BMJ Open Diabetes Research & Care

Efficacy and safety of flash glucose monitoring in patients with type 1 and type 2 diabetes: a systematic review and meta-analysis

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To cite: Castellana M, Parisi C, Di Molfetta S, *et al*. Efficacy and safety of flash glucose monitoring in patients with type 1 and type 2 diabetes: a systematic review and meta-analysis. *BMJ Open Diab Res Care* 2020;**8**:e001092. doi:10.1136/bmjdrc-2019-001092

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/bmjdrc-2019-001092).

Received 2 December 2019
Revised 1 May 2020
Accepted 8 May 2020

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ABSTRACT

Introduction Flash glucose monitoring (FGM) is a factory-calibrated sensor-based technology for the measurement of interstitial glucose. We performed a systematic review and meta-analysis to assess its efficacy and safety in patients with type 1 and type 2 diabetes.

Research design and methods PubMed, CENTRAL, Scopus and Web of Science were searched in July 2019. Twelve studies with a follow-up longer than 8 weeks, evaluating 2173 patients on prandial insulin, multiple daily insulin injections or continuous subcutaneous insulin infusion were included. The following data were extracted: HbA1c, time in range, time above 180 mg/dL, time below 70 mg/dL, frequency of hypoglycemic events, number of self-monitoring of blood glucose (SMBG) measurements, total daily insulin dose, patient-reported outcomes, adverse events, and discontinuation rate. A comparison with SMBG was conducted.

Results FGM use was associated with a reduction in HbA1c (−0.26% (−3 mmol/mol); p=0.002) from baseline to the last available follow-up, which correlated with HbA1c levels at baseline (−0.4% (−4 mmol/mol) for each 1.0% (11 mmol/mol) of HbA1c above 7.2% (55 mmol/mol)). Also, a decrease in time below 70 mg/dL was found (−0.60 hours/day; p=0.04). Favorable findings in patient-reported outcomes and no device-related serious adverse events were reported. When compared with SMBG, FGM was characterized by no statistically different change in HbA1c (p=0.09), with lower number of SMBG measurements per day (−3.76 n/day; p<0.001) and risk of discontinuation (relative risk=0.42; p=0.001). A limited number of studies, with a heterogeneous design and usually with a short-term follow-up and without specific training, were found.

Conclusions The present review provides evidence for the use of FGM as an effective strategy for the management of diabetes.

Significance of this study

What is already known about this subject?

- Glucose monitoring is an integral component of effective therapy of patients with diabetes.
- Discordant findings have been reported on the impact of flash glucose monitoring (FGM) on glycemic management; a high level of evidence on the comparison with self-monitoring of blood glucose (SMBG) is currently lacking.

What are the new findings?

- A limited number of studies, with a heterogeneous design and usually with a short-term follow-up and without specific training, are reported in the literature.
- In patients with type 1 and type 2 diabetes on insulin therapy, FGM use was associated with significant reductions in HbA1c, which correlated with HbA1c levels at baseline, and in time below 70 mg/dL from baseline to the last available follow-up. Favorable findings in patient-reported outcomes on FGM were reported.
- Compared with SMBG by finger pricking, FGM was characterized by a similar extent of change in HbA1c, with lower number of SMBG measurements per day and risk of discontinuation.

How might these results change the focus of research or clinical practice?

- Our findings indicate that FGM is an effective and safe strategy to monitor glucose levels in patients with diabetes.

INTRODUCTION

Glycemic management aiming at blood glucose concentrations close to the normal range is key for a successful diabetes care. The traditional method for assessing glucose exposure and oscillations is represented by HbA1c and self-monitoring of blood glucose (SMBG) by finger pricking. Though effective, this approach shows multiple limitations. HbA1c does not inform about intraday and interday glycemic variability, nor on postprandial hyperglycemia or hypoglycemia, which are linked to microvascular and macrovascular complications.[1 2] Also, its reliability is limited in some patients, such as those with

anemia, hemoglobinopathies, iron deficiency and during pregnancy and severe kidney disease. On the other hand, SMBG requires a fingerstick to get a capillary blood sample, can be painful, provides only intermittent 'point-in-time' measurements, and does not allow to predict impending changes in daily glucose control.[1 2] In order to overcome these limitations, new diabetes technologies have been introduced. These include real-time continuous glucose monitoring (RT-CGM) and flash glucose monitoring (FGM), also known as intermittently viewed CGM or intermittently scanned CGM. Both RT-CGM and FGM measure glucose concentrations in the interstitial fluid. RT-CGM is characterized by alarms for low and high glucose and may be integrated with insulin pumps. Although novel devices harbor improved characteristics, the widespread diffusion of previous versions has been often limited by the need of frequent calibration and the short wear time.[3–5]

