



ORIGINAL ARTICLE

Real-World Studies Support Use of Continuous Glucose Monitoring in Type 1 and Type 2 Diabetes Independently of Treatment Regimen

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Abstract

Numerous randomized controlled trials (RCTs) have demonstrated the glycemic benefits of continuous glucose monitoring (CGM) in management of type 1 diabetes (T1D) and type 2 diabetes. Although RCTs remain the gold standard clinical study design, findings from these trials do not necessarily reflect the effectiveness of CGM or reveal the feasibility and wider applications for use in broader real-life settings. This review evaluates recent real-world evidence (RWE) demonstrating the value of CGM to improve clinical outcomes, such as avoidance of severe hypoglycemic and hyperglycemic crises, and improved measures of psychological health and quality of life. Additionally, this review considers recent RWE for the role of CGM to enhance health care resource utilization, including prediction of T1D and applications in gestational diabetes, chronic kidney disease, and monitoring during surgery.

Keywords: CGM, Type 1 diabetes, Type 2 diabetes, RCTs, Observational, Hospitalizations.

Introduction

WELL-DESIGNED, RANDOMIZED CONTROLLED TRIALS (RCTs) have traditionally been considered the highest level of trial evidence. Although they provide critical information about the efficacy of a given intervention (medication or medical device) when applied within tightly controlled clinical conditions, the results may not replicate how or if individuals will actually integrate the intervention into their daily lives, potentially resulting in an overestimation of efficacy. Moreover, RCTs may not reflect the effects of an intervention within the populations that have been excluded from the trial.

Another limitation of RCTs concerns the assessment of rapidly evolving diabetes technologies in meta-analyses and systematic reviews (MASRs). By the time enough studies have been completed for a robust MASR, subsequent improvements in accuracy, reliability, and convenience will render the results from MASRs outdated and potentially misleading in terms of the efficacy and safety of current technologies. This is particularly relevant to continuous glucose monitoring (CGM).

Given these limitations, there is growing recognition for the role of real-world evidence (RWE) generated by prospective, retrospective, and observational studies that fill the knowledge gap between the responses of individuals to an intervention within a controlled setting compared with patterns of response and clinical impact in real life. Recognizing the importance of real-world study designs, many payers and regulatory agencies now request pharmaceutical and medical device manufacturers to submit RWE in conjunction with findings from their RCTs when assessing the safety, effectiveness, and cost–benefit parameters of new medications and medical devices.^{1–4}

Over the past decade, findings from several large RCTs have demonstrated the clinical value and utility of improving the overall glycemic status^{5–10} and reducing hypoglycemia risk^{5,7,11–13} in individuals with type 1 diabetes (T1D) and type 2 diabetes (T2D) who are treated with intensive insulin regimens. In this article, we review findings from recent real-world studies of CGM systems that provide greater insights into the clinical effectiveness and economic impact of this technology within various diabetic populations. We also discuss how CGM is being used to expand our understanding of diabetes in toto.

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Evidence of Clinical Effectiveness

As adoption of CGM continues to expand, we are seeing a growing number of large national and commercial database studies investigating the effects of CGM on A1C, hypoglycemia risk, and acute diabetes-related events in individuals with T1D^{14–24} and T2D.^{25–27}

Table 1 presents a summary of findings from the most recent real-world studies within the past 2 years.

T1D studies

A recent, prospective observational study assessed the impact of using flash CGM (FreeStyle Libre, Abbott Diabetes Care, Alameda, CA) in a cohort of 1913 T1D adults.¹⁵ During the 12-month study period, there was a significant reduction in admissions for severe hypoglycemia and/or ketoacidosis (from 3.3% to 2.2%, $P=0.031$), with fewer individuals reporting severe hypoglycemic events (from 14.6% to 7.8%, $P<0.0001$). Reductions in the percentages of individuals who experienced hypoglycemic coma (from 2.7% to 1.1%, $P=0.001$) and reported work absenteeism (from 5.8% to 2.9%, $P<0.0001$) were also observed. Results from an earlier study showed similar findings among patients using other CGM devices, namely MiniMed Enlite (Medtronic, Inc., Northridge, CA); G4 PLATINUM (Dexcom, Inc., San Diego, CA); and FreeStyle Navigator II (Abbott Diabetes Care).¹⁴ The use of these devices also showed favorable results in improving A1C, reducing hypoglycemia events and hospitalizations, and decreasing days absent from work.

