Diabetes Ther (2022) 13:1175–1185
https://doi.org/10.1007/s13300-022-01253-9

ORIGINAL RESEARCH

Reductions in HbA1c with Flash Glucose Monitoring Are Sustained for up to 24 Months: A Meta-Analysis of 75 Real-World Observational Studies

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Received: January 20, 2022 / Accepted: March 11, 2022 / Published online: April 27, 2022

ABSTRACT

Introduction: Real-world evidence (RWE) confirms that reductions in HbA1c for children and adults with type 1 diabetes (T1DM) and adults with type 2 diabetes (T2DM) are associated with use of the FreeStyle Libre system. This current meta-analysis aims to investigate whether HbA1c benefits are sustained over 24 months and to identify patterns of change in HbA1c for users of the FreeStyle Libre system for people living with T1DM or T2DM.

Methods: A bibliographic search up to December 2020 identified 75 studies reporting data on change in lab HbA1c in 30,478 participants with type 1 (n = 28,063; 62 trials) or type 2 diabetes (n = 2415; 13 trials) using the FreeStyle Libre system, including observations on children, adolescents and adults. Meta-analysis was performed using a random effects model.

Results: Reductions in HbA1c at 3–4 months were similar for adults with T1DM (− 0.53%, 95% CI − 0.69 to − 0.38) or with T2DM (− 0.45%, 95% CI − 0.57 to − 0.33), continuing through 4.5–7.5 months in T1DM (− 0.42%, 95% CI − 0.58 to − 0.27) and in T2DM (− 0.59%, 95% CI − 0.80 to − 0.39). Meta-regression analysis shows that higher starting HbA1c is correlated with greater reductions in HbA1c in T1DM and in T2DM. These patterns of change in HbA1c were sustained for 24 months in T1DM and for at least 12 months in T2DM.

Conclusions: Meta-analysis of RWE confirms that using the FreeStyle Libre system is associated with significant reductions in HbA1c for adults with T1DM or with T2DM. Reductions are greater for people with higher baseline HbA1c and are sustained for 24 and 12 months in T1DM and TD2M respectively.

Keywords: Flash glucose monitoring; FreeStyle Libre system; Self monitoring blood glucose; HbA1c; Meta-analysis; Real-world observational studies; Type 1 diabetes; Type 2 diabetes

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13300-022-01253-9.

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Key Summary Points

Meta-analysis of 75 observational studies confirms that using the FreeStyle Libre system is associated with a significant reduction in HbA1c for adults and children with type 1 diabetes (T1DM) and for adults with type 2 diabetes (T2DM).

Reductions in HbA1c associated with using the FreeStyle Libre system are sustained for 24 months for adults and children with T1DM and for at least 12 months for adults with T2DM, indicating that the fall in HbA1c is a consequence of using the FreeStyle Libre system rather than transient confounding factors around the time of initiation.

Both in T1DM and in T2DM, the degree of change in HbA1c is predicted by the HbA1c at baseline, such that a greater reduction in HbA1c is seen for users with a higher baseline HbA1c.

The observed patterns of change in HbA1c in T1DM and T2DM across 75 studies are not different after starting the FreeStyle Libre system, indicating that flash glucose monitoring can be used in the same way to reduce long-term glucose exposure for adults with either T1DM or T2DM.

INTRODUCTION

The use of continuous glucose monitoring (CGM) or flash glucose monitoring with the FreeStyle Libre system by people with type 1 diabetes (T1DM) or type 2 diabetes (T2DM) is associated with lowered HbA1c, increased time in range (TIR) and reduced time below range (TBR) in hypoglycaemia [1–3]. In a 2020 meta-analysis [4] of 25 real-world studies or clinical trials we showed that flash glucose monitoring was associated with a mean reduction in laboratory-measured HbA1c of − 0.56% (95% CI − 0.76, − 0.36) amongst adults and − 0.54% (95% CI − 0.84, − 0.23) in children and adolescents. A longitudinal analysis showed that HbA1c fell significantly within the first 2–4 months of use and changes were sustained up to 12 months in adult subjects (n = 1276). No significant differences were detected between T1DM and T2DM, and regression analysis indicated that the degree of change in HbA1c directly correlated with the initial HbA1c of the study population—i.e. the greater the HbA1c immediately prior to starting flash glucose monitoring, the larger the reduction in HbA1c with continued use.

