# Real-time continuous glucose monitoring in adults with type 1 diabetes and impaired hypoglycaemia awareness or severe hypoglycaemia treated with multiple daily insulin injections (HypoDE): a multicentre, randomised controlled trial

*Lutz Heinemann, Guido Freckmann, Dominic Ehrmann, Gabriele Faber-Heinemann, Stefania Guerra, Delia Waldenmaier, Norbert Hermanns*

## Summary

**Background** **The effectiveness of real-time continuous glucose monitoring (rtCGM) in avoidance of hypoglycaemia among high-risk individuals with type 1 diabetes treated with multiple daily insulin injections (MDI) is unknown. We aimed to ascertain whether the incidence and severity of hypoglycaemia can be reduced through use of rtCGM in these individuals.**

**Methods** **The HypoDE study was a 6-month, multicentre, open-label, parallel, randomised controlled trial done at 12 diabetes practices in Germany. Eligible participants had type 1 diabetes and a history of impaired hypoglycaemia awareness or severe hypoglycaemia during the previous year. All participants wore a masked rtCGM system for 28 days and were then randomly assigned to 26 weeks of unmasked rtCGM (Dexcom G5 Mobile system) or to the control group (continuing with self-monitoring of blood glucose). Block randomisation with 1:1 allocation was done centrally, with the study site as the stratifying variable. Masking of participants and study sites was not possible. Control participants wore a masked rtCGM system during the follow-up phase (weeks 22–26). The primary outcome was the baseline-adjusted number of hypoglycaemic events (defined as glucose ≤3·0 mmol/L for ≥20 min) during the follow-up phase. The full dataset analysis comprised participants who wore the rtCGM system during the baseline and follow-up phases. The intention-to-treat analysis comprised all randomised participants. This trial is registered with ClinicalTrials.gov, number NCT02671968.**

**Findings** **Between March 4, 2016, and Jan 12, 2017, 149 participants were randomly assigned (n=74 to the control group; n=75 to the rtCGM group) and 141 completed the follow-up phase (n=66 in the control group, n=75 in the rtCGM group). The mean number of hypoglycaemic events per 28 days among participants in the rtCGM group was reduced from 10·8 (SD 10·0) to 3·5 (4·7); reductions among control participants were negligible (from 14·4 [12·4] to 13·7 [11·6]). Incidence of hypoglycaemic events decreased by 72% for participants in the rtCGM group (incidence rate ratio 0·28 [95% CI 0·20–0·39], p<0·0001). 18 serious adverse events were reported: seven in the control group, ten in the rtCGM group, and one before randomisation. No event was considered to be related to the investigational device.**

**Interpretation** **Usage of rtCGM reduced the number of hypoglycaemic events in individuals with type 1 diabetes treated by MDI and with impaired hypoglycaemia awareness or severe hypoglycaemia.**

**Funding** **Dexcom Inc.**

Published **Online**
February 16, 2018
http://dx.doi.org/10.1016/S0140-6736(18)30297-6

See **Online/Comment**
http://dx.doi.org/10.1016/S0140-6736(18)30290-3

**Science-Consulting in Diabetes GmbH, Düsseldorf, Germany** (Prof L Heinemann PhD, G Faber-Heinemann MA); **IDT-Institut für Diabetes-Technologie, Forschungs-und Entwicklungsgesellschaft mbH an der Universität Ulm, Ulm, Germany** (G Freckmann MD, D Waldenmaier MSc); **Research Institute Diabetes of the Diabetes Academy Mergentheim (FIDAM) (FIDAM), Bad Mergentheim, Germany** (D Ehrmann PhD, Prof N Hermanns PhD); **Department of Clinical Psychology and Psychotherapy, University of Bamberg, Bamberg, Germany** (D Ehrmann, Prof N Hermanns); **and Dexcom Inc, San Diego, CA, USA** (S Guerra PhD)

Correspondence to:
Prof Norbert Hermanns, Research Institute Diabetes of the Diabetes Academy Mergentheim (FIDAM), 97980 Bad Mergentheim, Germany
**hermanns@fidam.de**

## Introduction

Hypoglycaemia remains a limiting factor in achievement of optimal glycaemic control in individuals with type 1 diabetes.[1] Use of real-time continuous glucose monitoring (rtCGM) systems in these individuals has the potential to avoid low glucose concentrations and severe hypoglycaemia through the availability of low-glucose alarms and use of trend information (eg, trend graphs and rate of change [ROC] arrows) to proactively respond to falling or near-low glucose values.

Results of meta-analyses have shown that use of rtCGM can help to optimise glucose control without increasing the incidence of hypoglycaemic events in individuals with type 1 diabetes.[2] These findings have encouraged research into the effect of rtCGM in individuals with problematic hypoglycaemia,[3,4] a subgroup of people with diabetes that faces substantial clinical challenges due to the high prevalence of impaired hypoglycaemia awareness or previous severe hypoglycaemia episodes, or a combination of both factors; both conditions predispose these individuals to future severe hypoglycaemia episodes.[5,6]

However, available evidence about the benefits of rtCGM in problematic hypoglycaemia is scarce. Most previous studies of rtCGM were not designed to reach a hypoglycaemia-specific primary endpoint[2,3] or had relatively small sample sizes.[3,4,7] Many studies also excluded individuals with frequent or severe hypoglycaemia or with impaired hypoglycaemia awareness.[8,9]

## Research in context

### Evidence before this study

We searched the PubMed database up to Oct 31, 2017, using the search terms "type 1 diabetes" and "continuous glucose monitoring or CGM" and "multiple daily insulin injections or MDI" and "hypoglycemia or hypoglycaemia" and "randomized or randomised or randomized trial or randomised trial" for randomised controlled trials that had investigated the effect of real-time continuous glucose monitoring (rtCGM) on hypoglycaemia-related outcomes in patients with type 1 diabetes treated by multiple daily insulin injections (MDI). The search identified 48 publications, of which only 11 met the inclusion criteria (rtCGM *vs* self-monitoring of blood glucose [SMBG] in patients with type 1 diabetes treated with MDI). Among these were two reviews: one examined the effect of continuous glucose monitoring (CGM) on glycaemic control in pregnant women, while the other investigated the effect of CGM with alarms versus CGM without alarms. We identified only five studies investigating the effect of rtCGM in patients with type 1 diabetes treated with MDI. Two studies (IN CONTROL and HypoCOMPaSS) selected patients with type 1 diabetes who had hypoglycaemia. However, both studies included patients with type 1 diabetes on MDI therapy or continuous subcutaneous insulin infusion (CSII) therapy. Both studies also had relatively small sample sizes, thus limiting the post-hoc analyses of rtCGM in patients with type 1 diabetes on MDI, and they were done in a small number of study sites (two for IN CONTROL, five for HypoCOMPaSS). Three studies (GOLD, DIAMOND, and the DIAMOND follow-up study) included only patients with type 1 diabetes on MDI. However, all three studies had the primary objective of studying the effect of rtCGM on the reduction of glycated haemoglobin ($HbA_{1c}$). Participants in these studies were selected on the basis of an elevated $HbA_{1c}$ and not the presence of problematic hypoglycaemia. In summary, we found no sufficient evidence from the available randomised controlled trials about the efficacy of rtCGM on hypoglycaemia-specific outcomes in adult patients with type 1 diabetes and with problematic hypoglycaemia, who are exclusively treated by MDI.

### Added value of this study

The results of the HypoDE study show the efficacy of rtCGM on hypoglycaemia-specific outcomes in patients with type 1 diabetes on MDI with impaired hypoglycaemia awareness or severe hypoglycaemia. These results also indicate the potential of rtCGM to avoid both biochemical and clinical hypoglycaemia in such patients. Avoidance of biochemical hypoglycaemia was corroborated by blood glucose measurements. Additionally, this study shows that, in a well controlled sample of adult patients with type 1 diabetes, avoidance of hypoglycaemia by rtCGM usage was not achieved at the expense of a deterioration in $HbA_{1c}$.

