Flash Continuous Glucose Monitoring: A Summary Review of Recent Real-World Evidence

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Optimizing glycemic control remains a shared challenge for clinicians and their patients with diabetes. Flash continuous glucose monitoring (CGM) provides immediate information about an individual's current and projected glucose level, allowing users to respond promptly to mitigate or prevent pending hypoglycemia or hyperglycemia. Large randomized controlled trials (RCTs) have demonstrated the glycemic benefits of flash CGM use in both type 1 and type 2 diabetes. However, whereas RCTs are mostly focused on the efficacy of this technology in defined circumstances, real-world studies can assess its effectiveness in wider clinical settings. This review assesses the most recent real-world studies demonstrating the effectiveness of flash CGM use to improve clinical outcomes and health care resource utilization in populations with diabetes.

During the past 5 years, increasing numbers of people with type 1 or type 2 diabetes have integrated continuous glucose monitoring (CGM) into their diabetes self-management regimens. Unlike traditional blood glucose meters, CGM systems provide immediate information about the concentration and the direction and rate of change of interstitial glucose. This information enables patients to intervene promptly to prevent or reduce acute hypoglycemia or hyperglycemia.

Flash CGM is among the most recent CGM technologies. Currently, the FreeStyle Libre 14-day system (Abbott Diabetes Care) and FreeStyle Libre 2 are the only flash CGM systems available, and these systems are being adopted rapidly. Large randomized controlled trials (RCTs) have confirmed the glycemic benefits of flash CGM use in people with type 1 diabetes (1,2) and those with type 2 diabetes (3–6). However, because RCTs are mostly focused on measures of efficacy in defined circumstances, real-world studies can usefully assess the effectiveness of flash CGM in wider clinical settings.

Although adoption of flash CGM continues to expand within endocrinology and diabetes specialty practices, primary care providers may be less familiar with this technology and how it can benefit patients with diabetes. This review assesses recent real-world studies demonstrating the impact of flash CGM use on clinical outcomes and health care resource utilization in both type 1 and type 2 diabetes populations.

Rationale for Intensive Interventions to Improve Glycemic Control

The International Diabetes Federation estimated the global prevalence of diabetes in 2019 to be 9.3% (463 million people), and this proportion is expected to rise to 10.2% (578 million people) by 2030 (7), with associated annual costs of ~$2.25 trillion (7). This figure includes $1.5 trillion in direct costs and $730 billion in indirect costs (e.g., absenteeism and societal costs) resulting from uncontrolled diabetes (7).

Therefore, preventing or reducing the severity of acute and long-term diabetes complications through patient-centered care remains a primary goal of diabetes management, and maintaining optimal glycemic control is central to achieving this goal (8,9). Although improvements in glycemic control should always be a priority, it is also important to strike a balance among the clinical benefits of new diabetes technologies, the initial and ongoing costs associated with their use, and the long-term gains for health and well-being.

Lowering A1C Levels Reduces Health Care Costs

Many studies have demonstrated that lower A1C levels result in lower health care resource utilization and associated costs (10–14). In a recent U.K. analysis using the IMS Core Diabetes Model, the per-person cost reductions

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TABLE 1 Cost Reductions per Person for an A1C Reduction From Baseline by 0.4% (4.4 mmol/mol) in U.K. Adults With Diabetes (12)

Baseline A1C	5 Years	10 Years	15 Years	20 Years	25 Years
Adults with type 1 diabetes					
<7.5%	£66 ($87)	£271 ($359)	£719 ($953)	£1,379 ($1,828)	£2,057 ($2,726)
7.5–8.0%	£89 ($118)	£358 ($474)	£901 ($1,194)	£1,713 ($,2270)	£2,621 ($3,473)
>8.0–9.0%	£103 ($137)	£494 ($655)	£1,224 ($1,622)	£2,138 ($2,833)	£2,831 ($3,752)
>9.0%	£184 ($244)	£808 ($1,071)	£1,880 ($2,491)	£3,147 ($4,171)	£4,136 ($5,481)
Adults with type 2 diabetes					
<7.5%	£83 ($110)	£317 ($420)	£682 ($904)	£1,280 ($1,429)	£1,280 ($1,696)
7.5–8.0%	£132 ($175)	£449 ($595)	£995 ($1,319)	£1,510 ($2,001)	£1,678 ($2,224))
>8.0–9.0%	£138 ($183)	£607 ($804)	£1,366 ($1,820)	£1,999 ($2,649)	£2,223 ($2,946)
>9.0%	£105 ($139)	£662 ($877)	£1,274 ($1,688)	£1,591 ($2,108)	£1,559 ($2,065)