The importance of implementing CGM and flash glucose monitoring in standard care is emphasized by data from national audits and diabetes registries that show that targets for glycaemic control as recommended by the International Society for Pediatric and Adolescent Diabetes (ISPAD) [5], the American Diabetes Association (ADA) [6] and the European Association for the Study of Diabetes (EASD) [7] are not met by substantial numbers of people with T1DM or T2DM [8–10]. Across the T1DM Exchange registry in the USA and the DPV German/Austrian registry no more than one-third of children and adults with T1DM achieve targets for HbA1c < 7.0% (53 mmol/mol) [8] and targets for < 7.5% (58 mmol/mol) were achieved by no more than half of registry participants. Similarly, glycaemic targets for < 7.0% (58 mmol/mol) are only met by 50% of people with T2DM across Europe and the USA [10]. Available evidence links CGM or flash glucose monitoring with substantially increased achievement of HbA1c targets [11, 12] for people with diabetes, which may lead to reduced risks of long-term macrovascular disease for people with T1DM [13] or T2DM [14].

Real-world studies have confirmed that reductions in HbA1c with flash glucose monitoring are sustained in adults with T1DM or T2DM for 12 months [3, 15]. Our first meta-analysis [4] revealed that both the pattern and the degree of HbA1c reduction within 3 months after starting flash glucose monitoring were similar between adults and children with T1DM, and also similar between adults with T1DM and T2DM. This observation indicates

that the benefits of flash glucose monitoring can be achieved across the spectrum of diabetes. The aims of this current meta-analysis are (1) to extend the previous analysis [4] of real-world outcomes in a larger group of subjects for reductions in HbA1c in people with diabetes using flash glucose monitoring when compared to self monitoring blood glucose (SMBG); (2) to investigate the pattern of changes in HbA1c longitudinally, from 1 month to up to 24 months; (3) to identify common and unique features of change in HbA1c for users of flash glucose monitoring between people with T1DM and people with T2DM based on length of study or type of diabetes.

METHODS

Search Strategy and Study Selection

A search was conducted across the following abstracting and indexing databases: Allied & Complementary Medicine™, Analytical Abstracts, BIOSIS Previews®, Embase®, EMCare®, International Pharmaceutical Abstracts, MEDLINE®, ToxFile®. The searched string of terms and the subsequent selection flow diagram are detailed in Fig. 1. The search covered the period from 2013 until December 31st 2020.

Our meta-analysis focuses on observed change in HbA1c at either 3–4 months and 4.5–7.5 months, as well as a longitudinal analysis up to 24 months. These data were drawn from the studies identified in our initial search, as indicated in Supplementary Table 1. Studies were included if data were based on continuous use of the FreeStyle Libre system during the study period and reported in a manner that could be used in a statistical meta-analysis. Where necessary, study investigators were solicited to supply basic statistical parameters regarding their cohorts not included in their initial reports. For the randomised controlled trials (RCTs) within this longitudinal analysis set, the within-intervention arm results have been included, not the between-arm results reported previously. All studies included here are reported as absolute change from baseline to ensure a consistent approach and to reflect the real-world patient-centred outcome. Although several studies reported on endpoints less than 3 months after commencement of flash glucose monitoring, we acknowledge that HbA1c may circulate in plasma for approximately 3 months after formation, despite a change in average glucose [16]. Therefore, where possible, we have used 3 months as the minimum timepoint to assess change in HbA1c, except for the longitudinal analysis. This is to minimise the inclusion of measurements that may include HbA1c reflective of the average glucose prior to the application of flash glucose monitoring. The inclusion only of flash glucose monitoring study arms accommodates the reality that many of the observational studies do not have control subject groups. This is an acknowledged limitation of this meta-analysis. Several of the included studies reported change in laboratory measured HbA1c for multiple timed endpoints. Each of these is included in the longitudinal analysis, up to 24 months.

