

Clinical Research Article

Flash CGM Is Associated With Reduced Diabetes Events and Hospitalizations in Insulin-Treated Type 2 Diabetes

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Abbreviations: ACH, all-cause hospitalization; ADE, acute diabetes-related event; CGM, continuous glucose monitoring; HbA1c, glycated hemoglobin; ICD-10, International Classification of Diseases, 10th Revision; NDC, National Drug Code; SMBG, self-monitoring of blood glucose.

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Abstract

Purpose: Suboptimal glycemic control among individuals with diabetes is a leading cause of hospitalizations and emergency department utilization. Use of flash continuous glucose monitoring (flash CGM) improves glycemic control in type 1 and type 2 diabetes, which may result in lower risk for acute and chronic complications that require emergency services and/or hospitalizations.

Methods: In this retrospective, real-world study, we analyzed IBM MarketScan Commercial Claims and Medicare Supplemental databases to assess the impact of flash CGM on diabetes-related events and hospitalizations in a cohort of 2463 individuals with type 2 diabetes who were on short- or rapid-acting insulin therapy. Outcomes were changes in acute diabetes-related events (ADE) and all-cause inpatient hospitalizations (ACH), occurring during the first 6 months after acquiring the flash CGM system compared with event rates during the 6 months prior to system acquisition. ICD-10 codes were used to identify ADE for hypoglycemia, hypoglycemic coma, hyperglycemia, diabetic ketoacidosis, and hyperosmolarity.

Results: ADE rates decreased from 0.180 to 0.072 events/patient-year (hazard ratio [HR]: 0.39 [0.30, 0.51]; P < 0.001) and ACH rates decreased from 0.420 to 0.283 events/patient-year (HR: 0.68 [0.59 0.78]; P < 0.001). ADE reduction occurred regardless of age or gender. **Conclusions:** Acquisition of the flash CGM system was associated with reductions in ADE and ACH. These findings provide support for the use of flash CGM in type 2 diabetes patients treated with short- or rapid-acting insulin therapy to improve clinical outcomes and potentially reduce costs.

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Key Words: continuous glucose monitoring, type 2 diabetes, hospitalizations, hypoglycemia, hyperglycemia

The global prevalence of diabetes is estimated to increase from 9.3% (463 million people) in 2019 to 10.2% (578 million people) by 2030 [1], with the total cost of care rising to US \$2.2 trillion [2]. Hospitalizations and emergency department utilization are primary contributors to these costs. In a recent American Diabetes Association report, the total direct cost of diabetes was estimated to be US \$237.3 billion in 2017 [3]. Approximately 38% of these costs were attributed to hospital inpatient care (\$69.7 billion), hospital outpatient treatment (\$12.1 billion), emergency department utilization (\$8.0 billion) and ambulance services (\$332.0 million).

Hospitalizations are prevalent among individuals with type 2 diabetes, who account for 90% to 95% of all diabetes cases [4]. Adults with type 2 diabetes are admitted for emergency department treatment or hospitalized for numerous health conditions, including severe hyperglycemia and hypoglycemia [5-9]. These events are particularly common among patients with large fluctuations in glycated hemoglobin (HbA1c) and very high or very low average HbA1c levels [10].

Suboptimal glycemic control using traditional blood glucose monitoring persists among a substantial number of patients with type 2 disease [11, 12]. However, randomized controlled trials have demonstrated that use of continuous glucose monitoring (CGM) significantly lowers HbA1c [13], with reductions in hypoglycemia [14, 15] and improved treatment satisfaction [13, 14] in various type 2 diabetes populations.

Unlike traditional self-monitoring of blood glucose (SMBG), CGM systems provide a continuous stream of glucose data, indicating the current interstitial glucose level and the direction and velocity of changing glucose. This information allows users to quickly intervene to prevent or reduce acute hypoglycemia or hyperglycemia.

