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The use of flash glucose monitoring significantly improves glycemic control in type 2 diabetes managed with basal bolus insulin therapy compared to self-monitoring of blood glucose: A prospective observational cohort study

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ABSTRACT

Aim: This prospective, observational cohort study aimed to measure HbA1c change over 3–6 months in type 2 diabetes managed with basal-bolus insulin and FreeStyle Libre® Flash Glucose Monitoring System (FSL) use compared to self-monitored blood glucose (SMBG).
Methods: Sixteen Italian hospitals enrolled patients with type 2 diabetes (n = 322, [109 FSL, 213 SMBG users]) using basal-bolus insulin therapy for ≥ 1 year, HbA1c 8.0–12.0% (64–108 mmol/mol), new to FSL use (<3 months) or continuing with SMBG (controls). Eligible FSL and SMBG users were matched (1:2 ratio) for baseline HbA1c (within ± 0.5%, recorded ≤ 3 months previously), study site and baseline data collection date.
Results: Overall, baseline HbA1c was 8.9 ± 0.8% (74 ± 9 mmol/mol), age 67.2 ± 10.0 years, BMI 30.5 ± 6.5 kg/m^2 and insulin use duration 8.6 ± 6.6 years (mean ± SD), 56.2% were males. After 3–6 months, 234 complete cases (83 FSL, 151 SMBG users) demonstrated significantly reduced HbA1c for FSL use compared to SMBG (0.3% ± 0.12 [3 mmol/mol ± 1.3, (mean ± SE)], p = 0.0112). The difference remained statistically significant after adjusting for confounders.
Conclusions: HbA1c significantly improved in basal-bolus treated type 2 diabetes after flash glucose monitoring use for 3–6 months compared to SMBG.

Abbreviations: CGM, Continuous glucose monitoring; FCS, Fully conditional specification; FSL, FreeStyle Libre flash glucose monitroing system; HbA1c, Glycated haemoglobin; MAR, Missing at random; SMBG, Self-monitored blood glucose

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1. Introduction

The use of continuous glucose monitoring (CGM) in individuals with diabetes is increasing globally along with evidence showing the benefit of its use in type 2 diabetes. International and Italian consensus statements recommend continuous glucose monitoring use for individuals with type 2 diabetes treated with basal-bolus insulin therapy [1,2]. However, there is still limited data reported by European clinical trials to support the use of CGM technology in type 2 diabetes treated with basal-bolus insulin therapy [3,4]. The aim of this prospective, observational cohort study was to evaluate glycated haemoglobin (HbA1c) change in this population after the initiation of flash glucose monitoring in a real-world setting compared to self-monitoring of blood glucose (SMBG).

2. Subjects

This prospective observational cohort study was conducted in 16 hospital diabetes centers in Italy. Each site created a list of current or potential FreeStyle Libre® Flash Glucose Monitoring System ([FSL], Abbott, Diabetes Care, Witney UK) users by evaluating all medical records from the previous three months. Study inclusion criteria were medical records for individuals age 18 years or over who had type 2 diabetes treated with basal-bolus insulin therapy for at least one year, had been using flash glucose monitoring for less than three months or were planning to start using the device within the next 30 days, and the most recently recorded HbA1c value (in the last 3 months, before baseline data collection) was between 8.0% and 12.0% (64 to 108 mmol/mol). Medical records were not included in the study for individuals who were pregnant or planning pregnancy, receiving or planning dialysis treatment, participating in another study that could affect glucose measurements or management, currently prescribed or requiring steroid therapy, had any disease or condition that made it inappropriate or unsafe to have an HbA1c goal of <7% (53 mmol/mol), or FSL had been used for longer than three months or any other continuous glucose monitoring system had been used in the last three months. Following the enrolment of a FSL user, the study site then searched and matched them to two SMBG using patients (within the site), if available. In addition to age 18 years or over with type 2 diabetes treated with basal-bolus insulin therapy for 1 year or more, the control group inclusion criterion was current use of self-monitoring of blood glucose (SMBG). Patients were matched for baseline HbA1c (within ± 0.5% and recorded in the previous three months or less), study site and the date of baseline data collection (the record date). Medical records for SMBG users in the control group were not included in the study if the patient was currently (at the time of enrolment into the study) using, or had used within the previous four months, any CGM or FSL device.