Costs are based on a 1.32 USD ($) to GBP (£) calculation.

that could be achieved over time were calculated based on a 0.4% (4.4 mmol/mol) reduction from baseline A1C (12). As shown in Table 1, the cost savings are most notable for individuals with the highest baseline A1C levels.

Reducing the Incidence and Severity of Hypoglycemia Reduces Health Care Costs

The global HAT (Hypoglycemia Assessment Tool) study, a 6-month retrospective and 4-week prospective investigation of 27,585 insulin-treated patients (type 1 diabetes, n = 8,022; type 2 diabetes, n = 19,563) in 24 countries noted the costs of inadequate glycemic control (15). During the prospective period, 83% of patients with type 1 diabetes and 46.5% of those with type 2 diabetes reported hypoglycemia, resulting in increased blood glucose monitoring, a marked increase in contact with health care providers, and increased hospitalizations. Significant indirect costs were incurred during the prospective period, with lost work time averaging 2.0 days for patients with type 1 diabetes and 1.8 days for those with type 2 diabetes. Other studies have had similar findings (15). Importantly, any level of hypoglycemia confers substantial indirect costs on employers as well as on individuals with diabetes because of increased work days lost (16–18).

Glycemic and Economic Benefits of Flash CGM Use in Real-World Studies

Although well-designed RCTs provide high levels of evidence, there is growing recognition for the complementary relationship between RCTs and real-world prospective and retrospective observational studies. An increasing number of payers and regulators now request that pharmaceutical and medical device companies provide real-world evidence alongside RCT findings when evaluating the safety and effectiveness of new drugs and medical devices (19–22).

Large RCTs have clearly established that use of flash CGM improves glycemic control, reduces hypoglycemia, and achieves higher treatment satisfaction scores among individuals with type 1 diabetes (1,2) or type 2 diabetes (4,5) who are treated with intensive insulin therapy. Now real-world studies are investigating the use of flash CGM within different clinical settings and diverse diabetes populations.

Recent Study Results

As presented in Table 2, results from recently published prospective, observational studies closely align with glycemic benefits reported in earlier RCTs and also demonstrate the value of flash CGM use on cost outcomes and quality of life (QoL) measures (23–31). While these studies confirm significant reductions in A1C (23–25,32) and hypoglycemia (23,24) within large populations with type 1 or type 2 diabetes, they also provide strong evidence linking metabolic outcomes of flash CGM use to reductions in health care resource utilization. For example, one prospective, observational study assessed the impact of flash CGM in an unselected real-world cohort of 1,913 adults with type 1 diabetes (23). Over the 12-month study period, admissions for severe hypoglycemia and/or diabetic ketoacidosis (DKA) decreased from 3.3 to 2.2%

TABLE 2 Summary of Recently Published Real-World, Prospective, Observational Studies