Similar findings emerged from an analysis of a large Dutch registry that included 1365 individuals with diabetes, the majority of whom had T1D (77%).¹⁶ Investigators reported that use of flash CGM was associated with significant A1C reductions after 12 months (from 8.0% to 7.4%, $P<0.001$). Significant reductions in the percentage of patients experiencing any hypoglycemic event (from 93.1% to 91.0%, $P<0.05$) and a decrease in the number of diabetes-related hospitalizations (from 144 to 22, $P<0.001$) were also observed along with reductions in work absenteeism (from 18.6% to 7.8%, $P<0.001$).

In a single-center cohort of 41 participants with T1D (aged 5–49 years), investigators assessed the long-term effects of initiating CGM (FreeStyle Libre, Dexcom G4, and MiniMed Guardian Sensor 3) in conjunction with insulin pump therapy on A1C and the incidence of hypoglycemia and microvascular disease. At follow-up (8.9 ± 2.8 years), A1C had decreased from 8.8% to 7.6% ($P=0.051$), with significant reductions in severe hypoglycemia (from 9.7 to 2.2 per 100 patient-years, $P=0.03$), but with a comparable incidence of newly diagnosed, diabetic microvascular complications.³²

Similar A1C reductions were observed in a prospective observational study that assessed A1C changes in 900 adult T1D patients using flash CGM compared with 518 patients who continued usual care with traditional blood glucose monitoring (BGM).¹⁸ Users of flash CGM with a baseline A1C $>7.5\%$ showed a significant reduction of A1C over an 8-month study period (median -0.6% , $P<0.001$), whereas no changes in A1C were observed with BGM use. Among flash CGM users, there was a 48.8% increase in those achieving an A1C $<7.5\%$ and the number of those with an A1C $>9.0\%$ was more than halved. Although flash CGM users reported more symptomatic and asymptomatic hypoglycemia, this is

likely to derive from heightened awareness due to having access to continuous glucose data through frequent scanning. Importantly, there were no significant changes in severe hypoglycemia.

An earlier study of 120 T1D adults who were followed for 12 months after initiating flash CGM found significant decreases in A1C levels from baseline at 3 months (from 8.5% to 7.8%, $P<0.001$), but with a slight increase to 7.9% at 12 months.²² These improvements were accompanied by reduction in fear of hypoglycemia, which is often a major obstacle to achieving optimal glycemic control.^{33,34} As noted in some other studies,²¹ there was a slight, but statistically significant, ($P<0.05$) increase in the number (but not duration) of hypoglycemic events at 12 months, which correlated with improvements in A1C and may be attributed largely to awareness with use of CGM. However, in a prospective observational study that compared flash CGM with BGM use in a cohort of 334 T1D children/adolescents, there was a 53% ($P=0.012$) reduction in cases of severe hypoglycemia among users of flash CGM compared with those using BGM, although A1C was not significantly altered in either group.³⁵ The majority (83.2%) of patients who switched from BGM to using flash CGM were still using their device after median use of 5.3 months.

T2D studies

About 20%–30% of patients with T2D eventually require insulin therapy, enabling substantial reductions in A1C levels, acute diabetes-related adverse events (ADEs), and all-cause hospitalizations (ACHs).^{21,27} Although a majority of insulin-treated T2D patients receive only basal insulin with or without other glucose-lowering agents (rather than basal-bolus injections or pump therapy), CGM still offers an opportunity to optimize glycemic control.

