

# THE **sensor** report

ISSUE 2/2021

## WELCOME TO THE SENSOR REPORT, ISSUE 2

We hope that you enjoyed the first issue of *The Sensor Report*! With Issue 2 we are starting a series of themed insights into recent evidence for improved outcomes for people with diabetes using the FreeStyle® Libre portfolio. In this issue of *The Sensor Report* we are bringing into focus the topic of FreeStyle Libre portfolio and how the frequency of hospital admissions for acute diabetes events (ADEs) is reduced by flash glucose monitoring. Central to this theme is the recent publication of the RELIEF study, a large retrospective investigation using the French national claims database of hospitalizations with diabetes as a contributing diagnosis in the 12 months before and after national reimbursement of the FreeStyle Libre system for people with type 1 diabetes (T1DM) or type 2 diabetes (T2DM). The outcomes from this important study are supported by a number of other investigations, which together show that use of flash glucose monitoring has significant implications for reducing ADEs and potentially for long-term health economic outcomes in managing care in T1DM and T2DM.

Of course, this issue of *The Sensor Report* will also provide you with a timely selection of other recent

insights on how the FreeStyle Libre portfolio is supporting children, adolescents and adults with diabetes, as well as looking at how the consistent improvement in accuracy and specificity of the FreeStyle Libre sensors is making it hard for comparative assessments of different CGM systems to stay current. Please enjoy Issue 2 of *The Sensor Report* and we look forward to hearing from you.



**Alexander Seibold,**  
*Regional Medical Director  
Europe, Middle East,  
Africa, Pakistan, Abbott's  
diabetes care division*

### CONTACT THE SENSOR REPORT

Wiebke Jessen, Medical  
Affairs Coordinator EMEAP  
Abbott's diabetes care  
division

[wiebke.jessen@abbott.com](mailto:wiebke.jessen@abbott.com)

## featurestory

# The impact of CGM and the FreeStyle Libre system in preventing acute diabetes events and associated hospital admissions

It has been established that use of CGM or flash glucose monitoring can significantly improve measures of short-term and longer-term glucose control, including HbA1c, TIR, TBR and TAR. Until recently, it was not conclusively demonstrated that glucose-sensing technologies had an impact on the rate of acute diabetes events (ADEs) and associated hospital admissions. Data on the efficacy of CGM and the FreeStyle Libre system in ADEs are now emerging.

In 2018 and in 2020, the FUTURE study looked at the rates of hospitalization for ADEs across three specialized centres in Belgium following the nationwide reimbursement of CGM and flash glucose monitoring systems. In the first, Charleer et al<sup>1</sup> studied 515 individuals with T1D on CSII therapy who



had recently been started on CGM systems, showing a significant -0.3% (-3.3 mmol/mol) reduction in HbA1c after 12 months of use. More notable was that 16% of patients were hospitalized for severe hypoglycemia or diabetic ketoacidosis (DKA) in the 12 months prior to starting CGM, which was reduced to 4% one year following initiation ( $p < 0.0005$ ). There was also a significant reduction in hospital length of stay, work absenteeism and significant improvement in quality of life (QOL), including less fear of hypoglycemia. The second FUTURE study<sup>2</sup> collected real-world data for 1,913 adults with T1D started on the FreeStyle Libre system. This showed that hospitalization for severe hypoglycemia and/or DKA were 3.3% in the year prior to introduction of the FreeStyle Libre system and decreased to 2.2% in the year after ( $p = 0.031$ ). These were supported by the FLARE-NL4 diabetes registry study<sup>3</sup> in the Netherlands, which showed that diabetes-related hospital admissions decreased from 13.7% to 4.7% of 1365 people with diabetes in the 12 months after initiating flash glucose monitoring ( $p < 0.05$ ). Although not reporting on hospital admissions, these data are also supported by a retrospective analysis of DPV registry data on 3,553 children with T1DM<sup>4</sup>. This showed that in the first year after starting with CGM or flash glucose monitoring systems, the rate of DKA was reduced by 50%, severe hypoglycemia was reduced by 24% and severe hypoglycemia with coma/convulsions by 43%. In fact, in another study, severe hypoglycemia in children and adolescents was reduced by up to 86% amongst long-term users of the FreeStyle Libre system<sup>5</sup>.

These notable findings were considerably extended by Roussel and colleagues in the RELIEF study<sup>6</sup>, a large retrospective real-world analysis of data extracted from the national French Système National des Données de Santé (SNDS) health claims database examined the nationwide rate of hospitalizations for ADEs among 74,011 people with T1DM or T2DM following initiation of the FreeStyle Libre system, after reimbursement was implemented in 2017. ADEs included hospitalizations for DKA, hypoglycaemia, diabetes-related comas and hyperglycaemia. The data showed that in the first 12 months of FreeStyle Libre system use, admissions for ADEs fell both in T1D (-49.0%) and T2D (-39.4%). More specifically, admissions for DKA fell in T1D by -56.2% and in T2D by -52.1%, with reductions in admissions for diabetes-related comas in T1D (-39.6%) and in T2D (-31.9%). Hospitalizations for hypoglycemia and hyperglycemia also decreased in T2D (-10.8% and -26.5%, respectively). Importantly, the data also showed that 98.1% of users persisted with the FreeStyle Libre system after 12 months use.

