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Flash forward: a review of flash glucose monitoring

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What's new?

- The FreeStyle Libre is a novel interstitial flash glucose monitor designed to replace finger-stick glucose tests, available through the UK National Health Service, subject to local health authority approval, from November 2017.

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- In this narrative review, we summarize the current evidence on the efficacy of the FreeStyle Libre with regard to HbA_{1c}, hypoglycaemia and quality of life from randomized and observational studies.
- Device accuracy data are presented, both as stand-alone data and in comparison to existing continuous glucose monitors and blood glucose meters.
- We discuss advantages, disadvantages and adverse events, and summarize key practice/safety areas aimed at helping clinicians and funders to make informed decisions about the future role of the FreeStyle Libre in diabetes management.

Abstract

The FreeStyle Libre flash glucose monitor became available on prescription (subject to local health authority approval) in all four nations of the UK from November 2017, a watershed moment in the history of diabetes care. Calibration free, the FreeStyle Libre is a disc worn on the arm for 14 days which is designed largely to replace the recommended 4–10 painful finger-stick blood glucose tests required each day for the self-management of diabetes. This review discusses clinical data from randomized and observational studies, considers device accuracy metrics and deliberates its popularity and the potential challenges that this new device brings to diabetes care in the UK. In randomized trials, FreeStyle Libre use is associated with a reduction in hypoglycaemia and, in observational studies, improvements in HbA_{1c} levels. User satisfaction is high and adverse events are low. Accuracy of the FreeStyle Libre is comparable to currently available real-time continuous glucose monitors in adults, children and during pregnancy; the cost of the FreeStyle Libre is lower. Glucose data can be visualized in multiple devices and platforms, and summarized in an ambulatory glucose profile to aid pattern recognition and insulin dose adjustment. There is a need for appropriate

education, of both users and healthcare professionals, to harness the full benefits. Further randomized studies to assess the long-term impact on HbA_{1c}, particularly in those with high baseline HbA_{1c} and in specific age groups, such as adolescents and young adults, are warranted. The potential impact on complications, is yet to be realized.

Introduction

Type 1 diabetes is a demanding lifelong condition. It requires individuals to measure blood glucose multiple times a day, facilitating insulin dose adjustment in the unrelenting endeavour to achieve normoglycaemia and minimize the future risk of micro- and macrovascular complications [1]. Despite major progress in the care of people living with Type 1 diabetes, many fail to achieve modern glycaemic targets. A key barrier to achieving near normal glucose levels is this need for frequent finger-stick blood glucose monitoring, perhaps only second to the risk and fear of hypoglycaemia [2]. Pain and inconvenience are recognized reasons for non-adherence to self-monitoring of blood glucose [3,4].

Remarkably, self-monitoring of blood glucose (SMBG) has only been an option since the 1970s [5]. Its introduction was met with controversy. Despite Sonksen reporting 'insulin dosage and type were found to be much easier and more predictable than with urine-glucose analysis…hypoglycaemic episodes were less frequent, 70% of patients preferred blood-tests to urine tests and 92% would like to buy their own meter if the price was right', it was not until the 1980s that uptake became more widespread. Blood glucose monitoring is now accepted as the standard of care, with the National Institute for Health and Care Excellence (NICE; NG17) recommending four to 10 measurements per day [6].

In 1999, MiniMed received US Food and Drug Administration approval for the first retrospective continuous glucose monitoring (CGM) device in the USA [7]. Since then, a number of retrospective and real-time CGM options have been introduced, including MiniMed iPro, Enlite 2, Enlite Enhanced, Enlite 3 (Medtronic Inc, Northridge, CA, USA), DexCom Short Term Sensor, Dexcom 3, 7, Gen 4 and 5 (Dexcom Inc, San Diego, CA, USA), and Navigator I and II (Abbott Diabetes Care, Alameda, CA, USA). These devices have been evaluated in a range of studies, which have shown that consistent use of real-time CGM is associated with improvements in HbA_{1c} and reductions in hypoglycaemia [8,9]. However, widespread adoption of these devices has been hampered by several factors including cost, accuracy of earlier devices and user acceptability.

In 2014, a new category of device was introduced: the FreeStyle Libre Flash Glucose Monitoring System (Abbott Diabetes Care, Alameda, CA). The FreeStyle Libre device is a white disc, worn on the arm for 14 days. As implied by the term 'flash glucose monitoring' the user can obtain glucose results instantly by scanning the glucose sensor with the reader, or their mobile phone, producing real-time on-demand glucose data. A recent International Consensus on CGM has coined the term ‘intermittently viewed CGM’ to describe flash glucose monitoring [10]. While both real-time CGM and the FreeStyle Libre will allow users to monitor interstitial glucose levels, only real-time CGM will trigger an alarm to alert users to the potential risk of hypoglycaemia or hyperglycaemia. With the FreeStyle Libre, such trends can only be viewed after physically scanning the sensor. A further contrast between real-time CGM and the FreeStyle Libre is the need for real-time CGM systems to be calibrated at regular intervals using finger-stick glucose levels. The FreeStyle Libre device, which uses wired enzyme technology, is factory calibrated and does not need finger-stick glucose calibration during use, with stability of the sensor up to 14 days.

Abbott provided users with the option of direct online purchase of the FreeStyle Libre, without prior healthcare professional approval. This, combined with the relatively low cost and advertising, led to a demand which exceeded the manufacturer's expectations. Shortly after launch, orders were suspended while a new factory was built. In the present review, we aim to explore the reasons underlying the popularity of this device, and discuss the clinical data, accuracy and challenges that this new device brings to diabetes care in the UK. To provide readers with the most up-to-date information we have included both published papers and conference abstracts (Table 1). Data presented in some conference abstracts are preliminary in nature.