3. Materials and methods

For both FSL and SMBG users, the study sites extracted information from the medical records which had been entered prior to the record date (the date of baseline data collection). This included: age, concomitant disease, duration of insulin use, glucose lowering medications, insulin therapy regimen, sex, and up to three HbA1c results measured within the three months prior to the record date. If more than one HbA1c test result was available, the average HbA1c result was used. The sites also extracted information from all the medical records three to six months (between days 90 to 194) after the record date for: insulin therapy regimen, non-insulin glucose lowering medications (initiation or cessation), resource use (such as an emergency department visit, ambulance call out, or hospital stay), the start date of flash glucose monitoring (for the FSL user group only), and up to three HbA1c results. The follow up HbA1c level was defined as being measured between three to six months (90 and 194 days) following the record date. If more than one follow-up HbA1c test result was available, the measurement taken closest to 135 days after the record date was used. All HbA1c results used in the analysis were extracted from the medical records. The analysis compared baseline HbA1c data to follow up HbA1c data at three to six months (90–194 days).

The chosen method of glucose monitoring (FSL or SMBG) was a clinical decision that was made independently from this study. The FSL systems used were prescribed and reimbursed by the national health system in Italy.

The Italian National Pharma Agency (AIFA, Agenzia Italiana del Farmaco) was informed of the study and the study was given ethics approval at each study site. All individuals gave their written informed consent for the study.

3.1. *Outcomes*

The primary outcome was evaluation of HbA1c change in individuals with type 2 diabetes managed with basal-bolus insulin therapy three to six months after initiation of flash glucose monitoring, compared to the control group using SMBG. Secondary outcomes included changes in insulin, glucose lowering medications and resource use. There were no safety endpoints, including hypoglycaemia.

3.2. *Statistical analysis*

Priori sample size was calculated based on results from a previous study [3]. With assumed population standard deviation of 1.0 and correlation coefficient 0.46 between baseline and final HbA1c, to detect a difference of 0.35% (3.8 mmol/mol) in HbA1c between the cohort means at the 5% level, 228 individuals (76 FreeStyle Libre users and 152 SMBG users) were required with 80% power.

Difference in HbA1c between groups was assessed using analysis of covariance (ANCOVA). We reported results from two models: "basic model" and "adjusted model". The basic model included baseline HbA1c and study site as covariates. Additional confounders (age, sex, BMI, duration of insulin) and their two-way interactions were considered for selection in an adjusted model. Backward selection method was used to select the optimal, parsimonious adjusted model.

To improve power and accuracy, missing final HbA1c values were imputed using multiple imputation (using fully conditional specification (FCS) method), under the missing at random (MAR) assumption [5]. Baseline HbA1c, group, age, sex, BMI and site were included in imputation models. 100 imputed datasets were created and parameters of interest combined using Rubin's rules [6]. Similar methods were used for the sensitivity analysis of change in HbA1c for different time windows of the baseline and final HbA1c. Data were analysed using SAS software version 9.4.

4. Results

All eligible medical records identified by the 16 study sites were included in the study (Fig. 1). The record date was between March 2019 and January 2020. Use of FSL commenced between February 2019 and December 2019. The total number (N = 332) included 114 in the FSL user group and 218 in the SMBG user (control) group. Of these, ten did not meet the inclusion criteria (n = 5 FSL users and n = 5 SMBG users) and a further 88 (26 FSL and 62 SMBG) were either lost to follow up or could not be included in the analysis (Fig. 1). Medical records which met all the inclusion criteria and had follow-up HbA1c recorded (complete cases, N = 234) were 83 for the FSL group and 151 for the SMBG group. Baseline demographics and baseline characteristics from all the medical records are shown in Table 1. Baseline HbA1c was 8.9% ± 0.8 (74 mmol/mol ± 9) and 8.9% ± 0.8 (74 ± 9) in the FSL and SMBG groups, respectively. Final HbA1c was 8.2% ± 1.0 (66 mmol/mol ± 11) and 8.5% ± 1.0 (69 ± 11) in the FSL and SMBG groups, respectively. In the complete case analysis with the basic model, the reduction in HbA1c for the FSL group was 0.8% ± 0.11 (8 mmol/mol ± 1.2, [adjusted mean ± SE]) compared to 0.5% ± 0.09 (5 mmol/mol ± 1.0) in the SMBG control group, an adjusted difference of −0.3% ± 0.12 (−3 mmol/mol ± 1.3, [mean ± SE], p = 0.0112) (Fig. 2 and Table 2). In the analysis including all eligible records with the basic model, the difference in HbA1c change between the two groups was −0.3% ± 0.12 (3 mmol/mol ± 1.3, [mean ± SE], p = 0.0197, Table 2).

