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Visser, Margaretha M; Charleer, Sara; Fieuws, Steffen; De Block, Christophe; Hilbrands, Robert; Van Huffel, Liesbeth; Maes, Toon; Vanhaverbeke, Gerd; Dirinck, Eveline; Myngheer, Nele; Vercammen, Chris; Nobels, Frank; Keymeulen, Bart; Mathieu, Chantal; Gillard, Pieter

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Comparing real-time and intermittently scanned continuous glucose monitoring in adults with type 1 diabetes: the six-month multicentre randomised controlled ALERTT1 trial

Margaretha M Visser, Sara Charleer, Steffen Fieuws, Christophe De Block, Robert Hilbrands, Liesbeth Van Huffel, Toon Maes, Gerd Vanhaverbeke, Eveline Dirinck, Nele Myngheer, Chris Vercammen, Frank Nobels, Bart Keymeulen, Chantal Mathieu, Pieter Gillard

Department of Endocrinology, University Hospitals Leuven – KU Leuven, Leuven, Belgium (MM Visser MD, S Charleer PhD, Prof C Mathieu MD, P Gillard MD);
Interuniversity Institute for Biostatistics and Statistical Bioinformatics, KU Leuven and University of Hasselt, Leuven, Belgium (S Fieuws PhD);
Department of Endocrinology-Diabetology-Metabolism, University Hospital Antwerp, Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium (Prof C De Block MD, E Dirinck MD);
Academic Hospital and Diabetes Research Centre, Vrije Universiteit Brussel, Brussels, Belgium (R Hilbrands MD, Prof B Keymeulen MD, P Gillard MD);
Department of Endocrinology, OLV Hospital Aalst, Aalst, Belgium (L Van Huffel MD, F Nobels MD);
Department of Endocrinology, Imeldaziekenhuis Bonheiden, Bonheiden, Belgium (T Maes MD, C Vercammen MD);
and Department of Endocrinology, AZ Groeninge, Kortrijk, Belgium (N Myngheer MD, G Vanhaverbeke MD)

Correspondence to:
Dr Pieter Gillard, Department of Endocrinology, University Hospitals Leuven – KU Leuven, Herestraat 49, 3000 Leuven, Belgium
pieter.gillard@uzleuven.be

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Abstract

Background

ALERTT1 compared real-time continuous glucose monitoring (rtCGM) with intermittently scanned continuous glucose monitoring (isCGM) in adults with type 1 diabetes (T1D), since it is unclear whether switching from isCGM to rtCGM with alert functionality offers additional benefits.

Methods

This prospective, multicentre, randomised controlled trial was conducted in adults with T1D previously using isCGM, at six Belgian hospitals. Participants were randomly assigned (1:1) to rtCGM (Dexcom G6®; intervention) or isCGM (FreeStyle Libre®; control). Randomisation was performed centrally using minimisation dependent on study centre, age, gender, HbA_{1c}, time in range (TIR; sensor-glucose 3·9–10·0 mmol/L [70–180 mg/dL]), insulin administration method, and hypoglycaemia awareness. Participants, investigators, and study teams were not masked to group allocation. Primary endpoint was mean between-group difference in TIR after six months (intention-to-treat). Pre-specified key secondary endpoints were HbA_{1c}, time <3·0 mmol/L (54 mg/dL), and Hypoglycaemia Fear Survey worry (HFS-worry) score. ClinicalTrials.gov: NCT03772600.

Findings

Between Jan 29 and Jul 30, 2019, 269 participants were recruited, of whom 254 randomly assigned to rtCGM (n=127) or isCGM (n=127); 124 and 122 participants completed the study, respectively.

After six months, TIR was higher with rtCGM compared to isCGM (59·6% vs 51·9%; mean difference 6·85 percentage points, 95% CI 4·36–9·34; p<0·0001), while HbA_{1c} was lower (7·1% vs 7·4%; p<0·0001), as was time <3·0 mmol/L (0·47% vs 0·84%; p=0.0070), and HFS-worry score (15·4 vs 18·0; p=0·0071). Fewer participants on rtCGM experienced severe hypoglycaemia (n=3 vs n=13; p=0·0082). Skin reaction was more frequently observed with isCGM; bleeding after sensor insertion was more frequently reported by rtCGM users.

Interpretation In an unselected adult T1D population, switching from isCGM to rtCGM significantly improved TIR, HbA_{1c}, time <3·0 mmol/L, and hypoglycaemia worry, implying that clinicians should consider rtCGM instead of isCGM to improve the health and quality of life of people with T1D.

Funding Dexcom.

Research in context

Evidence before this study

We searched PubMed for trial reports published in English up to February 2nd, 2021, comparing real-time continuous glucose monitoring (rtCGM) with intermittently scanned continuous glucose monitoring (isCGM) in non-pregnant adults with type 1 diabetes. We used 'intermittent' or 'flash', 'real time', 'continuous glucose monitoring', and 'type 1 diabetes' as search terms. We identified six manuscripts of four trials. Three manuscripts were based on the randomised controlled I HART trial, one was the randomised controlled CORRIDA trial, and two described observational trials, evaluating real-world data from France and Germany/Austria.

I HART (Reddy et al.) was an eight-week trial, followed by an eight-week extension phase, conducted in 40 adults with type 1 diabetes and impaired awareness of hypoglycaemia, treated with multiple daily insulin injections. Median HbA_{1c} was 7·3% (56 mmol/mol). CORRIDA (Hásková et al.) studied 60 adults with type 1 diabetes and normal hypoglycaemia awareness during a four-day exercise and four-week home phase. Mean HbA_{1c} was 7·8% (62 mmol/mol). Both trials included CGM naïve people. Of note, outcomes regarding glycaemic control were not measured with the same CGM device in I HART, which is an important limitation of the study design.
The French observational trial (Préau et al.) assessed the impact of switching from isCGM to rtCGM in 18 adults with type 1 diabetes and a high risk of hypoglycaemia (n=8), or an elevated HbA_{1c} (n=9), or both (n=2) after three and six months. Mean HbA_{1c} was 8·07% (65 mmol/mol). The German/Austrian trial (Sandig et al.) included 233 adults with type 1 diabetes using isCGM or rtCGM, with a median HbA_{1c} of 7·3% (56 mmol/mol), in a cross-sectional analysis. In both observational studies, the majority of participants used insulin pump therapy.

