Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: a multicentre, non-masked, randomised controlled trial

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Summary

Background Tight control of blood glucose in type 1 diabetes delays onset of macrovascular and microvascular diabetic complications; however, glucose levels need to be closely monitored to prevent hypoglycaemia. We aimed to assess whether a factory-calibrated, sensor-based, flash glucose-monitoring system compared with self-monitored glucose testing reduced exposure to hypoglycaemia in patients with type 1 diabetes.

Method In this multicentre, prospective, non-masked, randomised controlled trial, we enrolled adult patients with well controlled type 1 diabetes (HbA$_{1c}$ ≤58 mmol/mol [7·5%]) from 23 European diabetes centres. After 2 weeks of all participants wearing the blinded sensor, those with readings for at least 50% of the period were randomly assigned (1:1) to flash sensor-based glucose monitoring (intervention group) or to self-monitoring of blood glucose with capillary strips (control group). Randomisation was done centrally using the biased-coin minimisation method dependent on study centre and type of insulin administration. Participants, investigators, and study staff were not masked to group allocation. The primary outcome was change in time in hypoglycaemia (<3·9 mmol/L [70 mg/dL]) between baseline and 6 months in the full analysis set (all participants randomised; excluding those who had a positive pregnancy test during the study). This trial was registered with ClinicalTrials.gov, number NCT02232698.

Findings Between Sept 4, 2014, and Feb 12, 2015, we enrolled 328 participants. After the screening and baseline phase, 120 participants were randomly assigned to the intervention group and 121 to the control group, with outcomes being evaluated in 119 and 120, respectively. Mean time in hypoglycaemia changed from 3·38 h/day at baseline to 2·03 h/day at 6 months (baseline adjusted mean change −1·39) in the intervention group, and from 3·44 h/day to 3·27 h/day in the control group (−0·14); with the between-group difference of −1·24 (SE 0·239; p<0·0001), equating to a 38% reduction in time in hypoglycaemia in the intervention group. No device-related hypoglycaemia or safety issues were reported. 13 adverse events were reported by ten participants related to the sensor—four of allergy events (one severe, three moderate); one itching (mild); one rash (mild); four insertion-site symptom (severe); two erythema (one severe, one mild); and one oedema (moderate). There were ten serious adverse events (five in each group) reported by nine participants; none were related to the device.

Interpretation Novel flash glucose testing reduced the time adults with well controlled type 1 diabetes spent in hypoglycaemia. Future studies are needed to assess the effectiveness of this technology in patients with less well controlled diabetes and in younger age groups.

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Introduction

Tight glucose control and near-normal blood glucose concentrations delay the onset and progression of diabetic microvascular and macrovascular complications.[1,2] However, many patients do not achieve optimum glycaemic targets because of increased hypoglycaemia[1] and those attaining their glycaemic goals remain persistently at risk of low glucose concentrations.[3] Population-based data indicate that 30–40% of people with type 1 diabetes experience an average of one to three episodes of severe hypoglycaemia each year.[4] Nocturnal hypoglycaemia is particularly dangerous and accounts for approximately half of severe hypoglycaemic events.[5] Hypoglycaemia affects wellbeing and quality of life. A further concern is that recurrent exposure to hypoglycaemia might lead to attenuated hormonal

responses to falling glucose concentrations, and ultimately impaired awareness of hypoglycaemia (hypoglycaemia-associated autonomic failure), which is associated with a several-fold increased risk of severe hypoglycaemia.[6]

A reduction of 30% or higher in hypoglycaemia is considered clinically relevant[7]; structured patient education, individualised targets, and self-monitoring of blood glucose are cornerstones in treatment to prevent and manage hypoglycaemic risk. Over the past decade, the introduction of continuous glucose monitoring to facilitate self-management has shown improved glucose control and reduced exposure to hypoglycaemia,[8] favourable findings being especially noticeable when continuous glucose monitoring has been used in sensor-augmented pump therapy[9,10] and with low-glucose suspend systems.[11] However, there are some limitations

Research in context

Evidence before this study

We searched PubMed for any studies published in English up to May 25, 2016, using flash glucose monitoring technology. Our search terms were "flash glucose monitoring" and "blood glucose". Continuous glucose monitoring was not included as a search term because of differences in the technology and expected differences in terms of patient engagement with the technology and its features. Of the 12 search results, one clinical trial was identified that compared the accuracy of the flash glucose monitoring system with capillary blood glucose. The trial reported that the factory-calibrated flash glucose monitoring system showed good accuracy, sustained over 14 days, with mean absolute relative difference of 11·4% compared with capillary blood glucose monitoring.

Interpretation

There is a gap in published data related to assessing the impact of this technology on glycaemic control. To the best of our knowledge, this is the first randomised controlled trial that has compared the effect of new flash glucose monitoring technology to self-monitoring of blood glucose on hypoglycaemia in type 1 diabetes.

Implications of all the available evidence

Our findings showed that replacing self-monitoring of blood glucose with novel flash sensor-based glucose monitoring demonstrated superior reduction in time in hypoglycaemia without deterioration of glycated haemoglobin. This novel technology could empower individuals with type 1 diabetes by providing a potential alternative to conventional self-monitoring of blood glucose testing.

with current continuous glucose monitoring devices, including relatively short sensor lifetime and daily self-monitoring of blood glucose for device calibration to ensure sensor accuracy, which have restricted their widespread use.[12]

We used a novel sensor-based flash glucose monitoring system (Freestyle Libre; Abbott Diabetes Care, Witney, Oxon, UK). The sensor is calibrated in the factory and needs no calibration during the 14 day wear. Data are transferred to the reader when it is brought into close proximity to the sensor, which then displays current sensor glucose level, a glucose trend arrow, and glucose readings over the preceding 8 h. Scanning can be done as often as is needed for current glucose concentration; otherwise, glucose data are automatically captured and stored on the sensor (every 15 min). The reader stores data for 90 days. Data can be uploaded from the reader, using the device software[13] to generate summary glucose reports (including ambulatory glucose profile) that can be reviewed by the patient alone or with their clinician. In this randomised controlled trial, we aimed to assess the efficacy of this new flash glucose monitoring technology system compared with conventional self-monitoring of blood glucose testing to prevent hypoglycaemia in adults with well controlled type 1 diabetes.