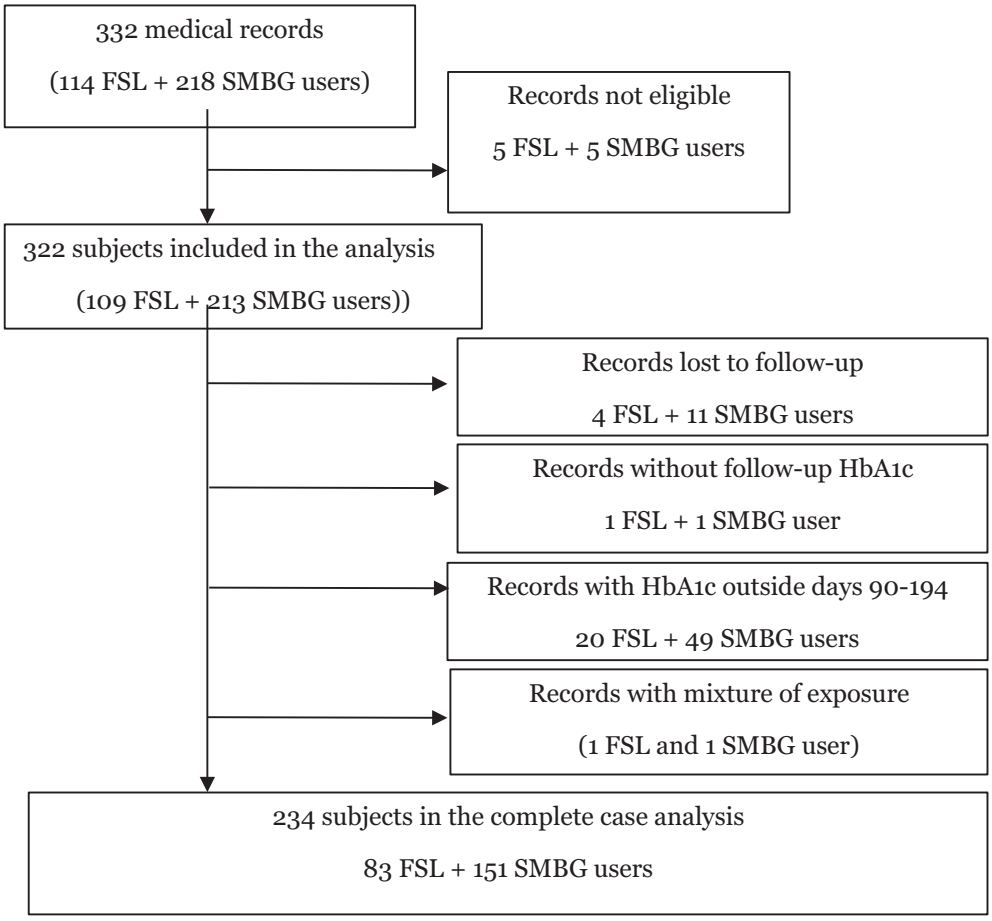

Fig. 1 – Study flow.

Table 1 – Demographics and baseline characteristics.