I HART, CORRIDA, and the observational trials concluded that rtCGM was superior to isCGM with regard to glycaemic control based on CGM metrics; time in range (sensor-glucose 3·9–10·0 mmol/L [70–180 mg/dL]) was higher, while time in hypoglycaemia (definitions ranged from a sensor-glucose <3·0 mmol/L [54 mg/dL] to <3·9 mmol/L [70mg/dL]) was lower with rtCGM compared to isCGM. In addition, I HART showed less worry about hypoglycaemia with the use of rtCGM. Only two trials evaluated HbA_{1c} and observed no benefit with rtCGM versus isCGM. However, as trials were limited in terms of study population (small and pre-specified), design, and/or duration (short follow-up), it is still not clear whether switching from isCGM to rtCGM with alert functionality offers additional benefits in a large and unselected population with type 1 diabetes over a longer period of time.

Added value of this study

The ALERTT1 trial is the first six-month, multicentre, prospective, randomised controlled trial comparing rtCGM with isCGM in 254 adults with type 1 diabetes, previously using isCGM. Mean HbA_{1c} was 7·4% (58 mmol/mol) and a minority of the study population was hypoglycaemia unaware (n=44 [17%]) and/or had a history of severe hypoglycaemia (n=29 [11%]). Most (n=205 [81%]) were treated with multiple daily injections.

Findings showed that in an unselected group of people with type 1 diabetes, six-month use of rtCGM with alert functionality improved time in range (sensor-glucose 3·9–10·0 mmol/L [70–180 mg/dL]), while HbA_{1c}, time in clinically significant hypoglycaemia (sensor-glucose <3·0 mmol/L [54 mg/dL]), and time in hyperglycaemia (sensor-glucose >10·0 mmol/L [180 mg/dL]) were reduced. In addition, more people on rtCGM achieved glycaemic targets as defined by international consensus guidelines, and experienced less frequently severe hypoglycaemia.

Besides glycaemic control, the ALERTT1 trial also evaluated patient reported outcomes through various validated questionnaires. Despite relatively high quality of life of all participants at baseline, rtCGM users experienced less hypoglycaemia worry and higher treatment satisfaction at the end of study.

Implications of all the available evidence

rtCGM showed significant benefits over six months compared to isCGM in terms of both glycaemic control and patient reported outcomes. This implies that clinicians should consider rtCGM to improve the health and quality of life of people living with type 1 diabetes.

Introduction

The majority of people with type 1 diabetes (T1D) do not achieve a glycated haemoglobin (HbA_{1c}) below 7% (53 mmol/mol)[1,2] and spend a considerable part of the day in hypo- and hyperglycaemia, exposing them to risk of hypoglycaemic coma, ketoacidosis, and chronic micro- and macrovascular disease. In recent years, progress has been made in the field of home glucose self-monitoring with the advent of subcutaneous sensors capable of reporting glycaemic levels on demand (intermittently scanned continuous glucose monitoring; isCGM) or in real-time (real-time continuous glucose monitoring; rtCGM). People on isCGM can check their glucose values by scanning the sensor transmitter with a receiver or smartphone, while the transmitter of rtCGM automatically sends a new value to a receiver, smart watch, or smartphone every one to five minutes. In contrast to isCGM, rtCGM has the option of (predictive) alerts for high and low blood glucose levels, but is generally more expensive than isCGM.[3] Several randomised controlled trials comparing the use of CGM with capillary blood glucose measurements, showed that isCGM and rtCGM have a beneficial effect on glycaemic outcomes and quality of life in people with T1D treated with multiple daily injections (MDI) or insulin pump therapy.[4-9] In order to address the question whether switching from isCGM to rtCGM offers additional benefits, we performed a multicentre, non-masked, randomised controlled trial comparing six-month rtCGM use with six-month isCGM use in adults with T1D who were previously using isCGM.

Methods

Study design and participants

ALERTT1 (Comparing Continuous With Flash Glucose Monitoring in Adults With Type 1 Diabetes) was designed as a six-month double arm, parallel-group, non-masked, randomised controlled trial comparing rtCGM (intervention group) with isCGM (control group), and was conducted in the diabetes clinics of three regional and three university medical centres in Belgium. Ethical approval was obtained centrally by the independent Ethics Committee of University Hospitals Leuven, in consultation with the local ethics committees. The trial was conducted in accordance with the Declaration of Helsinki in its latest form. All participants gave written informed consent before start of trial-related activities.

People aged 18 years or older with diagnosis of T1D for six months or more were eligible for inclusion. Additional inclusion criteria were treatment with MDI or insulin pump, HbA_{1c} ≤10% (86 mmol/mol), and exclusive isCGM use (FreeStyle Libre®, Abbott Diabetes Care, Alameda, CA) for at least six months. Key exclusion criteria were (planned) pregnancy, severe cognitive impairment limiting CGM usage, use of systemic corticosteroids, or concomitant pathology that could cause oedema at anticipated CGM insertion sites.

Randomisation and masking

Participants were randomly assigned (1:1) to rtCGM (Dexcom G6®, Dexcom, San Diego, CA; 10-day wear) or isCGM (FreeStyle Libre®; 14-day wear) based on an approach minimising deterministically the imbalance between both groups[10] in the following baseline characteristics: study centre, age, gender, HbA_{1c} (local laboratory analysis), time in range (TIR; sensor-glucose 3·9–10·0 mmol/L [70–180 mg/dL]), insulin administration method, and level of hypoglycaemia awareness (as reported by Clarke hypoglycaemia awareness survey [see Supplement 1]). The minimisation procedure was implemented in SAS software for Windows (version 9.4, SAS Institute, Cary, NC) by S.F. Randomisation was performed by a staff member of University Hospitals Leuven, who was not involved in the rest of the trial. The result of randomisation, which was coded for the staff member, was sent digitally to the study centres and communicated to each participant by the local study teams. Participants, investigators, and study teams were not masked to group allocation.