Randomized controlled trials

Table 1 lists the randomized controlled trials on the FreeStyle Libre device. The largest study is the IMPACT randomized controlled multicentre European trial [11]. That study included 239 participants with well-controlled [HbA_{1c} ≤59 mmol/mol (7.5%)] Type 1 diabetes and intact awareness of hypoglycaemia, a third of whom used continuous subcutaneous insulin infusion therapy. FreeStyle Libre use was associated with a 38% reduction in time spent in hypoglycaemia (<3.9 mmol/l) with no change in total daily insulin dose. The reduction in hypoglycaemia was achieved within 2 weeks, despite no training on glucose data interpretation and no healthcare professional contact during this period, suggesting that users intuitively understood how to react to the data (Fig. 1). There was an increase in glucose time in range, combined with a reduction in glycaemic variability. HbA_{1c} was unchanged. FreeStyle Libre users were scanning 15 times/day on average, a behaviour sustained over the 6-month follow-up. FreeStyle Libre utilisation was high at >90% with high treatment satisfaction. It is important to highlight that those with impaired awareness of hypoglycaemia were not included in IMPACT.

In a randomized, non-masked parallel group study conducted in London by Reddy *et al.* [12], the FreeStyle Libre was assessed compared with real-time CGM (Dexcom G5) in people with Type 1 diabetes who had experienced a severe hypoglycaemic event in the last 12 months or had impaired awareness of hypoglycaemia (Gold score ≥4). After a 2-week run-in period, 40 participants using intensified multiple daily injections were randomized to either Dexcom G5 real-time CGM or FreeStyle Libre for 8 weeks. The reduction in percentage of time spent in hypoglycaemia (<3.3 mmol/l) was significantly greater in those using the Dexcom G5 real-time CGM compared with the FreeStyle Libre (–4.3%; P=0.0006); however, there was no significant difference between the groups in the Gold score or HbA_{1c} level from baseline to endpoint. The authors concluded that real-time CGM has significantly greater benefit than the FreeStyle Libre monitor in those with impaired awareness of hypoglycaemia. These findings lend support to the NICE Type 1 diabetes in adults (NG17) recommendations for the use of real-time CGM in those who have either recurrent severe hypoglycaemia or loss of awareness of hypoglycaemia [6].

The FreeStyle Libre has also been assessed in people with Type 2 diabetes on intensive insulin therapy in a large multicentre European study of 224 participants [13]. Despite less frequent sensor scans than were seen in the IMPACT study (8 vs 15 per day), time in hypoglycaemia (<3.9 mmol/l) was reduced by 0.47±0.13 h/day compared with a control group, representing a 43% reduction in time spent in hypoglycaemia. HbA_{1c} was unchanged. Treatment satisfaction was higher in users and no device-related serious adverse events were reported, suggesting that flash glucose monitoring also offers a suitable replacement for SMBG in those with Type 2 diabetes who are on intensive insulin therapy.

Observational studies

Adults

A range of observational studies have evaluated the FreeStyle Libre (Table 1). Dover *et al.* [14] prospectively assessed the FreeStyle Libre in 25 participants and described improved glucose control, reduced hypoglycaemia and improved quality of life. The mean HbA_{1c} of 64 mmol/mol (8.0±0.14%) reduced to 59 mmol/mol (7.5±0.14%) after 16 weeks. Those with a baseline HbA_{1c} >58 mmol/mol (7.5%) experienced a greater (–0.59±0.15%) reduction. There was a significant reduction in hypoglycaemia and diabetes distress. A key behavioural change associated with FreeStyle Libre use was an increase in those delivering the insulin bolus 15–20 min pre-meal as per recommendations. McKnight and Gibb [15] subsequently reported FreeStyle Libre use in ~3% of their Type 1 diabetes clinic population in Edinburgh. FreeStyle Libre use was associated with a significant change in HbA_{1c} in users vs non users (–0.2% vs +0.1%). Of those with HbA_{1c} levels >58 mmol/mol (>7.5%), 32% of FreeStyle Libre users reached target HbA_{1c} compared with only 9.8% of non-users (P<0.001).

A study in Israel of 31 people with poorly controlled Type 1 or Type 2 diabetes noted an HbA_{1c} decrease of 1.33±0.29% after 8 weeks of FreeStyle Libre use [16]. For those who continued using the device (n=27), the change was maintained for 24 weeks (1.21±0.42%; P = 0.009).

Holcombe *et al*. [17] (conference abstract) assessed the FreeStyle Libre in a small group of 13 people with Type 1 diabetes. In their study, the mean HbA_{1c} fell from 75 to 65 mmol/mol (9.0% to 8.1%), with increased time in target (29% vs 24%) and reduced hypoglycaemia (82 vs 95 min). All participants demonstrated a reduction in their Problem Areas in Diabetes (PAID) questionnaire scores. Glucose monitoring increased from three finger-stick tests per

day to 11 scans per day. The authors also commented in their abstract that the device facilitated virtual contact and support.