FGM is a factory-calibrated sensor-based technology characterized by a small-sized patch lasting up to 14 days and a short warm-up period. On-demand sensor scanning provides patients with comprehensive glucose data, including current glucose levels, which are updated every minute, historical glucose readings from the last 8 hours, and trend arrows. Also, ambulatory glucose profiles can be reviewed and shared with the physician.[3 4 6] Clinical evidence showing relevant benefits of FGM use in patients with type 1 and type 2 diabetes in terms of sparing of hypoglycemia, with apparent no change in HbA1c, compared with SMBG has recently been provided.[7 8] Ease of use, convenience and expanding reimbursement policies have led to its growing adoption.[9] Despite the remarkable number of patients using FGM,[10] a high level of evidence on its efficacy and safety is currently lacking. Accordingly, we performed a systematic review and meta-analysis to evaluate the impact of this intervention on the management of patients with type 1 and type 2 diabetes. The primary outcome was the change in HbA1c from baseline to the last available follow-up while on FGM. As secondary outcomes, the changes in time in range, time above 180 mg/dL, time below 70 mg/dL, frequency of hypoglycemic events, number of SMBG measurements, and total daily insulin dose on FGM were assessed; also, patient-reported outcomes, adverse events and discontinuation of FGM were analyzed. Finally, a comparison with SMBG was conducted.

METHODS

The systematic review was registered in PROSPERO (CRD42019146926) and performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (online supplementary table S1).[11]

Data sources and searches

A five-step search strategy was planned. First, we searched sentinel studies in PubMed. Second, we identified keywords in PubMed. Third, the terms 'flash glucose monitoring' and 'FreeStyle Libre' were searched in PubMed in order to test the strategy (online supplementary table S2). Fourth, CENTRAL, Scopus and Web of Science were searched with the same strategy. Lastly, references of included studies were searched for additional papers. The last search was performed on 22 July 2019. No language restriction was adopted. Two investigators (MC, CP) independently searched papers, screened titles and abstracts of the retrieved articles, reviewed the full texts, and selected articles for their inclusion.

Study selection

Studies evaluating the efficacy and safety of FGM in patients of any age with type 1 and type 2 diabetes with a follow-up longer than 8 weeks were selected by two investigators (MC, CP). Letters, commentaries, posters, studies assessing the accuracy of FGM only, studies on FreeStyle Libre Pro, and papers on deidentified data from FGM monitors were excluded.

Data extraction and quality assessment

The following information was extracted independently by two investigators (MC, CP) in a piloted form: (1) general information on the study (author, year of publication, country, study type, follow-up period, number of patients, age, sex, diabetes duration, inclusion criteria); (2) information on FGM (training, compliance, number of sensor scans/day); (3) glycemic endpoints, including HbA1c, time in range (70–180 mg/dL), time above 180 mg/dL, time below 70 mg/dL, and frequency of hypoglycemic events; (4) total daily insulin dose; (5) number of SMBG measurements; (6) patient-reported outcomes; (7) adverse events; (8) number of patients discontinuing FGM or SMBG. Discontinuation was defined as the number of patients who withdrew for personal reasons or were excluded from the study. The main papers and supplementary data were searched; if data were missing, corresponding authors were contacted via email. Data were crosschecked, and any discrepancy was discussed.

The risk of bias of included studies was assessed independently by two reviewers (MC, CP). For observational studies, the National Heart, Lung, and Blood Institute Quality Assessment Tool was used, and the following aspects evaluated: study question; eligibility criteria; sample size calculation; description and delivering of intervention; definition of outcome measures; duration of follow-up; blinding; loss to follow-up; statistical methods; funding. Each domain was assigned absence, unclear or possible risk of bias.[12] For randomized controlled trials (RCT), the Cochrane Collaboration's tool for assessing risk of bias was used and the following aspects evaluated: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selecting reporting. For other bias, funding was assessed. Each domain was assigned low, unclear or high risk of bias.[13]

Data synthesis and analysis

The primary outcome was the change in HbA1c from baseline to the last available follow-up on FGM. Secondary outcomes included: (1) changes in time in range, time above 180 mg/dL, time below 70 mg/dL, frequency of hypoglycemic events, number of SMBG measurements, and total daily insulin dose from baseline to the last available follow-up; (2) patient-reported outcomes and adverse events; (3) number of patients discontinuing FGM. Endpoints were analyzed as: (1) continuous variables and summarized as weighted mean difference; (3) dichotomous variables, and the proportion was estimated. For endpoints under number (2), we only collected data in tables, given the heterogeneous reporting. According to a more conservative approach, the change from baseline and the last available follow-up was assessed for each study by unpaired statistics. For change in number of SMBG measurements, studies in which a substitutive use of FGM without any SMBG measurements was planned were excluded from the analysis. A comparison with SMBG was conducted when at least three studies were available; endpoints were summarized as: (1) weighted mean difference; (2) qualitatively; (3) relative risk (RR). If SD was missing in a study for a specific outcome, it was calculated from SE or 95% CI; if none of these were available, the largest among the other studies was reported. A subgroup analysis based on the type of diabetes was performed. A meta-regression on change in HbA1c from baseline to the last available follow-up on FGM based on baseline HbA1c and number of sensor scans per day was conducted. Pooled data were presented with 95% CI. Heterogeneity between studies was assessed by using I^2, with 50% or higher regarded as high. Publication bias was assessed with Egger's test; the trim-and-fill method was used for estimating its effect. All analyses were two sided and were carried out using RevMan V.5.3 (the Cochrane Collaboration) and Prometa V.3.0 (Internovi) with a random effects model. P<0.05 was regarded as significant.