Procedures

The trial was subdivided in a baseline phase of four to seven weeks (hereafter referred to as 'baseline') and a study phase of six months. For a schematic overview of the trial and its procedures, see Fig. S1.

At start of baseline, demographic data were collected during a screening visit. Maximal two weeks after screening, participants received uniform education with refreshment of basic principles of diabetes treatment, such as insulin dosing principles, glucose control with CGM use, and treatment of hypo- and hyperglycaemia. For details about the education moment, see Table S1.

Up to one week later, participants started rtCGM (Dexcom G6®) with a blinded receiver during a 28-30 day run-in period, while simultaneously using their isCGM device. After run-in, participants were randomised to rtCGM or isCGM (standard treatment).

After randomisation, the rtCGM group received oral and written instructions on unblinded use of the rtCGM device, using a smartphone or receiver. Sensor insertion was allowed on the abdomen, upper arm or thigh. Alerts were set according to preferences and needs of each participant. The control group continued with isCGM.

During study phase, both groups attended a visit three and six months after randomisation. For the control group, six-month visit was preceded by a verified 28- to 30-day blinded wear period of rtCGM, while using their isCGM device.

Participants were asked to report any (serious) adverse event, severe hypoglycaemia (third party assistance required for treatment), and/or change of alert settings in a diary. Participants attended usual diabetes consultations as provided by their diabetes teams.

By using blinded rtCGM during run-in and before the end of the trial (the latter only in the isCGM group), we were able to analyse sensor-glucose data collected by the same system in both groups at baseline and month 6. At baseline and the six-month visit, preceding 28-day rtCGM data were uploaded in Clarity® and used for the calculations of all CGM metrics.

Outcomes

The primary outcome was TIR, defined as a sensor-glucose of 3·9–10·0 mmol/L (70–180 mg/dL), at six months.

Key secondary outcomes, all evaluated at six months, were HbA_{1c} (analysed at a central laboratory), time in clinically significant hypoglycaemia (sensor-glucose <3·0 mmol/L [54 mg/dL]), and hypoglycaemia fear evaluated with the Hypoglycaemia Fear Survey version II worry subscale (HFS-worry).

Additional secondary outcomes were various CGM metrics at six months, namely: time in hypoglycaemia (sensor-glucose <3·9 mmol/L [70 mg/dL]); time in target (sensor-glucose 3·9–7·8 mmol/L [70–140 mg/dL]); time in hyperglycaemia (sensor-glucose >10·0 mmol/L [180 mg/dL]); time in clinically significant hyperglycaemia (sensor-glucose >13·9 mmol/L [250 mg/dL]); mean glucose concentration; glycaemic variability, expressed by coefficient of variation (CoV) and standard deviation; number of low glucose events (sensor-glucose ≤3·0 mmol/L [54 mg/dL] for at least 15 minutes, preceded by at least 30 minutes with sensor-glucose >3·0 mmol/L [54 mg/dL]). Patient reported outcomes at six months were evaluated by means of different questionnaires (Supplement 1).

Further exploratory endpoints (post-hoc) included the proportion of people able to achieve consensus targets for time in ranges and different combined endpoints as described in international guidelines on CGM.[11,12] Device- or diabetes-related adverse events were reported, along with any other serious adverse event.

Statistical analysis

Inclusion of 250 participants in total was planned. This sample size was determined to have at least 80% power for the primary and key secondary endpoints. The family-wise alpha was set at 5% and Bonferroni-Holm correction was planned for the key secondary endpoints. Sample size calculations were based on comparison between both groups of the mean value after six months, correcting for

differences at baseline and anticipating dropout rate of approximately 15%. With the planned sample size, there was more than 99% power to detect a difference of 5 percentage points in TIR, which is defined as clinically relevant based on literature.[12] Further, there was more than 80% power for each of the key secondary endpoints to detect standardised effect sizes (Cohen's d) equal to 0·3 for HbA_{1c} and HFS-worry, and to detect a 35% reduction in time in clinically significant hypoglycaemia. Supplement 2 describes the performed sample size calculation in detail.

Means (standard deviation [SD]), medians (interquartile range [IQR]) and percentages were used to describe characteristics in both groups. Comparisons of the primary and secondary outcomes were conducted on an intention-to-treat basis. For continuous outcomes, the mean value at six months was compared between both groups after correction for the baseline value. To handle the presence of missing data this ANCOVA approach was implemented using constrained longitudinal data analysis (cLDA).[13] As effect size, the difference in mean (95% confidence interval [95% CI]) obtained from this model was reported. This approach provides adjustment for observed baseline differences in estimating treatment effect at six months, without excluding subjects with a missing post-baseline value. For time <3·0 mmol/L (54 mg/dL) and time <3·9 mmol/L (70 mg/dL), distribution of model residuals was highly skewed and therefore results were also reported from a sensitivity analysis on log-transformed values yielding a ratio of means as effect size instead of a difference in means. For binary outcomes, effect size was obtained from an absolute risk model, constraining both groups to be equal at baseline (hence, applying the cLDA approach). The reported effect size (with 95% CI) refers to the difference in absolute risk after six months adjusted for baseline risk. For the primary outcome, a p value was considered significant when smaller than 0·05. To allow strong claims for the three key secondary outcomes, Bonferroni-Holm correction was applied. For other secondary outcomes, no correction for multiple testing was considered. Detailed description of the statistical analyses can be found in Supplement 3.

All analyses have been performed by an independent statistician, using SAS software for Windows (version 9.4, SAS Institute, Cary, NC) or SPSS software for Windows (IBM SPSS Statistics version 26, Armonk, NY). The trial is registered with ClinicalTrials.gov, number NCT03772600.

Role of the funding source

University Hospitals Leuven (Sponsor of the ALERTT1 trial) received a research grant from Dexcom (San Diego, CA, USA). Dexcom provided the experimental rtCGM device and technical support (to study teams only) in case of device issues. Representatives of Dexcom reviewed the manuscript, but had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the

decision to submit for publication. All authors had full access to all the data in the study, and had final responsibility for the decision to submit for publication.