Children and young adults

Campbell *et al.* [18] evaluated the use of FreeStyle Libre as a replacement for SMBG in young people (aged 4–17 years) with Type 1 diabetes [*n*=76, 58% continuous subcutaneous insulin infusion users, 46% boys aged 10.3±4.0 years, baseline HbA_{1c} 63 mmol/mol (7.9±1.0%), Type 1 diabetes duration 5.4±3.7 years] in a single-arm European multicentre trial. After 2 weeks' baseline masked (blinded) wear, participants used FreeStyle Libre for 8 weeks. Time with glucose values in range (70–180 mg/dl) and HbA_{1c} significantly improved vs baseline [mean (±SD) 1.0±2.8 h/day, P=0.0056 and –0.4±0.6%, P<0.0001 respectively]. The mean FreeStyle Libre scan frequency was 12.9/day, whereas SMBG reduced from a median of 8.0 (baseline) to 1.0 times/day during open use. The Diabetes Treatment Satisfaction Questionnaire scores showed improved treatment satisfaction for parents (*n*=70) and teenagers (age ≥13 years; *n*=23): mean (±SD) score change 21.7±6.6 (P<0.0001) and 18.7±5.6 (P<0.0001), respectively.

These studies add to the growing clinical perception that the FreeStyle Libre monitor is desirable and beneficial for people living with Type 1 diabetes. It is important to note, however, that improvements seen during observational studies cannot be solely ascribed to the FreeStyle Libre device as other factors, such as additional education or simply being observed, may contribute to improvements. Nonetheless, the authors of these studies observed striking reductions in HbA_{1c} with FreeStyle Libre use in those with very poorly controlled diabetes [HbA_{1c} >86 mmol/mol (10%)], who were doing little or no glucose monitoring. Unfortunately, such individuals are rarely included in clinical studies.

User satisfaction and insights

Adults

User feedback on the FreeStyle Libre is generally very positive. Olafsdottir *et al.* [19] explored treatment experience in 58 adults with Type 1 diabetes. The FreeStyle Libre scored favourably, with scores of 9/10 for 'My experience of the FreeStyle Libre was very positive' and 9.4/10 for 'I would like to use FreeStyle Libre in my daily life'. The participants reported the device was easy to use (9.8/10) and easy and trouble-free to insert (9.1/10) and, importantly, they felt it was easy to interpret information on the FreeStyle Libre screen (9.6/10). The authors also compared their findings for FreeStyle Libre user satisfaction (overall score 82.2–98/100) with their earlier studies of the Dexcom G4 and Enlite sensor which used the same questions (overall score 72.5–90/100 for Dexcom G4 and 42.1–86.1/100 for Enlite).

Ish-Shalom *et al.* [16] reported their experience in Israel with the FreeStyle Libre. All users (n = 31) were highly satisfied and stated that they would like to use flash glucose monitoring in the future. In addition, users unanimously stated that it was easy to use and painless. Healthcare professionals reported that the data presentation, particularly the ambulatory glucose profile, was an outstanding tool, enabling better and easier control of glucose levels.

Children/young adults

Families of children who have used the device are generally satisfied. McPhater *et al*. [20] contacted the families of 19 FreeStyle Libre users. They reported that the sensor was easy to insert and was an easier method of checking glucose than SMBG (preliminary analysis, conference abstract). The majority found the sensor lasted 14 days. Most perceived that glucose control had improved during use as a result of improved awareness of glucose levels,

and changes in self-management behaviour, particularly with regard to hypoglycaemia. Although trend data were useful, most users did not alter self-management as a result. Confidence in nocturnal glucose control was improved. A quarter of participants did not continue to use the sensors because of limited sensor duration and blood glucose discrepancies compared with SMBG.

Another user evaluation in the paediatric population also described high user satisfaction, with the majority rating the device favourably for sensor application (84.3–92.1%) and sensor wear and use (87.2–100%) when comparing use to SMBG (85.4–97.5%) [21] .

Real-world use of FreeStyle Libre

The manufacturer of the FreeStyle Libre evaluated the association of real-world scanning using the FreeStyle Libre monitor with glucose control measures [22]. In that study, a large number of real-time readers (50 831) with 279 446 sensors (86.4 million monitoring hours by 63.8 million scans) were analysed (Fig. 2). Users performed an average of 16.3 scans per day [median (interquartile range) 14 (10–20)]. Estimated HbA_{1c} levels decreased (P<0.001) as the scan rate increased, from 64 mmol/mol (8.0%) to 50 mmol/mol (6.7%) from the lowest (mean 4.4 scans/day) to the highest (mean 48.1 scans/day) groups, while time below 3.9, 3.0 and 2.5 mmol/l decreased by 15%, 40% and 49%, respectively (all P<0.001).

Adverse events

As one might expect, most adverse events were related to the medical grade adhesives used to secure the sensor for 14 days. Sensor-wear-related symptoms were recorded as adverse events in the IMPACT trial if the effects were severe and lasted for >7 days, or if the user required prescription medication for the event to resolve [11]. IMPACT reported 13 device-

related adverse events in 10/119 users in the intervention arm, which were related to wearing the sensor, and were categorized as mild (three cases), moderate (four cases) and severe (six cases). Six of 120 participants in the intervention arm and one of 121 participants in the control arm withdrew from the study because of adverse events. For participants with adverse events involving skin symptoms, the symptoms (including severe) were resolved by use of barrier products (e.g. Cavilon spray) or drug therapy (e.g. zinc ointment, Fenistil gel or hydrocortisone cream), or by relocating the device to another area [23]. Investigations have since identified isobornyl acrylate as the likely agent causing contact dermatitis [24]

Since completion of the IMPACT trial, minor design changes have been made to the FreeStyle Libre. These changes are expected to improve breathability of the skin that is in contact with the sensor and to facilitate the exclusion of moisture between the sensor–skin interface [23]. During the children's study, five device-related adverse events were reported in five (6%) participants: allergic reaction, blister, pink mark/scabbing and abrasion on sensor removal [21].

Assessing sensor accuracy

There are no consensus guidelines for the best metric by which to assess the accuracy of real-time CGM and flash glucose monitoring devices. As a result, a variety have been used, the majority of which are affected by glucose excursions, therefore, comparing across studies may lead to misleading conclusions [25]. Ideally different sensors should be compared in the same individual exposed to same glucose fluctuations.