RESULTS

Study characteristics

A total of 1081 papers were found, of which 234 were on PubMed, 198 on CENTRAL, 335 on Scopus, and 314 on Web of Science. After removal of 436 duplicates, 645 articles were analyzed for title and abstract; 600 records were excluded (studies assessing the accuracy of FGM only; reviews, letters, commentaries, posters, case reports, case series; cost-effectiveness analyses; interventions other than FGM; non-diabetic patients; not in humans). The remaining 45 papers were retrieved in full text and 13 articles corresponding to 12 studies were finally included in the systematic review (figure 1).[7 8 14–24] No additional study was retrieved from references of included studies.

Study quality assessment

The risk of bias of the included studies is shown in online supplementary tables S3 and S4. In regard to the observational studies, statement of the study question, eligibility criteria, description and delivering of intervention, definition of outcome measures, duration of follow-up, and statistical methods were adequate in all. A sample size justification was reported in one study only.[19] Outcome measures were not taken multiple times in three studies.[14 15 17] Loss to follow-up after baseline was higher than 20% in two studies.[17 19 20] Finally, one study was funded by industry.[16] In regard to the three RCTs, no information on random sequence generation was reported. Participants, investigators and outcome

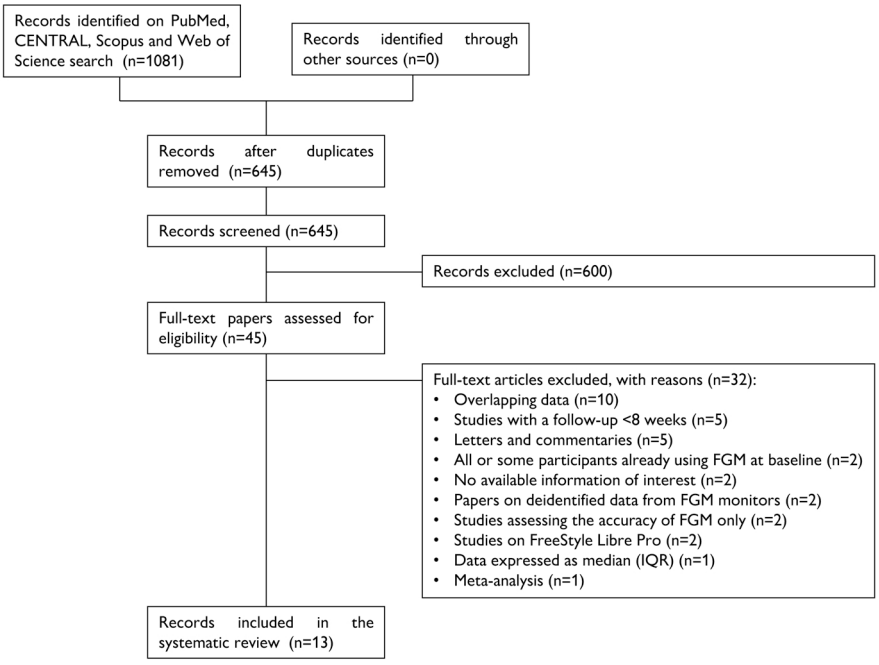

Figure 1 Flowchart of the systematic review. FGM, flash glucose monitoring.

assessors were not blinded to the intervention. It is worth noting that no other study design could have been adopted for the first two roles. The latter could have potentially been blinded, but outcome measurements were not likely to be influenced by lack of blinding (ie, change in time in range). A higher discontinuation rate in patients on SMBG was reported in one study.[8] All the study's prespecified outcomes were reported in the prespecified way. Finally, all three RCTs were funded by industry.[7 8 23]

Qualitative analysis (systematic review)

The characteristics of the included articles are summarized in table 1 and online supplementary table S5. The studies were published between 2016 and 2019, had sample sizes ranging from 36 to 838 patients, and a follow-up from 8 to 56 weeks. Three studies were RCTs, five prospective cohort, and three retrospective cohort; the design was not clearly stated in one paper.[17] Data on training and compliance to FGM are reported in online supplementary table S6. FGM was compared with SMBG in six studies.[7 8 19 20 23 24] Participants were children, adolescents and adult outpatients diagnosed with type 1 or type 2 diabetes, treated with multiple daily insulin injections (MDI) or continuous subcutaneous insulin infusion (CSII). The only exceptions were ref 8, in which patients on prandial insulin only were recruited too, and ref 24, in which also patients with other insulin-dependent forms of diabetes were enrolled (ie, postpancreatectomy). Overall, 2173 patients were included; of these, 55% were males, 1785 were diagnosed with type 1 diabetes, 325 with type 2 diabetes, and 63 with type 2 diabetes or other types of insulin-dependent diabetes (they were mentioned in ref 24, and could not be categorized any further); 1663 assessed glucose levels with FGM, while 510 with SMBG.

