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

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Use of continuous glucose monitoring (CGM) systems has become standard of care in type 1 diabetes (T1D) in many countries, particularly in children and adolescents (1,2). Results from clinical trials indicate that use of CGM leads to improved metabolic control and reduction in nonsevere hypoglycemia compared with self-monitoring of capillary blood glucose (3,4). Benefits are seen irrespective of insulin delivery method (pump or pen) (4,5) but are conditioned on near-daily sensor usage (4).

Trial participants, however, are often biased toward higher education level, greater therapy adherence, and better self-management. Small sample size and short trial duration very often preclude appropriate assessment of CGM impact on rare events such as severe hypoglycemia (SH) or diabetic ketoacidosis (DKA).

We therefore used real-world data from the German-Austrian-Swiss-Luxembourgian Diabetes Prospective Follow-up (DPV) registry to longitudinally assess HbA_{1c}, SH, and DKA during the first year after initiation of CGM, including real-time CGM and intermittently scanned/viewed CGM. Anonymized patient registry records were analyzed. SH was defined as events requiring external assistance by another person and events resulting in coma/convulsion. DKA was defined by pH level <7.3. All HbA_{1c} values were Diabetes Control and Complications Trial (DCCT) standardized.

Selection criteria included T1D, <18 years of age, >1 year of diabetes duration, available registry data 6 months prior to CGM start (baseline period), and at least 1 year of follow-up after CGM initiation. Documented sensor use for at least 50% of the time during both follow-up periods was required: *1*) the first 6 months following CGM initiation (excluding the first 6 weeks) and *2*) months 6–12 on CGM. All outcome measures were summarized over the 6-month periods. Data for this analysis were collected from 2005 to 2018 (2018, 23% of data; 2017, 49%; 2016, 24%; and $\leq$2015, 4%). Comparisons (follow-up periods vs. baseline) were performed using nonparametric tests for paired data (McNemar test and Wilcoxon signed rank test). Event rates were analyzed based on generalized estimation equation models with Poisson distribution and 1st-order autoregressive correlation structure to account for individual time under risk and longitudinal data. SAS, version 9.4 (SAS Institute, Cary, NC), was used for statistical analysis. Two-sided *P* values <0.05 were considered statistically significant.

Inclusion criteria were met by 3,553 pediatric patients (median age 12.1 years [quartile 1–quartile 3 9.2–14.6] and T1D duration 4.2 years [2.3–6.7]; 53% males), with 62% of subjects on insulin pumps. Fourteen percent of eligible patients were

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Table 1—Comparison of clinical outcomes at baseline with outcomes assessed during the first 6 months of CGM use and during months 6–12 after CGM initiation

	Baseline	Follow-up 1 (months 2–6)	*P*	Follow-up 2 (months 6–12)	*P*
HbA_{1c}					
%	7.58 (6.95, 8.23)	7.47 (6.89, 8.13)	<0.0001	7.48 (6.91, 8.18)	<0.0001
mmol/mol	59.3 (52.5, 66.5)	58.2 (51.8, 65.4)		58.2 (52.0, 65.9)	
Percentage of subjects with HbA_{1c} <7.5% (<58 mmol/mol)	47.1	52.3	<0.0001	50.5	<0.0001
DKA					
Percentage of subjects with at least 1 event	1.0	0.5	0.0055	0.5	0.0143
Event rate, events/100py (95% CI)	2.0 (1.4–2.9)	1.2 (0.7–1.9)	0.06	1.1 (0.7–1.7)	0.0254
SH					
Percentage of subjects with at least 1 event	3.4	1.8	<0.0001	2.6	0.0366
Event rate, events/100py (95% CI)	9.3 (7.3–11.8)	6.9 (5.1–9.5)	0.13	8.6 (6.4–11.4)	0.66
SH with coma/convulsion					
Percentage of subjects with at least 1 event	1.4	0.5	<0.0001	0.8	0.0153
Event rate, events/100py (95% CI)	2.5 (1.9–3.4)	1.2 (0.7–1.9)	0.0062	1.8 (1.2–2.6)	0.15

Data are median (interquartile range) unless otherwise indicated. Baseline, 6 months prior to CGM start; follow-up 1, outcomes assessed during the first 6 months of CGM use; follow-up 2, outcomes assessed during months 6–12 after CGM initiation ($n = 3,553$). McNemar test was used for dichotomous variables, and Wilcoxon signed rank test was used for continuous variables. Event rates were analyzed using a Poisson generalized estimation equation model. 100py, 100 person-years.

using real-time CGM, 46% were on intermittently scanned/viewed CGM, and for 39% of subjects no definitive sensor type was recorded.

