visit (y)	Pctl50 = 44	-0.43 (-0.58 to -0.29)	-4.73 (-6.31 to -3.16)	.49	.53
Sex	Male	-0.53 (-0.72 to -0.34)	-5.83 (-7.91 to -3.75)	.11	.13
	Female	-0.30 (-0.51 to -0.08)	-3.25 (-5.61 to -0.89)		
HbA1c (%) at randomization visit	Pctl25 = 7.92	-0.23 (-0.39 to -0.07)	-2.54 (-4.30 to -0.79)	<.0001	
	Pctl50 = 8.28	-0.36 (-0.50 to -0.22)	-3.95 (-5.47 to -2.44)		
	Pctl75 = 8.83	-0.56 (-0.71 to -0.41)	-6.11 (-7.72 to -4.50)		
HbA1c (mmol/mol) at randomization visit	Pctl25 = 63	-0.23 (-0.39 to -0.07)	-2.53 (-4.29 to -0.77)	<.0001	
	Pctl50 = 67	-0.36 (-0.50 to -0.22)	-3.97 (-5.48 to -2.45)		
	Pctl75 = 73	-0.56 (-0.71 to -0.41)	-6.12 (-7.73 to -4.50)		
SD of glucose levels (mg/dL) at randomization visit	Pctl50 = 77.72	-0.41 (-0.56 to -0.25)	-4.45 (-6.12 to -2.78)	.97	.18
CV of glucose levels at randomization visit	Pctl25 = 0.37	-0.54 (-0.71 to -0.37)	-5.92 (-7.80 to -4.04)	.0034	.15
	Pctl50 = 0.41	-0.41 (-0.56 to -0.26)	-4.49 (-6.10 to -2.88)		
	Pctl75 = 0.46	-0.25 (-0.43 to -0.06)	-2.70 (-4.68 to -0.71)		
% of time with low glucose levels below 54 mg/dL (<3.0 mmol/L) at randomization visit	Pctl25 = 0.35	-0.59 (-0.77 to -0.40)	-6.42 (-8.44 to -4.40)	.0020	.10
	Pctl50 = 1.28	-0.50 (-0.65 to -0.34)	-5.42 (-7.14 to -3.71)		
	Pctl75 = 3.26	-0.30 (-0.46 to -0.14)	-3.30 (-5.06 to -1.54)		
% of time with low glucose levels below 70 mg/dL (<3.9 mmol/L) at randomization visit	Pctl25 = 1.67	-0.59 (-0.79 to -0.40)	-6.49 (-8.62 to -4.37)	.0041	.33
	Pctl50 = 4.61	-0.44 (-0.59 to -0.29)	-4.85 (-6.48 to -3.21)		
	Pctl75 = 7.89	-0.28 (-0.45 to -0.10)	-3.01 (-4.90 to -1.13)		
% of time with high glucose levels above 250 mg/dL (>13.9 mmol/L) at randomization visit	Pctl25 = 13.57	-0.26 (-0.45 to -0.07)	-2.87 (-4.94 to -0.80)	.016	.61
	Pctl50 = 21.52	-0.39 (-0.54 to -0.24)	-4.27 (-5.91 to -2.64)		
	Pctl75 = 29.40	-0.52 (-0.69 to -0.34)	-5.66 (-7.57 to -3.76)		
Average number of experienced hypoglycaemia per week during the last 2 mo (not based on blood glucose values, but subjective estimation) at inclusion visit	Pctl50 = 2	-0.43 (-0.58 to -0.28)	-4.68 (-6.32 to -3.04)	.45	.66
Number of severe hypoglycaemias in the last year	Pctl50 = 1	-0.16 (-0.57 to 0.25)	-1.77 (-6.24 to 2.70)	.16	.20
Number of severe hypoglycaemias in the last 5 y	Pctl50 = 1	-0.44 (-0.58 to -0.29)	-4.77 (-6.38 to -3.16)	.86	.78
HCQ total scale	Pctl50 = 3.22	-0.44 (-0.59 to -0.29)	-4.78 (-6.41 to -3.16)	.60	.97
Mean number of SMBG measurements per day at screening based on last 60 d	Pctl50 = 2.51	-0.45 (-0.59 to -0.30)	-4.88 (-6.47 to -3.29)	.19	.20