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Statistical Analysis

Data Sufficiency

The meta-analysis statistical method requires at a minimum (1) mean change in HbA1c; (2) standard error (SE) of mean change in HbA1c; (3) mean initial HbA1c. Where the SD was not available it was calculated from p values or confidence intervals. SD was estimated from the IQR for Gibb and the mean was estimated from the median for Reddy (Supplementary Table 1).

Use of Single Timepoint in Meta-regression Analysis in Adults

A single timepoint from each study at each time range was used in this analysis, consistent with our previous report [4]. Analysis was conducted separately by type of diabetes and by time range (3–4 months and 4.5–7.5 months). Meta-analysis of change in HbA1c was performed using a random effects model. Analysis used trial-level

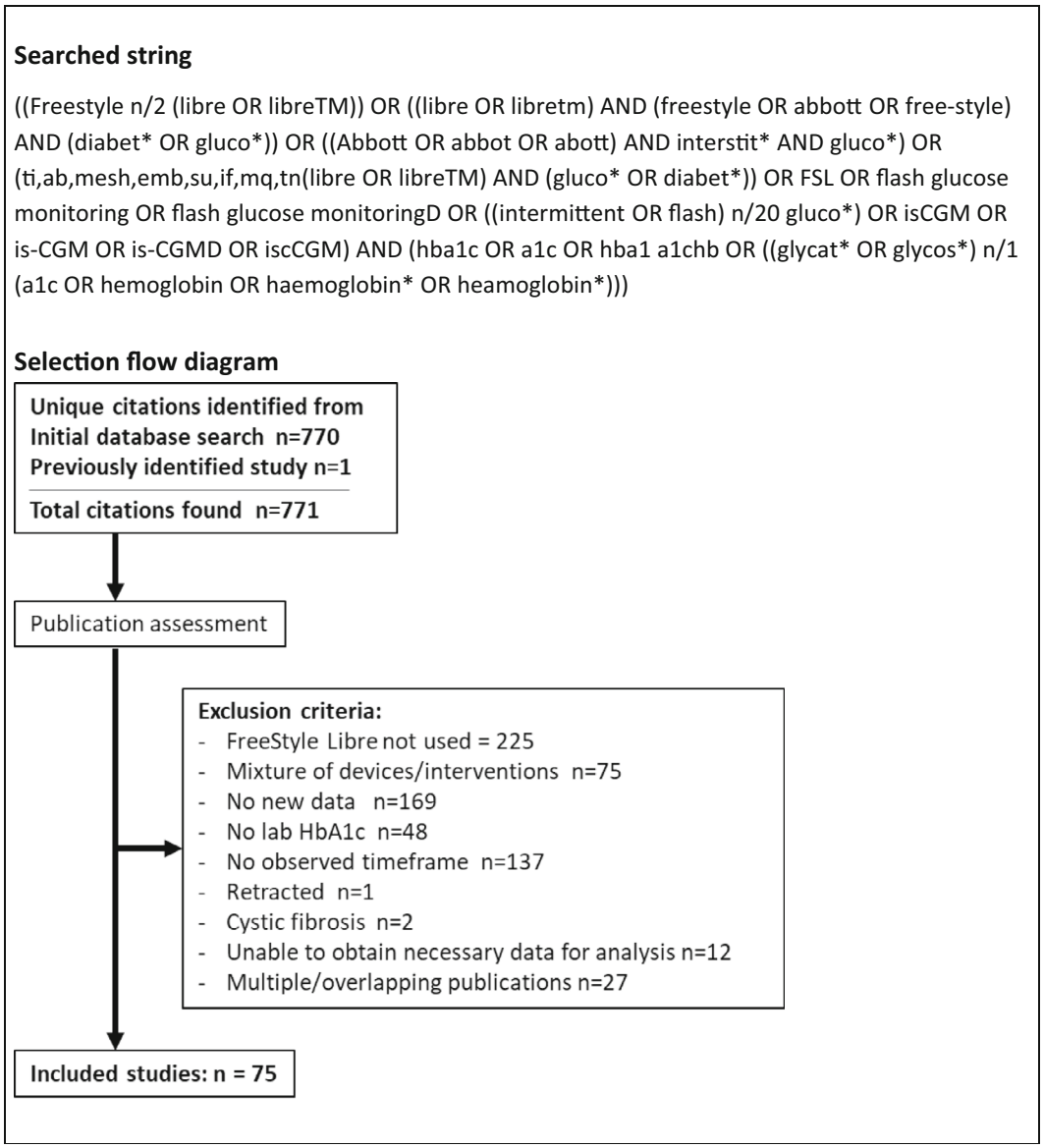

Fig. 1 Search strategy and study selection

data, weighting with the inverse of the within-trial variance. Cochran's heterogeneity statistic (Q) and the I^2 statistic were calculated [17]. Random effects meta-regression of change in HbA1c was performed versus initial HbA1c [18]. The proportion of variance explained by the regression, R^2 was calculated [18].