A retrospective chart review of 363 T2D adults from three European countries assessed the effectiveness of flash CGM use in conjunction with basal-bolus therapy.²¹ After >90 days following initiation of flash CGM, A1C levels were significantly lower: -0.9% (Austria), -0.8% (France), and -0.9% (Germany), all $P<0.0001$. The impact of this magnitude of A1C reductions after acquiring a flash CGM device is reflected in findings from an analysis of IBM MarketScan Commercial Claims and Medicare Supplemental databases.²⁷ This retrospective real-world analysis of a cohort of 2463 T2D adults treated with short- or rapid-acting insulin noted significant reductions in ADEs (from 0.180 to 0.072 events/patient-year, $P<0.001$) and ACHs (from 0.420 to 0.283 events/patient-year, $P<0.001$) during the 6 months after acquiring their flash CGM device compared with the 6-month period before acquisition. These improvements occurred regardless of age or gender.

Recent studies of flash CGM in T2D adults treated with nonintensive therapies have shown similar findings.^{30,31} In a Canadian chart review of 91 T2D adults managed with basal insulin therapy, there were significant A1C reductions (-0.8% , $P<0.0001$) after 3–6 months of flash CGM use.³⁰ A subgroup analysis comparing patients with baseline A1C of $<9.0\%$ and $>9.0\%$ showed clinically significant A1C reductions in both groups, but with most notable reductions occurring in the higher A1C group (-1.6% , $P<0.0001$). A U.S. chart review study of 100 T2D adults treated with basal

TABLE 1. REAL-WORLD STUDIES OF CONTINUOUS GLUCOSE MONITORING USE IN POPULATIONS WITH TYPE 1 DIABETES AND TYPE 2 DIABETES

Studies	Design	Study population	Outcome measures following CGM initiation	Findings
T1D Charleer ¹⁵	A 12-month, prospective, observational multicenter cohort (Belgium)	N=1913 T1D Age: 45.8 ± 15.3 years	Hospitalizations with DKA and/or SH Absenteeism Treatment satisfaction	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%, $P<0.0001$) Questionnaire-derived measures of treatment satisfaction improved
Sandig ¹⁷	Cross-sectional analysis (German/Austrian/Swiss Prospective Diabetes Follow-up [DPV] Registry)	N=233 T1D Age: ≥18 years	CGM metrics Time in range %TIR (70–180 mg/dL) Time below range %TBR (<70 mg/dL) Time above range %TAR (>180 mg/dL) Glycemic variability (% CV)	Participants aged ≥30 vs. <30 years spent more TIR (54% vs. 49%), more TBR (7% vs. 5%), less TAR (38% vs. 46%), and with a lower % CV (36% vs. 37%) Highest TIR and lowest time with sensor glucose >250 mg/dL observed in those treated with CSII and CGM
Šoupal ²⁴	A 3-year, nonrandomized, prospective 4-arm study	N= T1D 22 (CGM+MDI) N= T1D 26 (CGM+CSII) N= T1D 21 (BGM+MDI) N= T1D 25 (BGM+CSII) Age: ≥18 years	A1C change CGM metrics Time in range %TIR (70–180 mg/dL) Time below range %TBR (<70 mg/dL)	Greater A1C reductions from baseline at 3 years in the CGM+MDI and CGM+CSII groups (−1.2%, $P=0.0002$, and −1.3%, $P<0.0001$, respectively) compared with the BGM+MDI (−0.3%, $P=0.3574$) and BGM+CSII (−0.6%, $P=0.1000$) groups No significant difference in A1C reduction between the CGM+MDI and CGM+CSII groups ($P=0.61$) Significant increases in %TIR and reductions in %TBR in the CGM subgroups, but not in the BGM subgroups
T1D and T2D Rousse ²⁸	A 12-month, longitudinal retrospective cohort, pre- and postinitiation of flash CGM in France (French National Claims Database)	N=33,165 T1D Age: 8 to >75 years N=40,846 T2D Age: 16 to >75 years	Hospitalization for acute diabetes event Hospitalization for DKA	Significant reductions in hospitalizations for acute diabetes complications in T1D and T2D patients (−49.0% and −39.4%, respectively) Hospitalization rates for DKA fell by 55.0% (from 2508 patients to 1128 patients) Percentage of patients with at least one hospitalization for diabetes-related coma lower by 35.7% (T1D, −39.6%; T2D, −31.9%)