Accuracy of CGM devices is expressed using standards originally designed for assessing the accuracy of SMBG [26]. Numerical accuracy is based on mean or median absolute relative deviation (ARD; sensor glucose-reference glucose/reference glucose*100) and/or

International Standardization Organization (ISO) criteria [27]. Glucose data are non-normally distributed so the median ARD is usually lower than the mean ARD. In 2013, ISO criteria (ISO: 15197:2013) were drawn up, requiring that 95% of blood glucose results be within ± 0.83 mmol/l of laboratory results at concentrations of <5.6 mmol/l, or within ± 15% of laboratory results at concentrations of ≥5.6 mmol/l [27]. In contrast, clinical accuracy is often expressed using Clarke or consensus error grid analyses [28,29]. Error grid analyses assign a specific level of clinical risk to any possible error. Each point on the grid (true glucose, measured glucose) is associated with one of five risk levels. In both Clarke and consensus error grids, errors in zones A and B denote minimal risk to the user.

Accuracy of FreeStyle Libre

Accuracy in adults

The FreeStyle Libre monitor provides interstitial glucose results without the need for finger-stick glucose calibrations. This removes the risk of sensor inaccuracies attributable to user errors, such as not washing hands before a glucose test or delay in glucose entry [30].

In a study funded by the manufacturer, Bailey *et al.* [31] assessed the accuracy of the FreeStyle Libre in 72 study participants with Type 1 or Type 2 diabetes at four clinical sites in the USA. A sensor was inserted at the back of each upper arm for up to 14 days. Three sensor lots were used in the study. There were three scheduled in-clinic visits during the 14-day sensor wear period, where venous blood samples were collected every 15 min over an 8-h period for YSI analyser reference tests (Yellow Springs Instruments, Yellow Springs, OH, USA). At least eight capillary glucose tests, using the glucose meter built into the reader, were required to be performed on each day of the sensor wear, both at home and in the clinic.

In total, 13 195 capillary glucose and 12 172 YSI reference (venous) results were paired with sensor glucose results. The percentages of results in zone A of the consensus and Clarke error grids were 86.7% and 85.5%, respectively. The percentages of sensor results in zones A and B of the consensus and Clarke error grids were 99.7% and 99.0%, respectively, whereas 86.2% and 82.8% of sensor results were within 0.8 mmol/l or 20% of capillary glucose reference and venous reference, respectively (percentage within 0.8 mmol/l or 15% of reference data not reported).

The overall mean ARD was 11.4% for sensor results with capillary glucose reference. The overall mean ARD in the clinic alone for sensors' results with capillary glucose reference and with YSI reference was 12.1% and 12%, respectively. Mean ARD was comparable when the reference glucose was <100 mg/dl and >100 mg/dl. Looking at the performance of individual sensors, ~55% appear to have a mean ARD ≤10%, while ~10% of sensors had mean ARD values ≥16%. The percentage of sensor glucose levels in zone A of the Clarke error grid was lower on day 1 (~72%) compared with days 2 to 14 (85% to 89%).

During an independent study, Olafsdottir *et al*. [19] assessed the accuracy of the FreeStyle Libre device in 58 adults with Type 1 diabetes for 10–14 days and measured capillary blood glucose levels with the HemoCue blood glucose measurement system at least six times a day simultaneously. For the entire study period, the mean ARD was 13.2%. For glucose values <4, 4–10, and >10 mmol/l, the mean ARD was 20.3%, 14.7%, and 9.6%, respectively. Notably, during a *post hoc* analysis, authors found that 19.9% of glucose values measured by FreeStyle Libre deviated by >20%, and 7.9% of glucose values measured by FreeStyle Libre deviated by >30% from the HemoCue reference. Authors have raised concerns about the clinical impact of such high deviations when used for dosing insulin.

Accuracy during oral glucose tolerance test

Another study by Fokkert *et al.* [32] has compared the accuracy of the FreeStyle Libre monitor during 14 days of home use and during an oral glucose tolerance test. Interestingly, they also compared the accuracy of the device when worn in the back of the arm and in the abdomen. The percentage of data points in the zone A of the Clarke error grid was significantly higher when the sensors were worn in the back of the arm (85.5%) compared with the abdomen (64%). Authors found the FreeStyle Libre tended to report lower results in lower glucose ranges, and higher results than expected in the higher ranges. Following a standardized glucose load, a slower rise in glucose level was observed for FreeStyle Libre as compared with reference methods during the first 45–60 min after glucose load ingestion.

Accuracy in children

The accuracy of the FreeStyle Libre in children has been assessed during a multicentre UK-based study [21]. Those aged 4–17 years, with Type 1 or Type 2 diabetes treated with multiple daily injections of insulin or continuous subcutaneous insulin infusion, and monitoring blood glucose >2 times/day were eligible to participate. Participants wore the sensor for up to 14 days and were asked to perform four blood glucose tests daily (FreeStyle Optium test strips; Abbott Diabetes Care), each immediately followed by an interstitial fluid glucose sensor measurement (data masked to participants) to allow comparison of results between sensor and blood glucose. Clarke error grid analysis showed 83.8% of results in zone A and 99.4% of results in zones A and B. Overall, the mean ARD was 13.9% and the median ARD was 10.4%. For paired results at lower glucose concentrations, with capillary glucose <5.5 mmol/l (*n*=1468), the mean absolute difference was 0.75 mmol/l; for paired results at

higher glucose concentrations, capillary glucose 5.5–10.0 mmol/L (*n*=2090), the mean ARD was 13.5%, and at capillary glucose >10.0 mmol/l (*n*=1935), the mean ARD was 10.6%.