### Implications of all the available evidence

MDI therapy is the most common insulin therapy regimen in patients with type 1 diabetes. Worldwide, usage of MDI ranges from 70% to 99% of all patients with type 1 diabetes. Therefore, the finding that both biochemical and clinical hypoglycaemia can be avoided by use of rtCGM in patients on MDI therapy is of high importance for most patients with type 1 diabetes. Health-care expenditures for CSII are several times higher than for MDI. The same is true for the costs of rtCGM compared with those for conventional SMBG. The potential combination of the most expensive insulin delivery method with rtCGM could put considerable strain on health-care systems. Therefore, the finding that substantial benefits for avoidance of hypoglycaemia can be achieved by rtCGM in standalone mode in patients with type 1 diabetes treated with MDI and with impaired hypoglycaemia awareness or severe hypoglycaemia is both clinically and economically meaningful. Putting the findings of this study into context with those from the HypoCOMPaSS study and the post-hoc analysis of the IN CONTROL study (which showed that hypoglycaemia avoidance in patients with type 1 diabetes on CSII and rtCGM is not better than in patients on MDI and rtCGM), a head-to-head comparison between MDI and CSII with rtCGM is now needed.

The vast majority of individuals with type 1 diabetes are treated with multiple daily insulin injections (MDI), which is likely to be because of the increased costs associated with continuous subcutaneous insulin infusion therapy (CSII).[10] However, most evidence about the benefits of rtCGM in individuals with problematic hypoglycaemia was generated in clinical studies that had few or no participants treated with MDI.[3,4] Compared with MDI treatment, CSII enables individuals to adjust insulin doses in a more flexible manner to address circadian changes in insulin requirements and lifestyle factors (eg, physical activity), which facilitates avoidance of low glucose values;[11] therefore, the results obtained in these studies might not be generalisable to individuals treated with MDI.

GOLD[12] and DIAMOND,[13] two landmark studies investigating the effects of rtCGM exclusively in individuals with type 1 diabetes treated by MDI, showed significant reductions of glycated haemoglobin ($HbA_{1c}$), which were accompanied by an improvement in biochemical hypoglycaemia. However, because both studies selected their study sample on the basis of an unfavourable $HbA_{1c}$ value (>7·5% or 58·5 mmol/mol), individuals with problematic hypoglycaemia were (or might have been) excluded from the trials. For example, individuals with a history of recurrent severe hypoglycaemia were specifically excluded from participating in the DIAMOND trial,[13] whereas eligibility criteria for the GOLD study required investigators to exclude participants who were determined to be unsuitable for participation,[12] which might have been applied to individuals with problematic hypoglycaemia. Thus, the potential benefits of rtCGM in reducing hypoglycaemia

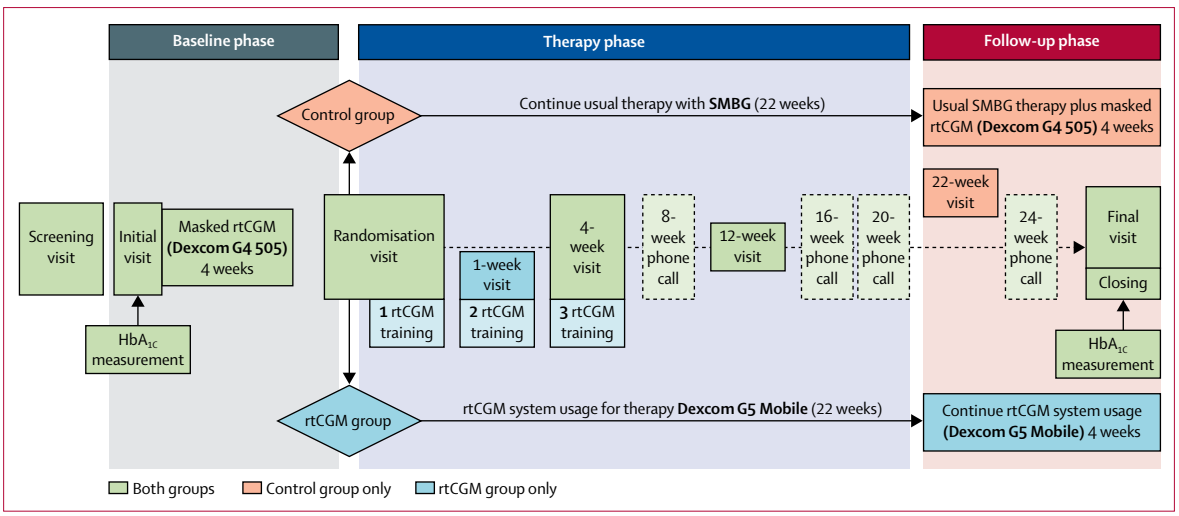


***Figure 1:*** **Study design**
SMBG=self-monitoring of blood glucose. rtCGM=real-time continous glucose monitoring. $HbA_{1c}$=glycated haemoglobin.

in high-risk individuals with type 1 diabetes treated by MDI remains an open question.

The aim of the investigator-initiated HypoDE study was to test the hypothesis that use of rtCGM reduces the frequency of hypoglycaemic events when compared with use of self-monitoring of blood glucose (SMBG) in high-risk adults with type 1 diabetes treated by MDI.

## Methods

### Study design and participants

The HypoDE study was a multicentre, open-label, parallel, randomised controlled trial with a 6-month study period fulfilling good clinical practice standards. Participants were recruited from 12 specialised diabetes practices in Germany. All sites had experience of conducting clinical trials and of rtCGM usage.

The clinical study protocol was approved by the ethics committee of Landesaerztekammer Baden Wuerttemberg, Stuttgart, Germany, and the respective local ethics committees. Full details of the HypoDE clinical study protocol have been previously published.[14]

Study participants were eligible for inclusion if they had type 1 diabetes for 1 year or more and problematic hypoglycaemia, which was defined as having had at least one severe hypoglycaemia event requiring third-party assistance for recovery in the previous year, or having impaired hypoglycaemia awareness as defined by a total score of 4 or more in the hypoglycaemia unawareness questionnaire developed by Clarke and colleagues.[15] Additional inclusion criteria were treatment with MDI (prandial insulin at each major meal and at least one dose of basal insulin), age 18 years or older, and screening $HbA_{1c}$ 75·0 mmol/mol or lower (≤9·0%). Exclusion criteria were treatment with CSII therapy, use of the rtCGM system or another rtCGM device in the previous 3 months, and pregnancy. All study participants had attended a structured diabetes teaching and treatment programme. Before inclusion, all participants were fully informed both orally and in writing about the study and provided written informed consent.

### Randomisation and masking

Following enrolment, participants had to complete a 4-week baseline phase with a masked rtCGM device (Dexcom G4 with software 505; Dexcom, San Diego, CA, USA) before they were eligible for randomisation. Participants in both groups were required to wear the masked rtCGM system more than 85% of the time (eg, for 6 of 7 days per week) during the 4-week period. If a participant was unable to meet this requirement, investigators had the option to allow one additional week of rtCGM system wear.

Following the baseline phase, eligible study participants were randomly assigned to one of two groups: rtCGM system use (rtCGM group) or continued use of SMBG (control group). Randomisation was done centrally at the study coordinating centre by staff who were not involved with recruitment or treatment of study participants. A randomisation sequence was generated with SYSTAT 12.0 with a 1:1 allocation; the study centre was a stratifying variable. Randomisation was done block-wise per site (four participants per block). Each study site received sealed envelopes with the respective group allocation. After successful completion of the baseline phase, the respective envelope was opened. Study site personnel informed participants about their group allocation. Because of the nature of the intervention, masking of study participants and study personnel was not possible.