		FSL users (N = 109)	SMBG users (N = 213)	All (N = 322)
Age (years)	Mean ± SD	66.3 ± 10.5	67.7 ± 9.7	67.2 ± 10.0
BMI (kg/m^2)	Mean ± SD	30.0 ± 7.1	30.7 ± 6.1	30.5 ± 6.5
Duration of insulin use (years)	Mean ± SD	8.9 ± 7.1	8.4 ± 6.4	8.6 ± 6.6
	Median [min, max]	8.0 [1, 39]	7.0 [1, 35]	7.0 [1, 39]
Baseline HbA_{1c} (%)	Mean ± SD	8.9 ± 0.8	8.9 ± 0.8	8.9 ± 0.8
Baseline HbA_{1c} (mmol/mol)	Mean ± SD	74 ± 9	74 ± 9	74 ± 9
Sex at Birth	Male	60 (55.0%)	121 (56.8%)	181 (56.2%)
	Female	49 (45.0%)	92 (43.2%)	141 (43.8%)
BMI	<18.5 kg/m^2	0 (0.0%)	3 (1.4%)	3 (0.9%)
	18.5 – 24.9 kg/m^2	22 (20.2%)	31 (14.6%)	53 (16.5%)
	25.0 –29.9 kg/m^2	44 (40.4%)	69 (32.4%)	113 (35.1%)
	30.0 – 34.9 kg/m^2	26 (23.9%)	64 (30.0%)	90 (28.0%)
	35.0 – 39.9 kg/m^2	13 (11.9%)	27 (12.7%)	40 (12.4%)
	≥40.0 kg/m^2	4 (3.7%)	19 (8.9%)	23 / 322 (7.1%)
Non-insulin glucose lowering medications at baseline	Metformin	41 (37.6%)	75 (35.2%)	116 (36.0%)
	SGLT-inhibitors	20 (18.3%)	32 (15.0%)	52(16.1%)
	DPP4 Inhibitors	1 (0.9%)	0 (0.0%)	1 (0.3%)
	Sulphonylureas	0 (0.0%)	2 (0.9%)	2 (0.6%)
	TZD's	0 (0.0%)	2 (0.9%)	2 (0.6%)
	Other (Acarbose)	1 (0.9%)	1 (0.5%)	2 (0.6%)
	Any oral diabetes medication	48(44.0%)	91(42.7%)	139(43.2%)
	GLP1- agonists	0 (0.0%)	3 (1.4%)	3 (0.9%)

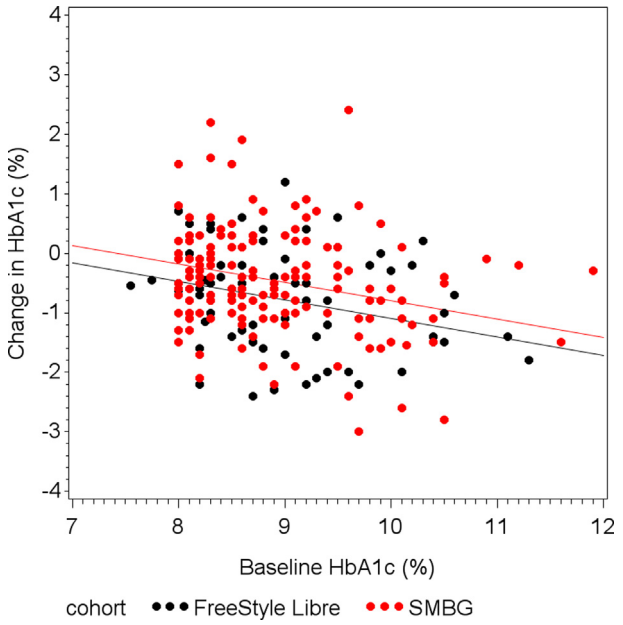

Fig. 2 – Change in HbA1c (%) between baseline and at three to six months (90 to 194 days) after record date (complete cases).

The difference in HbA1c remained statistically significant after adjusting for the confounders (Table 2).

4.1. *Sensitivity analysis*

The sensitivity analysis performed on the primary endpoint of change in HbA1c for different time windows of the final HbA1c value showed that the HbA1c improvement remained consistent. HbA1c change remained significant when different definitions of the baseline HbA1c window were used (Fig. 3 and Tables S1-S4, Supplementary Information).