The FreeStyle Libre 14-day system, manufactured by Abbott Diabetes Care, Alameda, CA, is the only flash CGM system currently available in the US. An earlier version (10day system) was available from 2017 to 2019. Unlike traditional blood glucose monitors, which provide only a single "point-in-time" glucose value, flash CGM systems utilize a single-use, factory-calibrated sensor that continuously measures interstitial glucose levels. By scanning the sensor with the reader or smartphone, the user can view the current glucose value as well as the glucose pattern over the past 8 hours with trend arrows, which indicate the direction and velocity of changing glucose levels.

Suboptimal glycemic control among individuals with diabetes is a leading cause of hospitalizations and

emergency department utilization. Use of flash continuous glucose monitoring (flash CGM) improves glycemic control in type 1 and type 2 diabetes, which may result in lower risk for acute and chronic complications that require emergency services and/or hospitalizations.

We analyzed the effects of system acquisition on inpatient and emergency outpatient acute diabetes-related event (ADE) and all-cause hospitalization (ACH) rates, in a large population of patients with type 2 diabetes who were treated with short- or rapid-acting insulin therapy. This represents the early real-world experience of patients using flash CGM systems.

Materials and Methods

Design and Study Sample

This retrospective database study assessed the effects of flash CGM system acquisition on occurrence rates of ADE and ACH within a large cohort of patients with type 2 diabetes treated with short- or rapid-acting insulin therapy. Both analysis structure and outcomes were prespecified. Patients were included if they had a diagnosis of type 2 diabetes, were \geq 18 years of age, received a prescription for short- or rapid-acting insulin, were naïve to CGM, and acquired either the 10-day or 14-day sensor system between November 2017 and September 2018. In addition, patients were required to be continuously enrolled in the inpatient, outpatient, and pharmacy databases for at least 6 months prior to system acquisition.

Diabetes type was determined from the closest relevant diagnosis claim prior to flash CGM acquisition. In the rare case the closest claim had billing codes related to both type 1 and type 2 diabetes, the patient was not included. In addition, patients with a gestational diabetes diagnosis in the 6 months prior to flash CGM acquisition were excluded.

Data Sources

Patient data were obtained from the IBM Watson Health MarketScan Commercial Claims and Medicare Supplemental databases, which capture paid and adjudicated billing claims from inpatient hospital stays, outpatient encounters, and pharmacy prescriptions for privately insured and Medicare Supplemental patients throughout the United States. This nationally representative database has been used to support publications in the field of diabetes research [16, 17]. A monthly patient enrollment indicator shows whether a patient is under observation, which allows for longitudinal analysis. Patients can be lost to follow-up for a wide variety of reasons, including switching employers, losing their jobs or death. The dataset does not provide information on why a patient is no longer under observation.

International Classification of Diseases, 9th and 10th Revision (ICD-10) codes were used to identify patients with diagnosed type 2 diabetes.

Existence of a comorbidity was defined by the presence of a related diagnosis code in either inpatient or outpatient claims at any time from the beginning of each patient's data availability through the day of flash CGM acquisition. Within the identified population, National Drug Code (NDC) data were used to identify patients who acquired a flash CGM system during the required observation period. We identified patients who were treated with short- or rapid-acting insulin therapy, as indicated by acquisition of short- or rapid-acting insulin in the NDC data within 6 months prior to system acquisition.

To ensure that patients were naïve to CGM, we excluded those with evidence of prior CGM purchase, including sensor, transmitter, or receiver, identified via either NDC codes or Healthcare Common Procedure Coding System (HCPCS) codes.

Outcome Measures

The primary outcome measure was change in ADE during the full 6 months following system acquisition compared with 6 months prior to use. Acute events included: hypoglycemia, hypoglycemic coma, clinical hyperglycemia, diabetic ketoacidosis, and hyperosmolarity. These were identified as either inpatient events with the associated ICD-10 code as the primary diagnosis code or emergency outpatient events, which included emergency department services, urgent care, or ambulance services with the associated ICD-10 code in any position. The ICD-10 codes for acute events were as follows: hypoglycemia (E16.1, E16.2, E10-11.649, E13.649), hypoglycemic coma (E10-11.641, E13.641), hyperglycemia (E10-11.65, E13.65), diabetic ketoacidosis (E10.1x, E13.1x), and hyperosmolarity (E11.00, E13.0x). For each patient, medical billing codes associated with the same service or admit date were counted as a single event. The change in ACH rates was assessed as a secondary outcome. Event rates are calculated by dividing the number of observed events by the total observation time. A patient that is lost to follow-up before 6 months results in a lower total observation time, leading to a higher estimate of the rate if the same number of events were still detected.