Methods

Study design and participants

We conducted this prospective, non-masked, randomised controlled study at 23 European diabetes centres (three in Sweden, six in Austria, five in Germany, three in Spain, and six in the Netherlands; the protocol is online). We enrolled participants aged 18 years or older who had been diagnosed with type 1 diabetes for 5 years or longer, had been on their current insulin regimen for at least 3 months before study entry, had a screening HbA_{1c} concentration of 58 mmol/mol (7·5%) or lower, reported self-monitoring of blood glucose levels on a regular basis (equivalent to ≥3 times a day) for 2 months or more before study entry, and were considered by the investigator to be technically capable of using the flash sensor-based glucose monitoring system. Any potentially eligible patient from the general diabetes population at each study site was invited to participate in the study (appendix p 1).

Patients were not included if they were currently diagnosed with hypoglycaemia unawareness; had diabetic ketoacidosis or myocardial infarction in the preceding 6 months; had known allergy to medical-grade adhesives; had used continuous glucose monitoring within the preceding 4 months; were currently using sensor-augmented pump therapy; were pregnant or were planning pregnancy; or were receiving oral steroid therapy for any disorders.

Approval was given by the appropriate competent authority in each country. All participating centres gave ethics approval before the study. Participants gave written informed consent. Original data are stored at each study centre.

Randomisation and masking

Participants were randomly assigned to flash sensor-based glucose monitoring (intervention group) or to self-monitoring of blood glucose (control group) in a 1:1 ratio by central interactive web response system (IWRS) using the biased-coin minimisation method; study centre and type of insulin administration were prognostic factors. Participants, investigators, and study staff were not masked to group allocation.

Procedures

At screening and enrolment, all participants had baseline HbA_{1c} samples measured (analysed by a central laboratory [ICON Laboratories, Dublin, Ireland]),

physical measures recorded (eg, blood pressure), and baseline values recorded for all questionnaire types. Questionnaires administered included Diabetes Distress Scale (DDS),[14] Diabetes Quality of Life Questionnaire (DQoL),[15] Diabetes Treatment Satisfaction Questionnaire (DTSQ),[16] Hypoglycaemia Fear Survey (HFS),[17] and a hypoglycaemia patient questionnaire[7] (used to record baseline perception of hypoglycaemia).

All participants wore a FreeStyle Libre device locked into masked mode for the 14 day baseline period; sensor glucose measurements were not visible to the participant or the investigator during this time (blinded). After randomisation, sensor data for participants in the intervention group were made available to them and the investigators. Glucose management was supported by self-monitoring of blood glucose, using the strip port built into the reader and compatible test strips (Abbott Diabetes Care, Witney, Oxon, UK). Participants were asked to record capillary glucose concentrations in a glucose diary and to log other events (eg, severe hypoglycaemia, hospitalisation, and additional health visits or treatment) in an event diary. Participants with sensor data for at least 50% of the blinded wear period (or ≥650 individual sensor readings) were then centrally randomised to the two groups.

After randomisation, the device was unblinded for participants in the intervention group who then continuously used sensor glucose data as per the device labelling for self-management of glucose throughout the duration of the study (6 months). Participants in the intervention group were given access to the device software, which they could use at home to review their sensor data if they wished. No training was provided to these participants for interpretation of glucose-sensor data.

Participants in the control group self-monitored glucose concentrations using the FreeStyle Lite meter and test strips (Abbott Diabetes Care, Witney, Oxon, UK). In the 14 days preceding the 3 month and 6 month time-points (days 91 and 194, respectively), participants in the control group wore the flash sensor while continuing to manage their diabetes with self-monitoring of blood glucose. All sensor glucose data were blinded for both participants and investigators.

No standardised treatment protocols or insulin titration algorithms were used in the trial. In line with standard diabetes care, all participants were encouraged to self-manage using current or historical glucose data to optimise glucose control. At clinic visits glycaemic control and glucose readings for both groups and sensor data reports using the software for participants assigned to the
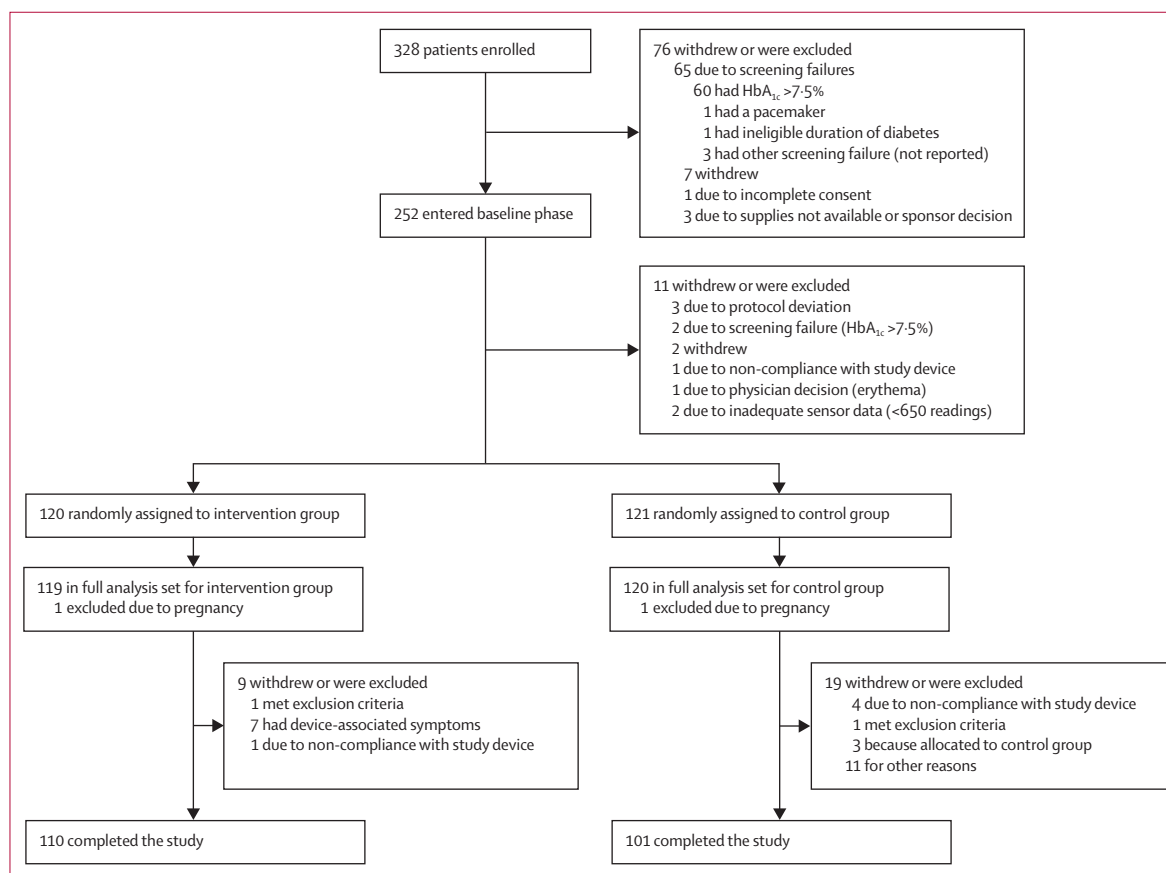