Another retrospective cohort study in Israel by Tsur and colleagues<sup>7</sup> looked at 3,490 adults with T1DM who were initiated on the FreeStyle Libre system during 2018 and followed for a median of 14 months. In 2,682 individuals with an HbA1c measured both at baseline and  $\geq 3$  months after initiation, average HbA1c declined from 8.1% (65 mmol/mol) to 7.9% (62.8 mmol/mol;  $p < 0.001$ ) at first measurement and this was maintained at 12 months. The largest decline (-0.5%; 5.5 mmol/mol) was seen in people with HbA1c  $\geq 8\%$  (63.9 mmol/mol). More significantly regarding ADEs, after 6 months of using the FreeStyle Libre system, there was a clinically significant decline in rate of internal medicine hospitalization, visits to primary care, or visits to endocrine/diabetes specialists ( $p < 0.001$ ). Admissions for DKA were reduced from 4.4 to 2.3 per 100 patient years ( $p < 0.001$ ) and for severe hypoglycemia admissions were reduced from 5.1 to 2.9 per 100 patient years ( $p < 0.001$ ).

Specifically focusing on the impact of the FreeStyle Libre system on ADEs in people with T2DM on rapid-acting insulin therapy, Bergenstal and colleagues<sup>8</sup> analyzed IBM MarketScan Commercial Claims and Medicare databases to assess the impact of the FreeStyle Libre system on ADEs and hospitalizations in a cohort of 2463 individuals in the 6 months before and after starting flash glucose monitoring. They found that hospital admission rates for any cause decreased by 35% from ( $p < 0.001$ ) and that ADE rates related to hypoglycemia fell by 29% and those related to hyperglycemia fell by 6% ( $p < 0.001$ ). Of particular note, a reduction in ADEs and hospitalizations was evident within the first 45 days of starting flash glucose monitoring.

Together, these findings at institutional and national level show that implementing CGM and flash glucose monitoring can have significant implications for the clinical care of people with T1DM or T2DM, as well as potential economic benefits through reduction in hospital admissions.

1. Charleer S, et al. Effect of continuous glucose monitoring on glycemic control, acute admissions, and quality of life: A real-world study. *J Clin Endocrinol Metab*. 2018 Mar 1;103(3):1224-1232. doi: 10.1210/je.2017-02498
2. Charleer S, et al. Quality of life and glucose control after 1 year of nationwide reimbursement of intermittently scanned continuous glucose monitoring in adults living with type 1 diabetes (FUTURE): A prospective observational real-world cohort study. *Diabetes Care* 2020 Feb;43(2): 389-397. doi: 10.2337/dc19-1610
3. Fokkert M, et al. Improved well-being and decreased disease burden after 1-year use of flash glucose monitoring (FLARE-NL4). *BMJ Open Diabetes Res Care* 2019;7, doi: 10.1136/bmjdr-2019-000809
4. Tauschmann M, et al. Reduction in Diabetic Ketoacidosis and Severe Hypoglycemia in Pediatric Type 1 Diabetes During the First Year of Continuous Glucose Monitoring: A Multicenter Analysis of 3,553 Subjects From the DPV Registry. *Diabetes Care*. 2020;43:e40-42. doi: 10.2337/dc19-1358
5. Messaoui A, et al. Flash Glucose Monitoring Accepted in Daily Life of Children and Adolescents with Type 1 Diabetes and Reduction of Severe Hypoglycemia in Real-Life Use. *Diabetes Technol Ther*. 2019; 21:329-335
6. Roussel R, et al. Important drop rate of acute diabetes complications in people with type 1 or type 2 diabetes after initiation of flash glucose monitoring in France: The RELIEF Study. *Diabetes Care* 2021 Apr 20; dc201690. doi: 10.2337/dc20-1690
7. Tsur A et al. Impact of flash glucose monitoring on glucose control and hospitalization in type 1 diabetes: A nationwide cohort study. *Diabetes Metab Res Rev*. 2021; Jan;37(1):e3355. doi: 10.1002/dmrr.3355
8. Bergenstal RM, et al. Flash CGM is associated with reduced diabetes events and hospitalizations in insulin-treated type 2 diabetes. *J Endocr Soc*. 2021 Feb 2;5(4):bvab013. doi: 10.1210/endo/bvab013

## Look out for a special issue of *The Sensor Report* that gives you an inside view of the 2021 ATTD, ADA and EASD Virtual Conferences

In recognition of the significant poster and oral presentations at these two major diabetes conferences, a special issue of *The Sensor Report* will capture the key learnings from ATTD, ADA and EASD 2021 Virtual Congresses.

These major annual congresses showcase the most-recent advances in diabetes care and we will bring you the highlights of those that focus on the FreeStyle Libre system, as well as other aspects of glucose-sensing technology and its impact on outcomes for people with diabetes. This special edition of *The Sensor Report* will make sure you can stay abreast of the latest research and its implications in this fast-moving field of diabetes therapy.

## Children under 12 show most frequent use of their FreeStyle Libre system and better metabolic control

Different age groups demonstrate significantly different behaviour with FreeStyle Libre, with consequences for glucose measures.

This cross-sectional study in Spain evaluated the use of flash glucose monitoring in 195 people with T1DM in different age ranges:  $\leq 12$  years; 13–19 years; 20–25 years and  $\geq 26$  years. Children aged 12 or younger scanned a mean of 15.9 times per day, 35% more than any other age group. They also had higher % time in range (%TIR) at 71.5%, and lower HbA1c, lower mean glucose and lower glycemic variability than any other population. Glycemic variability was highest in adolescents (13–19 years). As well as showing better glucose metrics, the 12 and under age group showed the greatest adherence to device use, which decreased during adolescence and into adulthood. More frequent device use was associated with better glycemic control in all age groups.