Published Report	Design/Intervention	Outcome Measures	Findings
Charleer et al., 2020 (23)	• 12-month, prospective, observational, multicenter, cohort study (Belgium) • 1,913 adults with type 1 diabetes • Use of flash CGM	• Hospitalization with DKA and/or severe hypoglycemia • Hypoglycemia • Absenteeism • QoL	• Hospitalizations decreased from 3.3 to 2.2% (P = 0.031). • Severe hypoglycemic events decreased from 14.6 to 7.8% (P <0.0001). • Hypoglycemic comas decreased from 2.7 to 1.1% (P = 0.001). • Fewer people were absent from work (2.9 vs. 5.8%). • Questionnaire-derived measures of treatment satisfaction improved.
Fokkert et al., 2019 (24)	• 12-month, prospective nationwide registry (the Netherlands) • 1,365 adults with type 1 diabetes (77%), type 2 diabetes (16%), or other diabetes (7%) • Use of flash CGM	• A1C • Hypoglycemia • Diabetes-related hospitalizations • Absenteeism • QoL	• A1C decreased from 64.1 to 60.1 mmol/mol (difference of −4 [95% CI −6 to 3] mmol/mol; P <0.001). • In participants with a baseline A1C >70 mmol/mol, the A1C decrease was −9 (95% CI −12 to 5) mmol/mol. • The proportion of participants who reported hypoglycemia decreased from 93.5 to 91.0% (P <0.05). • The diabetes-related hospital admission rate (per year) decreased from 13.7 to 4.7% (P <0.05). • Absenteeism (per 6 months) decreased from 18.5 to 7.7% (P <0.05). • Questionnaire-derived measures of QoL improved.
Kröger et al., 2020 (32)	• European pragmatic, parallel retrospective, noninterventional chart review study • 363 adults with type 2 diabetes • Use of flash CGM over 3–6 months	• A1C	• Mean (± SD) A1C levels were reduced by 9.6 ± 8.8 mmol/mol (0.9 ± 0.8%, P <0.0001) in Austria, 8.9 ± 12.5 mmol/mol (0.8% ± 1.1%, P <0.0001) in France, and 10.1 ± 12.2 mmol/mol (0.9% ± 1.1%, P <0.0001) in Germany compared with levels recorded up to 90 days before starting use of the device. • No significant differences were detected for age, sex, BMI, or duration of insulin use.
Tyndall et al., 2019 (25)	• 8-month, prospective observational study (United Kingdom) • 900 adults with type 1 diabetes • Use of flash CGM • SMBG comparator group (n = 518)	• A1C • Hypoglycemia • Hospitalization • QoL	• A1C levels decreased by 0.6% (P <0.001) among participants with a baseline A1C ≥7.5%; there was no change in the comparator group. • The percentage of participants who achieved an A1C <7.5% increased from 34.2 to 50.9% (P <0.001). • More symptomatic (OR 1.9, P <0.001) and asymptomatic (OR 1.4, P <0.001) hypoglycemia was reported with flash CGM. • Hospitalizations for DKA were reduced (P = 0.043) with flash CGM. • Participants experienced less regimen-related and emotional distress, but more patients had elevated anxiety and depression with flash CGM use.
Paris et al., 2018 (26)	• 12-month, observational study (Belgium) • 120 adults with type 1 diabetes • Use of flash CGM	• A1C • Scanning frequency • Hypoglycemia	• A1C levels decreased from 8.51 to 8.16% (P <0.0001) among participants with baseline A1C >7.5%. • Number of daily scans was negatively correlated with decreased A1C. • Number of hypoglycemic events (<70 mg/dL) increased from 16.9 to 22.9 events per month (P <0.05). • No severe hypoglycemic events were reported. • Less fear of hypoglycemia was reported.

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TABLE 2 Summary of Recently Published Real-World, Prospective, Observational Studies (continued)