### Procedures

The study was done in three phases: the baseline phase, therapy phase, and follow-up phase. The number of study visits was equal between the two groups, but differently distributed (figure 1). However, the distribution of

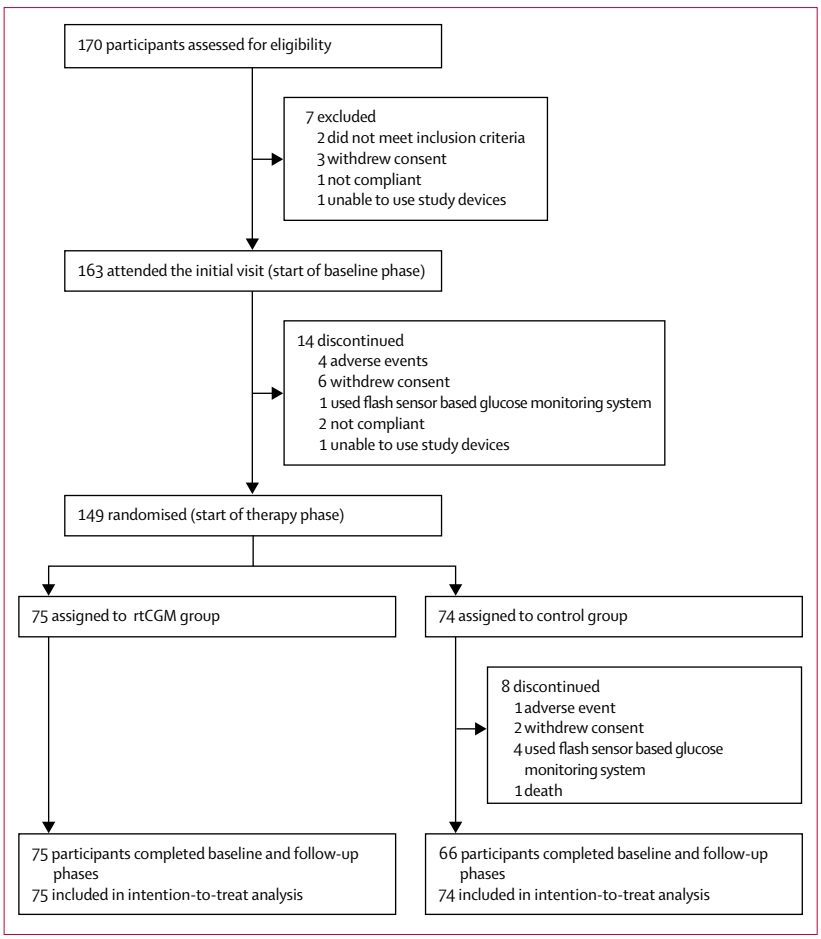


***Figure 2:*** **Trial profile**
rtCGM=real-time continous glucose monitoring.

visits did not have an effect on baseline or follow-up data collection.

In the baseline phase, after written informed consent was obtained from participants during the initial visit, baseline medical examinations were done, medical information was obtained from medical records, participants completed questionnaires, and blood samples for $HbA_{1c}$ measurement were collected. $HbA_{1c}$ analysis was done at a central laboratory (MLM Medical Labs, Moenchengladbach, Germany) by use of a certified high performance liquid chromatography method.

During the subsequent baseline phase, all participants wore a masked rtCGM system (Dexcom G4 with software 505) for 4 weeks. All participants were instructed on how to insert and secure the glucose sensor and how to calibrate the system. The SMBG systems used by study participants were assessed for accuracy. If accuracy was considered insufficient, an SMBG system with sufficient measurement accuracy was made available (a list of systems is provided in the appendix).

See Online for appendix

In the therapy phase, before randomisation, all rtCGM and SMBG data were uploaded at the study sites and downloaded at the study coordination centre via an electronic data management tool (DIASEND/Glooko, Goteborg, Sweden), and participant adherence to use of rtCGM was checked. Participants assigned to the rtCGM group received an unmasked rtCGM system (Dexcom G5 Mobile system, Dexcom Inc, San Diego, CA, USA). Analytical performance of the Dexcom G5 Mobile system and G4 505 system is identical.[16] The differences between the two systems are in the handheld device for data display and connectivity options, which the Dexcom G5 Mobile system offers. Glucose alerts were individualised to each participant at their respective study centre.

Participants in the rtCGM group received instructions on optimal use of rtCGM in three sessions. Topics included how to wear an rtCGM system, importance of calibration, when confirmation of results by SMBG is necessary, use of trend arrows and glucose profiles for treatment adjustments, and use and setting of hypoglycaemic or hyperglycaemic alerts. The first training session was done at the randomisation visit, the second at the additional 1-week visit, and the third at the regular 4-week visit, which was also attended by control group participants.

Control group participants continued SMBG measurements and received their usual care. Both groups used their respective glucose monitoring device (rtCGM or SMBG system) for the subsequent 22 weeks to make therapeutic decisions. Both groups attended a visit at 12 weeks and were contacted by phone calls at weeks 8, 16, 20, and 24 following randomisation; control group participants had an additional visit at week 22, when masked rtCGM systems were handed out again.

Study site clinicians were asked to review the rtCGM or SMBG data at each visit and during phone calls and make appropriate treatment modifications as needed. Study sites received a resource kit that provided recommendations for initiating therapy modifications (eg, change of basal insulin dose, prandial insulin, change of carbohydrate factors, and adjusting insulin to exercise). Study sites could use elements of the resource kit at their own discretion for treatment modifications for participants in both study groups.

The follow-up phase began at week 22. Control group participants again wore the masked Dexcom G4 505 system, and participants in the rtCGM group continued with the Dexcom G5 Mobile system during the next 4 weeks. At the final visit (week 26), rtCGM data were again uploaded at the study sites and downloaded at the study coordination centre. Patient questionnaires were administered and blood samples for $HbA_{1c}$ measurement were collected.

## Outcomes

The primary outcome was the number of hypoglycaemic events measured by rtCGM during the follow-up phase compared with baseline. The follow-up phase lasted from weeks 22 to 26. A hypoglycaemic event derived from

rtCGM was defined as glucose values of 3·0 mmol/L (≤54 mg/dL) or lower for at least 20 min, preceded by a minimum of 30 min with glucose values greater than 3·0 mmol/L (>54 mg/dL). The number of hypoglycaemic events was examined for each patient during each recording phase and standardised to an incidence of low glucose values per 28 days.

Secondary outcomes were changes in nocturnal hypoglycaemic events (0000 h to 0600 h); percentage and duration of glucose readings derived from continuous glucose monitoring per day in different glucose ranges (≤3·0 mmol/L [≤54 mg/dL], ≤3·9 mmol/L [≤70 mg/dL], >3·9 mmol/L to ≤10·0 mmol/L [>70 mg/dL to 180 mg/dL], and >10·0 mmol/L [>180 mg/dL]), and percentage of blood glucose readings based on SMBG measurements in these different glucose ranges. Glycaemic variability assessed by coefficient of variation and the low blood glucose index (LBGI),[17] as a risk indicator for severe hypoglycaemia, was calculated for the baseline and follow-up phases with rtCGM and SMBG data.

The following changes in patient-reported outcomes were also regarded as secondary endpoints: impaired hypoglycaemia awareness assessed with the hypoglycaemia unawareness questionnaire;[15] diabetes distress assessed with the Diabetes Distress Scale for type 1 diabetes (T1-DDS);[18] fear of hypoglycaemia assessed with the Hypoglycaemia Fear Survey;[19] self-reported health status assessed with the European Quality of Life 5 Dimensions questionnaire (EQ-5D);[20] and satisfaction with glucose measurement assessed with the Glucose Monitoring Satisfaction Survey.[21]

The frequency of severe hypoglycaemia events was defined as the number of hypoglycaemic events requiring third-party assistance to administer carbohydrate, glucagon, or intravenous glucose injections during the therapy and follow-up phases. Severe hypoglycaemia was further divided into two additional categories: events requiring medical assistance to inject glucagon or glucose or associated with hospital admission; and events requiring third-party assistance without medical assistance.