Figure 1: Trial profile

intervention group were formally reviewed with a health-care professional for personalised glucose management. Blood tests and physical measures were also taken at clinic visits. Questionnaires for the patient-reported outcomes were administered at the day 208 clinic visit.

Outcomes

The primary effectiveness endpoint was time spent in hypoglycaemia (<3·9 mmol/L [<70 mg/dL])[7] for the 14 days preceeding the end of the 6 month study period (days 194–208). Prespecified secondary endpoints were sensor-derived glycaemic measures at days 194–208, day 208 HbA$_{1c}$ concentrations, change in total daily dose of insulin from day 1 to day 208; system utilisation for days 15–208 (defined as the percentage of data collected, assuming continuous device wear), and frequency of glucose finger-sticks and sensor scans per day during the study period. Sensor-derived glycaemic measures comprised: number and duration of hypoglycaemic episodes (sensor glucose <3·9 mmol/L in 24 h, by day [0600–2300 h], and night [2300–0600 h]; <3·1 mmol/L in 24 h, and <2·2 mmol/L in 24 h [<70 mg/dL, <55 mg/dL, and <40 mg/dL, respectively]; an episode was defined as at least two consecutive readings, at 15 min intervals, outside the predefined glucose range, the end of an episode was one reading at or higher than the threshold); time with glucose in range 3·9–10·0 mmol/L (70–180 mg/dL); number and duration of hyperglycaemic episodes (>10·0 mmol/L and >13·3 mmol/L [>180 mg/dL and >240 mg/dL, respectively]); and glucose variability measurements.[18] Additional outcomes assessed in the clinical study report were proportion of participants who achieve time spent in hypoglycaemia (<3·9 mmol/L;

<70 mg/dL) ≤1 h/day; number of events of symptomatic hypoglycaemia; post prandial hyperglycaemia (>10·0 mmol/L, 180 mg/dL); prandial to basal insulin ratio; number of participants changing from once daily to twice daily basal insulin; body weight and body-mass index (BMI); fasting cholesterol and triglycerides; blood pressure; emergency room visits or admissions and non-protocol related additional clinic time; and medication usage (non-insulin related, including glucagon, self-reported from event diary).

Questionnaire results for the user questionnaire (participant [intervention group only] and health-care professional facing) were assessed at 6 months, with patient-recorded outcome measures (with the HFS, DTSQ, DDS, and DQoL) were assessed at baseline and at 6 months. Adverse events and sensor insertion-site symptoms were monitored throughout the study. Additionally, number of episodes of diabetic ketoacidosis and number of severe hypoglycaemia events[7] (requiring third-party assistance) were assessed and compared across the two study groups.

Statistical analysis

We calculated that a sample size of 178 participants was needed to provide 80% power to detect a difference of 30% between groups for the primary endpoint, with a two-sided significance level of 0·05. The primary endpoint and all secondary endpoints were assessed in the full analysis set, which included all randomised participants apart from those who had a positive pregnancy test during the study period. Safety outcomes were analysed in all participants who were enrolled.

We assessed the primary endpoint using analysis of covariance comparing treatment groups with study centre, insulin administration method, and baseline time in hypoglycaemia as covariates. Missing values were imputed by last observation carried forward. This included the baseline value if no measurements after baseline were available. Changes in patient-reported outcome measures and quality of life were calculated by comparing scores from control and intervention group participants using analysis of covariance on baseline values, study centre, and insulin administration method. Confidence intervals were calculated for the group least-square mean of each measure and the difference between group least-square means.

Data analysis was performed by a contract research organisation (ICON; Dublin, Ireland), managed by Abbott Diabetes Care, and by Abbott Diabetes Care. We used SAS version 9.2 or higher for all analyses. The trial is registered with ClinicalTrials.gov, number NCT02232698.

Role of the funding source

The sponsor designed the study protocol in collaboration with the principal investigator in each country and provided all the study materials. The sponsor was

	Intervention (n=119)	Control (n=120)
Men	77 (65%)*	59 (49%)*
Women	42 (35%)	61 (51%)
Race		
White	119 (100%)	119 (99%)
Black	0	1 (1%)
Age (years)	42 (33–51)	45 (33–57)
BMI (kg/m²)	25·2 (3·6)	24·8 (3·5)
Duration of diabetes (years)	20 (13–27)	20 (12–32)
Screening HbA$_{1c}$ (%; mmol/mol)	6·7 (0·5); 50·1 (5·7)	6·7 (0·6); 50·2 (6·5)
Self-reported blood glucose frequency per day	5·4 (2·0)	5·6 (2·3)
Insulin administration method		
Multiple daily injections	81 (68%)	80 (67%)
Continuous subcutaneous insulin infusion	38 (32%)	40 (33%)
Insulin, total daily dose		
Basal (units)	25·7 (13·9)	20·9 (10·0)
Bolus (units)	24·2 (13·5)	22·2 (13·4)
Continuous subcutaneous insulin infusion (units)	41·4 (17·1)	35·9 (15·6)

Data are n (%), median (IQR), or mean (SD). *p=0·0153.