Statistical Analysis

The analysis was structured as patient-as-own-control. Rates for all primary and secondary measures were calculated in the 6-month windows pre- and post-system purchase but are reported in units of events per patient-year (ev/pt-yr). Rates were adjusted for variable follow-up after system purchase. Cumulative events figures are based on Nelson-Aalen estimator. All hazard ratios, 95% confidence bounds, and P values are based on weighted Cox regression with Andersen-Gill extension for repeated events, adjusted for comorbidities listed in Table 1. Weighted Cox regression was used to account for nonproportionality of hazards, as tested via Schoenfeld residuals. Interactions were tested in the same model. All *P* values are reported without correction for multiple comparisons. RStudio version 1.0.153 (Boston, MA, USA) with R version 3.4.0 was used for statistical analysis.

Results

Patient Characteristics

We identified a cohort of 2463 patients with type 2 diabetes for assessment. Most patients were over the age of 50. The majority of patients had hypertension and dyslipidemia, and more than half were obese. Patient characteristics are presented in Table 1.

Outcomes

During the 6-month assessment period, we observed a reduction in ADE from 0.180 to 0.072 events/patient-year (hazard ratio [HR] 0.39 [0.30, 0.51]; P < 0.001) (Fig. 1A). Reductions in ACH were also observed, from 0.420 to 0.283 events/patient-year (HR 0.68 [0.59, 0.78]; P < 0.001). (Fig. 1B) The number of ADE, ACH, and patients experiencing these events dropped markedly during the 6-month postacquisition period. (Table 2)

Subgroup Analysis

Risk reductions were significant regardless of gender or age, with trends toward greater risk reductions among female patients (HR 0.30 [0.20 0.44]; P < 0.001) and patients age ≥ 50 years (HR 0.35 [0.25 0.48]; P < 0.001); however, neither interaction term P value, 0.054 and 0.183 respectively, achieved statistical significance (Fig. 2).

Causes of ACH

Circulatory system disorders continued to be the primary cause of ACH after flash CGM acquisition (Table 3).

| Mean age, years (mean ± SD [10%, 90% deciles]) | 54.2 ± 9.6 (41, 64) |
|--|---------------------|
| Male gender, % (n) | 52.9% (1304) |
| Follow-up days [10%, 90% deciles] | 173 [163, 182] |
| Comorbidities, % (n) | |
| Lipid disorder | 89.7% (2210) |
| Hypertension | 87.5% (2155) |
| Obesity | 60.0% (1479) |
| Neuropathy | 48.1% (1185) |
| Retinopathy | 31.2% (768) |
| Depression | 29.4% (724) |
| Pulmonary disease | 28.8% (709) |
| Hypothyroidism | 26.2% (646) |
| Anemia | 25.8% (635) |
| Myocardial infarction or coronary artery disease | 24.6% (606) |
| Liver disease | 20.8% (513) |
| Renal disease | 19.5% (480) |
| Peripheral vascular disease | 17.4% (429) |
| Heart failure | 13.1% (323) |
| Insurance type, % (n) | |
| Commercial insurance | 93.5% (2302) |
| Medicare supplemental insurance | 6.5% (161) |

However, Endocrine, Nutritional, and Metabolic system disorders, which is the category most related to diabetes, fell from the second to fifth most common major diagnostic category. Substantial decreases in infectious and parasitic diseases, respiratory system events, and kidney and urinary tract conditions were also observed.