Published Report	Design/Intervention	Outcome Measures	Findings
Messaaoui et al., 2019 (27)	• 12-month, prospective, observational study (Belgium) • 335 children/adolescents (10.9–16.3 years of age) with type 1 diabetes • Use of flash CGM	• Hypoglycemia • Hypoglycemia change • Use of SMBG • A1C • Acceptance • Adverse events	• Proportion of flash CGM continuers who experienced a severe hypoglycemic event decreased by 86% ($P = 0.037$); no change was seen in the SMBG group. • SMBG use decreased during use of flash CGM from 4.3 to 0 tests per day; SMBG use did not change in the SMBG group. • No significant changes in A1C occurred with either flash CGM or SMBG monitoring. • A total of 278 participants (83.2%) switched from SMBG to flash CGM, 234 participants were still using their device at end of the follow-up period, and 44 (15.8%) reverted to SMBG after a median use of 5.3 months. • Discontinuers reported more frequent occurrence of adverse events than continuers, including premature loss of sensor (31.8 vs. 12.4%), skin reactions (18.2 vs. 2.6%), and local pain (6.8 vs. 0%) (all $P < 0.001$). • Discontinuation of flash CGM was associated with longer duration of diabetes and higher baseline A1C level.
Pintus et al., 2019 (28)	• 12-month, prospective study (UK) • 52 children (4 months to 17 years of age) with type 1 diabetes • Use of flash CGM with education/support from health care professionals	• A1C • QoL	• Improvements were seen in A1C post–flash CGM compared with values at 12 ($P < 0.04$), 6 ($P < 0.04$), and 3 months ($P = 0.012$) pre–flash CGM use. • Questionnaire-derived measures of QoL improved ($P = 0.014$), diabetes symptoms decreased ($P = 0.018$), and treatment barriers were reduced ($P = 0.035$).
Al Hayek et al., 2019 (29)	• 12-week, prospective study (Saudi Arabia) • 33 adolescents/young adults (14–21 years of age) with type 1 diabetes • Use of flash CGM	• Well-being	• Questionnaire-derived measures of well-being improved: mean ($\pm$ SD) DTSQ score increased from 14.4 $\pm$ 6.5 to 32.1 $\pm$ 1.8 ($P < 0.001$), and percentage score for the WHO-5 Well-Being Index increased from 45.1% at baseline to 93.6% ($P < 0.001$).

DTSQ, Diabetes Treatment Satisfaction Questionnaire; OR, odds ratio.

($P = 0.031$), and fewer individuals reported severe hypoglycemic events (7.8 vs. 14.6%, $P < 0.0001$) or experienced hypoglycemic coma (1.1 vs. 2.7%, $P = 0.001$). Although measures of general and diabetes-specific QoL were relatively high at baseline and remained stable throughout the study, treatment satisfaction was increased by study end. Moreover, fewer subjects were absent from work (2.9 vs. 5.8%, $P < 0.0001$), a metric that is often not reported in RCTs and provides an informative indicator of economic benefit.

Similarly, an analysis of a Dutch registry assessed the impact of flash CGM use among 1,365 individuals with diabetes (77% with type 1 diabetes, 16% with type 2 diabetes, and 7% with other types of diabetes) (24). After 12 months of flash CGM use, A1C decreased from 8.0 to 7.4%, with the greatest reductions occurring among participants with a baseline A1C >8.6%. The percentage of patients experiencing any hypoglycemic event decreased from 93.5 to 91.0% ($P < 0.05$), and the number of diabetes-related hospital admissions decreased from 144 before baseline to 22 at 12 months ($P < 0.001$). Additionally, flash CGM users reported reduced diabetes burden with the SF-12 (12-item Short Form, v. 2) survey, EQ-5D-3 L (EuroQol 5-Dimension, three-level version) instrument, and DVN-PROM (Diabetes Vereniging Nederland Patient-Reported Outcomes Measure) questionnaire. The majority of study participants reported fewer hypoglycemic events (77%), less severe hypoglycemia (78%), more frequent insulin dose adjustments (80%), better understanding of their glucose fluctuations (95%), and less worry about their diabetes among housemates and family members (62%). Moreover, 81.7% felt no inhibitions about measuring their glucose in the presence of strangers, which was consistent with an increased frequency of sensor scanning. Also, in addition to the cost savings associated with reduced hospitalizations, there were fewer absences from work (7.8 vs. 18.55%, P <0.001).

While findings from these real-world studies further support the metabolic benefits associated with flash CGM use reported in RCTs, the reductions in hospitalizations (23–25,33) and in absenteeism (23,24) also demonstrate the immediate and substantial economic benefits of flash CGM use within populations with type 1 or type 2 diabetes. The improvements observed in treatment satisfaction (23,29), levels of hypoglycemia fear (26,29), sense of well-being (29), and other health-related measures (23–25,28,29) additionally support patient-reported outcomes described in RCTs (1,5).