Accuracy in pregnant women

Scott *et al.* [33] evaluated the accuracy of the FreeStyle Libre in 74 women during pregnancy (Type 1 diabetes, *n*=24, Type 2 diabetes, *n*=11 and gestational diabetes, *n*=39, average gestation 26 weeks, average age 30 years, and 66.2% using insulin). The study was conducted across nine UK sites and four in Austria. Compared with capillary glucose, consensus error grid analysis showed 88.1% of FreeStyle Libre readings were within zone A and 99.8% were within zones A and B. The overall mean ARD was 11.8%. Results show good agreement between the FreeStyle Libre and the capillary glucose for pregnant women with diabetes, indicating the device is safe and accurate for use by this population.

Head-to-head comparison with real-time CGM and blood glucose meters

Aberer *et al.* [34] recently compared the FreeStyle Libre with Dexcom G4 Platinum (Dexcom) and Medtronic MiniMed 640G (Medtronic) systems. A total of 12 individuals with Type 1 diabetes were included in a single-centre, open-label study over a 12-h period. Hypo- and hyperglycaemia were induced and venous plasma glucose values measured every 5 min for 12 h. The study also included a short bout of exercise (30 min, 50% maximum oxygen consumption). Across all glycaemic ranges including exercise, the FreeStyle Libre exhibited the lowest and Medtronic the highest mean ARD. The systems fulfilled ISO 15197:2013 criteria by 73.2% (FreeStyle Libre), 56.1% (Dexcom) and 52.0% (Medtronic). The mean (SD) ARDs in the entire glycaemic range were 13.2 (10.9)% (FreeStyle Libre), 16.8 (12.3)% (Dexcom) and 21.4 (17.6)% (Medtronic). All sensors performed less accurately during hypoglycaemia and best during hyperglycaemia.

In another study, Bonora *et al.* [35] compared the FreeStyle Libre with the Dexcom G4 real-time CGM sensor up to 14 days in eight individuals with Type 1 diabetes under usual care conditions. The average glucose profiles and mean ARD vs capillary glucose were broadly similar in the two systems, although the comparative performance varied significantly among individuals. For example, compared with SMBG, participant 5 had a mean ARD of 14.9% with FreeStyle Libre and a mean ARD of 37.4% with Dexcom G4 sensor. Compared with capillary glucose, the mean ARD for FreeStyle Libre among the eight participants ranged from 10.7% to 20.4% and with Dexcom G4, it ranged from 7% to 37%, indicating marked heterogeneity. There are no head-to-head studies comparing the FreeStyle Libre device with the latest generation of Dexcom G5 real-time CGM devices.

The accuracy of the Freestyle Libre, with a mean ARD of 11.4%, is comparable to many commercially available blood glucose meters. Blood glucose meters should fulfil the ISO criteria but when tested independently this was not found to be the case. Ekhlaspour *et al.* [36] assessed 17 different commercially available glucose meters against the Yellow Springs reference method (YSI 2300) to determine the mean ARD. The accuracy varied widely: mean ARD ranged from 5.6% to 20.8%. Overall, nine of 17 meters assessed had a mean ARD >12%, raising the possibility that some blood glucose meters could potentially be less accurate than the FreeStyle Libre.

Evaluation of FreeStyle Libre with potentially interfering substances

The manufacturer has undertaken tests to evaluate the FreeStyle Libre with 16 potentially interfering substances (Table S1) [37]. Testing confirmed no clinically significant interference for the substances tested, with the exception of ascorbic acid and salicylic acid.

Taking ascorbic acid may falsely raise and salicylic acid may slightly lower sensor glucose readings. The level of inaccuracy depends on the amount of interfering substance. Detailed information is available Table S1.

Summary of accuracy

In conclusion, FreeStyle Libre appears to have similar accuracy to that of currently available real-time CGM systems, such as Dexcom G4, and may even have superior accuracy to Medtronic Enlite sensors, without the need for calibration. A small number of sensors can have higher mean ARDs in the range of 16–20%. None of the currently available interstitial glucose sensors meet the ISO 15197:2013 criteria for capillary glucose meters; although in independent testing, many blood glucose meters also fail these criteria.

Adjunctive vs non-adjunctive use

The term non-adjunctive refers to the use of interstitial glucose data for insulin dosing without the need for additional finger-stick glucose checks. Presently, two glucose monitoring systems are licensed for non-adjunctive use in Europe and the USA: the Dexcom G5 system and FreeStyle Libre system.

FreeStyle Libre is designed to replace blood glucose testing in the self-management of diabetes including the dosing of insulin except in three main conditions. These are: during rapidly changing glucose values; to confirm sensor-reported hypoglycaemia or impending hypoglycaemia; and if symptoms do not correspond with the glucose value displayed. Under these circumstances, the manufacturer advises confirmation with a finger-stick glucose level. Further, Kovatchev *et al.* [38] using simulation techniques has calculated a minimal accuracy of a mean ARD of ≤10% for real-time CGM to reach sufficient safety when sensor glucose

data are used for insulin-dosing decisions. As outlined in the above accuracy studies, a small number of FreeStyle Libre sensors will have a mean ARD >15% and, unless the user cross checks with finger-stick glucose, it is not possible to know how an individual sensor is performing. The accuracy on day 1 of the sensor is lower than other days. A recent statement from the German Diabetes Society, as well as others, have highlighted pros and cons of using Dexcom G5/FreeStyle Libre in a non-adjunctive manner [39–41]. FreeStyle Libre users can perform a finger-stick (ideally fasting/when glucose not rapidly changing) to assess sensor accuracy. Also, the Driver and Vehicle Licencing Agency in the UK states that blood rather than interstitial glucose should be checked prior to driving [42].