Discussion

We hypothesized that the availability of glucose data provided by the flash CGM system would be associated with a reduction in diabetes-related complications and resultant hospitalizations in individuals with type 2 diabetes who were treated with short- or rapid-acting insulin therapy. Results from the current analysis showed a significant association between acquisition of flash CGM and reductions in ADE requiring emergency outpatient/inpatient hospital services and all-cause events requiring inpatient hospitalization. The change in number of events per patient, particularly in ADE (Table 2), suggests a corresponding reduction in readmissions. Moreover, although the rate of hypoglycemic ADE was low prior to the flash CGM acquisition,

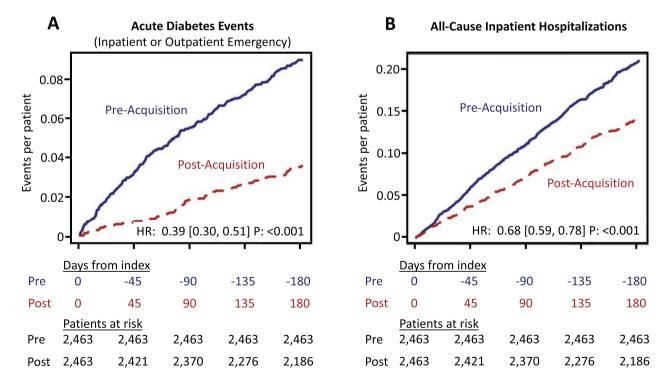


Figure 1. Changes in ADE (A) and ACH (B). Figure shows reduction in acute diabetes-related events (ADE) and all-cause inpatient hospitalizations (ACH) from the 6-month period pre-flash CGM acquisition (solid line, blue) to the 6-month period post-flash CGM acquisition (dotted line, red). Cumulative event rate is based on a Nelson-Aalen estimator. ADE include diabetes-related inpatient hospitalizations and diabetes-related outpatient emergency visits including ambulance, urgent care, and emergency room visits. Results of weighted Cox regression with Andersen-Gill extension are presented as a hazard ratio (HR) with 95% confidence bounds and *P* values.

the significant reduction in hyperglycemic ADE with slight reductions in hypoglycemia is a strong indicator of overall improved glycemic control. Both of these findings hold important clinical and financial implications. For example, hyperglycemia at hospital admission is a strong predictor of poor clinical outcomes for coronary artery bypass graft [18] and ischemic stroke [19-21]. As reported by Yun et al, each severe hypoglycemic event is significantly (P < 0.001) associated with increased risk for poor cardiovascular outcomes and all-cause mortality [22].

Because surveillance of hypoglycemia in the United States relies primarily on data from electronic health records (EHR) or administrative claims from hospital admissions and emergency department utilization, the actual incidence of severe hypoglycemia may be substantially

Table 2. Number of Events and Number of Patients Affected

| Event type | 6-months pre- acquisition # events (# affected) | 6-months post- acquisition # events (# affected) |
|--|---|--|
| All-cause inpatient hospitalizations (ACH) | 516 (357) | 331 (239) |
| Acute diabetes events (ADE) ^a | 221 (181) | 84 (73) |
| Hypoglycemic ADE | 24 (21) | 17 (16) |
| Hyperglycemic ADE | 199 (166) | 69 (62) |

Each event type shows number of events (number of patients with event). ^{*a*}In rare cases, when a hypoglycemic and hyperglycemic billing code appear on the same day, a single ADE is counted. So, totals on this row will be slightly lower than the sum of bottom 2 rows.

underreported. In a recent survey of 13 359 individuals with diabetes who were treated with glucose-lowering medications, 11.7% reported having one or more severe hypoglycemic events requiring third-party assistance in the previous 12 months; however, 0.8% had a documented hypoglycemia-related emergency department or hospital utilization during the same time period [23].

Apart from its acute clinical outcomes, episodes of severe hypoglycemia can impact patient adherence to therapy, which can lead to poor glycemic control and increased risk of long-term complications [24, 25]. An international survey of 27 585 diabetes patients found that 25.8% to 46.7% of people with type 2 diabetes reduced their insulin dosages in response to hypoglycemia [26].