Results

A total of 269 people with T1D were consecutively recruited between January 29 and July 30, 2019. Subsequently, 254 participants were randomly assigned to the intervention group (rtCGM; n=127) or control group (isCGM; n=127), of which 124 in the rtCGM and 122 in the isCGM group completed the study at six months (Fig. 1).

The rtCGM and isCGM groups had similar baseline characteristics (Table 1). Average age of participants was 42·9 years (SD 14·1), ranging from 18 to 76 years. The majority (n=239 [94%]) were Caucasian and highly educated. Most (n=205 [81%]) were using MDI with insulin analogues, had long experience with isCGM and were scanning frequently (median 11 scans/day, IQR 7–16). Mean HbA_{1c} was 7·4% (SD 0·9; range 5·3 to 9·9%) with a mean TIR of 51·9% (SD 15·1). A minority of the study population was hypoglycaemia unaware (n=44 [17%]) and/or had a history of severe hypoglycaemia (n=29 [11%]). During run-in, median sensor wear time was 96·0% (IQR 90·0–99·0) for isCGM and 97·6% (IQR 94·8–98·9) for blinded rtCGM. At six months, median sensor wear time was 96·0% (IQR 91·0–99·0) for isCGM and 96·9% (IQR 93·9–98·3) for rtCGM. Most participants utilised threshold-based alerts. Adaptation of alert settings by participants are described in Table S2.

TIR did not change in the isCGM group during the study (51·9% at month 6 vs 51·3% at baseline; Table 2). Starting from a similar baseline TIR of 52·5% in the rtCGM group, TIR increased to 59·6% at six months. Correcting for baseline TIR, this resulted in a mean difference of 6·85 percentage points (95% CI 4·36–9·34; p<0·0001) at six months, which corresponds to being on average 1 hour and 39 minutes per day more in range when using rtCGM (Table 2). Of note, baseline TIR was comparable for isCGM and rtCGM at every time of day and night. At month 6, higher TIR was observed in the rtCGM group over 24 hours and even more pronounced during night hours (Fig. S2).

HbA_{1c} levels at screening and start of study phase were similar. After three months, HbA_{1c} was lower with rtCGM compared to isCGM (mean difference -0·33 percentage points, 95% CI -0·45 to -0·22; p<0·0001) and this difference persisted up to six months (mean difference -0·36 percentage points, 95% CI -0·48 to -0·24; p<0·0001) (Table 2).

Time in clinically significant hypoglycaemia was low in both groups at baseline, given a mean of 0·9% in the rtCGM group and 1·1% in the isCGM group (Table 2). Still, after switching to rtCGM, time <3.0

mmol/L (54 mg/dL) almost halved, resulting at month 6 in a mean difference of -0·35% percentage points (95% CI -0·61 to -0·10; p=0·0070). The sensitivity analysis showed similar findings.

Fear of hypoglycaemia was similar in both groups at baseline (Table 2). Only in the rtCGM group, HFS-worry score decreased, resulting at month 6 in a mean difference of -2·62 points (95% CI -4·52 to -0·71; p=0·0071), indicating less worries about hypoglycaemia with use of rtCGM compared to isCGM.

Mean glucose concentration was equal at baseline for rtCGM and isCGM participants (9·9 mmol/L [95% CI 9·7–10·2] vs 10.1 mmol/L [95% CI 9·8–10·4]). It decreased with use of rtCGM to 9·3 mmol/L (95% CI 9·1–9·6), while staying the same in isCGM users (10·0 mmol/L, 95% CI 9·8–10·3). This resulted in a mean difference of -0·61 mmol/L (95% CI -0·88 to -0·35; p<0·0001). This difference was seen at every time of day and night (Fig. S3). A lower glycaemic variability was seen in the rtCGM group at month 6: mean CoV was 35·0% (95% CI 34·1–36·0) with rtCGM compared to 36·6% (95% CI 35·7–37·6) with isCGM (mean difference of -1·38% points, 95% CI -2·30 to -0·46; p=0·0034). Standard deviation was also lower in the rtCGM group at month 6 (3·3 mmol/L, 95% CI 3.2–3.4) compared to isCGM (3·7, 95% CI 3.6–3.8), resulting in a mean difference of -0·33 mmol/L (95% CI -0·45 to -0·22; p<0·0001). The number of low glucose events did not differ between rtCGM (5·6, 95% CI 4·2–7·0) and isCGM at month 6 (6·9, 95% CI 5·6–8·2; p=0·47).

Fig. 2 shows the distribution of time spent in different glucose ranges by study population, and the corresponding difference of each of these glucose ranges at six months. Distribution was equal for both groups at baseline, while after six months more people on rtCGM spent less time in hyper- and hypoglycaemic ranges and more time in the target ranges.

Percentage of participants achieving consensus targets at month 6 was higher in the rtCGM group, with exception of time <3·9 mmol/L (70 mg/dL) and CoV (Table 3). A higher percentage of participants achieved HbA_{1c} <7% at month 6 in the rtCGM group, while combined endpoints were also met in a higher percentage of rtCGM users (Table 3).

In general, participants experienced relatively high quality of life based on different questionnaires collected at screening (Table S3). At six months, participants on rtCGM scored better on the satisfaction subscale of the Diabetes Treatment Satisfaction Questionnaire status (DTSQs) (mean difference of 2·34 points, 95% CI 1·15–3·54; p=0·0001). This was also confirmed with the DTSQ change, given a mean difference of 6·76 points (95% CI 5·08–8·43; p<0·0001). Other patient reported outcome measurements did not differ between groups at month 6.

Adverse events during study phase are shown in Table S4. In total, 69 participants reported 91 adverse events, of which 44 were CGM related. Serious adverse events were reported 38 times in total, among which 30 severe hypoglycaemic events in the isCGM group, and three severe hypoglycaemic events and one acute hyperglycaemia leading to hospitalisation in the rtCGM group. None of these serious adverse events were caused by device malfunction.