Each severe hypoglycaemia event was recorded by the patient on a form provided. Study personnel inquired during each visit or phone call about the occurrence of adverse events and asked participants whether severe hypoglycaemia had occurred. Documented and reported severe hypoglycaemia events were assessed by medical staff to ascertain the severity of the event (eg, unconsciousness, seizure, emergency call) and type of intervention required (eg, glucose, glucagon, or hospital admission). If the severe hypoglycaemia event could be verified, this event was documented on a separate form. The number of severe hypoglycaemia events during therapy and the follow-up phase was standardised as the incidence of severe hypoglycaemia per patient-year. Other serious adverse events regardless of causality were recorded on respective forms.

| | Control group (n=74)* | rtCGM group (n=75)* |
|---|---|---|
| **Demographic and medical characteristics** | | |
| Age, years | 47·3 (11·7) | 45·8 (12·0) |
| Women | 25 (34%) | 35 (47%) |
| Men | 49 (66%) | 40 (53%) |
| Body-mass index, kg/m² | 26·0 (4·6) | 26·1 (6·7) |
| Diabetes duration, years | 21·6 (13·9) | 20·9 (14·0) |
| $HbA_{1c}$, %† | 7·3% (1·0) | 7·6% (1·0) |
| $HbA_{1c}$, mmol/mol† | 56·7 (10·6) | 59·3 (10·9) |
| **Treatment characteristics** | | |
| Treated with analogue basal insulin | 73 (99%) | 71 (95%) |
| Treated with one basal insulin injection per day | 47 (64%) | 39 (52%) |
| Daily dose of basal insulin, IU | 20·1 (10·8) | 23·9 (16·2) |
| Treated with analogue bolus insulin‡ | 66 (89%) | 67 (91%) |
| Daily dose of bolus insulin, IU§ | 24·3 (12·2) | 26·8 (29·5) |
| **Problematic hypoglycaemia** | | |
| Any severe hypoglycaemia in the past 12 months | 45 (61%) | 47 (63%) |
| Hypoglycaemia unawareness (hypoglycaemia unawareness score ≥4) | 68 (92%) | 71 (95%) |
| Hypoglycaemia unawareness score | 4·7 (1·3) | 5·0 (1·1) |

Data are mean (SD) or n (%). rtCGM=real-time continuous glucose monitoring. $HbA_{1c}$=glycated haemoglobin. *Numbers used in the analyses if not indicated otherwise. †$HbA_{1c}$ at baseline and follow-up was measured in central laboratory. ‡Based on data from 73 participants of the control group and 74 participansts of the rtCGM group. §Based on data from 64 participants of the control group and 75 participants of the rtCGM group.

***Table 1:*** **Baseline characteristics of randomised participants (intention-to-treat population)**

## Statistical analysis

In a meta-analysis,[2] effect sizes for reduction of biochemical hypoglycaemia in various rtCGM studies ranged between 0·19 SD and 0·48 SD. We considered an effect size of 0·5 SD to be clinically meaningful and realistic. Thus, a reduction in the frequency of low-glucose events by 0·5 SD was expected to be achieved by in the rtCGM group compared with the control group. Aiming to detect a reduction of low-glucose events by this magnitude and assuming a two-sided alpha of 0·05 and a power of 80%, we calculated that a sample size of 64 participants per group was required. Assuming a dropout rate of up to 20%, we determined that at least 160 participants were needed to secure data from 128 participants for analysis.

The full analysis dataset consists of participants who wore the rtCGM system during the baseline and follow-up phases. The intention-to-treat analysis was based on all randomised participants. For the intention-to-treat analysis, missing values were replaced with multiple imputation technique. This was done because the planned replacement method of carrying the baseline observation forward would have been disadvantageous for the control group, given the selective dropout in this

| | Baseline phase | | Follow-up phase | | Adjusted between-group differences (95% CI) | p value* |
|---|---|---|---|---|---|---|
| | Control group (n=66) | rtCGM group (n=75) | Control group (n=66) | rtCGM group (n=75) | | |
| Mean duration of rtCGM wear during baseline and follow-up phases, days | 26·4 (1·7) | 27·0 (1·5) | 27·0 (1·8) | 27·7 (1·5) | 0·02 (–0·49 to 0·54) | 0·9233 |
| Primary outcome, low glucose events ≤3·0 mmol/L | | | | | | |
| Mean number of hypoglycaemic events per 28 days | 14·4 (12·4) | 10·8 (10·0) | 13·7 (11·6) | 3·5 (4·7) | 0·28 (0·20 to 0·39)† | <0·0001‡ |
| Secondary outcomes, rtCGM characteristics | | | | | | |
| Mean number of nocturnal hypoglycaemic events per 28 days | 2·4 (2·6) | 2·3 (2·4) | 2·7 (2·8) | 1·0 (1·0) | 0·35 (0·22 to 0·56)† | <0·0001‡ |
| Mean rtCGM glucose, mmol/L | 8·7 (1·5) | 9·0 (1·6) | 8·9 (1·5) | 9·5 (1·6) | 0·28 (–0·05 to 0·62) | 0·0982 |
| Median percentage of rtCGM values ≤3·9 mmol/L | 6·9% (3·6 to 12·3) | 5·0% (2·7 to 9·0) | 6·4% (3·7 to 12·0) | 1·6% (0·9 to 3·7) | .. | <0·0001 |
| Median percentage of rtCGM values ≤3·0 mmol/L | 2·7% (1·0 to 5·7) | 1·7% (0·7 to 3·8) | 2·5% (1·0 to 6·1) | 0·3% (0·1 to 0·9) | .. | <0·0001 |
| Mean percentage of rtCGM values >3·9 mmol/L and ≤10·0 mmol/L | 59·1% (13·3) | 57·8% (15·4) | 56·5% (12·2) | 58·5% (17·7) | 3·1 (0·0 to 6·2) | 0·0535 |
| Mean percentage of rtCGM values >10·0 mmol/L | 32·8% (15·5) | 35·4% (17·5) | 35·3% (15·2) | 38·8% (18·7) | 1·3 (–2·3 to 4·9) | 0·4681 |
| Median duration of rtCGM ≤3·9 mmol/L per day, min | 99·5 (52·3 to 178·1) | 70·9 (38·8 to 130·2) | 92·2 (51·8 to 172·6) | 23·9 (12·9 to 54·5) | .. | <0·0001 |
| Median duration of rtCGM ≤3·0 mmol/L per day, min | 36·3 (13·1 to 79·7) | 24·1 (8·9 to 51·0) | 32·9 (13·1 to 83·9) | 3·8 (1·1 to 11·9) | .. | <0·0001 |
| Mean duration of rtCGM values >3·9 mmol/L and ≤10·0 mmol/L per day, min | 851·0 (191·7) | 831·9 (221·5) | 814·2 (176·0) | 842·9 (225·2) | 44·9 (–0·3 to 90·0) | 0·0513 |
| Mean duration of rtCGM values >10·0 mmol/L per day, min | 471·7 (223·1) | 509·8 (252·2) | 509·1 (219·1) | 558·6 (268·4) | –18·7 (–70·3 to 32·9) | 0·4744 |
| Mean rtCGM variability, coefficient of variation | 40·5% (7·0) | 39·3% (7·6) | 41·1% (6·9) | 34·1% (5·6) | 6·2 (5·0 to 7·5) | <0·0001 |
| Median low blood glucose index (rtCGM-LBGI) | 1·60 (0·88 to 2·92) | 1·26 (0·70 to 2·15) | 1·53 (0·84 to 2·97) | 0·52 (0·25 to 0·98) | .. | <0·0001 |
| Secondary outcomes, SMBG characteristics | | | | | | |
| Mean SMBG glucose, mmol/L | 8·8 (1·6) | 9·3 (1·7) | 9·1 (1·6) | 9·7 (1·8) | –0·23 (–0·62 to 0·15) | 0·2385 |
| Mean number of SMBG tests per day | 6·4 (1·7) | 6·8 (2·5) | 6·0 (1·3) | 3·7 (1·9) | –2·5 (–3·0 to 2·1) | <0·0001 |
| Median percentage of SMBG values ≤3·9 mmol/L | 9·0% (5·8 to 14·4) | 7·6% (4·1 to 11·5) | 8·6% (4·8 to 11·7) | 2·6% (1·0 to 6·2) | .. | <0·0001§ |
| Median percentage of SMBG values ≤3·0 mmol/L | 2·9% (1·0 to 7·2) | 2·4% (0·6 to 4·8) | 2·6% (1·0 to 4·9) | 0·0 (0·0 to 1·6) | .. | <0·0001§ |
| Mean percentage of SMBG values >3·9 mmol/L and ≤10·0 mmol/L | 55·5% (13·5) | 53·9% (14·5) | 53·6% (12·7) | 54·4% (16·6) | 3·4 (–1·0 to 7·9) | 0·1251§ |
| Mean percentage of SMBG values >10·0 mmol/L | 33·9% (18·9) | 37·5% (16·3) | 37·2% (15·2) | 41·4% (18·3) | 0·2 (–4·5 to 4·9) | 0·9422§ |
| Mean SMBG variability, coefficient of variation | 43·7% (6·8) | 43·0% (9·7) | 43·9% (7·4) | 37·8% (7·2) | 5·7 (3·4 to 8·0) | <0·0001§ |
| Median low blood glucose index (SMBG-LBGI) | 1·85 (1·20 to 3·24) | 1·58 (0·90 to 2·45) | 1·75 (1·11 to 2·71) | 0·61 (0·28 to 1·45) | .. | <0·0001§ |
| Secondary outcomes, glycaemic control | | | | | | |
| Mean $HbA_{1c}$, % | 7·4% (1·0) | 7·6% (1·0) | 7·3% (0·9) | 7·4% (0·8) | 0·03 (–0·12 to 0·19) | 0·6653 |
| Mean $HbA_{1c}$, mmol/mol | 57·1 (10·7) | 59·3 (10·9) | 55·8 (9·6) | 57·0 (9·1) | 0·37 (–2·07 to 1·32) | 0·6653 |