(continued)

TABLE 1. (CONTINUED)

<i>Studies</i>	<i>Design</i>	<i>Study population</i>	<i>Outcome measures following CGM initiation</i>	<i>Findings</i>
Eeg-Olofsson ²³	A 12-month, retrospective observational study, pre- and post-acquisition of flash CGM (Swedish National Diabetes Register)	N=39,554 T1D or T2D Age: ≥18 years	A1C change	Significant A1C reductions achieved and sustained at 12 months in T1D (-0.44%) and T2D (-0.66%)
Hirsch ²⁹	A 12-month, retrospective observational study, pre- and post-CGM acquisition (IBM MarketScan Commercial Claims and Medicare Supplemental databases)	N=12,521 T1D or T2D Age: ≥18 years Short- or rapid-acting insulin	ADEs for hypoglycemia or hyperglycemia	Reductions in from 0.245 to 0.132 events/patient-year (HR: 0.54 [95% CI: 0.49-0.59]; $P < 0.001$) No association between ADE reductions and history of BGM daily frequency (≥ 4 vs. < 4)
T2D Bergenstal ²⁷	A 12-month, retrospective observational study, pre- and post-CGM acquisition (IBM MarketScan Commercial Claims and Medicare Supplemental databases)	N=2463 T2D Age: ≥18 years Short- or rapid-acting insulin	ADEs and ACHs	ADE rates decreased from 0.180 to 0.072 events/patient-year HR: 0.39 [0.30, 0.51]; $P < 0.001$) ACH rates decreased from 0.420 to 0.283 events/patient-year (HR: 0.68 [0.59 0.78]; $P < 0.001$)
Miller ²⁵	A 12-month, retrospective observational study, pre- and post-CGM acquisition (IBM MarketScan Commercial Claims and Medicare Supplemental databases)	N=10,282 T2D Age: ≥18 years Basal insulin or noninsulin therapy	ADEs and ACHs	ADE rates decreased from 0.076 to 0.052 events/patient-year (HR: 0.68 [0.58 0.80]; $P < 0.001$) ACH rates decreased from 0.177 to 0.151 events/patient-year (HR: 0.85 [0.77 0.94]; $P = 0.002$)
Wright ²⁶	A 12-month, retrospective observational study, pre- and post-CGM acquisition (IBM Explorys database)	N=1034 T2D Age: ≥18 years Basal insulin or noninsulin therapy	A1C change	Reductions in A1C within the full cohort (from $10.1\% \pm 1.7\%$ to $8.6\% \pm 1.8\%$, $P < 0.001$) Greatest reductions in patients with baseline A1C $\geq 12.0\%$ (-3.7% , $P < 0.001$) Reductions in A1C in both treatment groups (basal insulin, -1.1% ; and noninsulin -1.6% , both $P < 0.001$) Reductions in A1C after ≥ 3 months of CGM use ($-0.8\% \pm 1.1\%$, $P < 0.0001$) Subgroup analysis by baseline A1C ($< 9.0\%$ vs. $\geq 9.0\%$) showed A1C reductions in both groups ($-0.5\% \pm 0.8\%$ and $1.6\% \pm 1.3\%$, $P < 0.0001$, respectively)
Elliot ³⁰	A 3- to 6-month, retrospective chart review	N=91 T2D Age: ≥18 years Basal insulin	A1C change	

(continued)

of POC values, and although some discordance between CGM and POC values was observed in 11 patients, the differences were not considered clinically significant. During the observation period, mean sensor glucose decreased from 235.7 ± 42.1 mg/dL to 202.7 ± 37.6 mg/dL with the use of CGM. Additionally, most (63%) of the attending nurses reported that CGM was helpful for improving patient care and 49% indicated that use of CGM reduced their personal protective equipment utilization.