At baseline, 16 participants (13%) on rtCGM and 13 participants (10%) on isCGM reported severe hypoglycaemia 12 months prior to screening (Table 1). A smaller percentage of rtCGM users experienced at least one severe hypoglycaemic event compared to isCGM users in the six-month study phase (2% [n=3] vs 11% [n=13]; difference of -8·2 percentage points, 95% CI -14·3 to -2·1; p=0·0082). Bleeding after sensor insertion was only reported by rtCGM users, leading to sensor replacement in a third of them. Skin reaction was more frequently observed in the isCGM group. Median body mass index did not change in the rtCGM group (25·5 kg/m^2 [23·3–28·4] at month 6 vs 25·6 kg/m^2 [23·3–28·4] at baseline), nor in the isCGM group (24·7 kg/m^2 [22·7–27·3] at month 6 vs 24·8 kg/m^2 [22·4–27·2] at baseline).

Discussion

To our knowledge, ALERTT1 is the first long-term, multicentre, prospective, randomised, controlled trial comparing rtCGM with isCGM in adults with T1D and a history of previous use of isCGM. The trial showed that six-month use of rtCGM with alert functionality improved time in range by 6·85 percentage points, and reduced time in hyperglycaemia >10·0 mmol/L (180 mg/dL) by 6·27 percentage points and time in hypoglycaemia <3·0 mmol/L (54 mg/dL) by 0·35 percentage points. The percentage of participants who achieved the consensus target of >70% TIR doubled (28% vs 15%) and nearly half of the participants had an HbA_{1c} <7% (49% vs 33%) at six months.

Current guidelines advise to use various CGM metrics in conjunction with HbA_{1c} for assessing glycaemic control in T1D.[11,12] Of these CGM metrics, TIR is probably the most meaningful in clinical practice; the metric is easy to understand for patients and their caregivers, and provides quick insight into current glycaemic control. Previous randomised[14,15] and observational trials[16,17] suggested that rtCGM can provide an increase in TIR versus isCGM in people with T1D. The long duration (six months), low dropout rate (3%), and size (254 people) of the ALERTT1 randomised trial now allow reliable conclusions on the primary endpoint TIR and other CGM metrics. The fact that all participants received a uniform education moment refreshing basic principles of diabetes treatment, and that sensor-glucose data were measured with the same CGM device with high sensor adherence, guaranteeing absolute comparability of sensor-glucose data in both groups at baseline and month 6, adds further validity to the reported observations. As such, we found a difference in TIR of 1 hour and 39 minutes

per day favouring rtCGM mainly due to people spending 1 hour and 17 minutes less in hyperglycaemia, which is important in view of the possible harm that is associated with high blood glucose levels.[18-22]

In clinical practice, high HbA_{1c} but even more hypoglycaemia and hypoglycaemia unawareness, are often considered as indications for switching to a device with (predictive) alerts for high and low blood glucose levels. In particular severe hypoglycaemia is a major clinical worry as it is associated with adverse health outcomes.[23] The ALERTT1 trial had unique features of including a large and broad population of people living with T1D, where only a minority had hypoglycaemia unawareness. We show that rtCGM protected against severe hypoglycaemia in the whole population, also in those not affected by hypoglycaemia unawareness.

Although we cannot differentiate whether our observations are due to the real-time connection and/or the alert functionality of rtCGM, we suggest that threshold-based high and low alerts, utilised by most rtCGM users in our study, mainly contributed to the observed improvements as they enable users to respond timely and adequately to abnormal glucose levels, especially during night time. A future comparison between the next generation isCGM with alert functionality (FreeStyle Libre 2®) and rtCGM could further elucidate if alerts are the main reason for the better outcome in rtCGM users, or rather the fact that sensor values are available in real-time, in contrast to only on demand in isCGM users. The fact that rise-rate alerts were used by less than half of the participants and that its use declined over time, may indicate that such alerts were of less added value in the observed benefits. This might be an expression of alarm fatigue, which can sometimes be experienced while using diabetes technology.[24]

Impact on quality of life of novel technologies is increasingly recognised as a clinically relevant outcome.[25] Through a wide range of validated questionnaires, we show relatively high quality of life in the ALERTT1 participants at baseline. At the end of study, hypoglycaemia worry was lower in rtCGM users, which may be due to a combination of the decrease in clinically significant hypoglycaemia, the high number of people using low alerts, and the default urgent low alert. Less worry about hypoglycaemia with rtCGM compared to isCGM was previously reported in people with T1D and hypoglycaemia unawareness.[26] In addition, we observed higher treatment satisfaction in rtCGM users, which is another patient reported outcome measurement that is increasingly accepted as an important outcome in diabetes care.[27] Of note, more frequent sensor replacement in the rtCGM group (every 10 days) versus the isCGM group (every 14 days), did not lead to a higher burden as measured by the Diabetes Treatment Satisfaction Questionnaire. CGM-related adverse events were mild and differed by device, with skin reaction being more frequently observed with isCGM and bleeding after sensor

insertion more frequently reported by rtCGM users. Longer follow-up will provide more information whether the observed higher frequency of skin reactions in isCGM users is due to different composition of the adhesive, or rather due to the difference in length of sensor use, which was shorter for rtCGM (<6 months) compared to isCGM (>6 months). Indeed, some skin reactions only occur after longer duration of use as shown in previous trials.[28,29]

We also acknowledge limitations of our study. Besides the non-masked design, the trial was conducted in a Belgian T1D population, where participants were well experienced with the use of isCGM. In the Belgian reimbursement system, free access to isCGM and some models of rtCGM, but not Dexcom G6®, was available for all people living with T1D and followed up in specialist endocrinology centres in Belgium (being virtually all people with T1D) at the time of the study. Also, the study population was overall highly educated, perceived a high (diabetes-related) quality of life at start of study, and seemed to be motivated in achieving good glycaemic control, reflected by mean HbA_{1c} of 7·4% and frequency of 11 scans per day at screening. A long-term and fully pragmatic trial, conducted in more diverse T1D populations, treated in different healthcare systems, would be needed to assess whether the findings of the ALERTT1 trial are also valid in these settings. To overcome the limitation of current data covering only the first six months after switching to rtCGM, we are conducting a pre-designed extension of the current ALERTT1 trial, which will evaluate the sustainability of the observed benefits for up to 24 months. Data of the current trial and its extension phase are needed for a pre-planned cost-effectiveness analysis, which might be useful in future decisions on reimbursement policies.