TABLE 1 (Continued)

Baseline variable	Baseline variable value	HbA1c (LOCF, %) LSM (95% CI) ^a for difference CGM-SMBG	HbA1c (LOCF, mmol/mol) LSM (95% CI) ^a for difference CGM-SMBG	P-value for interaction between study group and baseline variable	Adjusted ^b P-value for interaction between study group and baseline variable
Mean number of SMBG measurements per day at screening based on last 60 d or less	Pct150 = 2.06	−0.51 (−0.67 to −0.35)	−5.57 (−7.33 to −3.80)	.18	.43
Diabetes duration (y)	Pct150 = 22.15	−0.43 (−0.57 to −0.29)		.053	.28
C-peptide at inclusion	Below LLOD (≤0.04)	−0.38 (−0.53 to −0.22)		.085	.45
	Above LLOD (>0.04)	−0.73 (−1.10 to −0.36)			

Abbreviations: CGM, continuous glucose monitoring; CV, coefficient of variation; HCQ, hypoglycaemic confidence questionnaire; LLOD, lower limit of detection; LOCF, last observation carried forward; LSM, least square means; Pct125, 25th percentile; Pct150, 50th percentile; Pct175, 75th percentile; SD, standard deviation; SMBG, self-monitoring of blood glucose.

^aLSM (95% CI) and P-value are obtained from SAS procedure PROC GLM with sequence, patient(sequence), period and study group as class variables and fixed effects. Baseline variable and interaction between baseline variable and treatment is also modelled as fixed effect in the analysis.

^bAdjusted for interaction HbA1c at randomization × Treatment (post hoc analyses).

and less than 3.0 mmol/L (<54 mg/dL) were $r = -0.52$ ($P < .0001$) and $r = -0.38$ ($P < .0001$), respectively.

Correlation analysis between change in TIR and change in time in hypoglycaemia comparing SMBG with CGM showed that the more TIR improved, then less improvement was found for time in hypoglycaemia. The correlation coefficients between change in TIR and change in time in hypoglycaemia were $r = 0.55$ ($P < .0001$) and $r = 0.34$ ($P = .0001$) for hypoglycaemia thresholds of 3.9 mmol/L (70 mg/dL) and 3.0 mmol/L (54 mg/dL), respectively (Figure S1). The reduction in HbA1c comparing SMBG with CGM was related to increased TIR ($r = -0.66$; $P < .0001$), as shown in Figure 1C.

3.3 | HbA1c, hypoglycaemia and TIR responders

Responders analysis with improvement in HbA1c, time in hypoglycaemia and TIR revealed that 46.5% (95% CI 38.1%–55.0%) of participants had lower HbA1c values (reduction of >0.4% [>4.7 mmol/mol]) with CGM than with SMBG, 47.2% (95% CI 38.1%–56.4%) decreased their time in hypoglycaemia (glucose levels <3.9 mmol/L [<70 mg/dL]) by more than 20 minutes over 24 hours, and 43.9% (95% CI 35.0%–53.1%) improved their TIR by 5% or more. Overall, 78.1% (95% CI 70.2%–84.7%) of all participants either improved their HbA1c by more than 0.4% (>4.7 mmol/mol) or their time in hypoglycaemia by more than 20 minutes over 24 hours, and 80.5% (95% CI 72.4%–87.1%) improved either their TIR or time in hypoglycaemia. However, only

13.8% of participants experienced both HbA1c and hypoglycaemia reduction, and only 10.6% improved both TIR and hypoglycaemia (Figure 2A).

Analyses performed for 30 minutes of decreased time in hypoglycaemia showed a similar pattern (Figure 2B). A decrease in either HbA1c by more than 0.4% (>4.7 mmol/mol) or a decrease of time in hypoglycaemia was achieved by 74.5% (95% CI 66.3%–81.5%) of patients.

