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BRIEF REPORT

# Comparison Between Continuous Versus Flash Glucose Monitoring in Children, Adolescents, and Young Adults with Type 1 Diabetes: An 8-Week Prospective Randomized Trial

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## ABSTRACT

***Introduction***: To assess the impact of real-time continuous glucose monitoring (RT-CGM) instead of first-generation flash glucose monitoring (FGM) on hypoglycaemia in children and adolescents with type 1 diabetes.
***Methods***: In this randomized controlled interventional study, young individuals with type 1 diabetes used RT-CGM or FGM for 8 weeks. We evaluated changes in time below range (TBR), severe hypoglycaemia (SH), HbA1c, glycaemic variability, and impaired awareness of hypoglycaemia with RT-CGM (intervention group) in comparison with FGM.
***Results***: We randomly assigned 37 participants to either the intervention group ($n$ = 19) or the control group ($n$ = 18). At 8 weeks, we did not find a decrease in TBR in either group, but there was a significant reduction in SH in the intervention group. For participants with TBR $\geq$ 5% at baseline, we observed significant reductions in 24-h TBR, wake TBR, sleep TBR, and glucose variability at 8 weeks in the intervention group.
***Conclusions***: The use of RT-CGM versus FGM decreased SH in young individuals with type 1 diabetes, and TBR and glucose variability in patients with a higher TBR at baseline. The patient's history should be taken into account when advising on the method of blood glucose monitoring, as RT-CGM could be more effective in younger patients at high risk for SH.
***Trial registration***: ClinicalTrials.gov NCT04249102.

**Keywords:** Children; Continuous glucose monitoring; Flash glucose monitoring; Hypoglycaemia; Type 1 diabetes

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**Key Summary Points**

**Why carry out this study?**

In adults, real-time continuous glucose monitoring more effectively reduced impaired awareness of hypoglycaemia compared to flash glucose monitoring.

However, the added value of the low-glucose threshold alarm for hypoglycaemia prevention has not been clearly demonstrated in children and adolescents with type 1 diabetes who are already using flash glucose monitoring.

**What was learnt from this study?**

We showed that the use of real-time continuous glucose monitoring versus flash glucose monitoring reduces episodes of severe hypoglycaemia and time below range in young individuals with type 1 diabetes, especially in patients at higher risk for hypoglycaemia at baseline.

Continuous glucose monitoring with an alarm may therefore help to improve management of the risk of hypoglycaemia in young patients with type 1 diabetes, but selecting the right patient is very important, particularly given the higher cost of using real-time continuous glucose monitoring and the high discontinuation rate of this technology among young individuals with type 1 diabetes.

## INTRODUCTION

Hypoglycaemia remains a global issue and is underestimated in patients with type 1 diabetes (T1D). The reported incidence rate of severe hypoglycaemia (SH)—that is, hypoglycaemia associated with severe cognitive impairment (including coma and convulsions) which requires help from another person—is around 10 per 100 patient-years [1, 2]. Moreover, the patient's or their family's fear of experiencing SH is a serious barrier to achieving therapeutic goals [3–5].

The first-generation factory-calibrated flash glucose monitoring (FGM) system (FreeStyle Libre, Abbott Diabetes Care, Alameda, CA, USA) provides glucose values at any time when the patient scans the sensor. This technology has been fully covered by the Belgian public health insurance for patients with T1D since 2016, and FGM has been used since then by almost 80% of children and adolescents with T1D [6]. In a previous retrospective study, we demonstrated that the use of FGM significantly decreased the risk of SH in our paediatric population [7]. These results are more remarkable because the first-generation FGM system—unlike the real-time continuous glucose monitoring (RT-CGM) system—does not provide the option to activate glucose threshold alarms, which are useful because a significant number of young people with T1D have impaired awareness of hypoglycaemia (IAH) [8]. By providing real-time glucose data and low threshold alarms, RT-CGM could thus be beneficial for warning patients about a hypoglycaemic event before the development of clinical signs of neuroglycopenia and cognitive impairment. An international consensus recommends the time below range (i.e. 70 mg/dl) as a CGM metric [9]. This level gives patients enough time to react before experiencing the neuroglycopenic symptoms that commonly occur at or less than 54 mg/dl [3]. However, the added value of the low-glucose threshold alarm for preventing hypoglycaemia has not been clearly demonstrated for children and adolescents with T1D who are already using FGM.