Bahillo-Curienes MP, et al. Assessment of metabolic control and use of flash glucose monitoring systems in a cohort of pediatric, adolescents, and adults patients with Type 1 diabetes. *Endocrine* 2021 Mar 23. doi: 10.1007/s12020-021-02691-4



Image is for illustrative purposes only. Not real patient or data.

## Cost savings are associated with using the FreeStyle Libre 2 system in T2DM

This Spanish study compared the cost of FreeStyle Libre 2 system and self-monitoring of blood glucose (SMBG) in insulin-treated T2DM. The researchers conducted a literature review and applied a cost analysis model to estimate the economic impact associated with glucose monitoring, as well as costs associated with 2.5 severe hypoglycemic episodes/patient-year amongst a cohort of 1000 adults with T2DM. Cost analysis showed that SMBG costs were €2700/year/patient compared to FreeStyle Libre 2 system costs of €2120/year/patient. The authors estimate that for 1000 people with T2DM using basal-bolus insulin, 1220 severe hypoglycemic events could be prevented each year, equating to €580,953 of cost savings.

Oyagüez I, et al. Cost analysis of FreeStyle Libre 2 system in type 2 diabetes mellitus population. *Diabetes Ther*. 2021 May 4:1–14. doi: 10.1007/s13300-021-01064-4

## Higher scan rates for FreeStyle Libre users in Poland mean improved measures of glucose control

The wealth of de-identified glucose data from FreeStyle Libre sensors has allowed investigation of regional differences in metrics of glucose control.

This retrospective, real-world data analysis, looked at 113 million automatically recorded glucose readings from FreeStyle Libre system users in Poland from August 2016 and August 2020 and compared them with international data. On average, FreeStyle Libre system users in Poland demonstrated a much higher daily scan rate than the collected international pool (mean 21.2 vs. 13.2 scans/day). This was associated with a higher %TIR than the international mean (64.2% vs. 58.1%) and a lower %TAR (29.7% vs. 36.6%;  $p < 0.0001$  for all comparisons). Polish users were also more-likely to achieve TIR  $> 70\%$  (36.3% of users vs. 28.8%), but also had higher %TBR (4.7% vs. 3.6%). Of note, even at similar daily scan rates to the comparative group, users from Poland achieved higher %TIR, lower %TAR but higher %TBR, further emphasizing the diverse regional engagement with flash glucose monitoring.

Hohendorf J, et al. Intermittently Scanned Continuous Glucose Monitoring Data of Polish Patients from Real-Life Conditions: More Scanning and Better Glycemic Control Compared to Worldwide Data *Diabetes Technol Ther*. 2021 Apr 21. doi: 10.1089/dia.2021.0034

## Flash glucose monitoring in the Netherlands: more scanning means better glycemic outcomes

Using the international database of anonymized uploaded glucose-sensor readings the authors examined the association between daily sensor scan rates and measures of glucose control under real-world conditions in the Netherlands.

The analysis looked at the data from 27.9 million glucose scans performed by the users in the Netherlands. Users performed a median of 11.5 scans per day during the period between September 2014 and March 2020. People who scanned on average 3.7 times per day had the lowest TIR (43%), which increased with scan rates such that users scanning 40 times per day achieved 67% TIR. However, even at the highest scan rates users in the Netherlands did not reach the international consensus target for  $> 70\%$  TIR. In line with the data on %TIR, increasing scan rates were associated with reduced %TAR, with the lowest scan rates demonstrating almost twice as much time in hyperglycemia as the highest scanners (12.3 hrs/day versus 6.6 hrs/day). Of note was that %TBR did not correlate with increasing daily scan rates, since %TBR was lowest for the group with a median of 25.8 scans/day.

Laneijer A, et al. Flash Glucose Monitoring in the Netherlands: Increased monitoring frequency is associated with improvement of glycemic parameters *Diabetes. Res Clin Pract*. 2021 Jun 5;177:108897. doi: 10.1016/j.diabres.2021.108897

## ICU application of flash glucose monitoring during the COVID-19 pandemic

Individuals with T2DM who are hospitalized with COVID-19 have significantly higher mortality and studies are showing that telemonitoring in hospital can assist glycemic control and minimize risks for staff.

This small study from Wuhan in China, enrolled 17 adults with T2DM and hyperglycemia who were in the intensive care unit (ICU) during the study period. The study investigated whether the use of the FreeStyle Libre system would help ICU doctors better to control adverse glucose fluctuation. Remote monitoring of glucose levels in the ICU with the FreeStyle Libre system was shown to be safe, although accuracy was lower than that of standard point-of-care venous blood glucose testing. The authors acknowledge the small sample size, but suggest that the FreeStyle Libre system could potentially reduce workload and minimise risk of infection among medical staff.