3.4 | Baseline characteristics associated with the CGM effect on HbA1c

Five of the 16 studied variables at baseline showed a significant interaction with treatment effect on HbA1c after a 26-week CGM treatment period (Table 1). Those were HbA1c at randomization ($P < .0001$), time in hypoglycaemia for glucose less than 3.0 mmol/L (<54 mg/dL; $P = .0020$), time in hypoglycaemia for glucose less than 3.9 mmol/L (<70 mg/dL; $P = .0041$), time in hyperglycaemia for glucose greater than 13.9 mmol/L (>250 mg/dL; $P = .016$) and glycaemic variability measured with CV ($P = .0034$).

The higher the HbA1c at randomization then the greater the reduction between CGM versus SMBG treatment, with the mean difference ranging from -2.54 to -6.11 mmol/mol (-0.23% and -0.56%) for the 25th to 75th percentile, respectively.

We found that greater reductions in HbA1c between treatments were observed for patients with a lower percentage of time in hypoglycaemia (both <3.0 mmol/L [<54 mg/dL] and <3.9 mmol/L

[<70 mg/dL]) at randomization, lower CV of glucose levels, and greater time in hyperglycaemia (>13.9 mmol/L [>250 mg/dL]).

After performing pairwise analyses including adjustment for interaction between baseline HbA1c and treatment, the interacting effects of all variables but baseline HbA1c were attenuated to non-significance.

There was no significant interaction between treatment effect and the frequency of SMBG measurements before study start on HbA1c reduction, unadjusted or adjusted (Table 2).

3.5 | Baseline characteristics associated with the CGM effect on percentage of time in hypoglycaemia

Greater reductions in time of hypoglycaemia between CGM and SMBG after the 26-week treatment period were observed for women than for men ($P = .0071$ and $P = .012$), for higher CV of glucose levels ($P = .0049$ and $P = .014$), for greater time in hypoglycaemia (<3.0 mmol/L [<54 mg/dL]) at baseline ($P = .042$ and $P = .019$), for higher hypoglycaemic confidence score ($P = .019$ and $P = .021$), diabetes duration ($P = .0092$ and $P = .0002$) and C-peptide at inclusion ($P = .047$ and $P = .0008$). Following the adjustment for interaction between time in hypoglycaemia with respective cut-offs and treatment, the only remaining significant interactions were those for time in hypoglycaemia, hypoglycaemia confidence score, diabetes duration and C-peptide at inclusion.

There was no interaction between the frequency of SMBG at study start and reduction of time in hypoglycaemia, either in unadjusted or in adjusted analyses (Table 2).

4 | DISCUSSION

This study shows that the majority of people with type 1 diabetes treated with MDI and using CGM benefitted from the system. Almost half of users experienced an HbA1c benefit and equally as many decreased their time in hypoglycaemia and improved their TIR. Approximately 80% showed improvement in HbA1c, TIR or hypoglycaemia, but only 13.8% and 10.6% experienced an effect on time in hypoglycaemia and HbA1c or time in hypoglycaemia and TIR, respectively.

The baseline variables associated with greater reduction of HbA1c when using CGM were higher baseline HbA1c, less time with glucose levels below 3.9 mmol/L (<70 mg/dL) and 3.0 mmol/L (<54 mg/dL), lower CV, and greater time with glucose levels above 13.9 mmol/L (>250 mg/dL). The main predictive variable was baseline HbA1c. The participants who experienced the greatest effect in reducing time in hypoglycaemia were women, those with more time with blood glucose below 3.0 mmol/L (<54 mg/dL), greater CV, people with more confidence about their hypoglycaemias at baseline and those with greater diabetes duration and lower C-peptide. The main predictive variables were time in hypoglycaemia and the hypoglycaemia confidence score at baseline.