Table 1: Baseline characteristics

involved in collecting data and reporting results, but was not involved in the authors' interpretation or in writing text. The sponsor also funded medical writing services and gave approval to submit for publication. The corresponding author had full access to all the data in the study and, together with all authors, had final responsibility for the decision to submit for publication.

Results

We enrolled 328 participants between Sept 4, 2014, and Feb 12, 2015; 241 were subsequently randomly assigned to the intervention group (n=120) or control group (n=121) after completing the baseline phase (figure 1, table 1). The full analysis set included 239 randomised participants; one woman from each group was excluded due to pregnancy.

Time in hypoglycaemia (<3·9 mmol/L) changed from 3·38 h/day to 2·03 h/day in the intervention group (baseline adjusted mean change −1·39), and from 3·44 h/day to 3·27 h/day in the control group (baseline adjusted mean change −0·14). The adjusted between-group difference of −1·24 (SE 0·239 h/day) was highly significant (p<0·0001), equating to a 38% reduction in time in hypoglycaemia in the intervention group compared with the control group (figure 2; table 2).

The between-group differences for time in hypoglycaemia defined as sensor glucose lower than 3·1 mmol/L, 2·5 mmol/L, and 2·2 mmol/L were significant in favour of the intervention group (figure 2, table 2). The number of hypoglycaemic events registered at each hypoglycaemic threshold was significantly reduced (table 2).

Analysis by day and night showed that time below all hypoglycaemic thresholds and number of episodes were significantly improved in the intervention group compared with control (table 2, appendix pp 2–3). The between-group differences for AUC were also significant (table 2). At 6 months, 77 (65%) of the intervention group compared with 39 (33%) of the control group reduced their time in hypoglycaemia (<3·9 mmol/L) by at least 30% (p<0·0001). Time spent in hypoglycaemia was reduced almost immediately as sensor-based results became visible to participants (ie, before sensor results were reviewed with their clinician at study visits; figure 3).

Time spent in hyperglycaemia (>13·3 mmol/L) was reduced more in the intervention group than in the control group (table 2). There was no effect on time with sensor glucose concentrations higher than 10·0 mmol/L (appendix p 5). Time in range of sensor glucose 3·9–10·0 mmol/L was significantly increased in the intervention group compared with the control group at 6 months (table 2, figure 2B). Mean sensor glucose remained unchanged. Similar glycaemic data were observed after 3 months (appendix pp 6–7).

At 6 months, HbA$_{1c}$ concentrations in the intervention group were essentially unchanged compared with the control group (table 2). There were significant between-group differences favouring the intervention group compared with the control group in the glycaemic variability measures of glucose standard deviation, mean amplitude of glycaemic excursions, low blood glucose index, and blood glucose risk index, and in continuous overall net glycaemic action results (table 2, appendix p 8).

The mean number of self-monitored blood glucose tests performed per day by the intervention group immediately reduced from 5·5 (SD 2·0) tests per day in the 14 day baseline phase to 0·5 (0·7) tests per day during the treatment phase of the trial (figure 4A). This was an unprompted response by intervention participants that clinically equates to one self-monitoring of blood glucose test every 2–5 days. The mean number of sensor scans per day for the intervention group was 15·1 (SD 6·9) during the treatment phase (figure 4A), the pattern of daily scanning is in figure 4B. System utilisation, defined as the percentage of data collected, assuming continuous device wear for 6 months by the intervention group (n=112) was 92·8% (SD 7·3). The number of self-monitoring blood glucose tests performed by participants
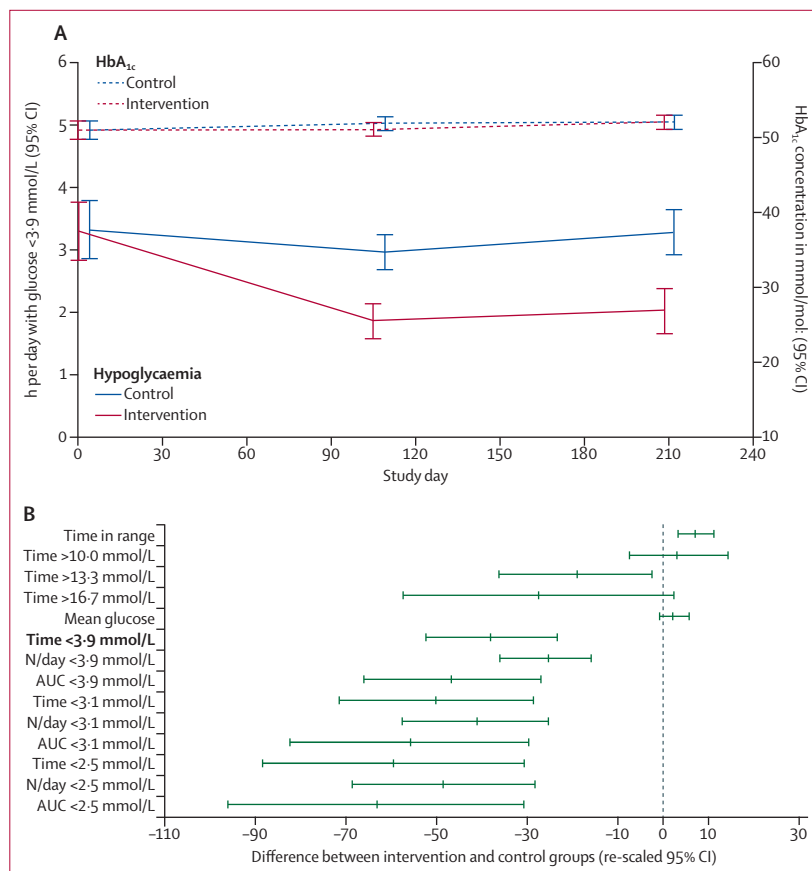

Figure 2: **Difference in groups for changes in time with hypoglycaemia and HbA$_{1c}$ (A) and with glucose higher or lower than glycaemic thresholds (B)**
In A, control and intervention study day offset for clarity. In B, re-scaled confidence intervals are confidence intervals for the difference in the intervention group from the control group at 6 months expressed as a percentage of the control group adjusted mean.