Additional Emerging Real-World Evidence

As use of flash CGM technology continues to grow, large national and commercial database studies are being investigated to discern the impact of flash CGM on both A1C and acute diabetes-related events (Table 3). Two recent analyses showed significant reductions in all-cause hospitalizations and diabetes-related events among adults with either type 1 or type 2 diabetes who acquired flash CGM.

Analysis of a French national reimbursement claims database identified 74,158 adults with diabetes (type 1: n = 33,203, type 2: n = 40,955) who initiated flash CGM during the last 6 months of 2017 (34). Over the next 12 months, yearly hospitalization rates for DKA and acute hyperglycemia were reduced by 52% among patients with type 1 diabetes and by 47% for those with type 2 diabetes. The reduced rates were most evident for people with very low or very high adherence to self-monitoring of blood glucose (SMBG).

Significant reductions in acute diabetes-related adverse events (ADEs) and all-cause hospitalizations (ACH) were noted among 1,244 adults with type 2 diabetes treated with rapid- or short-acting insulin who acquired flash CGM (35). At 6 months post-acquisition, ADE rates decreased from 0.158 to 0.077 events/patient-year (hazard ratio [HR] 0.49 [95% CI 0.34–0.69], P <0.001). Hospitalizations also decreased from 0.345 to 0.247 events/patient-year (HR 0.72 [95% CI 0.58–0.88], P = 0.002). These findings equate to numbers needed to treat of 12 and 10 for 1 year to avoid one ADE or 1 ACH, respectively.

Strong evidence for the clinical and economic benefits associated with use of flash CGM has also emerged from studies of individuals treated less intensively with insulin or noninsulin therapy (30,31,33). In addition to significant reductions in ADEs and hospitalization rates (33), there were substantial and sustained reductions in A1C among adults with type 2 diabetes treated with long-acting insulin or noninsulin therapies (30). For those not treated with insulin, the reductions in A1C were similar to what would be expected from adding insulin glargine (36). Further studies (34,37) have established that there is no correlation between previous frequency of daily blood glucose monitoring and ADEs.

These findings challenge the view that CGM should be made available only to patients who are treated with intensive insulin therapy and who have a documented history of frequent blood glucose monitoring. This perception may have reduced the coverage of CGM offered by some commercial and public insurers. For example, the Centers for Medicare & Medicaid Services currently limit coverage to patients who administer three or more insulin injections per day (or use an insulin pump) and perform four or more glucose tests per day.

Summary

Many individuals with diabetes experience poor glycemic control (38,39), which puts them at increased risk for acute adverse glycemic events (40,41) and the long-term development of microvascular and macrovascular disease (42–44). In addition to its clinical consequences, uncontrolled diabetes is driving an inordinate economic burden on private payers and national health care systems (7).

Numerous studies have shown that optimizing A1C levels and reducing the incidence of severe hypoglycemia and DKA can significantly lower health care costs (10–14,45–47). However, achieving optimal diabetes control necessitates expanded adoption of diabetes medications and technologies that are effective, safe, and feasible in real-world clinical settings.

Flash CGM provides immediate information about an individual's current and projected glucose level using rate-of-change arrows, which allows users to respond promptly to mitigate or prevent pending hypoglycemia or hyperglycemia. Findings from large RCTs and prospective, observational studies have shown that use of flash CGM is associated with improved overall glycemic control (23–26,28), reductions in hypoglycemia (23–25), fewer diabetes-related hospitalizations (23–25,33), decreased absenteeism (23,24), and improvements in treatment satisfaction (23,29) and measures of well-being (23,25,28,29). These outcomes indicate both clinical and economic benefits, and use of flash CGM can enable these