In conclusion, rtCGM showed significant benefits for over six months compared to isCGM in terms of both glycaemic control and patient reported outcomes. This implies that, within the limits of the current trial, clinicians should consider rtCGM to improve the health and quality of life of people living with type 1 diabetes.

Contributors

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

Declaration of interests

UZ Leuven received non-financial support for travel from Novo Nordisk for M.M.V. KU Leuven received non-financial support for travel from Medtronic, and financial support for travel from Roche for S.C. C.D.B. reports consulting fees and honoraria for speaking for Abbott, AstraZeneca, Boehringer-Ingelheim, A. Menarini Diagnostics, Eli Lilly, Medtronic, Novo Nordisk, and Roche. R.H. serves or has served on the advisory panel for Merck Sharp and Dohme, Boehringer-Ingelheim, and Eli Lilly. L.V.H. reports consulting fees and honoraria for speaking for Abbott, AstraZeneca, Boehringer-Ingelheim, Eli Lilly, Medtronic, Merck Sharp and Dohme, Novo Nordisk, and Sanofi-Aventis. G.V. serves or has served on the advisory panel for Merck Sharp and Dohme, Boehringer-Ingelheim, and Eli Lilly. G.V. reports consulting fees and honoraria for speaking from Merck Sharp and Dohme, Boehringer-Ingelheim, AstraZenica, Sanofi-Aventis, Novo Nordisk, and Eli Lilly. E.D. has served on the advisory panel for Novo Nordisk. E.D. reports speaking fees from Novo Nordisk, Boehringer-Ingelheim, Eli Lilly, and Astra Zenica. N.M. serves or has served on the advisory panel for Boehringer-Ingelheim. N.M. reports speaking fees from Merck Sharp and Dohme, Boehringer-Ingelheim, AstraZenica, Sanofi-Aventis, Novo Nordisk, and Eli Lilly. C.V. reports consulting and speaking fees from Medtronic, Boehringer Ingelheim, Astra Zeneca, and Sanofi Aventis. F.N. reports consulting fees and honoraria for speaking from Abbott, AstraZeneca, Boehringer-Ingelheim, Eli Lilly, Johnson and Johnson, Medtronic, Merck Sharp and Dohme, Novo Nordisk, Roche, and Sanofi-Aventis. C.M. serves or has served on the advisory panel for Novo Nordisk, Sanofi-Aventis, Merck Sharp and Dohme, Eli Lilly, Novartis, AstraZeneca, Boehringer-Ingelheim, Roche, Medtronic, ActoBio Therapeutics, Pfizer, and Zealand Pharma. Financial compensation for these activities has been received by KU Leuven; KU Leuven has received research support for C.M. from Medtronic, Novo Nordisk, Sanofi-Aventis, Merck Sharp and Dohme, Eli Lilly, Roche, Abbott, ActoBio Therapeutics, and Novartis; C.M. serves or has served on the speakers bureau for Novo Nordisk, Sanofi-Aventis, Merck Sharp and Dohme, Eli Lilly, Boehringer-Ingelheim, AstraZeneca, and Novartis. Financial compensation for these activities has been received by KU Leuven. P.G. serves or has served on the advisory panel for Novo Nordisk, Sanofi-Aventis, Boehringer-Ingelheim, Janssen Pharmaceuticals, Roche, Medtronic, and Bayer. Financial compensation for these activities has been received by KU Leuven. P.G. serves or has served on the speakers bureau for Merck Sharp and Dohme, Boehringer-Ingelheim, Bayer, Medtronic, Insulet, Novo Nordisk, Abbott, and Roche. Financial compensation for these activities has been received by KU Leuven. KU Leuven received for P.G. non-financial support for travel from Sanofi-Aventis, A. Menarini Diagnostics, Medtronic, and Roche. All disclosures were unrelated to the present work. S.F., T.M., and B.K. have nothing to disclose.

Data sharing

Anonymous data are shared with centres participating in the ALERTT1 trial, based on research questions mentioned in the ALERTT1 study protocol or based on a new study protocol approved by the relevant ethical committees.

Selected anonymous data collected in the study and additional documents can be made available to others not involved in the ALERTT1 trial, on the basis of a reasonable request.

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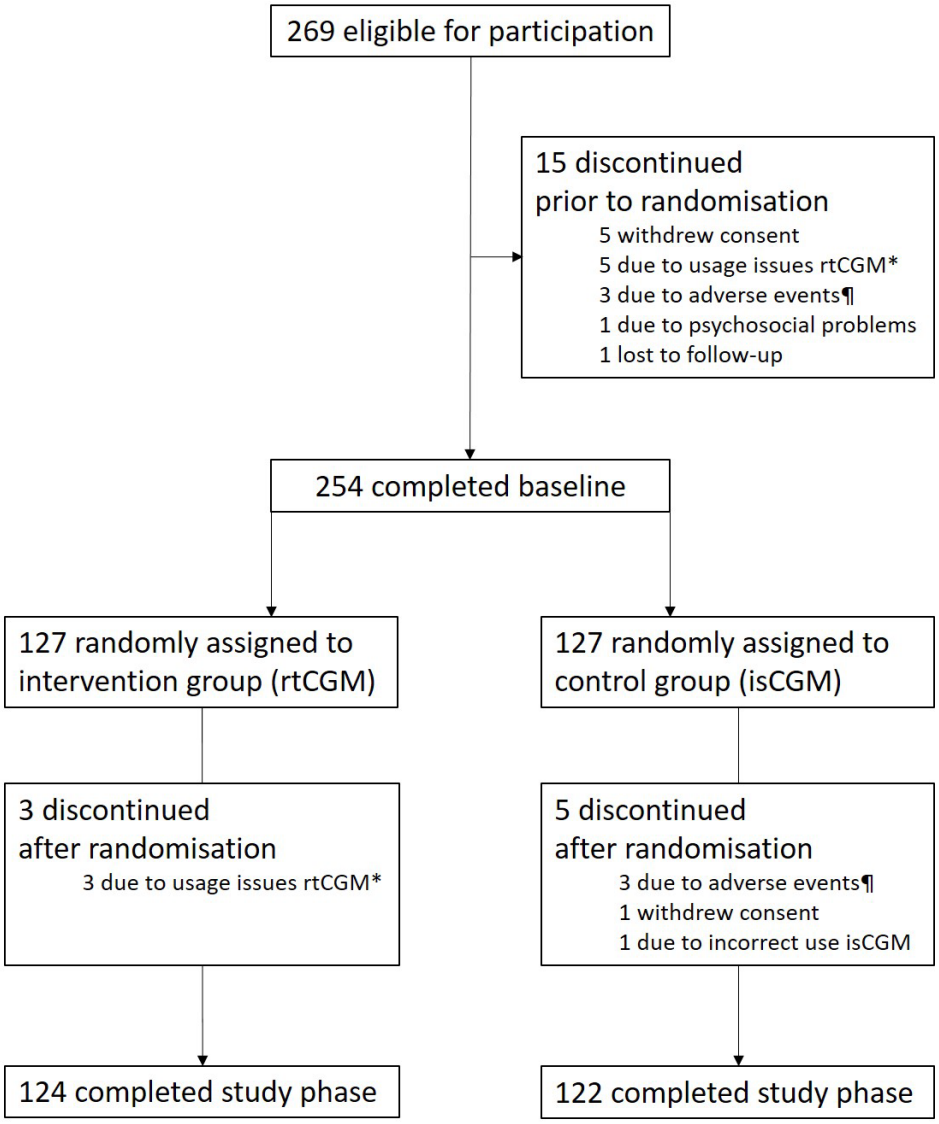
Figures