Quantitative analysis (meta-analysis)

The primary outcome was the change in HbA1c from baseline to the last available follow-up. FGM was associated with a reduction in HbA1c of −0.26% (−3 mmol/mol) (95% CI −0.43 to −0.09; I^2=78%) (figure 2). Also, FGM was associated with a reduction in time below 70 mg/dL (−0.60 hours/day; 95% CI −1.18 to −0.03; I^2=90%) and number of SMBG measurements per day (−4.55 n/day; 95% CI −5.74 to −3.35; I^2=95%). No changes in time in range, time above 180 mg/dL, frequency of hypoglycemic events, and total daily insulin dose from baseline to the last available follow-up on FGM were found (table 2, online supplementary figures S2–S7). Then, we conducted a meta-regression analysis to assess if our primary outcome could be predicted according to one or more explanatory variables. The change in HbA1c from baseline to the last available follow-up on FGM correlated with the HbA1c level at baseline (−0.4% for each 1.0% of HbA1c over 7.2% (−4 mmol/mol for each 11 mmol/mol of HbA1c over 55 mmol/mol), p=0.007) (online supplementary figure S1), but not with the mean number of sensor scans per day (p=0.98) (data not shown).

The overall prevalence of patients discontinuing FGM was 12.5%. Reasons included device-associated adverse events, switch to a CGM with alarms, being tired of the device, perception of inaccuracy, and costs. Concerning adverse events, there were no device-related serious adverse events. A limited number of patients with device-related adverse events were reported, while a higher one with anticipated sensor insertion site symptoms; the most frequent ones were represented by erythema (n=80), pain (n=55), bleeding (n=48), itching (n=38) and rash (n=24). Finally, regarding patient-reported outcomes, favorable findings at the end of follow-up or an improvement from baseline to the last available follow-up on FGM were reported (online supplementary tables S7 and S8).

When comparing FGM with SMBG, FGM was associated with a trend to greater HbA1c change (p=0.09) (figure 2) from baseline to the last available follow-up, but this difference was not statistically significant. No difference in total daily insulin dose changes from baseline to the last available follow-up was found (p=0.77). However, FGM was associated with a significant reduction in SMBG measurements (−3.76 n/day; 95% CI −4.79 to −2.72; I^2=86%) and a lower RR of discontinuation (0.42; 95% CI 0.25 to 0.71; I^2=0%) (table 2, online supplementary figures S8–S10) when differences in changes from baseline to the last available follow-up for these outcomes were assessed. There were not enough data to perform a meta-analysis for the following outcomes: (1) difference in change in time in range on FGM versus SMBG; (2) difference in change in time above 180 mg/dL on FGM versus SMBG; (3) difference in change in time below 70 mg/dL on FGM versus SMBG; (4) difference in change in frequency of hypoglycemic events on FGM versus SMBG. For patient-reported outcomes, conflicting findings were reported on the comparison between FGM and SMBG (online supplementary table S7).

There was no evidence of publication bias, with the exception of the change in HbA1c from baseline to the last available follow-up on FGM; the trim-and-fill method did not change the statistical significance of this result (online supplementary table S9).

DISCUSSION

The aim of this systematic review and meta-analysis was to identify the best available evidence on the efficacy and safety of FGM in patients with type 1 and type 2 diabetes. Twelve studies were found, including 2173 patients with type 1 and type 2 diabetes or other insulin-dependent forms of diabetes, treated with prandial insulin only, MDI or CSII. The overall results of our meta-analysis showed FGM to be associated with a reduction in HbA1c, time below 70 mg/dL and number of SMBG measurements from baseline to the last available follow-up. The number of serious adverse events and device-related adverse events on FGM was limited, while a higher frequency of anticipated sensor insertion site symptoms was reported. Favorable findings in patient-reported outcomes on FGM