Challenges

Funding and reimbursement in UK

In November 2017, the FreeStyle Libre became available on prescription in the UK, bringing the latter into line with several other European countries (France, Belgium, Sweden among others) where FreeStyle Libre is reimbursed. NICE has published a 'medtech innovation briefing' on the FreeStyle Libre [43] and has summarized the utility as well as gaps in the evidence base, including the uncertainties around resource impact which depends on the extent to which improved glucose control translates into fewer complications, reduced emergency admissions and less use of glucose test strips. However, in England funding is subject to local approval. Given the financial pressures on the National Health Service, there is concern that variation in local policies for funding will result in inequitable access, further widening variation in diabetes care. In an attempt to overcome this, the Regional Medicine Optimisation Committee has published recommendations for funding in select groups. (https://www.sps.nhs.uk/articles/regional-medicines-optimisation-committee-freestyle-libre-position-statement/).

Education

There is a recognized need for healthcare professionals to equip themselves with the skills required to support users of both flash glucose monitoring and real-time CGM [44]. Healthcare professionals can be reassured that, fundamentally, the skills required to make the most of the data are essentially the same principles as for intensive insulin therapy: aiming for a basal insulin which keeps the glucose relatively stable overnight, and aiming for insulin–carbohydrate ratios which bring the glucose into target by the next meal and insulin sensitivity factors which correct a higher glucose, bringing it into target 4–5 h later without causing hypoglycaemia. In the authors' experience, flash glucose monitoring is an educational tool. Many adjust basal insulin to minimize nocturnal hypoglycaemia and bolus 15–20 min pre-meal to reduce postprandial hyperglycaemia. These behavioural changes reflect the unique insights continuous glucose data provide vs isolated finger-stick glucose levels.

Ambulatory glucose profile

Flash glucose data can be displayed as an ambulatory glucose profile (Figure 3). The ambulatory glucose profile displays the data over a 24-h period, with median glucose levels, the 25--75th and 10--90th percentiles, as well as excursions and the tendency for hypo- or hyperglycaemia throughout the day. This display allows ease of hypothesis generation, while eliminating 'noise' from outliers. An expert group in the USA concluded that standardization of CGM data reporting using the ambulatory glucose profile would be of benefit [45] Matthaei *et al.* [46] have since developed a useful consensus statement on the interpretation of the ambulatory glucose profile.

Summary and personal perspectives

From the authors' perspective, FreeStyle Libre is a significant advance in the management of diabetes. Many users describe it as 'life changing'. Key advantages and disadvantages are summarized in Table 2. The FreeStyle Libre allows on-demand access to glucose data with no need for calibration and no risk of alarm fatigue. The sensor needs replaced infrequently and has a accuracy similar to real-time CGM. FreeStyle Libre data can be visualized in multiple devices and platforms as an ambulatory glucose profile to aid pattern recognition and insulin dose adjustment. We encourage appropriate education of both users and healthcare professionals, to harness the full benefits. As a more affordable option for CGM data, we support access to this technology for all people with diabetes who are treated with intensive insulin therapy. Further randomized studies to assess the long-term impact on HbA_{1c}, particularly in those with high baseline HbA_{1c} and in specific age groups such as adolescents and young adults are warranted.

Funding sources

None.

Competing interests

L.L. reports having received speaker honoraria from Minimed Medtronic, Animas, Roche, Sanofi, Insulet and Novo Nordisk, serving on advisory panel for Abbott Diabetes Care, Roche, Sanofi, Minimed Medtronic, Animas and Novo Nordisk, grants to attend educational meetings from Sanofi, Novo Nordisk and Takeda. EGW has received speaker honoraria from Abbott Diabetes Care, Diasend, Dexcom, Eli Lilly, Minimed Medtronic, Novo Nordisk, Sanofi Aventis and has served on advisory panels for Abbott Diabetes Care, Eli Lilly, Sanofi

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Supporting information

Additional Supporting Information may be found in the online version of this article:

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1 Evaluation of Abbott Diabetes Care FreeStyle Libre flash glucose monitoring system with potentially interfering substances.

Table 1 Summary of randomized and observational studies of Freestyle Libre evaluating changes in HbA_{1c} and/or hypoglycaemia

Reference	Study population	Intervention and duration	Outcomes
RCTs			
Bolinder *et al.* [11]	Adults with Type 1 diabetes, $HbA_{1c} \leq$ 7.5% and intact awareness of hypoglycaemia.	Parallel groups. FreeStyle Libre (*n*=120) vs self-monitoring (*n*=121) for 6 months.	38% reduction in time in hypoglycaemia (<3.9 mmol/l). No change in HbA_{1c}. FreeStyle Libre reduced glucose variability; mean number of scan 15/day and mean number of self-monitored blood glucose measurements 0.5/day.
Reddy *et al.* [12]*	Adults with Type 1 diabetes with impaired awareness of hypoglycemia or severe hypoglycaemia.	Parallel groups (*n*=40) FreeStyle Libre vs real-time CGM (Dexcom G5) for 8 weeks.	Higher reduction in % time in hypoglycaemia (<3.3 mmol/l) from baseline to endpoint with G5: median difference between groups 4.3%; *P*=0.006.
Haak *et al.* (13)	Adults with Type 2 diabetes with HbA_{1c} level 7.5–12.0%, on intensive insulin therapy.	Parallel groups FreeStyle Libre (*n*=149) vs self-monitoring (*n*=75) for 6 months.	43% reduction in time in hypoglycaemia (<3.9 mM; *P*<0.01). No change in HbA_{1c}. FreeStyle Libre reduced glucose variability; mean number of scans 8/day; mean number of self-monitored blood glucose measurements 0.3/day.
Observational studies			
Dover *et al.* [14]	Adults with Type 1 diabetes	16 weeks, use of FreeStyle Libre under routine care (*n*=25)	Mean HbA_{1c} reduced from of 8.0% to 7.5% (–0.48%, *P*<0.01). Episodes of hypoglycaemia <4.0 mM reduced from 17 in the first 2 weeks to 12 in the final 2 weeks of use (*P*=0.19). Significant reduction in the Diabetes Distress Scale (*P*<0.01).
McKnight *et al.* [15]	Adults with Type 1 diabetes	Routine clinic use of FreeStyle Libre (*n*=100	HbA_{1c} reduced by –0.2% compared with a 0.1% rise in non-users. HbA_{1c} >7.5% sub-group,