Figure 1: Trial profile

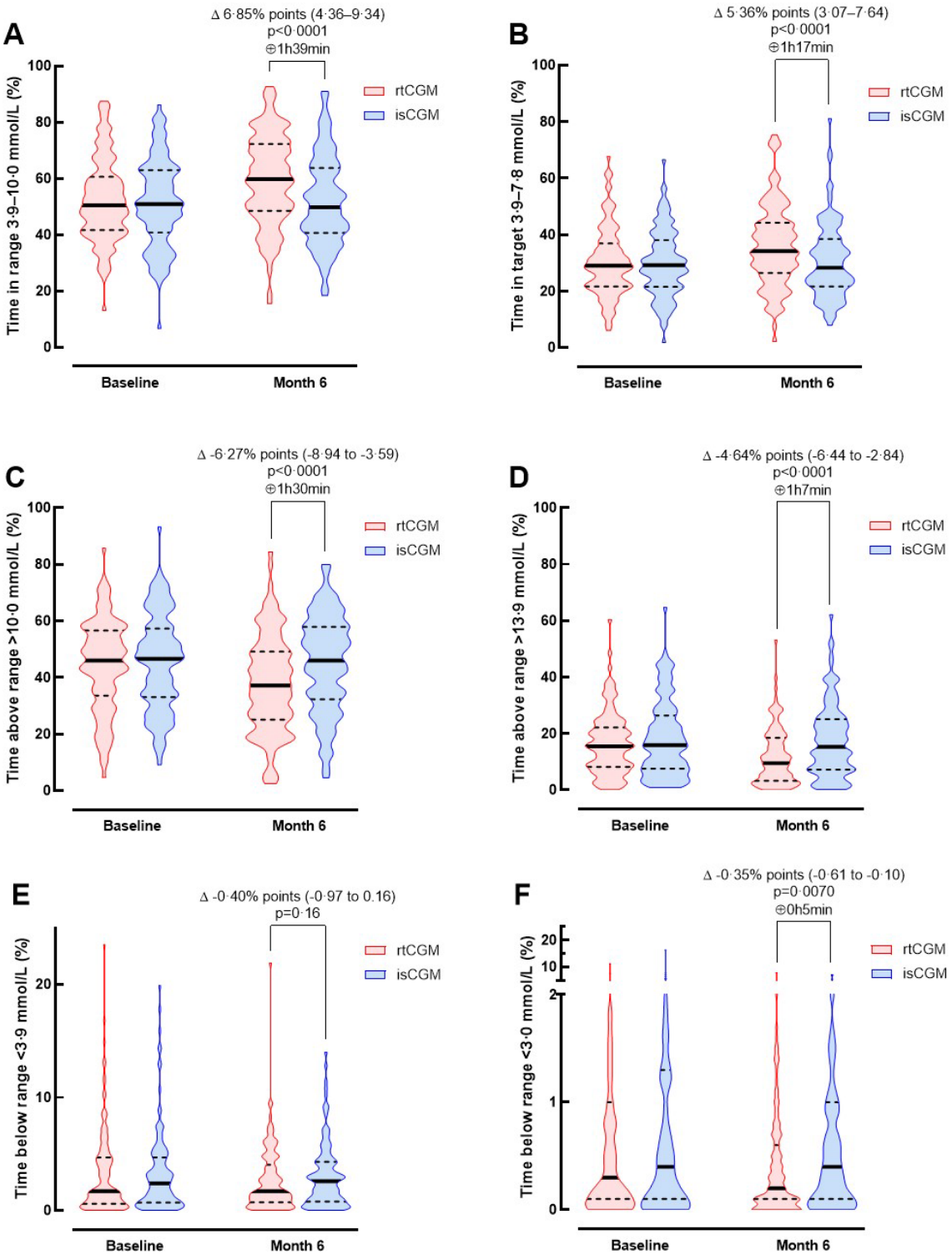


¶Adverse events during baseline consisted of a traffic accident (unrelated to hypoglycaemia), worsening of skin reaction to isCGM and development of skin reaction to rtCGM. Adverse events during the study phase leading to trial discontinuation consisted of multiple fractures due to fall of stairs (unrelated to hypoglycaemia), and worsening of skin reaction to isCGM (two times).

*Usage issues rtCGM prior to randomisation included: usage difficulties, problematic connectivity and/or sensor insertion during blinded use. Usage issues rtCGM after randomisation included: problematic connectivity, alarm fatigue, and/or doubts about accuracy during unblinded use.

rtCGM=real-time continuous glucose monitoring. isCGM=intermittently scanned continuous glucose monitoring.