Data are reported as mean absolute change in HbA1c after starting flash glucose monitoring compared to mean initial baseline, using bubble charts. In each case, the area of each bubble represents the weight of the trial and the regression line from meta-regression random effects model is displayed.

Longitudinal Analysis in Adults and in Children

Multiple timepoints up to 24 months from each study with adult or paediatric subjects were used in this analysis. Analyses were conducted separately for adults and for children. Mean change in HbA1c adjusted for initial HbA1c was estimated using random effects meta-regression versus initial HbA1c by type of diabetes with type of diabetes, month and interaction of type of diabetes and month as fixed effects [19]. For children the model did not include type of diabetes.

Analysis was performed using SAS version 9.4.

RESULTS

Studies Included

Seventy-five trials were identified to include in the meta-analysis, with a total of 30,478 participants with T1DM or T2DM using the FreeStyle Libre system over periods from 1 to 24 months (Supplementary Table 1). The analysis included 28,063 adults and children with T1DM from 62 trials and 2415 adults with T2DM from 13 trials.

Change in HbA1c in Adults at 3–4 months and 4.5–7.5 Months After Starting the FreeStyle Libre System

Meta-analysis of the overall mean change in HbA1c after starting the FreeStyle Libre system at each timepoint is shown in Table 1. At 3–4 months, HbA1c is reduced in adults by − 0.53% (95% CI − 0.69 to − 0.38) in T1DM and by − 0.45 (95% CI − 0.57 to − 0.33) in T2DM. At 4.5–7.5 months after starting the FreeStyle Libre system HbA1c is reduced by − 0.42% (95% CI − 0.58 to − 0.27) in T1DM and by − 0.59% (95% CI − 0.80 to − 0.39) in T2DM.

Meta-regression analysis of the reduction in HbA1c after starting the FreeStyle Libre system as a function of baseline HbA1c is shown in Fig. 2. At 3–4 months, no change in HbA1c is evident for study adult subjects with a baseline HbA1c level of 6.7% (50 mmol/mol) in T1DM or 6.6% (49 mmol/mol) in T2DM. On average, for each percentage point increase in mean initial HbA1c above this level, HbA1c at 3–4 months falls by − 0.32% (95% CI − 0.43 to − 0.21) in T1DM and by − 0.33% (95% CI − 0.92 to 0.25) in T2DM. The mean initial HbA1c explains a considerable proportion, 85.6%, of the heterogeneity between studies in the change in HbA1c in T1DM.

At 4.5–7.5 months after starting the FreeStyle Libre system no change in HbA1c is evident for adult subjects with a baseline HbA1c level of 7.2% (55 mmol/mol) in T1DM or for adults with T2DM and a baseline HbA1c of 6.7%

Table 1 Meta-analysis results for change in HbA1c by timepoint and type of diabetes

Timepoints (months)	Age group	Type of diabetes	Number of trials	Change in HbA1c (%)	Lower CL	Upper CL	*Q*	I^2	*P* value	τ^2
3–4	Adults	T1DM	16	− 0.53	− 0.69	− 0.38	181.1	91.7	< 0.0001	0.06574
3–4	Adults	T2DM	5	− 0.45	− 0.57	− 0.33	9.9	59.5	0.0427	0.00000
4.5–7.5	Adults	T1DM	23	− 0.42	− 0.58	− 0.27	336.5	93.5	< 0.0001	0.1030
4.5–7.5	Adults	T2DM	9	− 0.59	− 0.80	− 0.39	71.9	88.9	< 0.0001	0.06313