Zhang Y, et al. Evaluation for the feasibility and accuracy of FreeStyle Libre Flash Glucose Monitoring System used by COVID-19 Patients in Intensive Care Unit. *J Diabetes* 2021; Mar 31. doi: 10.1111/1753-0407.13181

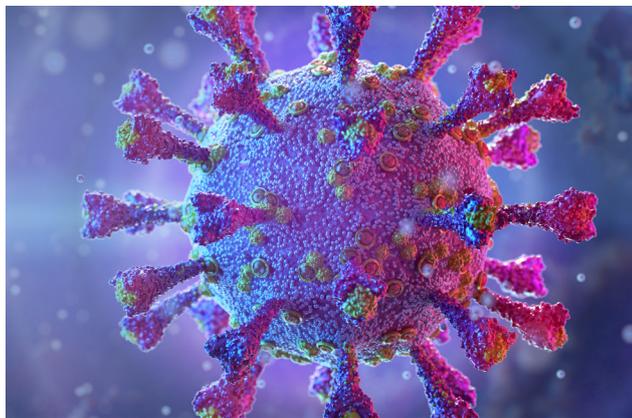


Image from Shutterstock.com

## Glucose monitoring with FreeStyle Libre can help people with diabetes in hospital with COVID-19

The need for close glucose monitoring and tight glycemic control of people hospitalized with COVID-19 is further emphasized.

This prospective cohort study included 60 hospitalized individuals with diabetes or hyperglycemia and COVID-19 infection and examined glycemic control metrics with temporary use of the FreeStyle Libre system while on insulin treatment in hospital. Clinical outcomes were also assessed. Most participants treated with the hospital's standard hyperglycemia protocol (basal-bolus insulin) improved their metabolic control, reaching time in range, low glycemic variability with low rates of hypoglycemia, similar to that of non-COVID populations. The study found no association between adverse outcomes and glycemic measures in people with known diabetes. Notably, in individuals without a history of diabetes, the study found an association between the rate of COVID-19 complications and %TAR >180 mg/dL (10 mmol/L).

Gómez AM, et al. Glycemic control metrics using flash glucose monitoring and hospital complications in patients with COVID-19. *Diabetes Metab Syndr*. 2021; 15: 499-503. doi.org/10.1016/j.dsx.2021.02.008

## Flash glucose monitoring in T1D improves outcomes amongst a large national cohort in Sweden

The Swedish National Diabetes Register (NDR) has included registration of CGM and FreeStyle Libre since 2016, allowing a before and after comparison of HbA1c levels and episodes of severe hypoglycemia.

This large study of 14,372 adults with T1DM looked at the impact of flash glucose monitoring on glycemic control and episodes of severe hypoglycemia. Data were collected for 3 years before and 2 years after initial use of the FreeStyle Libre system on 14,372 adults with T1DM and compared with 7,691 individuals using SMBG. HbA1c decreased in both cohorts, but the change was significantly greater in the FreeStyle Libre system user group, with an estimated mean absolute difference of -1.2 mmol/mol (-0.11%;  $P < 0.0001$ ) after 15–24 months. Importantly, change in HbA1c was most marked in individuals with the highest HbA1c at baseline (-8.5 mmol/mol [-0.78%]). Furthermore, risk of severe hypoglycemic episodes was significantly reduced by 21% in the cohort of FreeStyle Libre system users compared with the SMBG group ( $p = 0.0014$ ).

Nathanson D, et al. Effect of flash glucose monitoring in adults with type 1 diabetes: a nationwide, longitudinal observational study of 14,372 flash users compared with 7691 glucose sensor naive controls. *Diabetologia* 2021; doi: 10.1007/s00125-021-05437-z

## Use of the FreeStyle Libre system reduces HbA1c in T2DM in adults on insulin or non-insulin therapy

This large retrospective, observational study further confirms the significant improvements in long-term glucose control for people with T2DM using flash glucose monitoring.

The IBM Explorys database was used to assess changes in HbA1c after prescription of the FreeStyle Libre system in 1,034 adults with sub-optimally controlled T2DM (baseline HbA1c of  $\geq 8.0\%$ ), treated with basal insulin ( $n = 306$ ) or non-insulin therapy ( $n = 728$ ). After a mean follow-up of 159 days, HbA1c was significantly reduced by -1.5% ( $p < 0.001$ ) within the total study population. The largest reductions (-3.7%,  $p < 0.001$ ) were seen in patients with a baseline HbA1c  $\geq 12.0\%$ , and the proportion of patients with HbA1c  $\geq 12.0\%$  at baseline decreased by more than 50% following prescription of the FreeStyle Libre system. Significant falls in HbA1c were seen both in the basal insulin treatment group (-1.1%;  $p < 0.001$ ) and in the non-insulin cohort (-1.6%;  $p < 0.001$ ). The authors note that, as a consequence of the COVID-19 pandemic, clinicians are increasingly using telemedicine and digital glucose monitoring technologies to minimize face-to-face clinic visits whilst provide guidance and therapy adjustments via remote clinical consultation.

Wright EE, et al. Use of Flash Continuous Glucose Monitoring Is Associated With A1C Reduction in People With Type 2 Diabetes Treated With Basal Insulin or Noninsulin Therapy. *Diabetes Spectr*. 2021; 34:184–189.

## HbA1c variability is associated with hypoglycemia in T2DM, as confirmed using flash glucose monitoring

Glucose variability and risk of hypoglycemia are confirmed in T2DM.

This retrospective pilot study of 26 people with T2DM used flash glucose monitoring to ascertain whether intra-day glycemic variations is associated with HbA1c variability. The primary endpoint was standard deviation (SD) of HbA1c over a 6-month period. The study showed that adjusted SD of HbA1c is associated with %TBR and low blood glucose index (LBGI). For individuals with high HbA1c variability, the authors recommend that clinicians consider whether they are experiencing periods of hypoglycemia and adjust their glucose-lowering medications accordingly. The small sample size of this study, however, suggests that a further study with a larger cohort is warranted.