	Baseline		Study end		Difference in adjusted means in intervention vs control	Difference in intervention vs control (%)	p value
	Intervention (n=119)	Control (n=119)	Intervention (n=119)	Control (n=119)			
HbA₁c (mmol/mol)	50·7 (5·7)	50·6 (7·0)	52·4 (7·2)	52·4 (7·2)	0·0 (0·65)	NA	0·9543
HbA₁c (%)	6·79 (0·52)	6·78 (0·64)	6·94 (0·65)	6·95 (0·66)	0·00 (0·059)	NA	0·9556
Time with glucose 3·9–10·0 mmol/L (70–180 mg/dL) in h	15·0 (2·5)	14·8 (2·8)	15·8 (2·9)	14·6 (2·9)	1·0 (0·30)	NA	0·0006
Glucose <3·9 mmol/L (70 mg/dL) within 24 h							
Events	1·81 (0·90)	1·67 (0·80)	1·32 (0·81)	1·69 (0·83)	−0·45 (0·089)	−25·8%	<0·0001
Time in h	3·38 (2·31)	3·44 (2·62)	2·03 (1·93)	3·27 (2·58)	−1·24 (0·239)	−38·0%	<0·0001
AUC (h×mg/dL)	53·42 (43·46)	58·34 (57·22)	28·58 (31·15)	54·67 (60·08)	−25·14 (5·32)	−46·7	<0·0001
Glucose <3·9 mmol/L (70 mg/dL) at night (2300–0600 h) within 7 h							
Events	0·47 (0·32)	0·46 (0·29)	0·27 (0·23)	0·40 (0·29)	−0·14 (0·029)	−33·2%	<0·0001
Time in h	1·32 (1·07)	1·48 (1·29)	0·68 (0·97)	1·23 (1·10)	−0·47 (0·118)	−39·8%	<0·0001
Glucose <3·1 mmol/L (55 mg/dL) within 24 h							
Events	0·96 (0·65)	0·92 (0·73)	0·56 (0·55)	0·92 (0·74)	−0·38 (0·074)	−41·3%	<0·0001
Time in h	1·59 (1·42)	1·77 (1·86)	0·80 (0·96)	1·65 (1·97)	−0·82 (0·175)	−50·3%	<0·0001
AUC (h×mg/dL)	16·04 (17·46)	18·94 (23·22)	7·59 (10·25)	17·69 (26·34)	−9·67 (2·29)	−56·1%	<0·0001
Glucose <3·1 mmol/L (55 mg/dL) at night (2300–0600 h) within 7 h							
Events	0·34 (0·27)	0·36 (0·34)	0·19 (0·24)	0·30 (0·28)	−0·11 (0·03)	−34·9%	0·0005
Time in h	0·62 (0·60)	0·75 (0·83)	0·31 (0·43)	0·66 (0·080)	−0·32 (0·07)	−48·9%	<0·0001
Glucose <2·5 mmol/L (45 mg/dL) within 24 h*							
Events	0·56 (0·52)	0·59 (0·60)	0·29 (0·36)	0·56 (0·59)	−0·26 (0·06)	−48·5%	<0·0001
Time in h	0·85 (1·03)	1·04 (1·36)	0·38 (0·58)	0·96 (1·57)	−0·55 (0·14)	−59·5%	<0·0001
AUC (h×mg/dL)	3·99 (5·36)	5·00 (7·10)	1·74 (2·91)	4·73 (8·66)	−2·88 (0·75)	−63·1	0·0002
Glucose <2·5 mmol/L (45 mg/dL) at night (2300–0600 h) within 7 h*							
Events	0·23 (0·23)	0·27 (0·31)	0·11 (0·16)	0·21 (0·22)	−0·09 (0·02)	−44·9%	<0·0001
Time in h	0·36 (0·44)	0·48 (0·66)	0·15 (0·25)	0·43 (0·65)	−0·25 (0·06)	−60·4%	<0·0001
Glucose <2·2 mmol/L (40 mg/dL) within 24 h							
Events	0·39 (0·43)	0·44 (0·51)	0·19 (0·29)	0·43 (0·55)	−0·22 (0·050)	−55·0%	<0·0001
Time in h	0·59 (0·85)	0·75 (1·11)	0·26 (0·47)	0·73 (1·41)	−0·46 (0·122)	−65·3%	0·0003
Glucose >13·3 mmol/L (240 mg/dL) within 24 h							
Time in h	1·85 (1·44)	1·91 (1·70)	1·67 (1·36)	2·06 (1·61)	−0·37 (0·163)	−19·1%	0·0247
Glucose variability							
BGRI	8·2 (2·3)	8·3 (2·7)	7·3 (2·4)	8·4 (2·6)	−0·9 (0·26)	..	0·0004
CV glucose (%)	43·0 (7·0)	42·5 (6·6)	37·6 (5·7)	41·8 (6·8)	−4·4 (0·62)	..	<0·0001
LBGI	2·7 (1·5)	2·7 (1·7)	1·8 (1·4)	2·6 (1·7)	−0·8 (0·16)	..	<0·0001
MAGE (mg/dL; average)	142 (29)	144 (31)	132 (27)	141 (31)	−8 (3·0)	..	0·0055
Mean glucose (mg/dL)	141 (19)	142 (23)	146 (20)	143 (23)	3 (2·3)	..	0·1479
Standard deviation of glucose (mg/dL)	60·6 (12·6)	60·1 (12·9)	55·0 (10·9)	59·7 (13·8)	−5·0 (1·16)	..	<0·0001
CONGA							
2 h (mg/dL)	56 (13)	56 (14)	49 (12)	58 (13)	−9 (1·3)	..	<0·0001
6 h (mg/dL)	71 (25)	69 (26)	61 (25)	72 (28)	−12 (3·4)	..	0·0004

Data in parentheses are SDs, apart from when given with adjusted means where they are SEs. AUC=area under the curve. BGRI=blood glucose risk index. CV=coefficient of variation. LBGI=low blood glucose index. MAGE=mean amplitude of glycaemic excursions. CONGA=continuous overall net glycaemic action. *Post-hoc endpoint.