There was substantial heterogeneity between trials, with I^2 above 75% in T1DM at each timepoint. For T2DM, I^2 was also above 75% at 4.5–7.5 months, with other timepoints comprising 5 or fewer trials

T1DM, type 1 diabetes; T2DM, type 2 diabetes

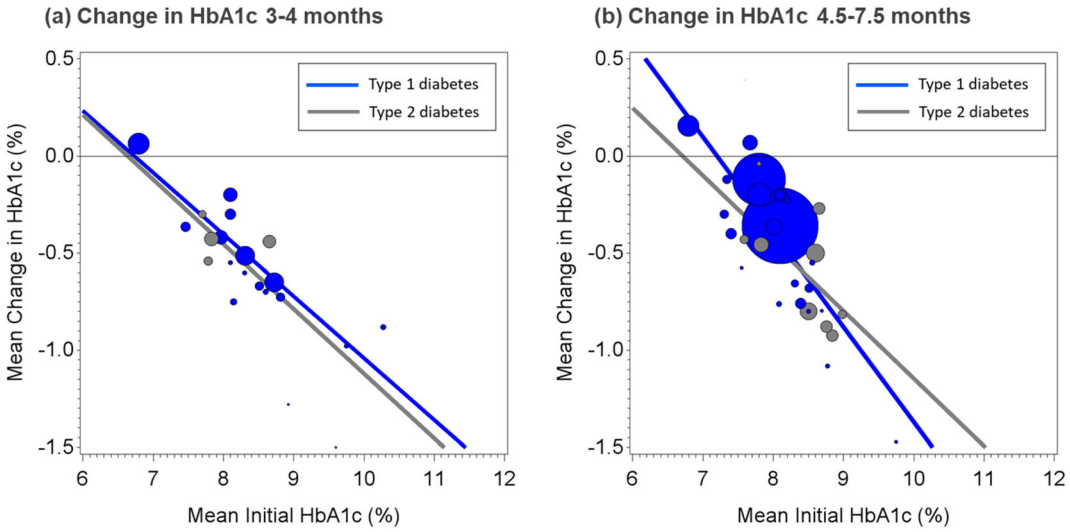

Fig. 2 Mean change in HbA1c in adults with T1DM or T2DM after starting the FreeStyle Libre system. Data shows a meta-regression analysis of mean change in HbA1c versus mean initial HbA1c as a bubble chart. The area of each bubble represents the weight of the trial. The regression line from meta-regression random effects model is displayed. Figure 2a Blue regression line = T1DM. Slope = − 0.32 (95% CI = − 0.43 to − 0.21). Heterogeneity: τ^2 = 0.0095. R^2 = 85.6%. Grey regression line = T2DM. Slope = − 0.33 (95% CI = − 0.92 to 0.25). Heterogeneity: τ^2 = 0.0030. R^2 cannot be calculated as estimate of heterogeneity in meta-analysis is zero. Figure 2b Blue regression line = T1DM. Slope = − 0.49 (95% CI = − 0.66 to − 0.32). Heterogeneity: τ^2 = 0.028. R^2 = 72.5%. Grey regression line = T2DM. Slope = − 0.35 (95% CI = − 0.74 to 0.05). Heterogeneity: τ^2 = 0.044. R^2 = 30.2%. T1DM, type 1 diabetes; T2DM, type 2 diabetes

(50 mmol/mol) (Fig. 2). For each percentage increase in mean initial HbA1c above this level, HbA1c at 4.5–7.5 months falls by − 0.49% (95% CI − 0.66 to − 0.32) in T1DM and by − 0.35 (95% CI − 0.74 to 0.05) in T2DM.

Longitudinal Change in HbA1c Over 12 months and 24 Months After Starting the FreeStyle Libre System

Adjusted mean change from baseline after starting the FreeStyle Libre system is shown for adults in Fig. 3 and for children and adolescents in Fig. 4. Both in T1DM and T2DM, mean HbA1c in adult subjects reduces each month to approximately 3 months. In T1DM this reduction is maintained to 24 months. In T2DM in adults, HbA1c reduction is maintained from 3 to 12 months, with no data available beyond this timepoint. The confidence intervals indicate that there is no evidence of a difference in