Previous studies have found that CGM reduces HbA1c and can decrease the amount of time spent in hypoglycaemia.^{7,9,15} The GOLD study showed a decrease of 0.43% (4.7 mmol/mol), the DIAMOND study a decrease of 0.6%, and the Switch study a decrease of 0.41% (4.4 mmol/mol); both the GOLD and DIAMOND studies included patients treated with MDI while the Switch study included patients with insulin pumps. For time in hypoglycaemia (<3.9 mmol/L [<70 mg/dL]), the reductions were 29, 20 and 12 minutes, respectively.^{7,9,15} Minimal data are available on how different baseline factors are associated with glycaemic improvements during CGM use, but the DIAMOND study did not find any interaction between baseline HbA1c and change in HbA1c during the study; however, in a post hoc analysis of the DIAMOND data, it was shown that the greater the HbA1c at baseline then the greater the reduction after 24 weeks of CGM use.^{7,16} Semi-closed loop and sensor-augmented pumps probably show an even greater effect in reducing HbA1c and time in hypoglycaemia.¹⁷

Earlier, it was shown that psychosocial factors were associated with improved glycaemic control and decreased time spent in hypoglycaemia. People who were more analytical in their approach, could better cope with frustration, and had the support of their loved ones, had better results after initiating CGM.¹⁸ It has also been shown that those with greater compliance (i.e. they wore their CGM devices more frequently) had a greater improvement in glycaemic control.^{10,19}

4.1 | Hypoglycaemia

To our knowledge there have been no previous analyses based on randomized trials that have evaluated which variables are associated with the effect on time in hypoglycaemia by CGM in people with type 1 diabetes treated with MDI. In the current study we show that CGM users seldom benefit both by decreasing their time spent in hypoglycaemia and HbA1c or TIR, but do appear to experience benefits within one of these areas. Few patients improved both HbA1c and time in hypoglycaemia or TIR and time in hypoglycaemia when using CGM. In this study we analysed the interaction of different baseline variables with regard to both improved hypoglycaemia for values below 3.0 mmol/L (<54 mg/dL) and 3.9 mmol/L (<70 mg/dL). Both of these hypoglycaemic cut-offs interacted with the same baseline variables. We found that people with lower C-peptide levels improved their time in hypoglycaemia by more than those with higher C-peptide levels, probably because people with higher C-peptide levels experience less hypoglycaemia and therefore probably benefit less from CGM.

4.2 | HbA1c

The effect to which HbA1c varies for different patient groups has not been well studied, but in the current study we have shown that people with higher HbA1c experience a greater reduction when CGM is introduced. This represents a strong argument for providing CGM devices to patients with high HbA1c levels because they may be able

TABLE 2 Interaction between study group and selected baseline variables on % of time with low glucose levels below 54 and 70 mg/dL (full analysis set population)

Baseline variable	Baseline variable value	% of time with low glucose levels below 54 mg/dL (<3.0 mmol/L)			% of time with low glucose levels below 70 mg/dL (<3.9 mmol/L)		
		RR (95% CI) ^a for CGM vs. SMBG	P-value for interaction between study group and baseline variable	Adjusted ^b P-value for interaction between study group and baseline variable	RR (95% CI) ^a for CGM vs. SMBG	P-value for interaction between study group and baseline variable	Adjusted ^b P-value for interaction between study group and baseline variable
Age at inclusion visit (y)	Pct150 = 44	0.42 (0.31-0.55)	.87	.69	0.58 (0.48-0.70)	.33	.20
Sex	Male	0.55 (0.38-0.80)	.0071	.053	0.71 (0.55-0.91)	.012	.051
	Female	0.28 (0.21-0.38)			0.45 (0.35-0.57)		
HbA1c (NGSP, %) at randomization visit	Pct150 = 8.28	0.42 (0.32-0.56)	.29	.77	0.59 (0.48-0.71)	.35	.96
HbA1c (IFCC, mmol/mol) at randomization visit	Pct150 = 67	0.42 (0.32-0.56)	.29	.77	0.59 (0.48-0.71)	.35	.96
SD of glucose levels (mg/dL) at randomization visit	Pct150 = 77.72	0.43 (0.33-0.57)	.54	.90	0.60 (0.50-0.73)	.32	.49
CV of glucose levels at randomization visit	Pct125 = 0.37	0.56 (0.43-0.73)	.0049	.13	0.71 (0.58-0.88)	.014	.22
	Pct150 = 0.41	0.47 (0.36-0.61)			0.63 (0.53-0.76)		
	Pct175 = 0.46	0.38 (0.27-0.53)			0.55 (0.44-0.68)		
% of time with low glucose levels below 54 mg/dL (<3.0 mmol/L) at randomization visit	Pct125 = 0.35	0.53 (0.40-0.72)	.042		0.71 (0.57-0.88)	.019	
	Pct150 = 1.28	0.49 (0.38-0.65)			0.66 (0.54-0.81)		
	Pct175 = 3.26	0.42 (0.31-0.56)			0.58 (0.47-0.70)		
% of time with low glucose levels below 70 mg/dL (<3.9 mmol/L) at randomization visit	Pct150 = 4.61	0.48 (0.37-0.62)	.12		0.64 (0.53-0.78)	.092	
% of time with high glucose levels above 250 mg/dL (>13.9 mmol/L) at randomization visit	Pct150 = 21.52	0.41 (0.32-0.54)	.18	.48	0.59 (0.49-0.72)	.54	.91
Average number of experienced hypoglycaemias per week	Pct150 = 2	0.40 (0.31-0.51)	.054	.12	0.56 (0.46-0.68)	.23	.38