What makes our findings unique is that we saw a notable reduction in ADE and ACH within the first 45 days of the flash CGM post-acquisition period. Additionally, our findings from a real-world large patient cohort are consistent with results from prospective, observational studies involving both type 1 and type 2 diabetes [27, 28]. The FLARE-NL4 study, a prospective, nationwide registry in the Netherlands, assessed the impact of flash CGM use over 1 year in 1365 patients with type 1 diabetes (n = 1054), type 2 diabetes (n = 223), and others (n = 88) [27]. During the first year of use, the percentage of diabetes-related hospital admissions decreased 66% from 13.7% to 4.7% (P < 0.05). A similar study in Belgium assessed the impact of flash CGM use in 1913 adults with type 1 diabetes [28]. Investigators reported significant reductions in hospital admissions for severe hypoglycemia and diabetic ketoacidosis (from 3.2% to 2.2%; P = 0.031), the number of patients

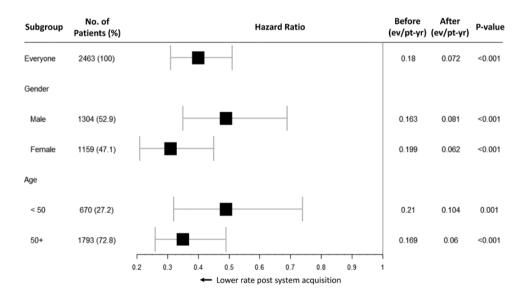


Figure 2. ADE by gender and age. Acute diabetes-related events (ADE) are analyzed for men and women and patients of different ages. Results of weighted Cox regression with Andersen-Gill extension for each patient group are presented as a hazard ratio with 95% confidence bounds and *P* values. Event rates per patient-year for the 6-month period before flash CGM acquisition and the 6-month period after flash CGM acquisition are illustrated.

reporting severe hypoglycemic events (from 14.6% to 7.8%; P < 0.0001), and rates of hypoglycemic comas (from 2.7% to 1.1%; P = 0.001) following one year of flash CGM use. While these studies highlighted benefits in primarily the type 1 diabetes population, we wanted to explore the potential benefits of flash CGM in the type 2 diabetes population.

Results from our study also highlight the need for reducing hyperglycemia without increasing the incidence and severity of hypoglycemia. Although recent data show similar rates for hypoglycemic and hyperglycemic ADE in the general diabetes population (8.8 vs 9.7 per/1000 patients, respectively) [29], the substantially larger number of hyperglycemic vs hypoglycemic ADE prior to flash CGM acquisition suggests that many study patients historically maintained elevated glucose levels. As reported by Gregg et al, there was a notable increase in hyperglycemia-related hospitalizations among young adults and middle-aged patients (aged 18-44 years) between 2009 and 2015 [30]. Although several factors may explain persistent hyperglycemia, it has been suggested that this may, in part, be an "unintended consequence" of relaxed treatment target recommendations from medical organizations [30]. Additionally, although cardiovascular disease remains the leading cause of mortality in both type 1 and type 2 diabetes, we are seeing an emergence in infectious, respiratory, renal, and liver diseases, which are likely attributable to persistent hyperglycemia [31]. Hospitalizations for all of these conditions were notably reduced after flash CGM acquisition. As shown in Table 3, we found notable decreases in hospitalizations for infections (41.7%), renal disease (48.5%), and liver disease (41.7%). Although the IBM Watson Health MarketScan datasets did not provide HbA1c values or other information regarding glycemic status, we believe that reductions in these comorbidities are likely due to improved glycemic control, as reported by McCoy et al [32].

An essential component of all available CGM systems is the ability to automatically transfer data to healthcare professionals via cloud-based software for interpretation and more informed decision making [33]. Although previously considered to be futuristic, the importance of telemedicine and digital medical device technologies has been demonstrated to be the best (or the only) option in delivering essential healthcare to patients as the COVID-19 pandemic progresses [34]. We expect use of telemedicine and cloudbased CGM data to expand and become a standard of diabetes care moving forward.