The aim of this study was to compare the clinical advantages of RT-CGM in providing low-threshold alarms to FGM without glucose alarms for hypoglycaemia in children and adolescents with T1D mostly treated with a regimen of two daily insulin injections.

# METHODS

## Study Design

GluMoCAY was an 8-week-long, double-arm, parallel-group, non-masked randomized controlled trial comparing RT-CGM (intervention group) with FGM (control group) (Fig. 1), which was conducted at the Diabetology Clinic at the Hôpital Universitaire des Enfants Reine Fabiola (Brussels, Belgium). This trial has been registered at ClinicalTrials.gov (number NCT04249102).

The inclusion criteria were as follows: (1) patients diagnosed with type 1 diabetes before 16 years of age; (2) duration of diabetes of more than 1 year; (3) patients without mental disability; (4) patients aged 4–20 years; and (5) patients had been using FGM for more than 6 months. Participants were excluded if they had ever used RT-CGM before the study or were already included in another study.

The participants were randomly allocated to the RT-CGM (intervention) or FMG (control) groups in a 1:1 ratio (Fig. 1) and were stratified by their IAH status (gold score $< 3$ [IAH not present] vs $\geq 3$ [IAH present]) using an online randomization tool. All participants entered a 7-day run-in phase during which they wore a blinded CGM sensor (Envision$^{TM}$ pro CGM system, Medtronic, Northridge, CA, USA) to record baseline glucose data. Then, according to their allocation, the participants were asked to continue with the FGM (control group) to manage their diabetes or were provided with an RT-CGM system (Guardian$^{TM}$ Connect, Medtronic, Northridge, CA, USA; intervention group) for 8 weeks. These patients and their families were trained by dedicated diabetes educators in the usage of the RT-CGM system and the calibration and interpretation of the data. A hypoglycaemia alert was activated at a threshold of 70 mg/dl, and calibration was requested at least twice daily for all participants in the RT-CGM group. The choice to set a high-glucose alert was left to the participants and/or their parents, if applicable. One week after randomization, all participants were contacted by a diabetes educator by telephone to reassess either their RT-CGM (intervention group) or FGM (control group) usage. For both groups, the insulin dosage was chosen by the participants and/or their parents according to the received education. During the final week (week 8) of the intervention phase, patients wore the blinded CGM sensor (Envision) again to record glucose data. At the end of the study, patients were asked to either return to FGM or use RT-CGM. Face-to-face study visits were planned at baseline (including the placement of the first blinded CGM sensor), at the start of week 8 (placement of the second blinded CGM sensor), and after week 8 (end of the study).