Table 2: **Glycaemic and glucose variability measures**

in the control group was consistent throughout the study, from 5·8 tests (SD 1·7) per day at baseline to 5·6 (2·2) per day at 6 months (figure 4A).

Over the study period, participants receiving multiple daily injection therapies changed their total insulin dose by a similar amount (mean −2·7 units [SD 7·3] in the

intervention group and −3·0 units [6·4] in the control group; p=0·7973). Participants receiving continuous subcutaneous insulin infusion therapy changed their total insulin dose by −0·5 units (SD 5·8) and −0·7 (3·4) units in the intervention and control groups, respectively (p=0·5860). At the end of the study there were no differences in total daily doses of insulin or bolus/basal insulin ratios between the study groups.

Patient satisfaction with treatment was significantly improved for intervention compared with control. (adjusted between-group difference −0·24 [SE 0·049]; p<0·0001). Diabetes quality of life score did not significantly favour either group in the full analysis set (−0·08 [0·039]; p=0·0524; appendix pp 14–15), but was significantly improved in the per-protocol set (appendix pp 10–13). The total treatment satisfaction (6·1 [0·84]; p<0·0001) and perceived frequency of hyperglycaemia (−1·0 [0·22]; p<0·0001) were significantly improved in the intervention group compared with the control group (figure 5). However there was no difference in diabetes distress (−0·03 [SE 0·089]; p=0·7634) or hypoglycaemia fear behaviour (0·0 [0·72]; p=0·9834) or worry scores (−1·2 [1·48]; p=0·4154; appendix pp 14–15).

276 adverse events or serious adverse events were experienced by 124 participants. There were 10 serious adverse events, five in each group, reported by nine participants. None of these were related to the device. 13 adverse events, reported by ten participants in the intervention group, were related to wearing the sensor (table 3). There were seven hypoglycaemia-related serious adverse events (requiring hospitalisation or third-party intervention) in six participants: two in the intervention group (n=2) and four in the control group (n=3). Additionally, there were three hypoglycaemia-related adverse events reported in the control group (n=2). None of the hypoglycaemic events were considered device related. There were no reported events of diabetic ketoacidosis during the study.

There were 248 sensor insertion-site signs and symptoms experienced by 65 participants across both groups. Signs can be subdivided into those expected due to sensor insertion (appendix p 17): pain (38), bleeding (25), oedema (eight), induration (five), and bruising (five), and those associated with sensor wear: erythema (85), itching (51), and rash (31). Seven participants withdrew from the study due to device-related adverse events or repetitive occurrences of sensor insertion-related symptoms.

Discussion

This randomised, controlled, multicentre, clinical trial assessed the effect of a novel glucose monitoring system on hypoglycaemia in adults with well controlled type 1 diabetes.[1] Our data show a reduced time in hypoglycaemia in the intervention group using the device compared with the control group, equating to a 38% decrease in time spent with sensor glucose lower than 3·9 mmol/L.

Notably, our trial resulted in both a decrease in time in hypoglycaemia and numerically fewer hypoglycaemic events. Previous studies of continuous glucose monitoring devices versus self-monitoring in adults with well
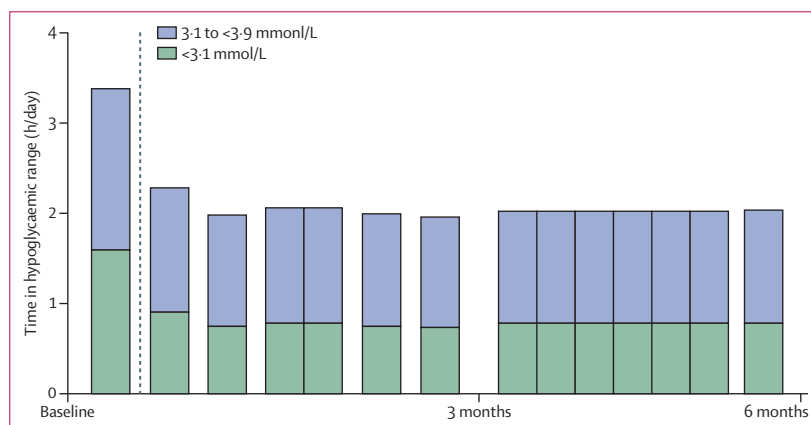

Figure 3: **Time in hypoglycaemic range during baseline and treatment phase (days 1–208) in the intervention group in the per-protocol set**
Grouped bars indicate analysis performed over 2 week periods and then averaged. Dashed line marks the start of the intervention.
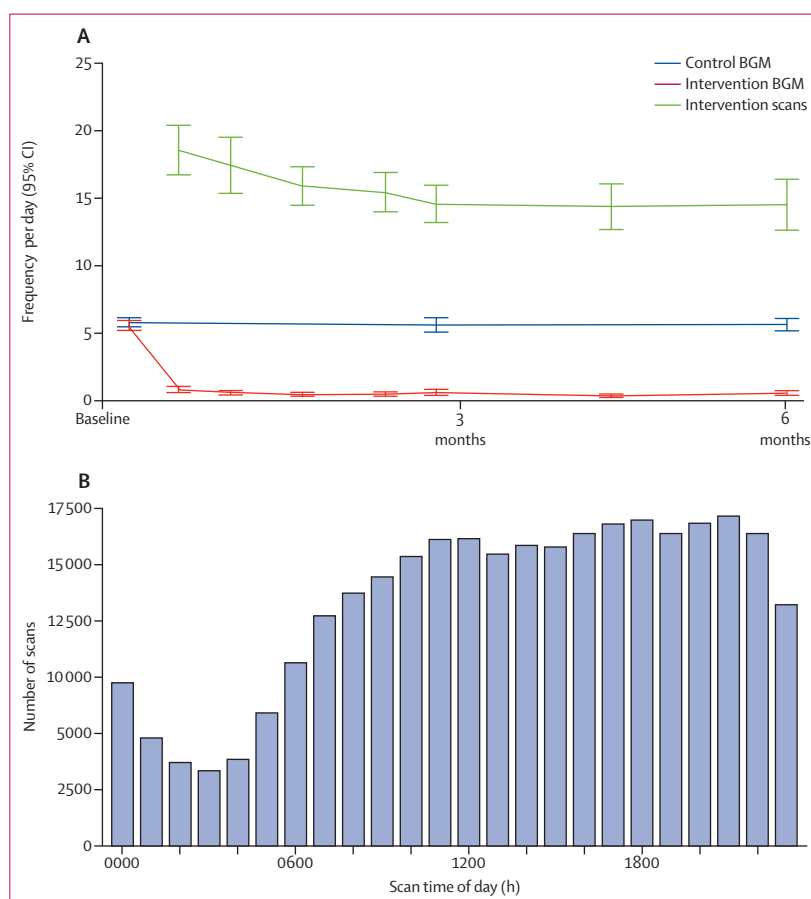