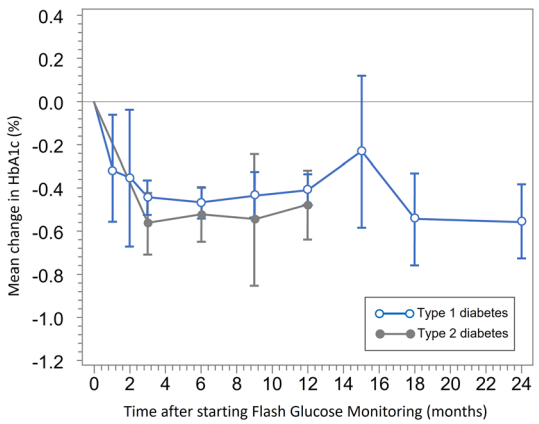

Fig. 3 Mean change in HbA1c with flash glucose monitoring is sustained over 12–24 months in adult subjects. Data show the longitudinal plot of adjusted mean change in HbA1c versus time for adults with T1DM or T2DM. For each timepoint, there is substantial overlap of the confidence intervals of the slope for T2DM and T1DM, indicating that there is no evidence that T2DM has a different pattern of change in HbA1c than T1DM after application of the FreeStyle Libre system

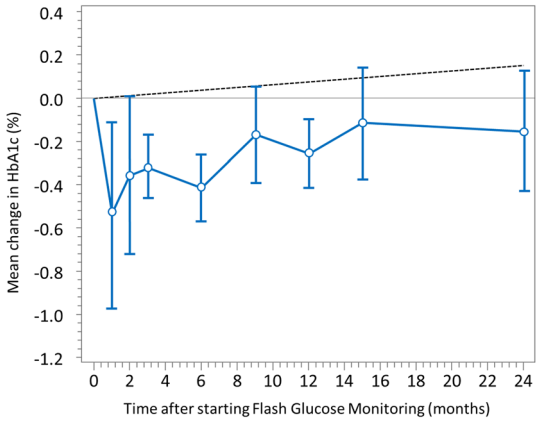

Fig. 4 Mean change in HbA1c with flash glucose monitoring is sustained over 24 months in children with T1DM. Data show the longitudinal plot of adjusted mean change in HbA1c versus time for children and adolescents with T1DM. The dotted line above the adjusted baseline indicates the predicted rise in mean HbA1c with age in children and adolescents observed by Rosenbauer et al. [20], calculated using the difference in HbA1c between > 5–10 and > 15–20 years

the HbA1c reduction by time in T1DM compared to T2DM.

In children and adolescents, mean HbA1c levels show the greatest reduction after 1 month to − 0.54% (Fig. 4), with this effect lessening with time up to 15 months, after which the reduction appears to stabilize through 24 months (Fig. 4). In this context, Rosenbauer et al. [20] have observed that mean HbA1c increases with age in children and adolescents, which we have calculated from the data in Rosenbauer et al. and represented by the dotted line (Fig. 4). This would suggest that a proportion of the attenuated reduction in longitudinal mean HbA1c when using the FreeStyle Libre system can be explained by the age effects as children mature.

DISCUSSION

The outcomes from this meta-analysis of 75 observational studies confirm that using the FreeStyle Libre system is associated with significant reductions in chronic exposure to hyperglycaemia, as measured by laboratory HbA1c. For adults these reductions are evident by 3 months after the introduction of flash glucose monitoring, with fall in HbA1c of − 0.53% in T1DM and by − 0.45% in T2DM. The meta-regression analysis shows that reductions in HbA1c are correlated with the starting HbA1c for FreeStyle Libre users. At the 4.5–7.5-month point, for every percentage point increase in mean starting HbA1c, adult users with T1DM will see an additional − 0.49% reduction in HbA1c and users with T2DM will see an additional − 0.35% fall. These gains are then shown to persist throughout the time period for which sufficient data exist (up to 24 months in T1DM and up to 12 months in T2DM). We acknowledge that there were only two studies with observations at 24 months. However, the model estimate at 24 months is calculated using the prior time points from each of these studies in comparison with other studies and the between-trial variation is taken into account in the confidence intervals. This persistence at 24 months supports the contention that confounding factors, other than use of the FreeStyle Libre system, are not responsible for the reductions in HbA1c. For example, initiation of the flash glucose monitoring might have been accompanied by device training or diabetes education, as well as more-focused time with healthcare professionals during the initiation process. However, the durability of the change in HbA1c at 12 and 24 months following initiation argues strongly that the fall in HbA1c is a consequence of using the FreeStyle Libre system for daily diabetes management.