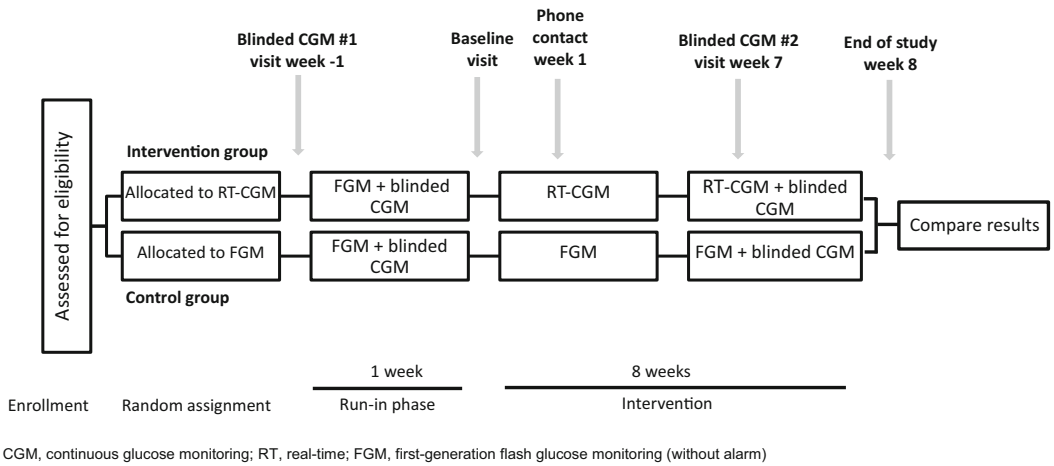


**Fig. 1** Study design

The primary aim was to assess the impact of RT-CGM on time below range (TBR), defined as sensor glucose of below 70 mg/dl. Pre-specified secondary outcomes were the impact of RT-CGM on SH, time spent below 54 mg/dl, time spent in the target range (TIR, 70–180 mg/dl), time spent above the target range (> 180 mg/dl and > 250 mg/dl), HbA1c, glycaemic variability (measured by the coefficient of variation, CV), IAH, and quality of life (QoL) [9]. Targets for the assessment of glycaemic control in T1D included TIR > 70% and TBR < 4% [10]. A certain proportion of the population did not meet these targets. Therefore, we wanted to analyse outcomes in a subgroup at high risk for hypoglycaemia; that is, with a TBR ≥ 5% at baseline. All outcomes were evaluated during the last week of the intervention (week 8).

## Study Population

Patients were treated with two daily insulin injections of an individualized mixture of rapid- and intermediate-acting insulins also called the Freemix Plus regimen, multiple daily injections (MDI), or pump (CSII). Patients were trained to perform flexible insulin therapy based on predetermined actions in response to glucose monitoring [11]. All patients were educated in the management of hypoglycaemia (oral resugaring either in the case of a low-glucose alarm in the intervention group or following a glucose measurement of < 70 mg/dl). Glucagon was prescribed, and parents were instructed about its appropriate use.

## Data Collection

Data on the patient's medical history, clinical data, and glucose profiles were collected, according to the case report form, at baseline and at the end of the intervention period. As young children require assistance to correct even mild hypoglycaemia, SH was defined for the purpose of this study as a hypoglycaemic event leading to the loss of consciousness [12]. SH and adverse events were assessed by reviewing the patient's logbook and were adjudicated by an endocrinologist. Moreover, patients and their parents were asked whether they experienced hypoglycaemic events that resulted in unconsciousness. If yes, they were asked how many episodes of SH they had experienced during the last 2 months.

Blinded CGM glucose data were uploaded using proprietary software (Medtronic Carelink®). As recommended, TBR was reported in three time blocks (sleep, wake, 24 h) [9]. For this study in a paediatric population, the default times for sleep (12:00 a.m. to 6:00 a.m.) and wake (6:00 a.m. to 12:00 a.m.) were adapted to 10:00 p.m. to 7:00 a.m. and 7:00 a.m. to 10:00 p.m., respectively.

Blood samples were collected without fasting. At baseline and at 8 weeks, HbA1c was measured by ion exchange, high-performance liquid chromatography (normal value < 6.0% or 42 mmol/mol), and glucagon by radioimmunoassay. C peptide was measured at baseline using electrochemiluminescence. A random C peptide level higher than 0.050 nmol/l in conjunction with glycaemia above 150 mg/dl was considered positive.

IAH was ascertained using the gold method (see the supplementary figure) [13–16]. Participants with scores < 3 were categorized as having normal hypoglycaemic awareness (NAH) [16]. Its noteworthy that the Clarke method is superior at identifying participants at risk of clinically significant hypoglycaemia, whereas the Gold method, which is easier to use in the clinical routine, is better at identifying those at risk of experiencing milder asymptomatic hypoglycaemia episodes, including those occurring during sleep [16].

QoL was determined using the three-level version of the EuroQol instrument, validated in children [17]. The parental questionnaire at baseline concerned the parent's fear of hypoglycaemia, which consisted of 25 items to measure parental concerns (15 items) and behaviours used to avoid hypoglycaemia (10 items) [18].

## Ethics

The study was performed according to the protocols approved by our institution. Approval

was received from the Ethics Committee of Erasme Hospital (references P2019/539/B406201942101). This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. Prior to enrolment in the study, written informed consent was obtained from each participant and their parents when needed.

### Statistical Analysis

Based on a previous study [7], we calculated that a sample size of 35 participants in each group would be sufficient to reach 80% power for the primary endpoint, considering a difference of 5% in TBR to be clinically significant ($\alpha = 0.05$).