Figure 4: **Glucose monitoring frequency (A) and total number of scans by time of day in the intervention group (B)**
Number of scans performed across all intervention participants over 6 months by time of day. BGM=blood glucose monitoring.
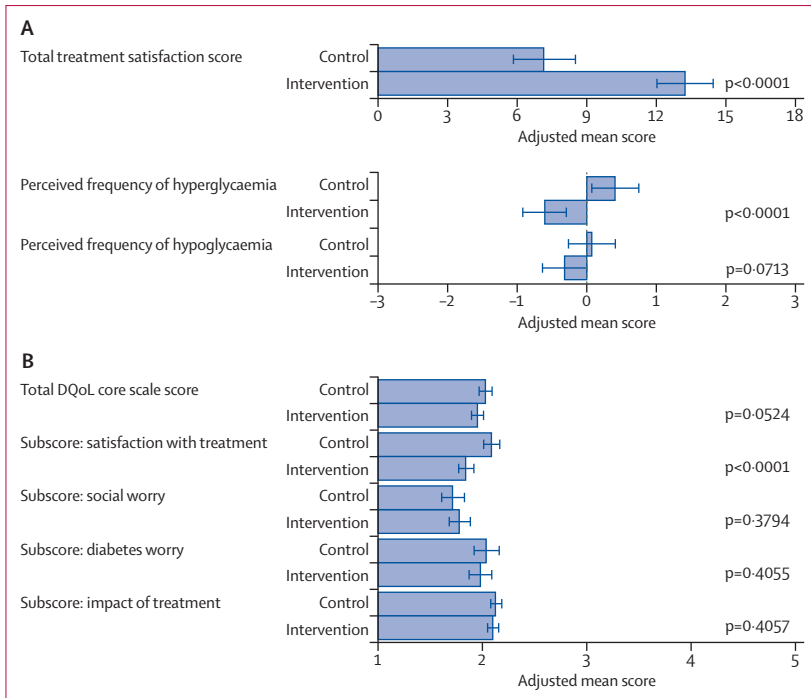
Figure 5: Scores from DTSQ (A) and DQoL (B) questionnaires

Data are presented for the full analysis set; for those for the per-protocol population please see appendix pp 10–13. Error bars show 95% CIs. DTSQ treatment satisfaction scores range from –18 to 18; high scores indicate much more satisfied, convenient, flexible, or likely to recommend treatment now. DTSQ perceived frequency scores range from –3 to 3; high scores indicate much more of the time now. DQoL scores range from 1 to 5; high scores indicate dissatisfaction, frequent impact, or frequent worry. DQoL=Diabetes Quality of Life Questionnaire. DTSQ=Diabetes Treatment Satisfaction Questionnaire.

	Intervention group (n=120)	Control group (n=121)
Participants with adverse or serious adverse events	63 (53%)	61 (50%)
Number of adverse or serious adverse events	138	138
Participants with serious adverse events	5 (4%)	4 (3%)
Number of serious adverse events	5	5
Participants with hypoglycaemic serious adverse events*	2 (2%)	3 (2%)
Number of hypoglycaemic serious adverse events*	2	4
Participants with hypoglycaemic adverse events	0	2 (2%)
Number of hypoglycaemic adverse events	0	3
Participants with device-related adverse events†	10 (8%)	0
Number of device-related adverse events	13	0
Participants who discontinued due to adverse events	6 (5%)	1 (<1%)‡

Table includes the full analysis set and two participants that became pregnant. *A hypoglycaemic serious adverse event was reported during the baseline phase. †Device-related adverse events were all related to wearing the sensor: four participants with allergy (one severe, three moderate); one with itching (mild); one with rash (mild); four with insertion-site symptom (severe); two with erythema (one severe, one mild); and one with oedema (moderate); all resolved. ‡Due to severe hypoglycaemia.

Table 3: Adverse events

Consequently, individuals with varying levels of hypoglycaemia awareness were included in our study (appendix p 1). Intervention participants achieved a clinically relevant reduction in hypoglycaemia and actively prevented further episodes over 6 months without depending on an alarm function or self-monitored blood glucose testing. Although we cannot delineate in detail the explanations of these consistent findings, our results might have been achieved because of the high system utilisation[21] (>90%) and scanning frequency, resulting in a three-times increase in daily self-monitoring of glucose control, which persisted throughout the 6 month study period. Time spent in hypoglycaemia was reduced almost immediately as sensor-based results became visible to participants (ie, before sensor results were reviewed with their clinician at study visits). This finding indicates fast adaptation to the device. Furthermore, it could suggest that real-time and glucose trend data, rather than retrospective analysis of the recordings, were predominantly used for proactive self-adjustments of glycaemic control. This notion is corroborated by findings showing that the effectiveness of continuous glucose monitoring depends largely on sufficient sensor utilisation[8] and that improvements in glucose control are rapidly reversed following cessation of monitoring.[10] Moreover, patient-driven use of real-time continuous glucose monitoring recordings is at least as effective as physician-led recommendations of therapy adjustments based on retrospective continuous glucose monitoring data analysis.[22] At study end, there were no differences in total daily doses of insulin or bolus/basal insulin ratios between the study groups. However, as shown previously in individuals with sensor-augmented pump therapy in whom insulin delivery was recorded in parallel with sensor glucose, day-to-day modifications of insulin administration patterns might take place without any noticeable overall changes in total insulin or relative proportion of bolus insulin.[10]