Tokutsu A, et al. Relationship between glycemic intraday variations evaluated in continuous glucose monitoring and HbA1c variability in type 2 diabetes: pilot study. *Diabetol Metab Syndr*. 2021 Apr 15;13(1):45. doi: 10.1186/s13098-021-00663-2

## Psychological wellbeing during COVID-19 is associated with %TIR for users of CGM or flash glucose monitoring systems

Here, the authors report on the impact of lockdown during the COVID-19 pandemic, both on glucose control and on measures of anxiety and depression, in youths with T1DM with access to CGM or flash glucose monitoring.

The study group of 117 adolescents with T1DM showed a increase in median %TIR of 10% during the period 30th March to 12th April 2020, compared to the same period in 2019 (59% vs. 49%;  $p < 0.001$ ). There was also a significant reduction in %TBR with low glucose and in %TAR with hyperglycemia ( $p < 0.001$  in both cases). Glucose variability did not differ between two comparative periods. Psychological wellbeing was investigated using the Test of Depression and Anxiety Scale (TAD). Higher score for depression and anxiety were associated with lower %TIR ( $p = 0.012$  for depression,  $p = 0.028$  for anxiety). It is not clear from the study if anxiety and depression contributed to lower %TIR, or whether their poorer glucose control was a contributing factor to decreased wellbeing. The authors note that, in youths with diabetes, anxiety and depression in particular are associated with increased risk of short and long-term complications, such as weight gain, severe hypoglycemia and hyperglycemia. This emphasizes the importance of psychological screening in the pediatric population during stressful periods, such as social isolation, in order to prevent a decline in mental wellbeing and consequent poor glycemic control.

Cusinato M, et al. Anxiety, depression, and glycemic control during Covid-19 pandemic in youths with type 1 diabetes. *J Pediatric Endocrinol Metabolism*. 2021; Jun 28. doi: 10.1515/jpem-2021-0153

## CGM improves glucose metrics in T1DM and T2DM: a meta-analysis

This meta-analysis looking at randomized controlled trials (RCTs) comparing CGM versus usual care for parameters of glycemic control, both in T1DM and T2DM.

Specifically, the analysis looked at changes in HbA1c, TIR, TBR, TAR and glucose variability (GV) expressed as coefficient of variation (CV). A total of 15 RCTs involving 2,461 individuals were included. Compared with usual care, CGM was associated with -0.17% reduction in HbA1c, a 5% increase in TIR, and 2% reductions TAR and TBR. GV was decreased by 3%. Of note, the RCTs using FreeStyle Libre showed a reduction in TBR  $< 3.9$  mmol/L (70 mg/dL) of 4% compared to the overall reduction across systems of 2%.

Maiorino MI, et al. Effects of continuous glucose monitoring on metrics of glycemic control in diabetes: A systematic review with meta-analysis of randomized controlled trials. *Diabetes Care*. 2020;43(5):1146-1156



Image is for illustrative purposes only. Not real healthcare professional or data.

## Insulin dosing adjustments using a 'slide rule' with CGM trend arrows

For people with diabetes on insulin, CGM trend arrows can be used for adjusting insulin dosing decisions.

Bruttomesso and colleagues have developed a 'slide rule' for adjusting insulin for people with T1D treated with multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII), who are using rapid or ultra-rapid acting insulin for meals and corrections. The slide rule was tested both *in silico* and in real life, and was based on current models using trend arrows, but with narrower blood glucose intervals and more classes of insulin sensitivity. When tested *in silico* and when the pre-prandial trend arrow was increasing, the slide rule reduced %TAR and increased %TIR ( $p < 0.05$ ). When the trend arrow was decreasing before meals, the slide rule approach reduced %TBR and slightly increased %TAR ( $p < 0.05$ ). Real-life testing showed that, in the postprandial period, the slide rule helped people to stay on target for 70.8% of the time when preprandial trend arrows were increasing, and 91.6% of the time when trend arrows were decreasing.

Bruttomesso D, et al. A "slide rule" to adjust insulin dose using trend arrows in adults with type 1 diabetes: Test in silico and in real life. *Diabetes Ther*. 2021; 12:1313-1324

## Inside the FLARE-NL diabetes registry: flash glucose monitoring lowers HbA1c, reduces hospital admissions and improves quality of life

The FLARE-NL diabetes registry was started in response to a lack of detailed medical and scientific evidence about the benefits of using the FreeStyle Libre system for people with diabetes in the Netherlands.

Two key studies have emerged from the FLARE-NL diabetes registry. FLARE-NL4 included 1365 FreeStyle Libre users<sup>1</sup> and showed that HbA1c fell at 6 months and 12 months by up to -4.9 mmol/mol, especially for people with T2DM. Just as important, FLARE-NL4 showed that diabetes-related hospitalizations amongst this group fell from 13.7% to 4.7% by 12 months after starting the FreeStyle Libre system, and that the number of people reporting loss of workdays due to illness fell from 18.5% to 7.7% in the 12 months after starting flash glucose monitoring.