Table 1 Characteristic of included studies

First author, year	Country	Study design	Intervention	Comparator	Follow-up (weeks)	Patients (n)	Inclusion criteria
Type 1 diabetes							
Al Hayek, 2017[14]	Saudi Arabia	PCS	FreeStyle Libre	NA	12	47	Type 1 diabetes, 13–19 years, MDI or CSII
Al Hayek, 2019[15]	Saudi Arabia	PCS	FreeStyle Libre	NA	12	47	Type 1 diabetes, 17–21 years, CSII, HbA1c >7% (53 mmol/mol)
Bolinder, 2016[7]	Austria, Germany, Netherlands, Spain, Sweden	RCT	FreeStyle Libre	SMBG	24	239	Type 1 diabetes, ≥18 years, MDI or CSII, HbA1c ≤7.5% (58 mmol/mol), SMBG ≥3 times/day, hypoglycemia awareness
Campbell, 2018[16]	Germany, Ireland, UK	PCS	FreeStyle Libre	NA	8	76	Type 1 diabetes, 4–17 years, MDI or CSII, SMBG ≥2 times/day
Kramer, 2019[17]	Germany	NR	FreeStyle Libre	NA	56	40	Type 1 diabetes, MDI or CSII
Landau, 2018[18]	Israel	RCS	FreeStyle Libre	NA	56	71	Type 1 diabetes, ≤25 years, MDI or CSII
Messaaoui, 2019[19]	Belgium	PCS	FreeStyle Libre	SMBG	56	334	Type 1 diabetes, 4–20 years, MDI or CSII
Moreno-Fernandez, 2018[20]	Spain	RCS	FreeStyle Libre	SMBG	24	36	Type 1 diabetes, 18–65 years, CSII
Paris, 2018[21]	Belgium	PCS	FreeStyle Libre	NA	56	120	Type 1 diabetes, ≥18 years, MDI or CSII
Type 2 diabetes							
Haak, 2017[8 22]	France, Germany, UK	RCT	FreeStyle Libre	SMBG	24*	224	Type 2 diabetes, ≥18 years, prandial insulin only or MDI or CSII, HbA1c 7.5%–12.0% (58–108 mmol/mol), SMBG ≥10 times/week
Yaron, 2019[23]	Israel	RCT	FreeStyle Libre	SMBG	10	101	Type 2 diabetes, 30–80 years, MDI, HbA1c 7.5%–10.0% (58–86 mmol/mol)
Mixed							
Gernay, 2018[24]	Belgium	RCS	FreeStyle Libre	SMBG	15	838	Type 1 diabetes or insulin-treated type 2 diabetes or other types of insulin-dependent diabetes, MDI or CSII

*In ref[8 22] patients randomized to flash glucose monitoring (FGM) continued into an additional 6-month open-access phase.
CSII, continuous subcutaneous insulin infusion; MDI, multiple dose insulin injection; NA, not applicable; NR, not reported; PCS, prospective cohort study; RCS, retrospective cohort study; RCT, randomized controlled trial; SMBG, self-monitoring of blood glucose.

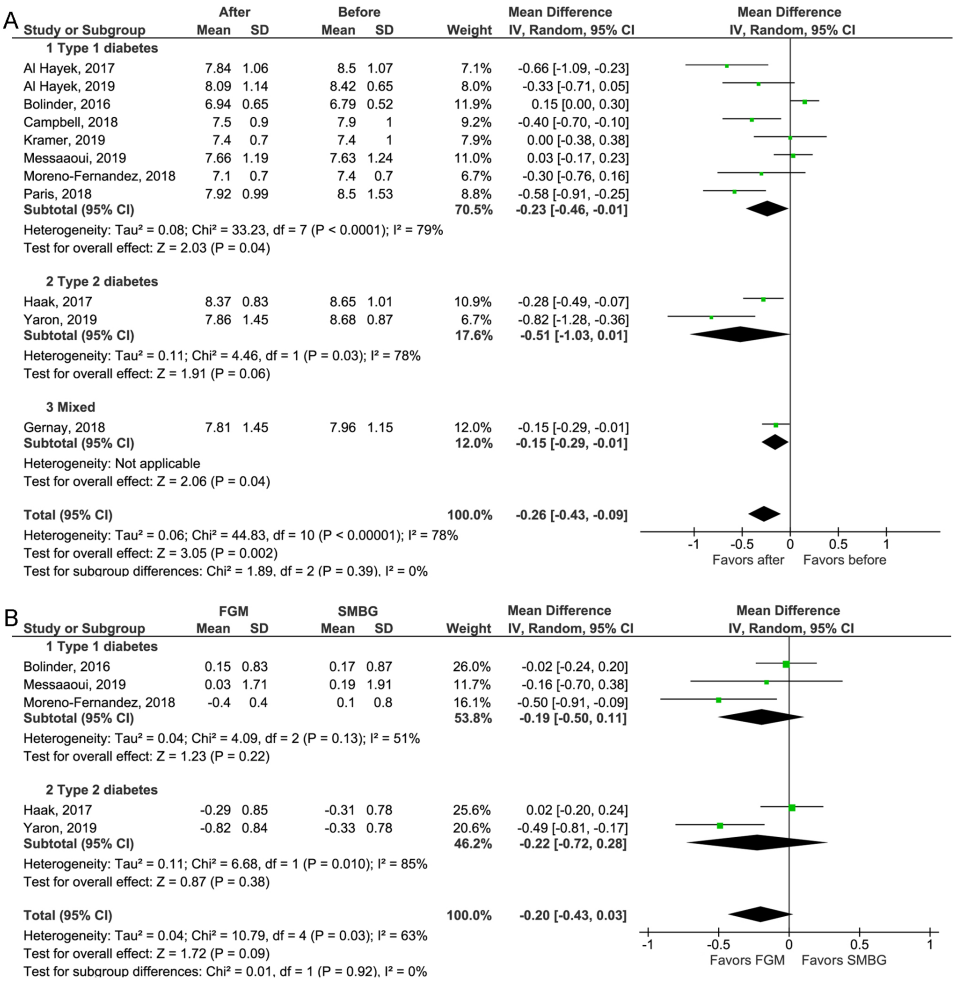

Figure 2 (A) Forest plot for change in HbA1c from baseline to the last available follow-up in patients on flash glucose monitoring (FGM). (B) Forest plot for the difference in change in HbA1c from baseline to the last available follow-up in patients on FGM versus patients on self-monitoring of blood glucose (SMBG).