Data are mean (SD) or median (IQR), unless otherwise stated. rtCGM=real-time continuous glucose monitoring. SMBG=self-monitoring of blood glucose. $HbA_{1c}$=glycated haemoglobin. Nocturnal=between 0000 h and 0600 h, measured by rtCGM. LBGI=low blood glucose index. *Unless stated otherwise, p values are based on covariance analysis with group allocation as independent factor and baseline values as covariates, and p values for data with skewed distributions are based on covariance analysis using van der Waerden scores. †Incidence rate ratio adjusted for baseline (reference category=control group). ‡p values are based on negative binominal regression analysis (model fit: Pearson $\chi^2$=0·92). §Adjusted for baseline and frequency of SBMG during follow-up phase.

***Table 2:*** **Primary and secondary glycaemic outcomes in both study groups**

study group. Missing data at the follow-up phase were imputed by use of a Markov Chain Monte Carlo multivariate imputation algorithm (missing data module in SPSS 24) with ten estimations per missing value by use of the following variables as estimators: age, diabetes duration, treatment allocation, unawareness score, number of low-glucose events in the baseline phase, and duration of the baseline and follow-up period.

The primary analysis comparing the number of hypoglycaemic events defined by rtCGM between both groups was done by negative binominal regressions analysis with adjustments for the number of hypoglycaemic events during the baseline phase and the duration of the follow-up phase.

For secondary outcomes, covariance analyses were used with group allocation as an independent factor and baseline values as covariates. For analysis of SMBG data, the number of SMBG tests during the follow-up phase was an additional covariate, because of the different frequency of SMBG in both groups in this phase. In case of skewed data distributions, covariance models based on ranks with van der Waerden scores were used instead of the raw data. Categorical data were analysed by $\chi^2$ tests or logistic regressions, adjusted for baseline values.

Rates of documented severe hypoglycaemia were reported as annual incidence per patient-year. A negative binominal regressions analysis was done to compare the frequency of severe hypoglycaemia between the two study groups during the treatment and follow-up phases, adjusted for baseline frequency of severe hypoglycaemia. To address overdispersion, a robust estimator was used in the covariance matrix. Incidence rate ratios (IRRs) with corresponding 95% CIs and p values were reported. Statistical analyses were done with SPSS 24.0 for Windows. The study is registered with ClinicalTrials.gov, number NCT02671968.

### Role of the funding source

The funder of the study (Dexcom Inc) had no role in study design, data collection, data analysis, data interpretation, or writing of this report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Results

Between March 4, 2016, and Jan 12, 2017, 170 participants were recruited and assessed for eligibility; 163 participants started the baseline phase and 149 were randomised to the control (n=74) or rtCGM (n=75) groups (figure 2). Among the 21 participants who were not randomised, seven discontinued before the baseline phase and 14 were excluded during or immediately after the baseline phase. All randomised participants were included in the intention-to-treat population. Among the 149 randomised participants, all rtCGM participants completed the study and eight in the control group terminated the study prematurely.

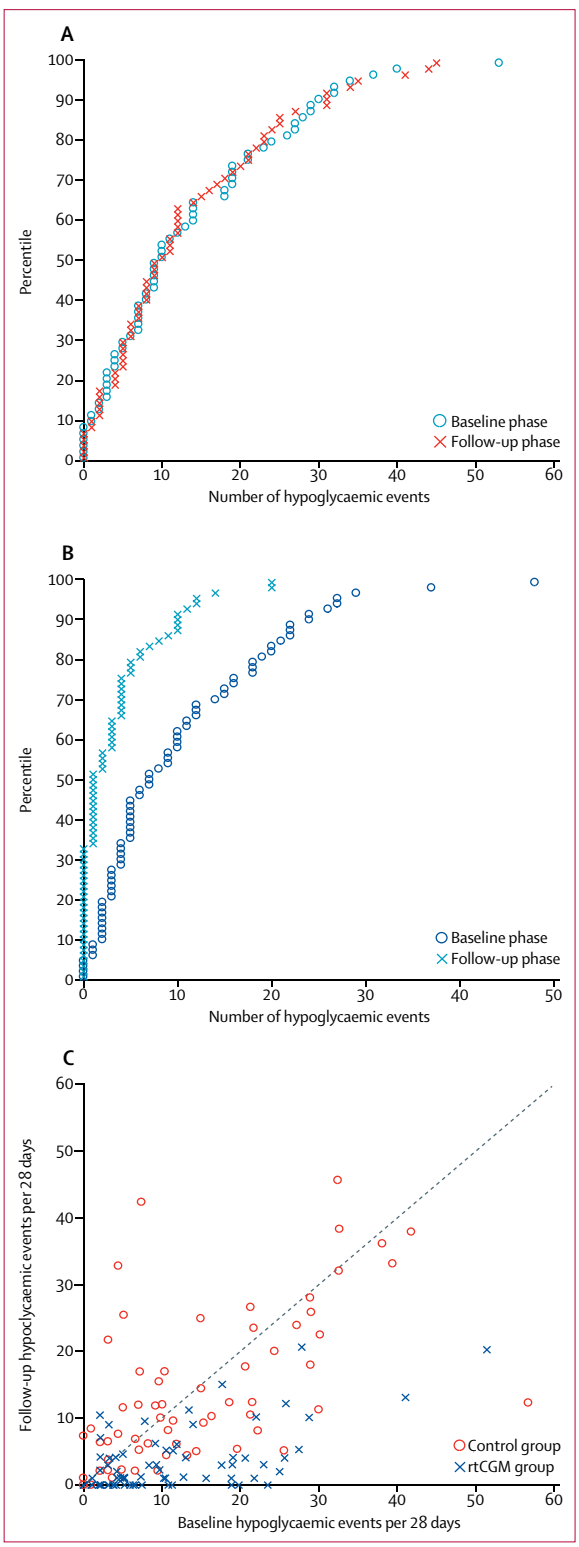


***Figure 3:*** **Hypoglycaemic values during the baseline phase and the follow-up phase for the rtCGM group and control group**
Cumulative distribution of hypoglycaemic events per 28 days at baseline and follow-up in the control group (A) and in the real-time continuous glucose monitoring (rtCGM) group (B). For any given number of hypoglycaemic events (x-axis) the percentage of participants with the number of events at that level or lower in baseline and follow-up phase (y-axis) can be determined from the graph. Scatterplot of hypoglycaemic events of all individual patients during baseline and follow-up phases (C). Points below the diagonal line represent participants in whom the number of events during the follow-up phase was lower than during the baseline phase.

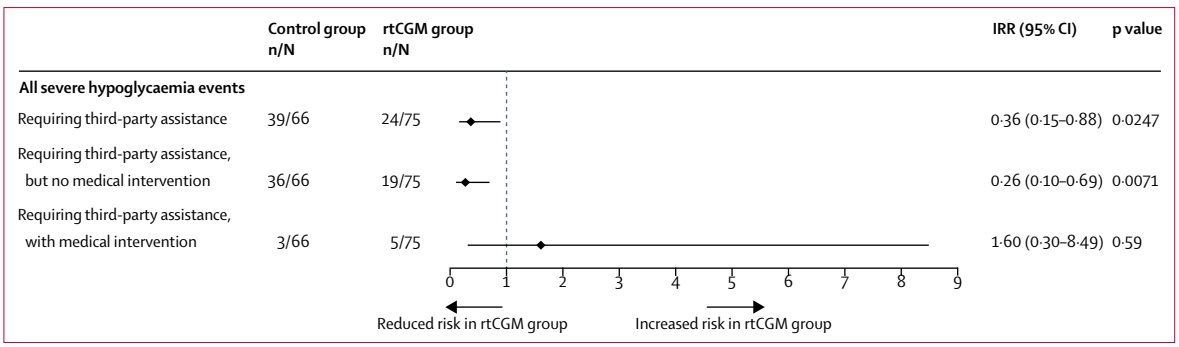


***Figure 4:*** **Severe hypoglycaemia events in the rtCGM group and the control group**
rtCGM=real-time continuous glucose monitoring. IRR=incidence rate ratio.