The FLARE-NL registry has also been used to assess which factors may be predictive of reductions in HbA1c through use of the FreeStyle Libre system. The FLARE-NL5 study<sup>2</sup> included 860 individuals with diabetes and used

multivariable regression analysis to assess the correlation between change in HbA1c and a host of characteristics, including: age; gender; medication; prior SMBG test frequency; incidence of hypoglycemia; prevalence of diabetes complications; quality of life measures. FLARE-NL5 confirmed a linear relationship between reduction in HbA1c after 12 months and baseline HbA1c at the initiation of flash glucose monitoring<sup>2</sup>. This confirms the observation from FLARE-NL4 that people with HbA1c of >70 mmol/mol (8.5%) saw HbA1c fall by -8.6 mmol/mol after starting the FreeStyle Libre system.

1. Fokkert M, et al. Improved well-being and decreased disease burden after 1-year use of flash glucose monitoring (FLARE-NL4). *BMJ Open Diabetes Res Care* 2019;7, doi: 10.1136/bmjdc-2019-000809
2. Lameijer A, et al. Determinants of HbA1c reduction with FreeStyle Libre flash glucose monitoring (FLARE-NL 5). *J Clin Transl Endocrinol*. 2020 Oct 12;22:100237. doi: 10.1016/j.jcte.2020.100237

## GMI differs significantly from HbA1c in assessing long-term mean glucose

This real-world study<sup>1</sup> reveals that long-term glucose exposure calculated from short-term CGM data rarely matches laboratory-measured HbA1c.

The glucose management indicator (GMI) is a measure of glucose control calculated from CGM data that provides an estimate of short-term glucose exposure that can be compared to a concurrent laboratory HbA1c. GMI is a replacement for the previously used eA1c (estimated HbA1c) metric and the intent is to use short-term CGM data to approximate long-term glucose exposure, as currently measured using HbA1c. Unlike eA1c, the method of calculating GMI is based solely on CGM data from 4 randomised clinical trials (RCTs), including people with T1DM or T2DM. In developing the GMI metric, Bergenstal and colleagues<sup>2</sup> also showed that there is a predicted difference between GMI and measured HbA1c levels for most people with diabetes, and that only 19% of people would have GMI and HbA1c values that differed by <0.1%. GMI is agreed to be most useful when there are discrepancies with measured HbA1c, since this can alert clinicians to the need for extra caution on further intensification of glucose control or additional risk for complications. Perlman and colleagues have compared GMI and laboratory HbA1c within each individual across a group of 641 people with diabetes on insulin therapy in a real-world clinical setting.

In contrast to the differences predicted on the basis of RCT data, this analysis found that only 11% of patients in the real-world setting had GMI and HbA1c levels that differed by <0.1%. In fact 50% of the study group had a difference between GMI and HbA1c of ≥0.5% and 22% had a difference ≥1%. These differences are considerably higher than those reported from RCTs by Bergenstal and colleagues, who indicated that the GMI-HbA1c gap would be >0.5% for 28% of people and >1.0% for only 3%. Across the study group, people with a lower HbA1c had lower contemporaneous GMI levels than the corresponding HbA1c, while at higher HbA1c levels the paired GMI would be higher than the HbA1c. This real-world study confirms the many cases reported of discordance between eA1c or GMI with a laboratory measured HbA1c within an individual with diabetes and also suggests that the differences are considerably wider than originally predicted for a significant number of individuals. The clinical implications of this will need to be considered.

1. Perlman JE, et al. HbA1c and Glucose Management Indicator Discordance: A Real-World Analysis. *Diabetes Technol Ther*. 2021; 23:253–258
2. Bergenstal RM, et al. Glucose Management Indicator (GMI): A New Term for Estimating A1C From Continuous Glucose Monitoring. *Diabetes Care* 2018; 42:2275–2280

## did you know...

Did you know that a panel of leading international diabetes experts delivered a digital symposium in which each expert provided local-language insights in English, French, German, Italian and Spanish into the use of GMI as a complementary indicator to HbA1c and its implications for clinical practice from their own national perspectives? These e-Learning activities are CME accredited by the European Accreditation Council for Continuing Medical Education (EACCME) and can be viewed on demand at <https://www.diabetes-symposium.org/GMI>

# PUBLISHING PRACTICES TIMELY PUBLICATION IS CRITICAL FOR COMPARATIVE ASSESSMENTS OF CGM SYSTEMS IN A FAST-MOVING CLINICAL ARENA

Several recent publications have highlighted the challenge of reporting objective comparisons between different continuous glucose monitoring (CGM) devices, such that they maintain their value to the wider clinical community in diabetes. The issue in question is one of researching and reporting on the performance of different interstitial-fluid (ISF) glucose sensing systems in a timely manner such that the outcomes are clinically relevant.

A 2021 paper in *Biosensors* from Moser et al<sup>1</sup> reported on the accuracy of the FreeStyle Libre system at different rates of change in plasma glucose during two oral glucose tolerance tests (OGTT) in 19 adults with T1DM. They concluded that the FreeStyle Libre system is accurate when compared to reference plasma glucose during OGTT challenge, but that its performance was dependent on the rate of change in glucose and when reference blood glucose values were in hypoglycemia. Although published in 2021, the report from Moser et al used the FreeStyle Libre sensors available in June 2018, during enrolment for their study. By the time of publication, the FreeStyle Libre sensor algorithm had been updated, with proven superior accuracy (MARD 9.2%) and reduced time lag ( $2.4 \pm 4.6$  mins)<sup>2,3</sup>, invalidating any contemporaneous conclusions based on ISF sensor readings and reference blood glucose at higher rates of glucose change. A similar lack of timeliness has invalidated the potentially useful conclusions of a 2020 report in *Pediatric Diabetes* from Nagl et al<sup>4</sup> on the comparative accuracy of three continuous glucose monitoring (CGM) systems in children with T1DM during a diabetes summer camp in 2019, since the FreeStyle Libre sensors were using the earlier algorithm, a fact that has been the subject of a clarifying Letter to the Editor in the journal<sup>5</sup>.