(Continues)

TABLE 2 (Continued)

Baseline variable	Baseline variable value	% of time with low glucose levels below 54 mg/dL (<3.0 mmol/L)			% of time with low glucose levels below 70 mg/dL (<3.9 mmol/L)		
		RR (95% CI) ^a vs. SMBG	P-value for interaction between study group and baseline variable	Adjusted ^b P-value for interaction between study group and baseline variable	RR (95% CI) ^a for CGM vs. SMBG	P-value for interaction between study group and baseline variable	Adjusted ^b P-value for interaction between study group and baseline variable
Number of severe hypoglycaemias in the last year	Pctl50 = 1	0.22 (0.07-0.69)	.26	.32	0.38 (0.18-0.79)	.24	.27
Number of severe hypoglycaemias in the last 5 y	Pctl50 = 1	0.41 (0.31-0.53)	.15	.26	0.58 (0.48-0.70)	.56	.60
HCQ total scale	Pctl25 = 2.89	0.56 (0.41-0.77)	.019	.038	0.73 (0.57-0.92)	.021	.048
	Pctl50 = 3.22	0.43 (0.34-0.55)			0.62 (0.52-0.74)		
	Pctl75 = 3.56	0.33 (0.24-0.46)			0.52 (0.42-0.65)		
Mean number of SMBG measurements per day at screening based on the last 60 d or less or estimated number of measurements	Pctl50 = 2.51	0.42 (0.32-0.56)	.55	.53	0.58 (0.48-0.71)	.76	.73
Mean number of SMBG measurements per day at screening based on the last 60 d or less	Pctl50 = 2.06	0.41 (0.31-0.59)	.65	.80	0.59 (0.48-0.74)	.94	.79
Diabetes duration (y)	Pctl25 = 12.60	0.53 (0.39-0.71)	.0092	.011	0.74 (0.60-0.92)	.0002	.0003
	Pctl50 = 22.15	0.41 (0.32-0.54)			0.58 (0.48-0.70)		
	Pctl75 = 31.10	0.33 (0.23-0.47)			0.46 (0.37-0.58)		
C-peptide at inclusion	Below LLOD (≤0.04)	0.39 (0.29-0.52)	.047	.17	0.53 (0.44-0.65)	.0008	.0048
	Above LLOD (>0.04)	0.72 (0.41-1.26)			1.14 (0.77-1.70)		

Abbreviations: CGM, continuous glucose monitoring; CV, coefficient of variation; HCQ, hypoglycaemic confidence questionnaire; IFCC, International Federation of Clinical Chemistry; Pctl25, 25th percentile; Pctl50, 50th percentile; Pctl75, 75th percentile; LLOD, lower limit of detection; NGSP, National Glycosylation Standard Program; RR, relative risk; SD, standard deviation; SMBG, self-monitoring of blood glucose.