A key strength of our analysis was use of claims data from a large dataset, which provided reliable information about acquisition of the flash CGM system over time in 2463 patients with insulin-treated type 2 diabetes. Similarly, assessments of complications and utilization of healthcare resources (eg, emergency room visits, inpatient

| Before flash CGM | | | After flash CGM |
|---|--|---|--|
| Hospitalizations (events/100 pt-yr) Major diagnostic category | Major diagnostic category | Hospitalizations (events/100 pt-yr) Major diagnostic category | Major diagnostic category |
| 7.8 | Circulatory system | 6.9 | Circulatory system |
| 6.4 | Endocrine, nutritional, and metabolic system | 2.8 | Infectious and parasitic DDs (systemic or unspecified sites) |
| 4.8 | Infectious and parasitic DDs (systemic or unspecified sites) | 2.8 | Musculoskeletal system and connective tissue |
| 3.5 | Respiratory system | 2.7 | Digestive system |
| 3.3 | Kidney and urinary tract | 2.6 | Endocrine, nutritional, and metabolic system |
| 3.2 | Musculoskeletal system and connective tissue | 2.1 | Respiratory system |
| 3.1 | Digestive system | 1.7 | Kidney and urinary tract |
| 2.9 | Nervous system | 1.6 | Nervous system |
| 2.4 | Hepatobiliary system and pancreas | 1.4 | Hepatobiliary system and pancreas |

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hospitalizations) based on ICD-10 codes allowed us to accurately quantify actual events and utilization without reliance on patient-reported data.

A notable limitation was the inability to empirically assess patient behaviors relevant to using the system. Specifically, we cannot conclude whether or to what degree patients used their system. Did they use their glucose data to make therapy decisions? Did they use it appropriately? In addition, as discussed earlier, because the IBM Watson datasets provided no information regarding HbA1c values, we could not assess changes in overall glycemic control. We also could not assess the socioeconomic, educational characteristics, or participation in a formal diabetes self-management education program, all of which could have affected outcomes. This is a limitation inherent to all claims data studies. Additionally, because our analysis only included data from commercial claims and Medicare Supplemental databases, our findings cannot be generalized to lower socioeconomic populations. Furthermore, although it was assumed that all of the study patients were using some form of short- or rapid-acting therapy we could not confirm through our database query the exact composition of the insulin regimen used by each patient. Importantly, since they comprise a small fraction of our study cohort, our findings cannot be generalized to older diabetes patients (≥ 65 years), who account for approximately 27% of diabetes in the United States [29], and in whom the risk for hypoglycemia is substantially greater [35-37] due to higher rates of hypoglycemia unawareness [38] and cognitive impairment [39]. However, an earlier randomized controlled trial showed significant reductions in time spent with glucose levels <70 mg/dL (<3.9 mmol/L) among flash CGM users compared with controls [15]. Nor did our population include Medicaid patients, who often develop diabetes at an earlier age with an increased level of severity, and who have different patterns of technology use compared with Medicare beneficiaries and privately insured patients [40]. Lack of a comparison group is an important limitation but is inherent to the retrospective design of the study. Although we were able to show associations between system acquisition and clinical outcomes, a causal relationship cannot be established.

Our findings provide evidence for the use of flash CGM in insulin-treated type 2 diabetes to improve clinical outcomes and potentially reduce the financial burden associated with hospitalizations and emergency department utilization due to ADE. Wider use of flash CGM may address the changing trends of increasing all-cause hospitalizations among younger and middle-age adults and the newly emerging trends of increased mortality due to infections, respiratory illness, and renal and hepatic complications. Further investigation of how patients utilize their glucose data in day-to-day diabetes management might provide additional insights that could guide the development of educational strategies and mechanisms for ongoing patient support systems that would encourage both persistent and appropriate use of the system.

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Additional Information

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Data Availability: Restrictions apply to some or all the availability of data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

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