Equally problematic is a pair of 2021 publications from Pleus, Freckmann and colleagues<sup>6,7</sup>, both of which report on a small-scale single-arm study from 2018, comparing the FreeStyle Libre system with the Dexcom G5 CGM system. In this study, 24 adults with T1D wore the sensors in parallel in a

head-to-head comparison over 8 calendar days. In the first report<sup>6</sup>, the overall mean absolute relative differences (MARD) of the systems were 12.5% (FreeStyle Libre) and 13.2% (G5) but there was marked variability of MARD observed throughout the day, particularly before and after meals. In the second report<sup>7</sup>, the authors found that the G5 and FreeStyle Libre system were identical in measuring time in range (TIR), with glucose 70-180 mg/dL, but differed significantly in time below range (TBR) and time above range (TAR). Overall, the conclusions were that the analytical performance of both systems was variable as a consequence of activities of daily life, and that differences in measuring %TBR and %TAR had potential implications for the health of users. As reported in a Letter to the Journal editors<sup>8</sup>, Pleus and Freckmann's conclusions are not relevant because of the new sensor-glucose algorithm<sup>2</sup>, with improved accuracy and sensitivity at all glucose ranges, which robs them of timeliness.

Lastly, in this context, are two recent publications by Reddy and Oliver<sup>9,10</sup> who have reported on the predicted need for adults with T1DM to perform self-monitored blood glucose (SMBG) tests when using the FreeStyle Libre system. They report on separate small cohorts of adult FreeStyle Libre users with T1D, 20 from the IHART CGM study at high risk of hypoglycemia and 67 adults reporting real-world data, to predict a mean of 3.86-5.43 confirmatory SMBG test readings each day, according to the labelling for the FreeStyle Libre system that was current in 2018. The authors then question the known cost-effectiveness for the FreeStyle Libre system in the UK<sup>11</sup>, based on use of SMBG testing for people with T1DM during sensor-glucose readings in the hypoglycemic range or at times of rapid glucose change. However, by the time of their 2020 publications, the newer advanced glucose algorithm<sup>2</sup> for the FreeStyle Libre system, means that the SMBG-indicated conditions referred to by Reddy and Oliver are no longer part of the product labelling for FreeStyle Libre sensors. The single remaining SMBG test requirement is for when glucose

readings do not match symptoms or a user suspects a reading may be inaccurate, i.e. that users should not ignore symptoms that may be due to low or high blood glucose. The problems with the relevance and timeliness of these data have also been the subject of a published comment<sup>12</sup>.

The outdated conclusions reported in the papers discussed here reflect the pace of change in glucose-sensing technologies in diabetes that, in these instances, has outpaced the process of publishing clinical data. As a consequence, inaccurate and inappropriate advice may be put forward on which clinical decisions and clinical choices may be made. This highlights a need for timely and effective two-way communication between industry and healthcare professionals to ensure that the most current knowledge is always brought to bear in making clinical decisions and supporting device selection for glucose management in diabetes.

1. Moser O, et al. Performance of the Intermittently Scanned Continuous Glucose Monitoring (isCGM) System during a High Oral Glucose Challenge in Adults with Type 1 Diabetes—A Prospective Secondary Outcome Analysis. *Biosensors* 2021; 11: 22. doi:10.3390/bios11010022
2. Alva S, et al. Accuracy of a 14-Day Factory-Calibrated Continuous Glucose Monitoring System With Advanced Algorithm in Pediatric and Adult Population With Diabetes. *J Diabetes Sci Technol*. 2020, 193229682095875. doi:10.1177/1932296820958754
3. Bailey T, et al. The Performance and Usability of a Factory-Calibrated Flash Glucose Monitoring System. *Diabetes Technol Ther*. 2015, 17, 787–794. doi:10.1089/dia.2014.0378
4. Nagl K, et al. Performance of three different continuous glucose monitoring systems in children with type 1 diabetes during a diabetes summer camp. *Pediatr Diabetes* 2020; 22:271-278. doi: 10.1111/pedi.13160
5. Jessen W, Seibold A. Comparisons between accuracy of CGM systems in a pediatric setting can be outdated before they are published. Comment on Nagl et al. *Pediatr Diabetes* 2021; doi: 10.1111/pedi.13230
6. Pleus S, et al. Variation of Mean Absolute Relative Differences of Continuous Glucose Monitoring Systems Throughout the Day. *J Diabetes Sci Technol*. 2021; Feb 20. doi: 10.1177/1932296821992373
7. Freckmann G, et al. Choice of Continuous Glucose Monitoring Systems May Affect Metrics: Clinically Relevant Differences in Times in Ranges. *Exp Clin Endocr Diab*. 2021; doi: 10.1055/a-1347-2550
8. Seibold A. Outdated assumptions regarding labelling of isCGM sensor performance and requirement for SMBG confirmation. Comment on Reddy and Oliver. *Diabetes Technol Ther*. 2021; in press
9. Reddy M, Oliver N. Self-monitoring of Blood Glucose Requirements with the Use of Intermittently Scanned Continuous Glucose Monitoring. *Diabetes Technol Ther*. 2020; 22(3):235-238. doi: 10.1089/dia.2019.0369
10. Reddy M, Oliver N. Self-monitoring of Blood Glucose Requirements with the Use of Intermittently Scanned Continuous Glucose Monitoring: A Follow-up Analysis using Real-life data. *Diabetes Technol Ther*. 2020; doi: 10.1089/dia.2020.0477
11. Hellmund R, et al. Cost Calculation for a Flash Glucose Monitoring System for Adults With Type 2 Diabetes Mellitus Using Intensive Insulin – a UK Perspective. *European Endocrinol*. 2018;14(2):86-92
12. Seibold A. Outdated assumptions regarding labelling of isCGM sensor performance and requirement for SMBG confirmation. Comment on Reddy and Oliver. *Diabetes Technology Ther*. 2021; Apr 16. doi: 10.1089/dia.2021.0146