^aRR (95% CI) and P-value are obtained from SAS procedure PROC GLIMMIX with binomial distribution and log-link function, with sequence, subject, period and study group as class variables and fixed effects. Baseline variable and interaction between baseline variable and study group is also modelled as fixed effect in the analysis. Within-subject effect is modelled as random residual effect.

^bAdjusted for interaction time in hypoglycaemia (<3.0 mmol/L and <3.9 mmol/L in respective analysis) × Treatment (post hoc analyses).

to avoid diabetes complications through subsequent improvements in HbA1c.

A CGM device gives continuous feedback to the user regarding current glucose values and trends, and leads to increased awareness. The possibility of alarms providing warnings about values being too high or low enables users to react quickly and thereby improves their overall glucose control. It is important to understand that it is not just those with very high HbA1c or very low HbA1c who experience the benefits of CGM use, but also those with moderate glycaemic control (HbA1c ~7.92%-8.83% [\sim 63-73 mmol/mol]) can experience both decreased HbA1c and a reduction in time in hypoglycaemia, and even improved TIR.

4.3 | Frequency of SMBG

Different reimbursement guidelines frequently state that patients must perform at least four SMBG tests to be prescribed CGM. It is worth stating that this study found no interaction between improved HbA1c and time in hypoglycaemia in relation to the number of SMBG tests taken before starting CGM.

This study implies that the majority of people with type 1 diabetes and MDI benefit from using CGM devices. It is important to view all patients with type 1 diabetes as potential candidates for CGM, but to also recognize that they might benefit in different ways. Patients with moderate glycaemic control who have problems with too much time spent in hypoglycaemia may not substantially improve their HbA1c after CGM initiation, but will probably substantially decrease their time in hypoglycaemia, which in turn decreases the risk of developing hypoglycaemia unawareness.^{20,21} The study also shows that higher hypoglycaemia confidence was a predictor of greater reduction of time in hypoglycaemia; the current study cannot explain this relationship but it needs to be examined in future research.

The impression given by healthcare professionals is that it is mainly those patients who can improve their HbA1c who are prioritized to receive CGM treatment, but this study shows that an equal number may improve their time spent in hypoglycaemia. Hypoglycaemia is related to an increased risk of severe hypoglycaemia and cardiovascular events and reduced quality of life.²²⁻²⁴ It is important to view all patients as possible candidates for CGM to improve HbA1c, TIR or time in hypoglycaemia.

A limitation of the current study is that treatment could not be blinded, thereby participants were aware of the intervention. This may have influenced the effects of treatment to some extent. In addition, the current results are restricted to adults with an HbA1c greater than 58 mmol/mol ($>$ 7.5%). These analyses were not the original endpoint of the Gold study, therefore they should be viewed as exploratory. Another limitation was that there was no possibility of evaluating how patients used their own data uploads to improve their glucose management.

A strength of the study is its randomized, cross-over design, where each participant acted as their own control between the two treatments, and that a masked CGM was used during the

SMBG period, which enabled more efficient analysis of glycaemic ranges.

In conclusion, the majority of adults with type 1 diabetes treated with MDI experience benefits when initiating treatment with CGM, and these benefits are equally divided between improvements in HbA1c and time spent in hypoglycaemia. There is no association between frequency of SMBG and these improvements. Patients who have a longer time in hypoglycaemia experience greater effects in reducing their time in hypoglycaemia, while patients with a shorter time in hypoglycaemia and higher HbA1c levels primarily benefit through HbA1c reduction. It is important that healthcare professionals and decision-makers for reimbursement and diabetes guidelines consider these factors and that there are no clear factors predictive of whom will respond to CGM monitoring or not.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

AFO, AP and ML contributed to the design of this study. All authors contributed to the analysis and interpretation of the data. AFO drafted the manuscript. All authors revised the manuscript and gave the final approval of the version to be published.

PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/dom.14257>.

DATA AVAILABILITY STATEMENT

Data can be accessed after a written research proposal and support from investigators. After formal request, legal procedures have to be assessed to secure data security according to GDPR and local laws.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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