The reduction in HbA1c in adults with T1DM using the flash glucose monitoring has now been well established, both through the current and the previous meta-analysis [4]. We have confirmed that this is a persistent benefit, at least up to 2 years after initiation. Importantly, we have also established that the same benefit is achieved by FreeStyle Libre users with T2DM up to 12 months after starting with flash glucose monitoring. Both in T1DM and in T2DM, greater reductions in HbA1c are shown for users with higher starting baselines. In T2DM, recent publications indicate that reductions are not only of greater magnitude in FreeStyle Libre users with higher baseline HbA1c but that adults with T2DM on non-insulin therapy see a

greater reduction by comparison with those on insulin therapy and similar HbA1c levels at initiation [21]. Overall, our analysis makes it clear that the patterns of change in HbA1c in T1DM and T2DM are not different after starting the FreeStyle Libre system, indicating that flash glucose monitoring can be used in the same way to reduce long-term glucose exposure for adults with either T1DM or T2DM.

For children and adolescents with T1DM, starting the FreeStyle Libre system is associated with reductions in HbA1c from 1 month (− 0.54%) to 6 months (− 0.42%). However, although a lower HbA1c is still evident at 12 and 24 months after starting flash glucose monitoring, the earlier reductions have been attenuated. Although we have included a single study that includes the 24-month timepoint, this trial also includes 6- and 12-month observations, thereby allowing a credible comparison across time from starting FreeStyle Libre. The blunted reduction at later time points in paediatric subjects contrasts with the observations in adults with T1DM, where the early fall in HbA1c was maintained at 24 months. One interpretation of this trend in children is that the change in HbA1c as children mature, as noted in the German and Austrian DPV diabetes register by Rosenbauer et al. [20], provides an opposing driver for HbA1c change despite use of the FreeStyle Libre system. This trend to increasing average glycaemia for paediatric subjects, as measured by HbA1c, has been subsequently confirmed in several studies that show this is a general feature of children growing into young adults with T1DM [22–25]. A separate analysis as part of the SWEET diabetes registry has reported that the mean HbA1c of youth is highest at diagnosis and lowest between months 4 and 5 post-diabetes diagnosis, but that it then continues to increase steadily through the first 18 months after diagnosis [26]. It is not clear from our data when children were started on the FreeStyle Libre system relative to time of diagnosis, but we must consider that this may be a factor. In this context, the psychological and emotional changes that accompany puberty may also affect use of the FreeStyle Libre system, with changes in the frequency of daily sensor scanning, that can impact glycaemic outcomes. However, despite the attenuation of the HbA1c reduction shown in our data, the use of the FreeStyle Libre system has provided a relative benefit compared to the natural history of HbA1c in this population.

We acknowledge that our current meta-analysis has limitations. These include that we were limited to inclusion only of studies that met our conditions for statistical analysis. Also, recruitment of subjects into the included observational studies was not standardized and only flash glucose monitoring arms were considered, and no comparison to control subjects was possible, since many of the real-world observational studies did not contain a control group. It is also a limitation that other metrics of potential interest were not included in our analysis. For example, average sensor scanning frequencies in relation to change in HbA1c, where noted, have not been included and no other information regarding the system use by individual patients or groups of patients are available. Studies may also have introduced bias in recruitment of the patients, since entry criteria were not standardised across the studies with few eligibility criteria specified. As with all real-world studies, there is potential publication bias. Also, not all studies report how any missing data were handled.

Strengths of our analysis are the large number of studies and patients included. The substantial heterogeneity between the studies analysed here was accommodated using a random effects model, as is indicated for such an analysis. This heterogeneity is an acknowledged limitation of observational studies in general [27, 28].