Figure 2: Time in ranges



Violin plots showing the distribution of time spent in target ranges (**A** and **B**), hyperglycaemia (**C** and **D**) and hypoglycaemia (**E** and **F**) by the study population at baseline and month 6. The violin width gives an indication of the number of participants. Solid black lines represent the median, black dashed lines represent the interquartile range.

The difference Δ (95% CI) in means obtained with the cLDA model (including the p value) is reported on top of the violins representing six-month data. These differences are also expressed in percentage points (% points), and hours and minutes (Θhmin). To convert glucose ranges from mmol/L to mg/dL, multiply by 18.

rtCGM=real-time continuous glucose monitoring. isCGM=intermittently scanned continuous glucose monitoring.

Tables

Table 1: Baseline characteristics		
	rtCGM (n=127)	**isCGM (n=127)**
Sex		
Male	81 (64%)	76 (60%)
Female	46 (36%)	51 (40%)
Age (years)	42·8 (13·8)	43·0 (14·5)
Body mass index (kg/m^2)	25·6 (23·2–28·4)	24·8 (22·4–27·2)
Highest level of education		
Primary education	2 (2%)	2 (2%)
Secondary education	38 (30%)	41 (32%)
Higher education	87 (69%)	84 (66%)
Duration of diabetes (years)	18 (10–30)	17 (8–28)
HbA_{1c} (%)	7·4 (0·9)	7·4 (0·9)
HbA_{1c} (mmol/mol)	57·9 (9·5)	57·6 (9·6)
Insulin therapy		
Multiple daily injections	103 (81%)	102 (80%)
Insulin pump therapy	24 (19%)	25 (20%)
Total bolus insulin (IU/kg)	0·3 (0·2–0·4)	0·3 (0·2–0·4)
Total basal insulin (IU/kg)	0·2 (0·2–0·3)	0·3 (0·2–0·3)
Duration of use of isCGM (months)	29 (25–31)	27 (22–31)
isCGM scan frequency (number/day)	11 (7–16)	11 (7–16)
Participants with hypoglycaemia unawareness	24 (19%)	20 (16%)
Participants with severe hypoglycaemia in the past 12 months	16 (13%)	13 (10%)
Participants with ketonaemia in the past 12 months*	5 (4%)	6 (5%)

Data are n (%), mean (SD), or median (IQR).

*Ketonaemia was defined as a ketone value >1 mmol/L.

rtCGM=real-time continuous glucose monitoring. isCGM=intermittently scanned continuous glucose monitoring.

Table 2: Primary and key secondary outcomes							
	Baseline			Month 6			
	rtCGM	isCGM		rtCGM	isCGM	Δ (95% CI)	p value
Primary outcome							
Time in range 3·9–10·0 mmol/L (%)	52·5 (49·8–55·1)	51·3 (48·7–54·0)		59·6 (56·8–62·4)	51·9 (49·1–54·7)	6·85% points (4·36–9·34)	<0·0001
Key secondary outcomes							
HbA_{1c} (%)	7·4 (7·3–7·6)	7·4 (7·3–7·6)		7·1 (6·9–7·2)	7·4 (7·3–7·6)	-0·36% points (-0·48 to -0·24)	<0·0001
Time in hypoglycaemia <3·0 mmol/L (%)	0·91 (0·60–1·22)	1·05 (0·74–1·36)		0·47 (0·28–0·66)	0·84 (0·65–1·03)	-0·35% points (-0·61 to -0·10)	0·0070
HFS-worry (points)	18·8 (16·7–21·0)	18·7 (16·5–20·8)		15·4 (13·3–17·5)	18·0 (15·8–20·1)	-2·62 (-4·52 to -0·71)	0·0071

Data are mean (95% CI) or difference in means (95% CI).

To convert glucose ranges from mmol/L to mg/dL, multiply by 18.

rtCGM=real-time continuous glucose monitoring. isCGM=intermittently scanned continuous glucose monitoring. Δ=difference in means at six months obtained with the cLDA model. % points=percentage points. HFS-worry=Hypoglycaemia Fear Survey version II worry subscale.

Table 3: Time in ranges consensus targets						
	Baseline		Month 6			
	rtCGM	isCGM	rtCGM	isCGM	Δ (95% CI)	p value
Participants achieving consensus targets						
<5% of time >13·9 mmol/L	18 (14%)	21 (17%)	38 (31%)	20 (17%)	16·3 (8·5–24·2)	<0·0001
<25% of time >10·0 mmol/L	18 (14%)	16 (13%)	30 (24%)	15 (12%)	10·8 (2·8–18·9)	0·0080
>70% of time 3·9–10·0 mmol/L	17 (13%)	16 (13%)	35 (28%)	18 (15%)	12·8 (4·8–20·9)	0·0017
<4% of time <3·9 mmol/L	84 (66%)	90 (71%)	93 (75%)	85 (70%)	7·5 (-2·4 to 17·4)	0·14
<1% of time <3·0 mmol/L	94 (74%)	87 (69%)	106 (86%)	89 (74%)	9·8 (7·0–18·9)	0·034
Coefficient of variation ≤36%	61 (48%)	49 (39%)	68 (55%)	52 (43%)	7·1 (-3·6 to 17·9)	0·19
HbA_{1c} <7%	36 (28%)	38 (30%)	60 (49%)	40 (33%)	18·3 (8·3–28·3)	0·0003
HbA_{1c} <7% and <1% of time <3·0 mmol/L	27 (21%)	24 (19%)	49 (40%)	26 (22%)	17·9 (7·9–27·8)	0·0004
HbA_{1c} <7% and no severe hypoglycaemia	32 (25%)	35 (28%)	59 (48%)	39 (32%)	18·7 (8·4–29·1)	0·0004
>70% of time 3·9–10·0 mmol/L and <1% of time <3·0 mmol/L	13 (10%)	12 (9%)	32 (26%)	14 (12%)	13·7 (5·4–22·0)	0·0012

Data are n (%) or difference in percentages (95% CI).

To convert glucose ranges from mmol/L to mg/dL, multiply by 18.

rtCGM=real-time continuous glucose monitoring. isCGM=intermittently scanned continuous glucose monitoring. Δ=difference in the percentage of participants at six months obtained with the cLDA model.