Many variables were not normally distributed, and summary statistics are presented as medians (interquartile range). The outcomes at baseline and at 8 weeks were analysed.

Comparisons within groups were performed using the paired Wilcoxon rank sum test or the McNemar test, and comparisons between groups were performed using either the Wilcoxon–Mann–Whitney test or the $X^2$ test, and the Fisher's exact test. Linear regression analysis was performed to ascertain the effect of the TBR at baseline on the change in TBR at the end of the study. Two-tailed statistical tests were performed using MedCalc® statistical software version 20.023 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2021). Statistical significance was set at $P < 0.05$.

## RESULTS

Due to Medtronic's decision to withdraw the Envision CGM from the market, we could only enrol 38 participants in the study. Thirty-seven patients were randomly assigned to either the intervention group ($n = 19$) or the control group ($n = 18$); one patient cancelled their appointments and was thus excluded from the analyses. Participants diagnosed with IAH were well balanced between the groups (53% in the intervention group vs 56% in the control group, $p$ = NS). All 37 participants completed the intervention period (Fig. 2). The baseline characteristics of the participants are presented in Table 1. There were no significant differences in the baseline characteristics between the groups. The use of RT-CGM in the intervention group was 87% (74–95%) during the study, with a minimum value of 65%.

### Time Below Range

At week 8, TBR did not change significantly in either of the two groups (see the supplementary table). The level of TBR reduction at the end of the study was positively correlated with baseline

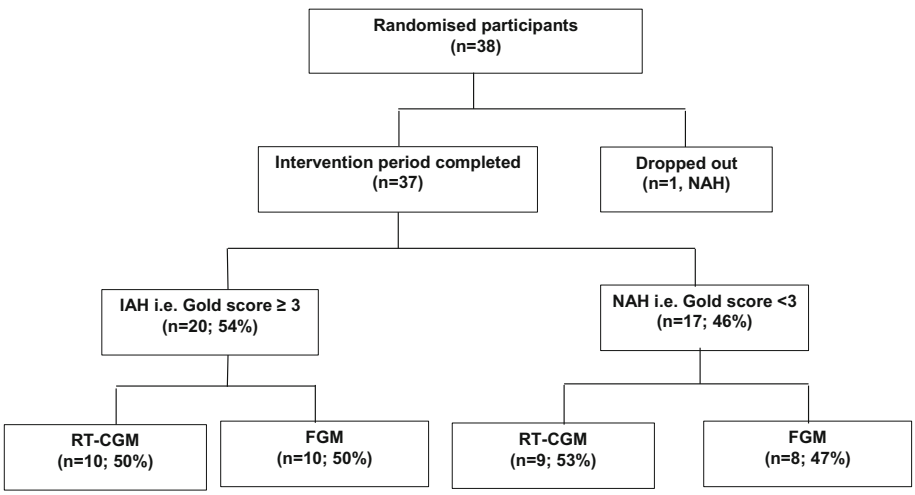


**Fig. 2** Flow diagram of the study

**Table 1** Characteristics of the study population at baseline

| | **All patients *n* = 37** |
|---|---|
| *Clinical characteristics* | |
| RT-CGM/FGM, *n* | 19/18 |
| Age, yrs | 13.8 (11.8–16.4) |
| Male, *n* (%) | 15 (41) |
| Age at diagnosis, yrs | 8.9 (5.8–10.8) |
| Diabetes duration, yrs | 4.4 (2.9–8.5) |
| Insulin daily dose, UI/kg/d | 1.1 (0.8–1.4) |
| Insulin schema, *n* (%) | |
| Freemix | 31 (84) |
| MDI | 4 (11) |
| CSII | 1 (3) |
| Premix | 1 (3) |
| HbA1c, % | 7.8 (7.2–8.4) |
| C peptide negative, *n* (%) | 38 (84) |
| Gold score positivity, *n* (%) | 20 (54) |
| Severe hypoglycaemia, *n* (%) | 8 (22) |
| QoL (children) | 13 (12–14) |
| Mobility | 3 (3–3) |
| Self-care | 3 (2–3) |
| Usual activity | 3 (2–3) |
| Pain/discomfort | 3 (2–3) |
| Anxiety/depression | 3 (2–3) |
| *Glucose metrics** | |
| TBR 24 h, % | 9 (4–12) |
| TBR wake, % | 7 (3–12) |
| TBR sleep, % | 7 (1–11) |
| Time below 54 mg/dl 24 h, % | 3 (1–5) |
| Time below 54 mg/dl wake, % | 2 (0–5) |
| Time below 54 mg/dl sleep, % | 2 (0–3) |
| Time in target range, % | 50 (38–60) |
| Time above 180 mg/dl, % | 43 (27–53) |
| Time above 250 mg/dl, % | 17 (8–26) |
| Coefficient of variation, % | 44 (38–52) |