A key aspect of guidance on inclusion of observational studies with inherent heterogeneity is the obligation to consider alternative hypotheses for the treatment effect proposed. Because many of the included studies are interpreted to be prospective in design, the most obvious alternative explanation of the consistent reduction in HbA1c reported here is a study effect which has then prompted a significant change in self-care, as discussed above, independent of the capabilities of the FreeStyle Libre technology itself. However, we argue against this for several reasons. Firstly, across

the studies included, no evidence of specific changes in standard self-care were reported that might result in improved HbA1c. Rather, where noted, SMBG testing frequencies decreased. Secondly, the longitudinal analysis on adult subjects (Fig. 3) shows the reduction in HbA1c is sustained over 12 months (T2DM) and 24 months (T1DM), which mitigates against a study effect.

Although HbA1c has been the gold standard as a marker for diabetes health since the outcomes of the DCCT and UKPDS studies [13, 29], it is not the only measure of glycaemic control. Even in the case of absence of a significant reduction in HbA1c, using the FreeStyle Libre system is associated with a reduction in the amount of time that adults with T1DM or T2DM on insulin spend with glucose in the hypoglycaemic zone below 3.9 mmol/L (70 mg/dL) [1, 2], with significant improvements both in daytime and nocturnal hypoglycaemia. In the IMPACT study [1], these benefits were evident in the intervention arm with a mean baseline HbA1c of 6.8%, indicting that the benefits of using the FreeStyle Libre System are evident in markers of diabetes health other than HbA1c. Similarly, adults, children and adolescents with T1DM see reductions in measures of glycaemic variability with the FreeStyle Libre system, as do adults with T2DM on insulin [1, 2, 30]. Also emerging are observational studies confirming the association of flash glucose monitoring with reduced hospitalization admissions for acute diabetes events (ADEs), such as diabetic ketoacidosis, severe hypoglycaemia or coma. The RELIEF study across the French national SNDS healthcare database [31] showed that across 74,011 people with T1DM or T2DM using the FreeStyle libre system, hospitalizations for ADEs fell in T1DM by − 49.0% and by − 39.4% in T2DM in the 12 months after FreeStyle Libre initiation compared to the 12 months before. This included reductions in admissions for DKA in T1DM (− 56.2%) and in T2DM (− 52.1%). Similar outcomes are also seen in the ABCD FreeStyle Libre nationwide audit in the UK [32].

CONCLUSIONS

The meta-analysis of 75 real-world observational studies and RCTs reported here confirms and extends our previous analysis. Initiating flash glucose monitoring with the FreeStyle Libre system is associated with a significant reduction in HbA1c for adults and children with T1DM and for adults with T2DM. The degree of change in HbA1c is predicted by the HbA1c at baseline, such that a greater reduction in HbA1c is seen over the study period for users with a higher baseline HbA1c, both in T1DM and T2DM. Importantly, longitudinal analysis of the data for adult subjects with T1DM or T2DM showed that using the FreeStyle Libre system results in a sustained reduction in HbA1c, which argues against a study effect. Just as important is that the pattern of change in HbA1c is common in T1DM and T2DM, indicating that flash glucose monitoring can be used in exactly the same way to drive reductions in HbA1c for adults with either type of diabetes. Longitudinal analysis of children and adolescents with T1DM indicates that using the FreeStyle Libre system is associated with sharp falls in HbA1c from 1 to 6 months but that the scale of these reductions is lessened over 12–24 months. This pattern of response may be a consequence of the observed trend for HbA1c to rise in children over time during their youth.

ACKNOWLEDGEMENTS

Funding. Funding for this meta-analysis, preparation of the manuscript and the journal's Rapid Service Fee were funded by Abbott Diabetes Care.

Editorial Assistance. Support for the writing of the manuscript was provided by Dr Robert Brines of Bite Medical Consulting, which was paid for by Abbott diabetes care division.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this

article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Author Contributions. All named authors contributed to the concept and design of the manuscript and worked collaboratively to review and prepare the final manuscript.

Disclosures. Zoë Welsh and Alexander Seibold are employees of Abbott Diabetes Care. Mark Evans has been a member of Advisory panels/ received speakers fees and/or received travel support from Abbott Diabetes Care, NovoNordisk, Eli Lilly, Medtronic, Dexcom, Roche, Zucara, Pila Pharma.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Data Availability. The datasets analyzed during the current study are available from the corresponding author on reasonable request.

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