4.2. *Secondary outcomes*

The total daily dose of insulin units was similar for the FSL (n = 105) and SMBG (n = 202) groups at baseline (58.8 ± 24.0 and 60.8 ± 35.2, respectively, [mean insulin units ± SD]) and at follow up (58.0 ± 26.6 and 60.3 ± 35.9, respectively) with no difference in the change between the two groups (p = 0.7108). The total daily doses of basal and bolus insulin were also similar between the two groups at baseline (26.1 ± 12.4 and 27.2 ± 15.6 [basal], respectively, and 32.6 ± 16.5 and 33.1 ± 21.4 [bolus], respectively) and at follow up (26.4 ± 13.5 and 27.4 ± 15.9 [basal], respectively, p = 0.7999 and 31.6 ± 17.4 and 32.5 ± 21.9 [bolus], respectively, p = 0.7393). Detailed information can be found in Table S5, Supplementary Information.

The use of non-insulin glucose lowering medications was also similar at baseline between the two groups (Table 1) and there was no difference observed between the FSL and SMBG groups for changes (initiation or cessation) in these medications at the end of the study, (Tables S6 and S7, Supplementary Information). The number of emergency department visits, hospital admissions and paramedic callouts were low in each group. There were no emergency department visits or hospital admissions for hypoglycaemia. The mean number of paramedic callouts for hypoglycaemia were 0.03 (3 callouts in 105 patients) in the FSL group and 0.03 (7 in 202) in the control group. There were no other call outs in the FSL group.

Post hoc analysis in the current study found HbA1c improvement was observed in the FSL group versus the control group for BMI $\geq$ 30 kg/m^2 (p = 0.0418) and there was no difference between the groups for BMI < 30 kg/m^2 (p = 0.0717, Table S8, Supplementary Information).

5. Discussion

This prospective, observational cohort study from Italy demonstrated significant HbA1c improvement in type 2 diabetes treated with basal-bolus insulin therapy after commencing flash glucose monitoring use compared to the control group who continued with SMBG. The observed primary outcome of HbA1c reduction with FSL use compared to SMBG, is validated by the sensitivity analyses which rebuts speculation that this difference may be due to sensor use before the baseline of the current study.

Our findings, based on a prospective observational study, show a beneficial effect of glucose monitoring technology on glucose control of type 2 diabetes and intensive insulin treatment. Similar results were obtained in some [7,8], but not all randomised controlled trials [3], and are comparable to a recently reported retrospective observational study including type 1 and insulin treated type 2 diabetes [9]. On the same line of evidence is the report of a retrospective European chart review study [4]. In addition, a baseline HbA1c value more than > 8.5% (69 mmol/mol) can be a predictor for significant HbA1c reduction with FSL use and meta-analyses in the effectiveness of flash glucose monitoring use in type 2 diabetes to improve HbA1c support the observed HbA1c improvement in the FSL user group [10–12].

Explanations for the significant change of HbA1c in the present study are uncertain, as there was no difference in daily insulin doses or other glucose lowering medication between the two groups. However, insulin titration may have occurred without impacting upon overall total daily doses of insulin [3,8]. Previously unseen glucose information and a large number of glucose values from the FSL system were available to both the user and their healthcare team. Most likely, the observed HbA1c improvement was due to a combination of lifestyle behaviour change, such as improved food choices, portion control and prevention of out of range glucose levels, regardless of any insulin dose adjustments. Additional life style change due to the COVID-19 pandemic, in particular the reduction of physical activity and the increased stress linked to the outbreak, might have limited a further reduction in HbA1c at the end of the study considering the high baseline HbA1c [13]. Italy was the first European country to be severely impacted by the COVID-19 outbreak and went into lockdown from March to May 2020, which was during the study period. The change in HbA1c observed in the con-

Table 2 – Change in HbA1c (%) at study end.