*From Envision

All values are shown as the median (IQR), excluding gender, insulin schema, C peptide negativity, severe hypoglycaemia, and gold score positivity, which are shown as *n* (%)

*RT-CGM* real-time continuous glucose monitoring, *FGM* flash glucose monitoring, *MDI* multiple daily injections, *CSII* continuous subcutaneous insulin infusion, *TBR* time below range (< 70 mg/dl), *QoL* quality of life

Comparisons between groups (CGM vs FGM)—which were performed using the Wilcoxon–Mann–Whitney test, $X^2$ test, or Fisher's exact test, depending on the subgroup size (gender, insulin schema, C peptide negativity, severe hypoglycaemia, Gold score positivity)—were not significant at baseline

TBR in the intervention group but not in the control group (Fig. 3). Participants with a TBR ≥ 5% at baseline in the intervention group showed aeductions in 24 h, sleep, and wake TBR, along with less time spent below 54 mg/dl and a reduced CV. In contrast, this effect was not observed in the control group (Table 2). In this specific population, the median change in TBR from baseline to endpoint was significantly higher in the intervention group than in the control group [− 6% ( − 8 to − 1%) vs. − 2% (− 4 to 2%); $p = 0.031$].

## Severe Hypoglycaemia

Severe hypoglycaemic episodes were significantly lower at week 8 in the intervention group but not in the control group (supplementary table). In the high-risk subgroup (TBR ≥ 5% at baseline), 67% of the participants who had SH at baseline did not have SH at week 8 in the intervention group. There was no change in HbA1c or IAH status at the end of the study.

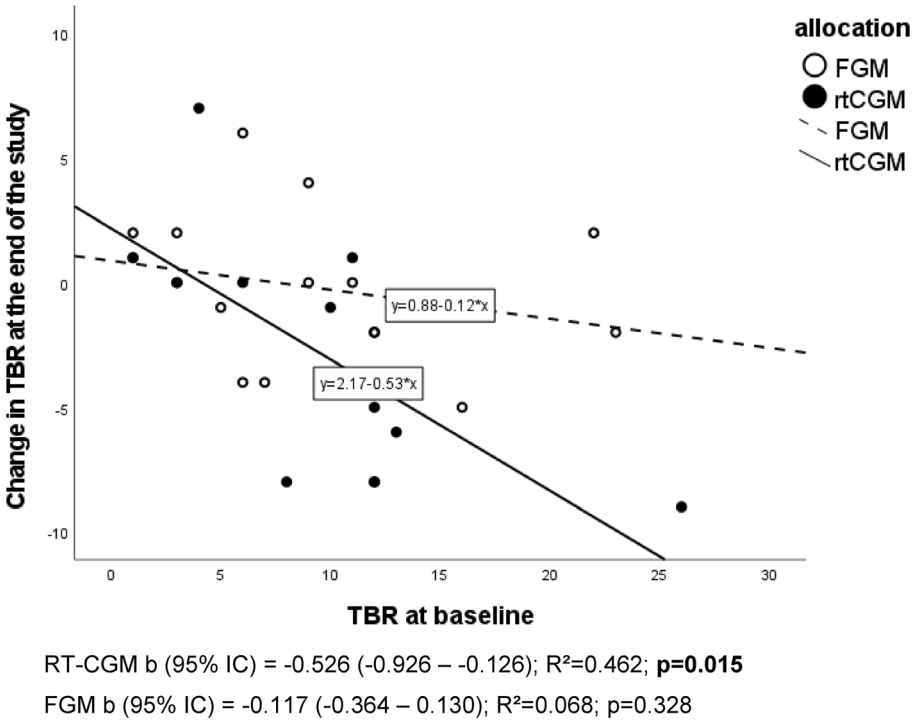


**Fig. 3** Change in time below range (70 mg/dl) depending on the time below range at baseline: intervention (RT-CGM) vs control (FGM)