We also found that the reduction in hypoglycaemia exposure (time and events) was similar during both day-time and night-time. The pattern of daily scanning (figure 4B) shows that the highest frequency occurred in the evening, probably allowing necessary adjustments in overnight insulin supplementation or carbohydrate intake to counteract low glucose concentrations before sleep. Moreover, although scanning frequency during night-time was much lower than the day, there was still an average of one to two scans per night; together with historical data and less variable glucose in general, this might have been sufficient to reduce the incidence of nocturnal hypoglycaemia.

The observed lessening of hypoglycaemia was not at the expense of increasing the general blood glucose concentration (supported by the essentially unchanged mean sensor glucose and HbA$_{1c}$ levels), in addition to significantly reduced time in hyperglycaemia (>13·3 mmol/L). Thus, the combination of decreases in both hyperglycaemia and hypoglycaemia resulted in an

controlled type 1 diabetes have only reported a decreased time spent in hypoglycaemia,[19,20] for which the presence of a low glucose alarm is expected to have had some beneficial contribution. In this study, participants with a diagnosis of severe hypoglycaemia unawareness were excluded.[7]

increase in time within optimum glucose control for participants in the intervention group.

Frequency of self-monitoring of glucose was maintained by participants in the control group throughout the study period, whereas it was decreased in the intervention group and replaced with sensor scanning. This is an important indication of confidence in using current, historic, and trend sensor glucose data for self-management. Moreover, the change in behaviour in the intervention group, indicated by the negligible number of self-monitoring tests performed and high sensor scanning, might be associated with the individuals in the intervention group being able to view their glucose values more easily, rapidly, and frequently during the day or night. By comparison, self-monitoring of glucose readings provides single, intermittent measurements, which might not capture intervals of high glycaemic variability or nocturnal events that precipitate hypoglycaemia.[23] Device acceptance was further supported by the high sensor utilisation rate and the improvement in some patient-reported measures and some aspects of quality of life at 6 months. The intervention group agreed with positive aspects, including use of the system, improved treatment satisfaction, and diminished anxiety. Reduced self-monitoring of glucose[24] and hypoglycaemia[25] are factors related to subject burden that might contribute to these improvements. This concords with a recent study suggesting that perceived increased control of diabetes is associated with improved quality of life.[26] However, despite these clinically relevant reductions in hypoglycaemia, there was no change in patient-reported fear of hypoglycaemia, which supports similar findings from sensor-augmented pump therapy[10,19,27] and insulin-suspend technology studies.[11]

Several studies have shown a strong association between glucose variability and severe hypoglycaemia.[28,29] Episodes of severe hypoglycaemia in type 1 diabetes have been shown to be preceded and followed within 48 h by measurable disturbances in blood glucose.[30] Kilpatrick and colleagues[29] reported an 1·07-times increase in incidence of time to first hypoglycaemic event for every 1 mmol/L (18 mg/dL) increase in glucose standard deviation. Both glucose variability[31] and hypoglycaemia[32] are associated with inferior clinical outcomes. In this study, the use of the flash sensor-monitoring device was associated with significant improvements in several different measures of glucose variability, including a lowering of the low blood glucose index to a level compatible with low risk of severe hypoglycaemia.[32] In absolute terms, there were fewer serious adverse events and adverse events associated with hypoglycaemia in the intervention (two) than in the control group (seven). It should be noted, however, the study was not powered to detect any statistically significant differences in the incidence of adverse events associated with hypoglycaemia.

With regard to safety, adverse events relating to major sensor insertion-site events were reported by few participants. With all types of medical devices attached to the body, skin reactions are an occasional reported problem. In the present study, skin reactions occurred in 8% of participants, which we consider typical of medical-grade adhesive use.

Our trial results add to those from continuous glucose monitoring studies that have showed a reduction in hypoglycaemia alone[27] or in combination with modest improvement in HbA$_{1c}$ levels or reduced time in hypoglycaemia without increasing HbA$_{1c}$ levels.[11,19,20] However, there are a number of study limitations that might affect the generalisability of our findings. For individuals diagnosed with severe hypoglycaemia unawareness, this technology might not be ideal and predictive or low-threshold glucose insulin-suspend technology might be preferable.[33] Our inclusion criteria of well controlled diabetes (HbA$_{1c}$ <7·5%) implies that participants were highly motivated and successful in their self-management compared with other populations; although a concern for this group is susceptibility to hypoglycaemia. The relative proportion of continuous insulin infusion users in the trial was higher than usually seen in most European type 1 diabetes populations,[34] and only adults were enrolled. Future studies are needed to assess the effectiveness of this novel glucose monitoring system in younger age groups in addition to less well controlled and less motivated people with type 1 diabetes. All participants experienced periods of sensor wear; consequently, the intervention was not masked to participants, investigators, and study staff. As such, treatment decisions and assessment were based on the same sensor glucose values. This is a common limitation in glucose technology studies and it is recognised that there is no practical alternative to this approach.[35] The trial took place over a period of 6 months and therefore there are limitations around expected compliance to device use over a longer period. No adjustment was made for multiple testing of secondary endpoints. Many of the endpoints, particularly those derived from sensor glucose values, are highly inter-related and should not be considered in isolation.

In summary, use of the novel flash glucose sensor system resulted in a significant reduction in time and incidence of hypoglycaemia, without deterioration in HbA$_{1c}$ levels, demonstrating that the system is a safe replacement for self-monitoring of blood glucose and is highly acceptable to individuals with type 1 diabetes. For many individuals, hypoglycaemia is a barrier to optimum glucose control. Novel sensor-based systems to monitor glucose hold great promise as an effective alternative to conventional self-monitoring of blood glucose.

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