were found. Compared with SMBG, FGM was associated with a lower number of SMBG measurements and risk of discontinuation. No difference was found for change in time in range, time above 180 mg/dL, frequency of hypoglycemic events, and total daily insulin dose from baseline to the last available follow-up on FGM, as well as

Table 2 Meta-analysis for changes in other outcomes from baseline to the last available follow-up

Parameter	Number of patients (number of studies)	Estimate (95% CI)*	I^2 (%)	P value
Changes in patients using FGM				
Time in range (70–180 mg/dL) (hours/day)	343 (3)	0.55 (–0.17 to 1.26)	48	0.14
Time above 180 mg/dL (hours/day)	343 (3)	0.19 (–0.90 to 1.29)	73	0.73
Time below 70 mg/dL (hours/day)	621 (4)	–0.60 (–1.18 to –0.03)	90	0.04
Hypoglycemic events (n/day)	597 (7)	–0.04 (–0.23 to 0.15)	91	0.67
SMBG measurements (n/day)	401 (5)	–4.55 (–5.74 to –3.35)	95	<0.001
Total daily insulin dose (IU/day)	517 (6)	–1.22 (–4.29 to 1.86)	0	0.44
Differences in changes in patients using FGM versus patients using SMBG				
SMBG measurements (n/day)	832 (4)	–3.76 (–4.79 to –2.72)	86	<0.001
Total daily insulin dose (IU/day)	498 (3)	0.23 (–1.34 to 1.80)	0	0.77
Discontinuation	564 (3)	0.42 (0.25 to 0.71)	0	0.001

*Data are expressed as relative risk for discontinuation and as weighted mean differences for the other outcomes.
FGM, flash glucose monitoring; SMBG, self-monitoring of blood glucose.

for differences in change in HbA1c or total daily insulin dose on FGM versus SMBG. To our knowledge, this is the first systematic review and meta-analysis focusing on outcomes other than HbA1c and comparing FGM with SMBG.

Conflicting results were published on the efficacy of FGM in reducing HbA1c (figure 2), with some authors describing an improvement only in specific subgroups of patients.[17 24] A positive relationship between HbA1c at baseline and the change in HbA1c has already been reported for other interventions.[25 26] Thus, we performed a meta-regression accordingly and found FGM to be associated with a reduction in HbA1c of −0.4% for 1.0% of HbA1c over 7.2% (−4 mmol/mol for each 11 mmol/mol of HbA1c over 55 mmol/mol) (online supplementary figure S1). Of note, this result was achieved without changes in total daily insulin dose, possibly meaning that a day-to-day variation took place without any detectable overall dose difference.[7] Given the results found for the primary outcome, a reduction in time above 180 mg/dL and/or an increase in time in range were to be expected. However, only a reduction in time below 70 mg/dL from baseline to the last available follow-up was found, as reported. The limited number of studies reporting data for this outcome and differences in patients' characteristics may potentially explain these findings. For example, concerning the time above 180 mg/dL in patients with type 1 diabetes, FGM showed discordant findings in ref 7 and 16; however, the HbA1c at baseline in these studies was also significantly different (6.8±0.5% vs 7.9±1.0%, respectively; p<0.01). Also, no change in the frequency of hypoglycemia was found. The accuracy of FGM may play a role in this setting, even though a higher mean absolute relative difference has generally been reported during hypoglycemia rather than hyperglycemia.[27–29] It is worth noting that the definition of hypoglycemia differed among the included studies. According to current guidelines, it should be defined as any measurable glucose concentration <70 mg/dL, either symptomatic or asymptomatic.[2] However, in some studies it was described as any glucose level ≤70 mg/dL[14 15], while in other studies it was represented by any FGM-derived glycemic measures <70 mg/dL, confirmed by a second reading in the following 15 min.[7 8 16] One paper assessed hypoglycemia at baseline and during the study with SMBG and FGM, respectively; a higher rate of hypoglycemic events at follow-up was found with FGM, which may detect values unrecognized by SMBG.[17] Finally, the detection of hypoglycemia, either with SMBG or FGM, was unclear in three studies.[14 15 21] Therefore, the result of the present meta-analysis, showing no change in the frequency of hypoglycemic events with FGM, could potentially be biased.

Despite the recommendations on when blood glucose levels should be assessed, it is common experience that several issues, including handling, pain or lack of time, limit the real number of SMBG measurements, often to three or less per day.[2 30] In the included studies, the mean number of sensor scan per day ranged from 7.5±4.2 to 17.8±9.9.[19 20] This implies that patients or their caregivers feel confident in measuring glucose any time they believe this to be necessary, anyway more often than with SMBG. Moreover, they opt to rely on these data to take the appropriate decisions when needed, and this is confirmed by favorable findings in patient-reported outcomes with FGM. In order for an intervention to impact on a disease, it should be both effective and durable. We found that approximately 1 out of 10 patients discontinued FGM. One of the leading reasons was represented by device-associated adverse events, including erythema, pain, bleeding, itching and rash, which can be caused by contact irritation or contact allergy mechanisms.[31] Patients should be informed about these issues, and sensor application sites regularly checked.