### Other Secondary Outcomes

We did not find any change in either the QoL scores or the parental fear of hypoglycaemia at the end of the study. There were also no differences between the parents of children with IAH and those of children with NAH. Nevertheless, parents with the highest parental fear scores for hypoglycaemia had younger children [11.7 (8.0–12.8) vs 13.2 (12.0–15.1) years; $p = 0.044$.]

There were more adverse events reported in the intervention group than in the control group (42% vs 11%; $p = 0.034$). The most common adverse events were premature sensor loss (8% vs 11%; $p$ = NS) and system calibration problems (21% in the intervention group). Among the 19 patients in the intervention group, 7 (37%) chose to return to FGM at the end of the study, mainly due to mild adverse events or system requirements (calibration).

## DISCUSSION

We have previously shown that switching from capillary blood sugar controls to FGM decreases SH [7] in children and adolescents with T1D. We show here the superiority of RT-CGM over FGM in terms of protection against SH.

Consistent with the reduction in SH, our trial also showed the benefit of CGM over FGM for improving TBR in a subgroup of patients at higher risk of hypoglycaemia (i.e. with a TBR $\geq$ 5% at baseline). This impact is crucial in younger individuals with a longer life expectancy, as the presence of lifetime SH could be associated with worse cognition among adults with T1D [19, 20].

In this specific population, the use of CGM makes it easier to achieve the optimal objectives [21]. Selecting the right technology for the right patient is important, especially given the higher cost of using CGM and the high rate of CGM

**Table 2** Change during study: CGM versus FGM in TBR ≥ 5

| | **CGM** ***N*** **= 12** | **FGM** ***N*** **= 12** | ***P*** **value** |
|---|---|---|---|
| ΔHbA1c, % | 0.0 (− 0.3 to 0.4) | 0.1 ( − 0.1 to 0.4) | 0.616 |
| ΔGold score | 0 (− 1 to 0) | 0 (− 1 to 2) | 0.802 |
| ΔSevere hypoglycaemia, *n* (%) | 0 (− 1 to 0) | 0 (0 to 0) | 0.676 |
| ΔTBR 24 h*, % | − 6 (− 8 to − 1) | − 2 (− 4 to 2) | **0.031** |
| ΔTBR wake*, % | − 3 (− 7 to − 1) | − 3 (− 6 to − 1) | 0.972 |
| ΔTBR sleep*, % | − 6 ( − 12 to − 1) | 0 (− 5 to 6) | **0.041** |
| ΔTime below 54 mg/dl 24 h*, % | − 3 (− 5 to 0) | − 1 (− 1 to 2) | 0.066 |
| ΔTime below 54 mg/dl wake*, % | − 2 (− 5 to − 1) | − 3 (− 6 to − 1) | 0.917 |
| ΔTime below 54 mg/dl sleep*, % | − 3 (− 6 to 2) | 0 (− 2 to 7) | 0.107 |
| ΔTime in target range*, % | − 1 (− 9 to 5) | − 1 (− 10 to 10) | 0.821 |
| ΔCoefficient of variation*, % | − 10 (− 18 to 0) | − 1 (− 4 to 3) | **0.043** |
| ΔLow blood glucose index* | − 1 (− 2 to 0) | 0 (− 1 to 0) | **0.043** |

*From Envision

All values are shown as the median (IQR), excluding severe hypoglycaemia and Gold score positivity, which are shown as *n* (%)

Δ indicates the change between baseline and the end of the study; *CGM* continuous glucose monitoring, *FGM* flash glucose monitoring, *TBR* time below range (< 70 mg/dl)

Comparisons between groups were performed using the Wilcoxon–Mann–Whitney test, $X^2$ test, or Fisher's exact test, depending on the subgroup size

discontinuation among unselected young people with T1D [22].