TABLE 3 Summary of Emerging Real-World Evidence

Published Reports	Design/Intervention	Outcome Measures	Findings
A1C reductions			
Miller et al., 2020 (30)	• 6- and 12-month retrospective, observational analyses using medical/pharmacy claims database and Quest laboratory A1C values (United States) • 6- and 12-month: 774 and 207 adults, respectively, with type 2 diabetes treated with long-acting insulin or premixed insulin (n = 277 and 87, respectively) or noninsulin therapy (n = 497 and 120, respectively) • Acquisition of flash CGM	• A1C	• A1C decreased by −0.8% (P <0.0001) in the 6-month cohort: long-acting insulin by −0.6% (P <0.0001), noninsulin by −0.9% (P <0.0001). • A1C decreased by −0.6% (P <0.0001) in the 12-month cohort: long-acting insulin by −0.5% (P = 0.0014), noninsulin by −0.7% (P <0.0001).
Wright et al., 2020 (31)	• 12-month, retrospective, observational study using IBM Explorys, a U.S. EHR database • 1,183 adults with type 2 diabetes using long-acting insulin or premixed insulin (n = 378) or noninsulin (n = 805) therapy • 12-month, retrospective, observational study using IBM Explorys, a U.S. EHR database	• A1C	• A1C decreased by −1.38% (from 10.16 to 8.78%, P <0.0001) at 6 months post–flash CGM acquisition. • Greatest reductions of A1C were seen in participants with highest baseline A1C levels.
Eeg-Olofsson et al., 2020 (48)	• 12-month, retrospective, observational study using Swedish National Diabetes Register • 538 adults with type 1 or type 2 diabetes • Flash CGM use	• A1C	• A1C decreased by −0.52% (P <0.0001) at 12 months.
Reductions in events/hospitalizations			
Hirsch et al., 2020 (37)	• 12-month, retrospective, observational study using IBM MarketScan Commercial Claims and Medicare Supplemental databases • 12,521 adults with type 1 or type 2 diabetes • Acquisition of flash CGM	• Acute ADEs for hypoglycemia or hyperglycemia	• ADE decreased from 0.245 to 0.132 events/patient-year (HR: 0.54 [95% CI 0.49–0.59], P <0.001). • Similar reductions in ADE were seen in participants with a history of performing four or more or less than four glucose tests per day.
Bergenstal et al., 2020 (35)	• 12-month, retrospective, observational study using IBM MarketScan Commercial Claims and Medicare Supplemental databases • 1,244 adults with type 2 diabetes • Acquisition of flash CGM	• Acute ADEs for hypoglycemia or hyperglycemia • ACH	• ADEs decreased from 0.158 to 0.077 events/patient-year (HR: 0.49 [95% CI 0.34–0.69], P <0.001). • ACH decreased from 0.345 to 0.247 events/patient-year (HR: 0.72 [95% CI 0.58–0.88], P = 0.002).
Miller et al., 2020 (33)	• 12-month, retrospective, observational study using IBM MarketScan Commercial Claims and Medicare Supplemental databases • 7,167 adults with type 2 diabetes treated with long-acting insulin or noninsulin therapy • Acquisition of flash CGM	• Acute ADEs • Hospitalization or outpatient emergency for hypoglycemia or hyperglycemia	• ADEs decreased at 6 months post-acquisition of flash CGM from 0.071 to 0.052 events/patient-year (HR: 0.70 [95% CI 0.57–0.85], P <0.001). • Hospitalizations decreased from 0.180 to 0.161 events/patient-year (HR: 0.87 [95% CI 0.78–0.98], P = 0.025).
Roussel et al., 2020 (34)	• 12-month, retrospective, observational study using the French nationwide reimbursement claims database • 33,203 individuals with type 1 diabetes and 40,955 individuals with type 2 diabetes • Flash CGM use for 12 months	• Hospitalizations for DKA	• DKA hospitalizations decreased by 52% in participants with type 1 diabetes and by 47% in those with type 2 diabetes.

EHR, electronic health record; IBM, International Business Machines.

outcomes regardless of therapy and previous blood glucose monitoring frequency (30,31,33,34,37).

Given the growing global prevalence of diabetes and its associated costs, there is an opportunity to take advantage of flash CGM to facilitate improvements in metabolic control and patient QoL while reducing the projected costs of diabetes care.

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AUTHOR CONTRIBUTIONS

C.J.B. and J.R.G. wrote, reviewed, and approved the manuscript for submission. C.J.B. is the guarantor of this work and takes responsibility for the integrity of the data and the accuracy of the content.

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