		current users). Duration of follow-up not available.	32.2% of FreeStyle Libre users and 9.8% of non-users ($P< 0.01$) had reached target at their last clinic visit.
Ish-Shalom *et al.* [16]	Adults; Type 2 and Type 1 diabetes HbA1C ≥7.5%	12 to 24weeks use of FreeStyle Libre (n=31).	HbA_{1c} reduced by −1.3% at 8 weeks ($P< 0.01$). For those patients who continued using FreeStyle Libre (n = 27), the change was maintained for 24 weeks, –1.2% ($P<0.01$).
Holcombe *et al.* [17]*	Patients with Type 1 diabetes	FreeStyle Libre use. Duration of follow-up not specified (n=13).	HbA_{1c} improved from 9.0% to 8.1%. Time spent in target increased (24% vs 29%), time spent below target reduced (95 min vs 82 min).
Campbell *et al.* [18]*	Children (age 4–17 years) with Type 1 diabetes	2 weeks masked use (baseline) followed by 8 weeks open label use (n=76).	Time in range (3.9 to 10 mM) improved vs baseline by 1.0±2.8 h/day; $P<0.01$. HbA_{1c} improved vs baseline, –0.4±0.6%; $P<0.01$. Scan frequency of FreeStyle Libre was 13/day. Number of self-monitored blood glucose measurements reduced from 8.0 to 1.0/day during open use.

CGM, continuous glucose monitoring; RCT, randomized controlled trial.

*Conference abstract.

Table 2 Advantages and disadvantages of flash glucose monitoring.

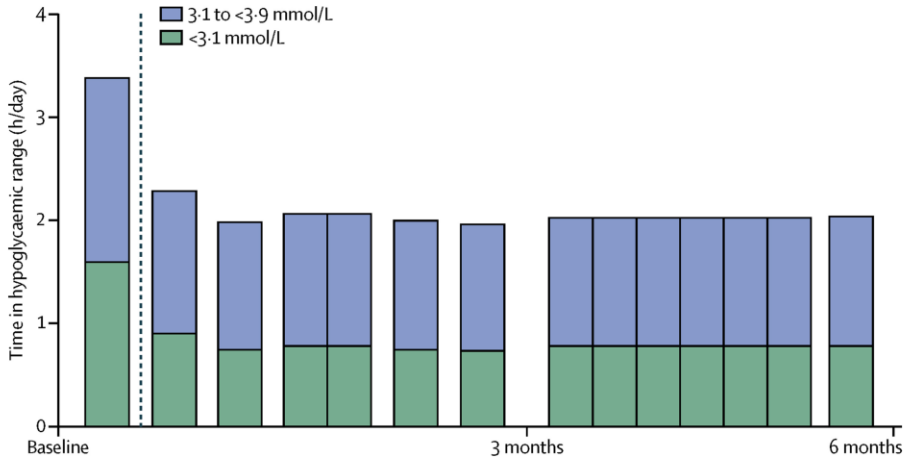
	Advantages	**Disadvantages**
Set-up and ease of use	User friendly, easy to set up and insert and generally well tolerated [31]. The 'on demand' glucose data may be preferable for some to real-time CGM which features alarms to alert to rising/falling glucose.	Some experience skin reactions related to the adhesive, or sensor may fall off within the intended 14-day use.
Hypo-glycaemia	FreeStyle Libre leads to a reduction in biochemical hypoglycaemia in patients with both Type 1 and Type 2 diabetes [11,13]. In the IMPACT trial this occurred within the first 2 weeks of use, despite no training on glucose data interpretation.	There is a ~5-min lag between FreeStyle Libre and blood glucose; therefore, falling blood glucose may read higher on the reader than blood glucose. In this instance, blood glucose should be relied on. Dexcom G5 real-time CGM is likely to be superior to FreeStyle Libre for reducing hypoglycaemia in those with impaired awareness [12].
Glucose control	FreeStyle Libre facilitates frequent glucose monitoring which has been associated with lower HbA_{1c} [2,4]. IMPACT RCT demonstrated increased time in range and reduced glycaemic variability while observational studies have reported reduction in HbA_{1c} [14,15,16, 17, 18]. Provides insight into glycaemic variability, easily viewed as an ambulatory glucose profile in clinic. Because of low cost can also be used intermittently, for instance for 2 weeks pre-clinic to provide detailed insight into glucose levels.	FreeStyle Libre use is associated with lower HbA_{1c} in observational studies. However, to date no randomised controlled trials have demonstrated a reduction in HbA_{1c}. Bolus calculators are useful tools which assist with accurate insulin dose calculation. The bolus calculator in the FreeStyle Libre reader requires the user to perform a finger-stick blood glucose measurement to use the calculator; interstitial glucose values cannot be entered.
Finger-stick	FreeStyle Libre reduces the need for the NICE	Blood glucose must be relied on when:

blood glucose monitoring	recommended 4–10 blood glucose finger sticks per day; in IMPACT self-monitored blood glucose measurements reduced from 5.5 to 0.5 tests per day.	• Glucose levels are rapidly changing • If hypoglycaemia or impending hypoglycaemia is displayed • When scanned glucose results do not correspond with user symptoms • To use the FreeStyle Libre reader bolus calculator • For driving as per UK DVLA regulations
Postprandial glucose	FreeStyle Libre use provides information on postprandial glucose excursions, leading to a significant increase in user delivery of insulin bolus 15–20 min pre-meal [14].	Users need to consider the ~4-h action profile of rapid-acting insulin analogues when contemplating the need for a post-meal insulin correction dose which carries the risk of insulin stacking and hypoglycaemia.
Driving	FreeStyle Libre trend arrows allow corrective action to be taken, facilitating informed decision making and hypoglycaemia avoidance as an adjunct to blood glucose monitoring in relation to driving.	The DVLA in the UK currently requires that blood glucose, not interstitial glucose, must be checked and relied on prior to driving (38).
Accuracy	Accuracy is similar to other available real CGM systems, (no data comparing dexcom G5) although there are few head to head studies published [33,34]. The FreeStyle Libre mean ARD is lower than many commercially available blood glucose meters [36].	To ensure the accuracy of the FreeStyle sensor, a blood glucose in the fasting state can be useful for cross-reference as a small number of sensors may have mean ARD > 15%.
Calibration	The FreeStyle Libre does not require calibration which is a benefit; calibration of real time CGM requires ≥2 blood glucose measurement per day. Calibration alarms can be an unwelcome intrusion.	In the event of an inaccurate FreeStyle Libre sensor, it cannot be calibrated and should be returned to the manufacturer for a replacement.
Alarms	No alarms, therefore no risk of 'alarm fatigue'.	The lack of alarms is a concern for those with impaired awareness of hypoglycaemia who are likely to be dependent on alarms to alert them to impending hypoglycaemia [12].
14 day wear	Replacing the sensor every 14 days, compared to every 6 or 7 days can reduce the 'diabetes burden' associated with the number of tasks needed for diabetes management. Most report sensor insertion as quick and painless [31].	Once placed on the skin, FreeStyle Libre cannot be moved for 14 days which may limit clothing options for some who prefer to have the device hidden from view. A minority will experience skin reactions to the FreeStyle Libre or sensor may fall off before 14 days
Data display	The LibreLink app allows integrated use of FreeStyle Libre with android smart phones. The mobile phone is used to scan the sensor which reads glucose data using near field communication, removing the need to carry an additional reader. LibreLink can be used to review glucose data, the ambulatory glucose profile and estimated HbA_{1c}, facilitating user review of results without the need to download data to a computer. The LibreLinkUp up also allows parents and carers to 'follow' the user and their glucose results remotely using the app on their mobile phone.	Users should carry blood glucose monitoring equipment with them as back up.

Cost	Flash glucose monitoring in the UK NHS will cost £35 per sensor, less than half the price of alternative CGM systems, potentially making it more accessible to a greater proportion of people living with diabetes. At this price it is cost equivalent to ~8 blood glucose tests per day.	None of the currently available randomised controlled trials have demonstrated cost savings in terms of reduced acute admissions, HbA_{1c} or long term complications.

ARD, absolute relative deviation; CGM, continuous glucose monitoring; DVLA, Driver and Vehicle Licencing Agency; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; RCT, randomized controlled trial.

Figure 1. IMPACT study, Bolinder et. al. (11): Time in hypoglycaemic range during baseline and treatment phase in the intervention group using flash glucose monitoring. Grouped bars indicate analysis performed over 2 week periods and then averaged. Dashed line marks the start of the intervention.



Reprinted from the Lancet, Bolinder J, Antuna R, Geelhoed-Duijvestijn P, Kroger J, Weitgasser R. Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: a multicentre, non-masked, randomised controlled trial. Lancet 2016; 388:2254 with permission from Elsevier.

Figure 2. Dunn et al. Real world data from >51,000 FSL readers demonstrating an association between glucose monitoring frequency and estimated HbA1c [22]

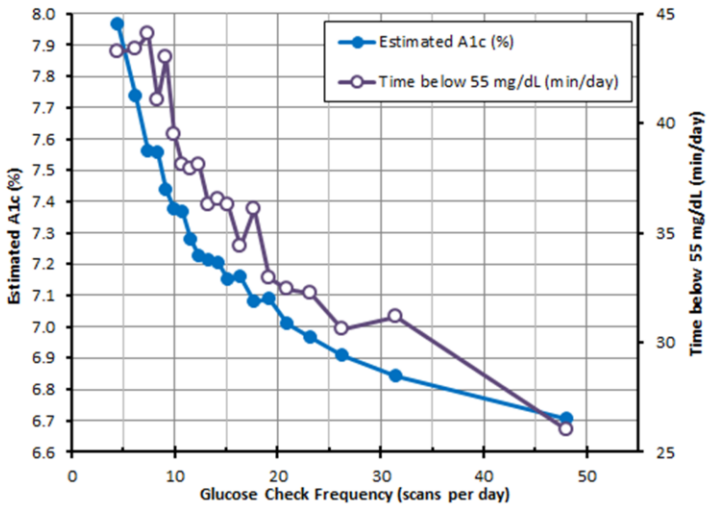


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Figure 3. Example of an Ambulatory Glucose Profile.