The results of the comparison between SMBG and FGM should be correctly interpreted as SMBG versus FGM with or without SMBG. The majority of included studies had such a design, exploiting the feature of the FGM reader that allows glucose measurements both by scan and finger pricking. We found FGM to be associated with a reduction in SMBG measurements when compared with SMBG, without any difference in change in HbA1c or total daily insulin dose from baseline to the last available follow-up. Also, despite the conflicting results reported for differences in patient-reported outcomes (see below), a lower risk of discontinuation for patients randomized to FGM compared with SMBG was found. It is worth noting that the impact of FGM technology is influenced by the characteristics of training performed in the included studies, and effective training is considered by diabetes experts as a key factor in exploiting diabetes technologies.[6] Indeed, in an untrained patient with stable glycemia, there is no difference between obtaining the current glucose levels by using FGM or SMBG.[3] Relevant to this concept, a reference to the interpretation of FGM data was reported only in three studies,[17 19 20] while the majority of the other papers described a training merely on scanning and sensor change or no training for interpretation of glucose sensor data.[7 8 14–16 21 23] One study specifically focused on the role of training in patients on FGM. Compared with the control group, patients randomized to the training program (named FLASH) achieved a lower HbA1c and higher time in range, with a similar rate of severe hypoglycemic events. This study was excluded from the present meta-analysis, since participants already using FGM were included.[32] Concerning patient-reported outcomes, the detailed assessment of this endpoint was limited by the following factors. First, only three out of six studies in which FGM was compared with SMBG reported data for this particular outcome.[7 8 23] Second, different scales were adopted. Considering all adopted scales, a higher satisfaction on FGM was found in four of them, while no difference was reported in the others. Nevertheless, there was no scale in which FGM was associated with worse patient-reported outcomes. Third, in each scale different domains were assessed. Despite the lack of difference in the overall scale, a significant advantage in patients on

FGM was reported for specific domains, such as the satisfaction with treatment in ref 8. Finally, patient-reported outcomes did not represent the primary endpoint of the studies, and thus sample size calculation was not based on this particular outcome making it possible that lack of adequate statistical power may have resulted in failure to find differences between FGM and SMBG.[23] Compared with SMBG, FGM could be potentially regarded as a strategy to improve patient compliance to glucose monitoring; however, further studies in which patients receive a specific training on FGM seem to be needed to fully compare these two options.

While the present manuscript found no difference in change in HbA1c between FGM and SMBG, meta-analyses in the literature showed a significantly greater HbA1c reduction from baseline with RT-CGM versus SMBG in patients with type 1 or type 2 diabetes.[33 34] Indeed, RT-CGM presents with alarms for immediate and/or impending hypoglycemia or hyperglycemia,[33 34] and these alarms can also be associated with fatigue or perceived as signaling personal failure to achieve optimal glycemic control.[35 36] On the other hand, in FGM, the patients are informed about current glycemic level only following scanning and, if this is performed more than 8 hours after the last scan, some data can be lost.[3–5] Moreover, a negative bias at low glucose concentrations has been reported with FGM, possibly resulting in the patient inadvertently adapting to higher 'true' glucose concentrations and thus higher HbA1c.[37 38] Thus, while both FGM and RT-CGM can be regarded as effective options for CGM, some patient's characteristics (eg, hypoglycemia unawareness) and the glycemic goals may lead to consider one over the other device.[39]

In October 2019, a meta-analysis was published on the impact of FGM in patients with type 1 and type 2 diabetes. Twenty-nine studies were found, of which 25 were included in the meta-analysis. The authors concluded that FGM use was associated with an overall reduction in HbA1c of −0.55% (−6 mmol/mol) (95% CI −0.70 to −0.39) at 2–4 months, which correlated with the HbA1c level at baseline (−0.31% for each 1.0% of HbA1c over 6.6% (−3 mmol/mol for each 11 mmol/mol of HbA1c over 49 mmol/mol)). Also, they found that HbA1c improved within the first 2 months and changes were sustained up to 12 months. While the results of our primary outcome are in line with this report, it was based on results published also as letters, posters or theses. We decided to exclude those documents since only full-text articles undergo peer review before publication and have a complete description of the research methods; moreover, in our analysis, three additional studies were considered,[15 17 24] additional outcomes other than change in HbA1c were addressed, and a comparison with SMBG was performed.[40]