The full analysis dataset consists of data from 141 participants (control group, n=66; rtCGM group, n=75) who completed the baseline and follow-up phases. Mean baseline $HbA_{1c}$ was 58·5 mmol/mol (7·5%) for all study participants, which is considered satisfactory according to German treatment guidelines for individuals with type 1 diabetes.[22] Approximately 90% or more of participants used insulin analogues for coverage of basal and prandial (bolus) insulin requirements. Among rtCGM participants, the average percentage of sensor wear time was 90·7% of study days assessed (first 4 weeks subsequent to randomisation, 30 days before 12-week visit, and 30 days before 26-week visit). Assessment of adherence during the total therapy phase and the follow-up phase was not possible because rtCGM data were overwritten after 30 days with the most recent data. A breakdown of sensor wear frequency is presented in the appendix. The mean frequency of daily SMBG was significantly lower in the rtCGM group than in the SMBG groups (3·7 [SD 1·9] *vs* 6·0 [1·3], p<0·0001).

Approximately two-thirds of participants reported at least one severe hypoglycaemia episode in the past year and more than 90% had impaired hypoglycaemia awareness. Other baseline demographic and medical characteristics are presented in table 1. We observed no significant differences in demographic characteristics between participants who completed the study and those who discontinued (appendix). Wear times of the rtCGM systems during the baseline and follow-up phases were similar between study groups (table 2).

The mean number of hypoglycaemic events per 28 days defined by rtCGM was reduced from 10·8 (SD 10·0) to 3·5 (4·7) among rtCGM group participants and from 14·4 (12·4) to 13·7 (11·6) among control group participants. Incidence of hypoglycaemic events decreased by 72% for rtCGM participants (IRR 0·28, 95% CI 0·20–0·39, p<0·0001; table 2; figure 3). Analysis of the intention-to-treat population by use of multiple imputation techniques yielded similar results: the mean number of hypoglycaemic events dropped from 10·4 (SD 9·6) to 3·4 (4·5) in the rtCGM group but remained relatively unchanged in the control group (13·2 [11·4] to 13·2 [10·9]) with an IRR of 0·27 (95% CI 0·20–0·38; p<0·0001). 25 (33·3%) of 75 rtCGM group participants had no hypoglycaemic events during the follow-up phase compared with five (7·6%) of 66 control group participants. This difference corresponds to an odds ratio of 6·1 (95% CI 2·2–17·1; p=0·0006) for avoidance of hypoglycaemia in the rtCGM group compared with the control group.

The number of nocturnal hypoglycaemic events was significantly reduced in the rtCGM group, but not in the control group (table 2). The percentages of glucose values 3·0 mmol/L or lower and 3·9 mmol/L or lower were reduced in the rtCGM group compared with the control group. The LBGI was also reduced in the rtCGM group, whereas it remained relatively unchanged in the control group (table 2). The time in range increased by 0·7 percentage points in the rtCGM group, whereas the control group showed a reduction by 2·6 percentage points (p=0·0513; table 2). The percentage of hyperglycaemic glucose values was increased slightly in both study groups but with no significant between-group differences (table 2). Reductions in glycaemic variability were observed in rtCGM group participants but not in control group participants (table 2). Glycaemic variability was improved over the whole day by rtCGM (appendix). The frequency of SMBG was substantially lower in the rtCGM group than in the control group during the outcome phase. Therefore, the SMBG frequency during the follow-up phase was adjusted. The adjusted SMBG data are consistent with those from the rtCGM group (table 2). $HbA_{1c}$ values remained stable in both groups, with only a marginal between-group difference.

63 severe hypoglycaemia events were observed during the therapy and follow-up phases: 24 in the rtCGM group and 39 in the control group. The incidence of all severe hypoglycaemia events among control group participants during follow-up was approximately twice the incidence seen in the rtCGM group (1·18 [SD 3·46] *vs* 0·64 [1·92] events per patient-year; IRR 0·36 [95% CI 0·15–0·88], p=0·0247; appendix). Severe hypoglycaemia events requiring third-party assistance without medical assistance for recovery were also less frequent in the rtCGM group than in the control group (19 *vs* 36 events),

with a similar difference in incidence (0·51 [SD 1·75] *vs* 1·09 [3·41] events per patient-year; IRR 0·26 [95% CI 0·10–0·69], p=0·0071; appendix). Of the eight severe hypoglycaemia episodes requiring medical assistance for recovery, five occurred in rtCGM group participants and three in control group participants (0·13 *vs* 0·09 events per patient-year; IRR 1·60 [95% CI 0·30–8·49], p=0·59). The baseline adjusted IRRs for these severe hypoglycaemia events are shown in figure 4. The proportion of participants affected by these severe hypoglycaemia events did not differ significantly between the groups (appendix).

Total scores for patient-reported outcome questionnaires are shown in the appendix. The hypoglycaemia unawareness score improved in both groups by approximately 40%, with no between-group differences. The glucose monitoring satisfaction score showed that participants in the rtCGM group were more satisfied with their method of glucose monitoring than were those in the control group. At study end, fear of hypoglycaemia was lowered in both groups (between-group difference p=0·067). The diabetes distress total score was also reduced in both groups. A significant between-group effect was observed only for the hypoglycaemia distress subscale score of the T1-DDS (appendix). Self-reported health status, measured by the EQ-5D questionnaire, showed no significant difference between both groups.

18 serious adverse events were reported for 15 participants: seven events occurred in the control group (two severe episodes of hypoglycaemia, one kidney transplantation, one myocardial infarction, two colon polyps, and one seizure) and ten occurred in the rtCGM group (four episodes of severe hypoglycaemia, two diabetic foot ulcers, one allergic reaction following a wasp sting, two fractures, and one kidney tumour removal). One serious adverse event occurred before randomisation (whiplash after a car accident). No event was considered to be related to the investigational device.

## Discussion

The results of this multicentre randomised study in individuals with type 1 diabetes treated with MDI and with impaired hypoglycaemia awareness or severe hypoglycaemia show that the number of hypoglycaemic events can be markedly reduced by use of rtCGM compared with reliance on SMBG. Other measures of biochemical hypoglycaemia or markers of future hypoglycaemic risk, such as percentage of hypoglycaemic values and the LBGI, were also significantly improved in the rtCGM group. Additionally, use of rtCGM lowered the frequency of clinical severe hypoglycaemia and reduced glycaemic variability. Importantly, the slight improvement in $HbA_{1c}$ values in the rtCGM group and the similar $HbA_{1c}$ values between both study groups indicate that hypoglycaemia reduction was not achieved at the expense of a deterioration of overall glycaemic control. These findings show that use of rtCGM can effectively address problematic hypoglycaemia in individuals with type 1 diabetes treated by MDI.

According to recent international consensus recommendations, a rtCGM reading below a threshold of 3·0 mmol/L (<54 mg/dL) for at least 15 mins is considered a hypoglycaemic event.[23] Glucose concentrations below this threshold cause severe neuroglycopenic dysfunction of the brain that limits the ability to self-treat.[24] This dysfunction not only increases the risk of severe hypoglycaemia[24] but is also associated with hazards in daily life if it occurs during potentially dangerous activities such as driving or while operating machines.[1] In the absence of third-party assistance, severe hypoglycaemia has a high probability of resulting in a life-threatening condition such as a coma or seizure. Thus, a reduction in the frequency of hypoglycaemic episodes requiring any third-party assistance could also be protective against further deterioration of severe hypoglycaemia resulting in coma or seizure.[25]

We found no difference in the incidence of severe hypoglycaemia requiring medical assistance for recovery. This result indicates that, despite use of rtCGM, a subgroup of participants had a persistently elevated hypoglycaemia risk.[6] Because these events are rare, this study might not have had sufficient statistical power to detect differences within this subgroup of participants with severe hypoglycaemia.[26]

We noted no relevant difference in the self-reported hypoglycaemia unawareness score between study groups. This observation corroborates findings from other studies, which showed a reduction in the incidence of severe hypoglycaemia but no difference in hypoglycaemia unawareness scores.[3,4] Self-reported unawareness might be a good predictor of future hypoglycaemia in epidemiological studies,[15] but it is less suited to measure the physiological effect of hypoglycaemia avoidance on hypoglycaemia-associated autonomic failure in the context of rtCGM.