Improvements in psychosocial measures

In many of the current studies that showed significant associations between CGM use and improvements in glycemic measures, investigators have also reported increased treatment satisfaction,^{15,20} less hypoglycemia fear,^{20,22} enhanced sense of well-being,²⁰ and improvements in other health-related measures^{15,16,18–20} associated with CGM use. For example, further analysis of a cohort of mostly T1D individuals described earlier¹⁶ found improvements in quality of life (QoL) measures and better patient engagement with their self-management regimens.⁴³ Flash CGM users reported reduced diabetes burden, as assessed with the SF-12^{v2} and EQ-5D-3L questionnaires. Participants also reported more frequent insulin dose adjustments (80%) and less worry about their diabetes among family members (62%). The majority (81.7%) stated that they felt no inhibitions about measuring their glucose in the presence of strangers.

Studies that focused primarily on QoL outcomes in T1D children, adolescents, and young adults using CGM have shown similar improvements in psychosocial measures, including significant improvements in overall QoL ($P=0.014$), lessening of diabetes symptoms ($P=0.018$), and reductions in barriers to treatment ($P=0.035$).¹⁹ In a 2019 study of 33 T1D adolescents and young adults, investigators reported significant increases in treatment satisfaction and overall well-being, both $P<0.001$, after 12 weeks of flash CGM use.²⁰

An Australian study that recruited 38 T1D adolescents (aged >12 years) and their parents ($n=60$) assessed changes in psychosocial measures after 2 months of CGM use.⁴⁴ Among parents, significant reductions in the total hypoglycemia fear score and worry subscore were observed (both $P=0.004$), with improvements in reported sleep quality. Treatment satisfaction increased in both the patient and parent groups, and significant reductions in the Gold hypoglycemia awareness score were reported (from 26.3% to 10.5%, $P=0.031$).

Use of advanced CGM features

Innovations in CGM technologies have resulted in a number of advanced features that have been shown to improve glycemic control and reduce hypoglycemia risk in individuals with T1D and T2D. For example, in a retrospective analysis of 15,000 T1D children and adolescents, 94.8% of whom used the Dexcom sharing feature,⁴⁵ use of this feature was associated with lower mean glucose values, a higher percentage of time spent in the target glucose range (70–180 mg/dL), and fewer episodes of hypoglycemia and hyperglycemia.

A recent study of the Guardian Connect System with the MiniMed Enlite sensor retrospectively analyzed CGM data from individuals with T1D ($n=2692$), T2D ($n=93$), or ges-

tational diabetes ($n=5$). When patients utilized the predictive alerts function, 59% of low glucose excursions and 39% of high glucose excursions were prevented.⁴⁶

Studies that Inform Clinicians and Guide Therapy

In addition to improving daily self-management, CGM has broadened our appreciation of risk factors and clinical assessments associated with diabetes.

Risk factors

Gender differences in hypoglycemia risk were examined in a post hoc analysis of a single-center prospective trial of 102 adult T2D inpatients (male, $n=52$; female, $n=50$) treated with intensive insulin therapy.⁴⁷ Patients underwent a standard bread meal test at baseline and were monitored with CGM during the last 4 of 7 days on insulin pump therapy. Although male patients required lower doses of insulin to maintain optimized glycemic control, they spent more time with glucose levels <70 mg/dL than their female counterparts (3.2% vs. 0.9%, $P<0.01\%$, respectively), with a higher of incidence of hypoglycemia (20/52 vs. 9/50, $P=0.022$).