Limitations of the present paper should be discussed. First, a limited number of studies (and patients) usually with a short-term follow-up were found. This clashes with the number of readers reported in real-world studies, which is up to 50 831. Our results are in line with those studies showing improvements in HbA1c and time in hypoglycemia, while a shorter time in hyperglycemia was found in real-life settings.[41] Also, the reason for the discrepancy between the number of posters, letters and commentaries versus published articles is unclear. The limited number of retrieved data implied that endpoints could be analyzed only by pooling studies with a different design and including patients with different type of diabetes, and this is a second limitation. Ideally, a meta-analysis of randomized controlled studies only should be performed since they are more likely to provide unbiased information about the differential effects of alternative health interventions. However, when the question of interest cannot be fully answered by randomized trials due to the paucity of such trials, the inclusion of non-randomized studies is justified.[42] Also, non-randomized studies should not be combined with randomized studies in a meta-analysis given the very different design features.[42] However, this approach has been adopted in previous meta-analyses published as Cochrane reviews as well or conducted by other authors.[40 43–45] Concerning the inclusion of patients with different types of diabetes, according to current guidelines, FGM can be considered in patients with type 1 diabetes or type 2 diabetes to lower HbA1c levels and/or reduce hypoglycemia.[3] In general, the pooling of results from patients with different types of diabetes can lead to biased results. However, the included studies were all conducted in patients taking insulin, for which there is an indication to consider the use of FGM. No patients with type 2 diabetes on oral or injectable therapy other than insulin (eg, glucagon-like peptide-1 receptor agonists) were retrieved. Thus, patients included in the present meta-analysis could be considered as relatively homogeneous on the basis of the pharmacological therapy they were on, making pooling of the result reasonable. Differences between the types of diabetes were taken into account, a subgroup analysis was planned, and results were presented graphically (figure 2). Third, a relatively conservative approach was adopted in the present meta-analysis for the assessment of all outcomes. Ideally, to assess changes from baseline to the last available follow-up on a specific intervention, the mean change and SDs for the change from baseline should be pooled, calculating this SD by a paired analysis, given that two sets of measurements from the same subjects are available and can be compared.[46] In the absence of this information in several studies and to include the largest number of studies, we estimated the data using an unpaired statistic, as stated. While this approach can be considered as conservative and appropriately adopted in our meta-analysis, according to differences in included studies and patients,[47 48] it is not explicitly supported by published recommendations, and one should be aware that it may yield some discrepancies between data reported in our forest plots and data reported in some of the original studies. Fourth, a high heterogeneity for 7 out of 11 evaluated outcomes was found. This could be due to heterogeneity in study design or patient characteristics. We demonstrated that change in HbA1c on FGM correlates with HbA1c level at baseline; however, other parameters, including age or diabetes duration,

may play a role. Caution should thus be taken in generalizing these results to clinical practice. Fifth, a comparison between FGM and SMBG could not be performed for some secondary outcomes, and we found only three studies in which patients were specifically trained on interpretation of FGM data (ie, trend arrows) and time of scan.[17 19 20] Further studies comparing SMBG with trained FGM are needed to fully assess potential differences in outcomes other than SMBG measurements and risk of discontinuation. Lastly, studies included in the present meta-analysis adopted FreeStyle Libre only as FGM. A new version has been recently released (FreeStyle Libre 2), which is characterized by alarms; whether similar results can be obtained using this system remains to be assessed.

Gathering as much evidence as possible for an intervention that is currently part of clinical practice is necessary. A limited number of studies on FGM are reported in the literature, using different study designs, including patients with different characteristics at baseline, and with a heterogeneous reporting. Particularly, we believe that the general lack of a specific training in patients on FGM represented the most relevant finding of our systematic review. Acknowledging these limitations, FGM proved to be a reliable option to achieve a significant reduction in HbA1c and time below 70 mg/dL in uncontrolled patients with type 1 or type 2 diabetes or other insulin-dependent diabetes on prandial insulin only, MDI or CSII. When compared with SMBG, FGM was associated with a similar change in HbA1c, a lower number of SMBG measurements, and a reduced risk of discontinuation. FGM should thus be regarded as an effective intervention to be proposed to properly selected patients, as a part of a multicomponent strategy. Further studies on the comparison between SMBG and trained FGM are however needed.

Acknowledgements The authors thank Dr Anissa Messaaoui (Bruxelles, Belgium) for providing the requested data.

Contributors MC conceived the meta-analysis. MC and CP developed the search strategy and provided statistical expertise. MC drafted the manuscript. All authors contributed to the development of the selection criteria, the risk of bias assessment strategy and data extraction criteria. All authors read, provided feedback, and approved the final manuscript. FG is the guarantor and takes responsibility for the contents of the article.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests AC: Eli Lilly, Novo Nordisk, Sanofi Aventis, AstraZeneca, Bruno Farmaceutici, Roche, Alfasigma. FG: Abbott, Medtronic, Roche Diabetes Care Italy, LifeScan. LL: Abbott, Medtronic, Movi, Roche Diabetes Care Italy. SDM: Roche Diabetes Care Italy.

Patient consent for publication Not required.

Ethics approval This systematic review and meta-analysis was in accordance with the principles of the Declaration of Helsinki. Analyses were performed on data extracted from published papers.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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