Glycaemic variability was also reduced by use of rtCGM. This result indicates that rtCGM participants achieved a more stable glucose profile than did participants in the control group, which is also a protective factor against hypoglycaemia.[27] As reported, rtCGM participants showed a significant reduction in glycaemic variability, from 39·3% at baseline to 34·1% at follow-up; glycaemic variability less than 36% is considered stable.[23]

Patient-reported outcomes showed a positive effect of rtCGM use on hypoglycaemia-related distress and on satisfaction with glucose monitoring systems. No effects were seen on fear of hypoglycaemia and overall diabetes-related distress or self-reported health status. This result indicates that use of rtCGM specifically affected participants' satisfaction with this method for glucose monitoring and participants' hypoglycaemia-related distress.

Findings from the most recent studies that investigated use of rtCGM exclusively in individuals with type 1 diabetes treated by MDI were similar to the results reported here. In the GOLD study,[12] an open-label crossover randomised trial, use of rtCGM was associated with a notably lower percentage of time participants spent in the hypoglycaemic range (<3·0 mmol/L) compared with conventional treatment with SMBG (0·79% *vs* 1·89%). Similar differences in the percentage of time spent with glucose concentrations less than 3·3 mmol/L were observed in the DIAMOND trial[13] among rtCGM users compared with SMBG users (1·4% *vs* 2·7%, p=0·002).

Conversely, the hypoglycaemic outcomes reported in the IN CONTROL trial[3] and the sensor-augmented CSII study by Ly and colleagues[4] were less robust. For example, the percentage of glucose values less than or equal to 3·9 mmol/L was notably higher among rtCGM users in the sensor-augmented study[4] (4·2%) and the IN CONTROL study[3] (6·8%) than in our study (median 1·6%; IQR 0·9–3·7). Glycaemic variability was also higher with use of rtCGM in the IN CONTROL study than in our study (39·5% *vs* 34·1%). However, there are substantial differences between the three studies. Whereas the HypoDE study included only participants treated by MDI, 44% of participants in the IN CONTROL study and 100% of those in the study by Ly and colleagues used CSII therapy. The differences in these findings might also be a consequence of demographic differences; duration of diabetes within the IN CONTROL population was 10 years longer than in the HypoDE study population. The analytical performance of different rtCGM systems used in these studies might also be an important contributor to these findings. Nevertheless, considering that rtCGM combined with CSII is the most expensive choice of therapy in type 1 diabetes, the finding that MDI combined with rtCGM has similar effects on hypoglycaemia could have significant health-economic implications. Therefore, head-to-head studies with MDI and CSII combined with rtCGM are clearly needed.

A key strength of the HypoDE study is that we only enrolled individuals with type 1 diabetes treated by MDI and with impaired hypoglycaemia awareness or severe hypoglycaemia. As discussed earlier, this population has not been well studied in previous trials. Thus, this study provided evidence of the significant effect of rtCGM on problematic hypoglycaemia in individuals treated by MDI. Findings from a recent study comparing outcomes of rtCGM in participants treated with MDI or CSII[28] and comparative effectiveness research[29] suggest that the combination of CSII and rtCGM has an unexpectedly limited ability to reduce hypoglycaemia. A further strength of the HypoDE study is that the glycaemic outcomes related to rtCGM could be confirmed by SMBG measurements, thus excluding the possibility that these outcomes were an artifact. Absence of external validation of the rtCGM results was a major criticism of the IN CONTROL study.[30]

Some limitations should also be considered. First, neither participants nor study personnel could be masked to the intervention. Second, participants were required to wear their rtCGM device 85% of the time during the baseline phase to continue in the study. This requirement might have resulted in selection bias, which could potentially limit the generalisability of our findings to all high-risk individuals with type 1 diabetes. The use of SMBG data to assess the effect of rtCGM on glycaemic outcomes could also be problematic since the control group might have tested blood glucose several times during one hypoglycaemic event. This repeated testing might have biased the effect of SMBG on hypoglycaemia-related outcomes. Additionally, the frequency of SMBG was substantially different during the follow-up period between the groups, which necessitated the use of a post-randomisation covariate. The absence of adjustment for multiplicity for secondary outcomes can be regarded as another limitation.

In summary, our findings indicate that individuals with type 1 diabetes treated by MDI and with impaired hypoglycaemia awareness or severe hypoglycaemia can minimise both biochemical and clinical hypoglycaemia through use of rtCGM without compromising overall glycaemic control. Since the majority of individuals with type 1 diabetes are treated by MDI, this finding has high clinical relevance.

#### Contributors

LH designed and helped to conduct the study, and was actively involved in analysing the data and writing the manuscript. GF contributed to study design and its coordination, analysis of data, and writing and editing of the manuscript. DE contributed to analysis of data, and writing and editing of the manuscript. GF-H was involved in designing and conducting the study and was actively involved in writing the manuscript. SG contributed to writing and reviewing the manuscript. DW contributed to coordination of the study, analysis of data, and writing and editing of the manuscript. NH contributed to study design, analysis of data, and writing and editing of the manuscript, and was the principal investigator of this study.

#### Declaration of interests

LH reports grants from Dexcom Inc during the conduct of the study; and personal fees from Roche Diagnostics, Integrity Ltd, Medtronic, and Sanofi outside the submitted work. LH owns shares of Profil Institut für Stoffwechselforschung GmbH (Neuss, Germany) and ProSciento (San Diego, CA USA). GF reports grants from Dexcom Inc during the conduct of the study; personal fees from Abbott, Berlin-Chemie, Becton-Dickinson, Dexcom Inc, LifeScan, Menarini, Novo Nordisk, Sanofi, Sensile, and Ypsomed; and grants and personal fees from Ascensia and Roche outside the submitted work. GF-H reports grants from Dexcom Inc during the conduct of the study. SG reports personal fees from Dexcom Inc during the conduct of the study. Additionally, SG has two patents (US 61/257,288 and US 61/551,773) licensed to Dexcom Inc. DE reports grants from Dexcom Inc during the conduct of the study and personal fees from Berlin-Chemie AG outside the submitted work. DW reports grants from Dexcom Inc during the conduct of the study. NH reports grants from Dexcom Inc during the conduct of the study; personal fees from Novo Nordisk; and grants and personal fees from Abbott, Berlin Chemie, Ypsomed, and Roche outside the submitted work.

**Acknowledgments**
This investigator-initiated trial was funded by Dexcom Inc, San Diego, USA. We thank Peter Wintergerst (IDT, Ulm, Germany) for coordination of the study and support of the study sites. We also thank Stefan Pleus (IDT, Ulm, Germany) and Michael Krichbaum (FIDAM, Bad Mergentheim, Germany) for assistance in data management and verification. The members of the steering committee of the HypoDE study were helpful in designing and conducting this study (D Deiss, Berlin, Germany; M Kaltheuner, Leverkusen, Germany; and A Liebl, Bad Heilbrunn, Germany). We thank Chris Parkin for assistance with editing the final version of the manuscript (funded by Dexcom Inc). We thank all study sites for their excellent cooperation and for their effort in the HypoDE study: Gemeinschaftspraxis Drs. Klausmann, Gerhard Klausmann (Aschaffenburg, Germany); Diabetologische Schwerpunktpraxis mit Fußambulanz, Ralf-Achim Bierwirth (Essen, Germany); Medicover Berlin-Mitte, Dorothee Deiss (Berlin, Germany); Diabetologische Schwerpunktpraxis, Matthias Kaltheuner (Leverkusen, Germany); Diabetologische Schwerpunktpraxis, Ralf Kolassa (Bergheim, Germany); Zentrum für Diabetologie Bergedorf, Jens Kröger (Hamburg, Germany); Diabetes-und Stoffwechselzentrum an der Fachklinik Bad Heilbrunn, Andreas Liebl (Bad Heilbrunn, Germany); Diabetologicum Duisburg, Diabetologische Schwerpunktpraxis, Hansjörg Mühlen (Duisburg, Germany); Diabetes Praxis Essen, Helga Zeller-Stefan (Essen, Germany); Diabetes Schwerpunkt Praxis Zentrum für Hormone und Stoffwechsel, Stephan Beck (Marktredwitz, Germany); Schwerpunktpraxis für Diabetes und Ernährungsmedizin, Winfried Keuthage (Münster, Germany); Diabetes Zentrum Mergentheim, Thomas Haak; and Bernhard Lippmann-Grob (Bad Mergentheim, Germany).