		Complete Case*			All Patients (Imputed)		
		FreeStyle Libre (N = 83)	SMBG (N = 151)	Difference	FreeStyle Libre (N = 109)	SMBG (N = 213)	Difference
n		83	151		109	213	
HbA1c (%)							
Baseline (Day 1)							
	Mean (SD)	8.9 (0.8)	8.9 (0.8)		8.9 (0.8)	8.9 (0.8)	
Final (Day 194)							
	Mean (SD)	8.2 (1.0)	8.5 (1.0)		8.2 (1.0)	8.5 (1.1)	
Change from Baseline							
	Mean (SD)	−0.7(0.8)	−0.5(0.9)		−0.7 (0.9)	−0.4 (0.9)	
Basic Model†	Adjusted mean (SE)	−0.8 (0.11)	−0.5 (0.09)	−0.3 (0.12)	−0.7 (0.11)	−0.5 (0.09)	−0.3 (0.12)
	95% CI for adjusted mean	−1.0, −0.5	−0.6, −0.3	−0.5, −0.1	−0.9, −0.5	−0.6, −0.3	−0.5, −0.0
	p-value vs. Control (*)			0.0112			0.0197
Adjusted model ‡	Adjusted mean (SE)	−0.7 (0.11)	−0.4 (0.09)	−0.3 (0.12)	−0.7 (0.11)	−0.4 (0.10)	−0.3 (0.12)
	95% CI for adjusted mean	−0.9, −0.5	−0.6, −0.3	−0.5, −0.0	−0.9, −0.5	−0.6, −0.2	−0.5, −0.0
	p-value vs. Control (*)			0.0270			0.0237
HbA1c (mmol/mol)							
Baseline (Day 1)							
	Mean (SD)	74 (9)	74 (9)		74 (9)	74 (9)	
Final (Day 194)							
	Mean (SD)	66 (11)	69 (11)		66 (11)	69 (12)	
Change from Baseline							
	Mean (SD)	−7 (9)	−5 (10)		−8 (10)	−5 (10)	
Basic Model †	Adjusted mean (SE)	−8 (1.2)	−5 (1.0)	−3 (1.3)	−8 (1.2)	−5 (1.0)	−3 (1.3)
	95% CI for adjusted mean	−11, −6	−7, −3	−6, −1	−10, −6	−7, −3	−6, −1
	p-value vs. Control (*)			0.0112			0.0197
Adjusted model ‡	Adjusted mean (SE)	−8 (1.2)	−5 (1.0)	−3 (1.3)	−8 (1.2)	−5 (1.1)	−3 (1.3)
	95% CI for adjusted mean	−10, −5	−7, −3	−5, −0	−10, −5	−7, −2	−6, −0
	p-value vs. Control (*)			0.0270			0.0237

*26 FSL group and 62 SMBG group records were missing HbA1c values in days 90–194.

† Adjusted for baseline HbA1c and site only.

‡ Adjusted for baseline HbA1c, site, age, Duration of insulin use, sex, BMI and two-way interactions between baseline HbA1c and group, age and BMI, site and sex, duration of insulin use and sex.