## Improved TIR using the FreeStyle Libre system in conjunction with a social media app in non-insulin-treated T2DM

This study investigated the potential benefit of flash glucose monitoring when combined with using a food and exercise mobile app amongst 665 adults, including non-diabetic subjects (n=473) and non-insulin-treated T2DM (n=192). Amongst the non-diabetic subjects, CGM identified glucose excursions in the diabetic range among 15% of healthy and 36% of those with prediabetes. In the group as a whole, TIR improved significantly ( $p<0.001$ ). Among the 51.4% of participants who improved, TIR increased by an average of 6.4% ( $p<0.001$ ). Of those with poor baseline TIR, defined as TIR below comparable A1c thresholds for T2D and prediabetes, 58.3% of T2D and 91.7% of healthy/prediabetes participants improved their TIR by an average of 22.7% and 23.2%, respectively. Predictors of improved response included absence of prior diagnosis of T2DM and lower BMI.

Zahedani AD, et al. Improvement in Glucose Regulation Using a Digital Tracker and Continuous Glucose Monitoring in Healthy Adults and Those with Type 2 Diabetes. *Diabetes Ther.* 2021; May 28. doi: 10.1007/s13300-021-01081-3

## FreeStyle Libre is associated with reduced frequency and severity of recurrent DKA episodes in T1DM

**DKA is associated with poorly managed or undiagnosed diabetes with significant morbidity, mortality, and healthcare costs.**

This retrospective chart review of 47 people with T1DM and recurrent DKA showed that the frequency of DKA was reduced by 93% in the 2-year period after starting the FreeStyle Libre system, compared with the 2 years before. Severity of DKA was also significantly reduced across the study period, with no severe events recorded after commencing flash glucose monitoring (mean 0.3 events/person before), with moderate and mild DKA events falling by a mean of 98% and 93% over the same period. A reduction in mean HbA1c from 9.9% (mmol/mol) to 7.4% (mmol/mol) was also seen 2 years after starting the FreeStyle Libre system. All of these changes were associated with a change in glucose testing from a mean 2.2 SMBG tests/day to 8.1 scans/day before and after beginning flash glucose monitoring.

Al Hayek AA, et al. Frequency of Diabetic Ketoacidosis in Patients with Type 1 Diabetes Using FreeStyle Libre: A Retrospective Chart Review. *Adv Ther.* 2021; May 19;1-11. doi: 10.1007/s12325-021-01765-z

## Using a social media app alongside flash glucose monitoring encourages glycemic control in young people with T1DM

**Young people are avid users of mobile technology and this may be an advantage for their diabetes care.**

This study from China looked at using the WeChat social networking platform alongside flash glucose monitoring in the self-management of T1DM in 60 young people, aged 10–19 years. WeChat is an app that uses video and graphic elements. Subjects were randomly assigned to either group A using self-monitoring blood glucose (SMBG); group B using FreeStyle Libre system; or group C using FreeStyle Libre system plus WeChat. After 6 months, HbA1c levels decreased significantly in groups B (-0.28%) and C (-0.5%, both  $p<0.05$ ) with the WeChat group being significantly lower than flash glucose monitoring alone ( $p=0.04$ ). Hypoglycemic episodes also decreased most significantly in the WeChat group C ( $P<0.001$ ). This research indicates that glucose management in young people can be optimised using interactive messaging platforms.

Xu Y, et al. Effectiveness of a WeChat combined continuous flash glucose monitoring system on glycemic control in juvenile type 1 diabetes mellitus management: Randomized controlled trial. *Diabetes Metab Syndr Obes.* 2021; 14:1085-1094. doi: 10.2147/DMSO.S299070

## in brief...

## Flash glucose monitoring can support acute treatment outcomes for DKA in hospital

Insulin infusion therapy for 10 people with diabetes being resuscitated from acute DKA episodes was studied using SMBG or flash glucose monitoring, to guide insulin infusion rates using duplicate paired readings. SMBG and flash glucose monitoring determined insulin infusion rates were similar, with differences in predicted insulin infusion rates noted in 2/10 patients with higher glucose levels. However, the authors noted that using the FreeStyle Libre system in the acute treatment setting may improve patient comfort, reduce staff workload and potentially reduce length of stay.

Richard LK, et al. Flash glucose monitoring compared to capillary glucose levels in patients with diabetic ketoacidosis; potential clinical application. *Endocr Pract.* 2021; Apr 21;S1530-891X(21)00162-2. doi: 10.1016/j.eprac.2021.04.005