Results of our analysis are summarized in Table 1. HbA_{1c} levels were statistically lower during the first 6 months ($P < 0.0001$) and months 6–12 ($P < 0.0001$) after CGM start compared with baseline. The percentage of people achieving HbA_{1c} levels <7.5% (58 mmol/mol) was higher after 6 and 12 months of CGM use (for both baseline vs. 6 months and baseline vs. 12 months, $P < 0.0001$). The proportion of people experiencing at least one DKA episode was significantly lower after 6 ($P = 0.0055$) and 12 ($P = 0.0143$) months on CGM compared with baseline, as were DKA event rates (events/100 patient-years) during months 6–12 on CGM ($P = 0.0254$).

Six months and 12 months after CGM initiation, significantly fewer patients experienced at least one SH event requiring external help (baseline vs. 6 months, $P < 0.0001$; baseline vs. 12 months, $P = 0.0366$) and there were significantly fewer patients with one or more episodes of SH coma (baseline vs. 6 months, $P < 0.0001$; baseline vs. 12 months, $P = 0.0153$). Although not statistically significant, SH event rates requiring external assistance, and event rates for SH with coma/convulsion, were lower with CGM use compared with self-monitoring of capillary blood glucose. This discrepancy in significance might suggest that some patients had experienced repeated SH events despite CGM use.

Our longitudinal analysis of real-world data confirms results from randomized clinical trials showing that regular CGM use is associated with improved metabolic control. We observed a persistent reduction in the proportion of patients experiencing DKA when using CGM and a reduction in DKA event rates. The proportion of patients experiencing SH events (with or without coma/convulsion) was significantly lower with CGM use. In large CGM randomized clinical trials (4,5), DKA and SH episodes were infrequent and did not differ between groups. However, neither of these trials was powered to detect differences in DKA or SH. Our findings complement the existing evidence on CGM benefits in pediatric T1D.

One strength of this study is its population-based multicenter database including real-world data from >80% of pediatric patients in Germany, Austria, and Luxembourg. Limitations are its observational design and possible reporting biases due to the registry structure. No subgroup analysis on baseline metabolic control, diabetes treatment type, or type of CGM was performed.

In summary, initiation and regular use of CGM in children and adolescents with T1D was associated with a reduction in DKA and SH and a modest improvement in metabolic control. Further analyses looking into differences between CGM sensor types are warranted.

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References

1. DeSalvo DJ, Miller KM, Hermann JM, et al.; T1D Exchange and DPV Registries. Continuous glucose monitoring and glycemic control among youth with type 1 diabetes: international comparison from the T1D Exchange and DPV Initiative. Pediatr Diabetes 2018;19:1271–1275

2. Ludwig-Seibold CU, Holder M, Rami B, Raile K, Heidtmann B, Holl RW; DPV Science Initiative; German Working Group for insulin pump treatment in pediatric patients; German BMBF Competence Network Diabetes. Continuous glucose monitoring in children, adolescents, and adults with type 1 diabetes mellitus: analysis from the prospective DPV diabetes documentation and quality management system from Germany and Austria. Pediatr Diabetes 2012;13:12–14

3. Battelino T, Phillip M, Bratina N, Nimri R, Oskarsson P, Bolinder J. Effect of continuous glucose monitoring on hypoglycemia in type 1 diabetes. Diabetes Care 2011;34:795–800

4. Slover RH, Welsh JB, Criego A, et al. Effectiveness of sensor-augmented pump therapy in children and adolescents with type 1 diabetes in the STAR 3 study. Pediatr Diabetes 2012;13:6–11

5. Beck RW, Riddlesworth T, Ruedy K, et al.; DIAMOND Study Group. Effect of continuous glucose monitoring on glycemic control in adults with type 1 diabetes using insulin injections: the DIAMOND randomized clinical trial. JAMA 2017; 317:371–378