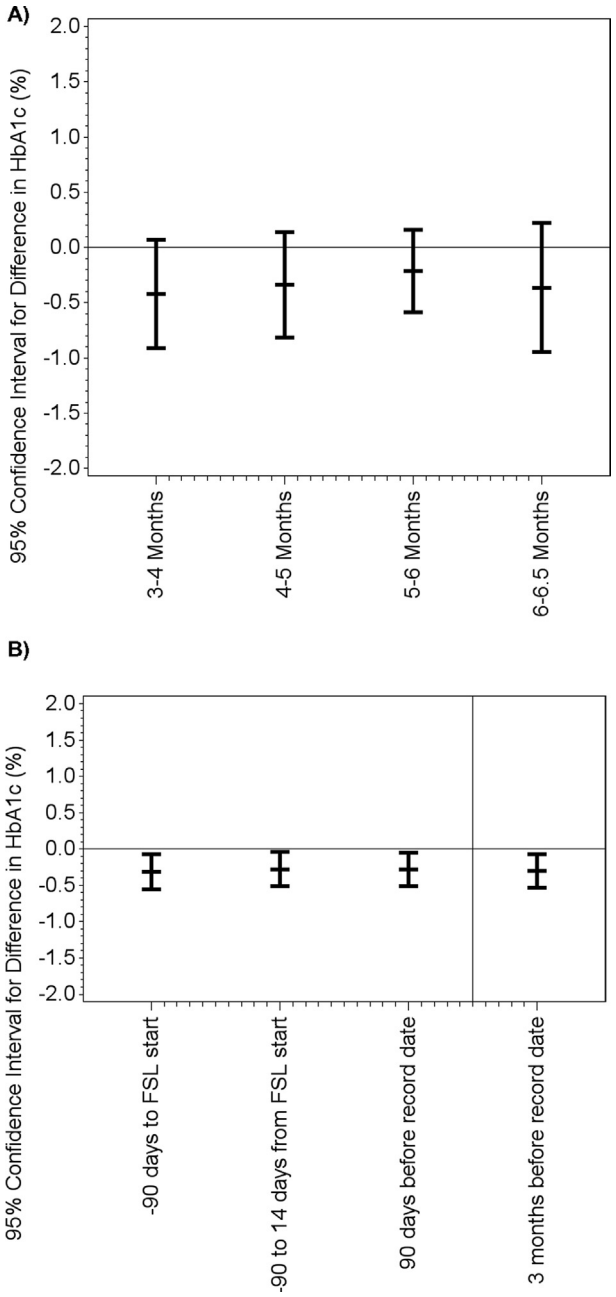

Fig. 3 – Change in HbA1c (%) for each month of the three to six months after record date (A) and for different baseline time windows (B).

trol group in the current study is supported by the findings of Beck et al (2017) [7] for real time CGM and Yaron et al (2019) [8].

To date, it has been acknowledged that improvement in type 2 diabetes with coexisting obesity managed with basal bolus insulin therapy is challenging. The HbA1c improvement observed in the FSL group versus the control group for BMI $\geq$ 30 kg/m^2 supports findings from retrospective studies in a similar population utilising FSL [4,14].

There was a large number of follow up HbA1c measurements taken outside the pre-specified time period. This was due to the fact that the current study was being conducted during the 2020 COVID-19 lockdown period for the pandemic, possibly resulting in delayed collection of routine HbA1c test samples at clinics. Hospitals in Italy, and all over Europe, experienced unprecedented admissions and an increased care load due to the COVID-19 outbreak and users may have avoided contact with these clinical settings [15]. Interestingly, the results from the whole population of users were substantially superimposable to that of the completed cases.

Similarly, to reported data from other European countries, the current cohort benefited from sensor provision via reimbursement from the National Health System in Italy [4]. Although it is not known if similar improvements in HbA1c would be observed with self-funding of the device in this population, this has been shown in type 1 diabetes and by earlier real world Italian and European data in an unspecified diabetes cohort which reported frequent scanning rates linked to improved glycaemic markers [16–19].

As expected, the most commonly prescribed glucose lowering medication in addition to insulin in the current study was metformin. Mean age, BMI, baseline HbA1c and duration of insulin use were similar to those reported by other studies in the same population (Table 1) [3,4,8]. Overall, medical history data in the current study (Table S9, Supplementary Information) were comparable to other European countries.

This study's main strengths are its methodology that includes a time and HbA1c matched control group, and the real world setting where flash glucose monitoring was prescribed as standard of care for individuals with type 2 diabetes on basal-bolus insulin therapy. Matching of the two groups' baseline characteristics and medical history and the supportive results after adjustment for potential confounding factors suggest that the current findings may be generalised. However, the observational nature of the study is a limitation as bias cannot be ruled out and it restricted more detailed clinical data capture such as time in ranges and potentially other glycaemic benefits for this cohort. The current study is also relatively short and the observed reduction in HbA1c may not be maintained on the longer term and more prolonged studies in this cohort are warranted.

This real-world, prospective cohort study demonstrated significantly improved HbA1c in individuals with type 2 diabetes treated with basal-bolus therapy three to six months after initiation of flash glucose monitoring therapy compared to SMBG use.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Authorship contribution statement

The corresponding author was involved in the design of the study protocol, prepared the first draft of the manuscript and worked collaboratively with the named authors to prepare the final manuscript. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship, had full access to all of the study data and take complete responsibility for the integrity of the data, the accuracy of the data analysis and integrity of the work as a whole. The authors have given their approval for this version to be published.

Author disclosure statements

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Data availability

The data sets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2021.109172.

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