**References**

1 Frier BM. Hypoglycaemia in diabetes mellitus: epidemiology and clinical implications. *Nat Rev Endocrinol* 2014; **10:** 711–22.
2 Pickup JC, Freeman SC, Sutton AJ. Glycaemic control in type 1 diabetes during real time continuous glucose monitoring compared with self monitoring of blood glucose: meta-analysis of randomised controlled trials using individual patient data. *BMJ* 2011; **343:** d3805.
3 van Beers CA, DeVries JH, Kleijer SJ, et al. Continuous glucose monitoring for patients with type 1 diabetes and impaired awareness of hypoglycaemia (IN CONTROL): a randomised, open-label, crossover trial. *Lancet Diabetes Endocrinol* 2016; **4:** 893–902.
4 Ly TT, Nicholas JA, Retterath A, Lim EM, Davis EA, Jones TW. Effect of sensor-augmented insulin pump therapy and automated insulin suspension vs standard insulin pump therapy on hypoglycemia in patients with type 1 diabetes: a randomized clinical trial. *JAMA* 2013; **310:** 1240–47.
5 Geddes J, Schopman JE, Zammitt NN, Frier BM. Prevalence of impaired awareness of hypoglycaemia in adults with type 1 diabetes. *Diabet Med* 2008; **25:** 501–04.
6 Gubitosi-Klug RA, Braffett BH, White NH, et al. Risk of severe hypoglycemia in type 1 diabetes over 30 years of follow-up in the DCCT/EDIC study. *Diabetes Care* 2017; **40:** 1010–16.
7 Little SA, Leelarathna L, Walkinshaw E, et al. Recovery of hypoglycemia awareness in long-standing type 1 diabetes: a multicenter 2 x 2 factorial randomized controlled trial comparing insulin pump with multiple daily injections and continuous with conventional glucose self-monitoring (HypoCOMPaSS). *Diabetes Care* 2014; **37:** 2114–22.
8 Battelino T, Phillip M, Bratina N, Nimri R, Oskarsson P, Bolinder J. Effect of continuous glucose monitoring on hypoglycemia in type 1 diabetes. *Diabetes Care* 2011; **34:** 795–800.
9 Battelino T, Conget I, Olsen B, et al. The use and efficacy of continuous glucose monitoring in type 1 diabetes treated with insulin pump therapy: a randomised controlled trial. *Diabetologia* 2012; **55:** 3155–62.
10 Joshi M, Choudhary P. Multiple daily injections OR insulin pump therapy: choosing the best option for your patient—an evidence-based approach. *Curr Diab Rep* 2015; **15:** 81.
11 Pickup JC. Insulin-pump therapy for type 1 diabetes mellitus. *N Engl J Med* 2012; **366:** 1616–24.
12 Lind M, Polonsky W, Hirsch IB, et al. Continuous glucose monitoring vs conventional therapy for glycemic control in adults with type 1 diabetes treated with multiple daily insulin injections: the GOLD randomized clinical trial. *JAMA* 2017; **317:** 379–87.
13 Beck RW, Riddlesworth T, Ruedy K, et al. Effect of continuous glucose monitoring on glycemic control in adults with type 1 diabetes using insulin injections: the DIAMOND randomized clinical trial. *JAMA* 2017; **317:** 371–78.
14 Heinemann L, Deiss D, Hermanns N, et al. HypoDE: research design and methods of a randomized controlled study evaluating the impact of real-time CGM usage on the frequency of CGM glucose values <55 mg/dl in patients with type 1 diabetes and problematic hypoglycemia treated with multiple daily injections. *J Diabetes Sci Technol* 2015; **9:** 651–62.
15 Clarke WL, Cox DJ, Gonder-Frederick LA, Julian D, Schlundt D, Polonsky W. Reduced awareness of hypoglycemia in adults with IDDM. A prospective study of hypoglycemic frequency and associated symptoms. *Diabetes Care* 1995; **18:** 517–22.
16 Laffel L. Improved accuracy of continuous glucose monitoring systems in pediatric patients with diabetes mellitus: results from two studies. *Diabetes Technol Ther* 2016; **18** (suppl 2)**:** S223–33.
17 Kovatchev B, Cox DJ, Gonder-Frederick LA, Young-Hyman D, Schlundt D, Clarke WL. Assessment of risk of severe hypoglycemia among adults with IDDM. *Diabetes Care* 1998; **21:** 1870–75.
18 Fisher L, Polonsky WH, Hessler DM, et al. Understanding the sources of diabetes distress in adults with type 1 diabetes. *J Diabetes Complications* 2015; **29:** 572–77.
19 Gonder-Frederick LA, Schmidt KM, Vajda KA, et al. Psychometric properties of the hypoglycemia fear survey-ii for adults with type 1 diabetes. *Diabetes Care* 2011; **34:** 801–06.
20 Greiner W, Claes C, Busschbach JJ, von der Schulenburg JM. Validating the EQ-5D with time trade off for the German population. *EurJHealth Econ* 2005; **6:** 124–30.
21 Polonsky WH, Fisher L, Hessler D, Edelman SV. Development of a new measure for assessing glucose monitoring device-related treatment satisfaction and quality of life. *Diabetes TechnolTher* 2015; **17:** 657–63.
22 Boehm BO, Dreyer M, Fritsche A, Fuechtenbusch M, Goelz S, Martin S. Therapie des Diabetes mellitus Typ 1 (S3-Leitlinie) [Therapy of type 1 diabetes (evidence-based guideline of the German Diabetes Association)]. https://www.deutsche-diabetes-gesellschaft.de/fileadmin/Redakteur/Leitlinien/Evidenzbasierte_Leitlinien/AktualisierungTherapieTyp1Diabetes_1_20120319_TL.pdf (accessed Feb 7, 2018).
23 Danne T, Nimri R, Battelino T, et al. International consensus on use of continuous glucose monitoring. *Diabetes Care* 2017; **40:** 1631–40.
24 Fanelli CG, Pampanelli S, Porcellati F, Bolli GA. Shift of glycemic thresholds for cognitive function in hypoglycaemia unawareness. *Diabetologia* 1998; **41**: 720–23.
25 The DRG. Hypoglycemia in the diabetes control and complications trial. *Diabetes* 1997; **46:** 271–86.
26 Beck RW, Kollman C, Xing D, Buckingham BA, Chase HP. Outcome measures for outpatient hypoglycemia prevention studies. *J Diabetes Sci Technol* 2011; **5:** 999–1004.
27 Malkani S, Kotwal A. Frequency and predictors of self-reported hypoglycemia in insulin-treated diabetes. *J Diabetes Res* 2017; **2017:** 7425925.
28 Beck RW, Riddlesworth TD, Ruedy KJ, et al. Effect of initiating use of an insulin pump in adults with type 1 diabetes using multiple daily insulin injections and continuous glucose monitoring (DIAMOND): a multicentre, randomised controlled trial. *Lancet Diabetes Endocrinol* 2017; **5:** 700–08.
29 Yeh HC, Brown TT, Maruthur N, et al. Comparative effectiveness and safety of methods of insulin delivery and glucose monitoring for diabetes mellitus: a systematic review and meta-analysis. *Ann Intern Med* 2012; **157:** 336–47.
30 El Youssef J. IN CONTROL of type 1 diabetes, despite hypoglycaemia unawareness. *Lancet Diabetes Endocrinol* 2016; **4:** 874–75.