Most of our participants were on the Freemix twice a day insulin regimen, which is easy to use by the patient and their parents and gives good results in paediatrics [11]. The Freemix regimen is usually considered a conventional non-intensive treatment. However, the use of analogue injections makes this treatment more intensive and flexible. Since in Belgium it is not possible to have a nurse intervene to perform the injections (or boluses), and there is no legal framework for teachers, our school-age patients are regularly put on the Freemix regimen, which allows good results without systematic intervention during school hours. Later, as the child becomes autonomous, the treatment evolves towards MDI or CSII. This approach has already been recognized internationally [23]. On the other hand, with a Freemix regimen, insulin dose adjustments are less straightforward than with MDI or CSII. Interestingly, we were able to demonstrate a decrease in SH and in the risk of hypoglycaemia in this population despite the relative barrier of Freemix to insulin adjustment. We interpret this as a direct benefit of the CGM hypoglycaemic threshold alarm.

More adverse events were reported with CGM than with FGM, resulting in one-third of the patients discontinuing this method at the end of the study. As already shown, the need for timely calibration is considered the main drawback of CGM [24].

The strength of this trial is that it is, to our knowledge, the first randomized study to compare CGM and FGM use in a paediatric population. In addition, we used a standard reference methodology (blinded CGM) to compare

glucose-related metrics in both groups. The fact that the two groups were well balanced in terms of IAH status is another strength of this study. In addition, this study investigated the effect of CGM on patients treated with a twice-daily Freemix insulin injection regimen, whereas most CGM studies have been conducted on insulin pump users [25, 26]. In our population, we could not demonstrate any difference in TBR or insulin requirements during follow-up depending on the insulin regimen used by the patient.

The main limitation of our study was the small number of participants. Indeed, because of Medtronic's decision to withdraw the Envision CGM from the market, we were not able to recruit the expected number of patients to be able to demonstrate an overall improvement in TBR. Nevertheless, as it will be increasingly difficult to recruit young patients to participate in trials using CGM without alarms in the future, given the worldwide replacement of the FreeStyle Libre 1 by the FreeStyle Libre 2 and other calibration-free RT-CGMs, the significant secondary outcomes we obtained here, especially in the subgroup of patients at high hypoglycaemic risk, are worth considering in clinical practice.

Another limitation of our study was the large proportion of patients treated with the Freemix Plus regimen, which may preclude the extrapolation of our results to patients treated with other insulin regimens such as CSII or MDI.

## CONCLUSION

The use of RT-CGM versus FGM decreased SH in young individuals with type 1 diabetes and TBR and glucose variability in patients with a higher TBR at baseline. The patient's history should be taken into account when advising on the method of blood glucose monitoring, as RT-CGM could be more effective in younger patients at high risk for SH and given the higher cost of using RT-CGM and the high discontinuation rate of this technology among young individuals with type 1 diabetes.

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***Authorship.*** All authors (1) made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data; or the creation of new software used in the work; (2) drafted the work or revised it critically for important intellectual content; (3) approved the version to be published; and (4) agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy of integrity of any part of the work are appropriately investigated and resolved.

***Author Contributions.*** Anissa Messaaoui designed the study, collected the data, undertook analysis, interpreted results, wrote the manuscript, reviewed and edited the manuscript, and takes full responsibility for the integrity of the data and the accuracy of data analysis. Sylvie Tenoutasse and Lucia Hajselova reviewed the manuscript. Laurent Crenier designed the study, undertook analysis, interpreted results, wrote the manuscript, and reviewed and edited the manuscript. All authors read and approved the final manuscript.

***Disclosures.*** Anissa Messaaoui, Sylvie Tenoutasse, and Lucia Hajselova have nothing to disclose. Laurent Crenier serves or has served on the advisory panel for Medtronic and Abbott Laboratories. Financial compensations for these activities have been received by Hôpital Erasme, Brussels.

***Compliance with Ethics Guidelines.*** The authors state that they have received approval from the Ethics Committee of Erasme Hospital (references P2019/539/B406201942101). This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. All subjects provided informed consent to participate in the study.

***Data Availability.*** The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.



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