A study of CGM in 77 women with gestational diabetes (GDM) investigated whether specific patterns of hyperglycemia at different times of the day could predict maternal–fetal complications.⁴⁸ After placing the women on prospective CGM for 6 days between 26 and 32 weeks of gestation, investigators observed a statistically significant relationship between the time spent in hyperglycemia after lunch and fetal complications, including macrosomia ($P=0.035$) and large-for-gestational age infants ($P=0.010$). There was also a 24% increase in the probability of initiating glucose-lowering therapies for every additional percentage point of time above range.

CGM has also been used to predict glycemic control based on socioeconomic status based on the Index of Relative Socio-economic Disadvantage (IRSD),⁴⁹ which measures disadvantage (e.g., poverty, deprivation, and social exclusion) at an area level (e.g., neighborhood and community), not at an individual level.⁵⁰ Among 300 adult T2D patients assessed in the General Practice Optimising Structured Monitoring To Improve Clinical outcomes (GP-OSMOTIC) randomized study, glucose data from the FreeStyle Libre Pro CGM system revealed that those who were least disadvantaged had higher TIR and lower A1C values than those who were most disadvantaged.⁵¹ However, there was no association between the educational level and glycemic status.

CGM has been used to assess the appropriateness of a hospital protocol for managing patients postcardiovascular surgery.⁵² Glycemic variability was recorded in 76 patients during elective cardiovascular surgery and postoperative management with continuous intravenous insulin infusion in the intensive care unit (ICU) and when injection therapy was introduced after oral food intake was initiated. While the study confirmed that the protocol was adequate during continuous subcutaneous insulin infusion treatment, it exposed changes needed to improve the injection therapy protocol.

Assessments

Although measurements of A1C and fructosamine are often used to monitor glycemic status in individuals without chronic kidney disease, these methods are limited in their

utility to predict the risk of acute glycemic events and to assess glycemic control in patients treated with dialysis. In a prospective study of 104 T2D patients with end-stage renal disease, blinded CGM was recorded for two 6-day periods separated by 2 weeks, in conjunction with A1C and fructosamine measurements.⁵³ When compared with CGM data, fructosamine was significantly biased by age, body-mass index, serum iron concentration, transferrin saturation, and albuminuria. In addition, A1C values were underestimated in patients with albuminuria.

The utility of CGM in predicting the onset of T1D was assessed in 23 antibody-positive (Ab+) participants in the Diabetes Autoimmunity Study in the Young (DAISY), which prospectively follows children who are at increased risk for developing islet autoantibodies and T1D.⁵⁴ Investigators found that spending $\geq 18\%$ of time at >140 mg/dL was a strong predictor of progression to clinical diabetes in Ab+ children. These findings are particularly valuable in light of the development of new medications such as anti-CD3 monoclonal antibodies that have been shown to delay progression to T1D in high-risk individuals.^{55,56}

Conclusions

Large RCTs have clearly demonstrated the benefits of CGM use in individuals with diabetes who are treated with intensive insulin therapy.^{5–13} A growing number of real-world observational and prospective studies are confirming these findings and demonstrating similar benefits in T2D patients who are treated with less-intensive therapy.^{25,26,30,31} Results from these studies suggest that wider use of CGM within the broader diabetic population could increase overall glycemic control and improve the effectiveness while reducing the enduring cost of diabetes health care. Moreover, as studies emerge to further elaborate on the utility of CGM to identify risk of complications, improve care of inpatients, and predict the development and progression of T1D, we anticipate applications of CGM in broader disease management and research.

Authors' Contributions

J.R.G. III and C.J.B. wrote, reviewed, and approved the manuscript for submission. C.J.B. and J.R.G. III are the guarantors of this work and take responsibility for the integrity of the data and accuracy of the content.

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