Continuous glucose monitoring versus blood glucose monitoring for risk of severe hypoglycaemia and diabetic ketoacidosis in children, adolescents, and young adults with type 1 diabetes: a population-based study

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Summary

Background The effect of continuous glucose monitoring on the risk of severe hypoglycaemia and ketoacidosis in patients with diabetes is unclear. We investigated whether rates of acute diabetes complications are lower with continuous glucose monitoring, compared with blood glucose monitoring, and which metrics predict its risk in young patients with type 1 diabetes.

Methods In this population-based cohort study, patients were identified from 511 diabetes centres across Austria, Germany, Luxembourg, and Switzerland participating in the Diabetes Prospective Follow-up initiative. We included people with type 1 diabetes aged 1·5–25·0 years, with a diabetes duration of more than 1 year, who had been treated between Jan 1, 2014, and June 30, 2021, and had an observation time of longer than 120 days in the most recent treatment year. Severe hypoglycaemia and ketoacidosis rates during the most recent treatment year were examined in people using continuous glucose monitoring and in those using blood glucose monitoring. Adjustments of statistical models included age, sex, diabetes duration, migration background, insulin therapy (pump or injections), and treatment period. Rates of severe hypoglycaemia and diabetic ketoacidosis were evaluated by several continuous glucose monitoring metrics, including percentage of time below target glucose range (<3·9 mmol/L), glycaemic variability (measured as the coefficient of variation), and mean sensor glucose.

Findings Of 32 117 people with type 1 diabetes (median age 16·8 years [IQR 13·3–18·1], 17 056 [53·1%] males), 10 883 used continuous glucose monitoring (median 289 days per year), and 21 234 used blood glucose monitoring. People using continuous glucose monitoring had lower rates of severe hypoglycaemia than those using blood glucose monitoring (6·74 [95% CI 5·90–7·69] per 100 patient-years *vs* 8·84 [8·09–9·66] per 100 patient-years; incidence rate ratio 0·76 [95% CI 0·64–0·91]; p=0·0017) and diabetic ketoacidosis (3·72 [3·32–4·18] per 100 patient-years *vs* 7·29 [6·83–7·78] per 100 patient-years; 0·51 [0·44–0·59]; p<0·0001). Severe hypoglycaemia rates increased with percentage of time below target glucose range (incidence rate ratio 1·69 [95% CI 1·18–2·43]; p=0·0024, for 4·0–7·9% *vs* <4·0% and 2·38 [1·51–3·76]; p<0·0001, for ≥8·0% *vs* <4·0%) and glycaemic variability (coefficient of variation ≥36% *vs* <36%; incidence rate ratio 1·52 [95% CI 1·06–2·17]; p=0·022). Diabetic ketoacidosis rates increased with mean sensor glucose (incidence rate ratio 1·77 [95% CI 0·89–3·51], p=0·13, for 8·3–9·9 mmol/L *vs* <8·3 mmol/L; 3·56 [1·83–6·93], p<0·0001, for 10·0–11·6 mmol/L *vs* <8·3 mmol/L; and 8·66 [4·48–16·75], p<0·0001, for ≥11·7 mmol/L *vs* <8·3 mmol/L).

Interpretation These findings provide evidence that continuous glucose monitoring can reduce severe hypoglycaemia and ketoacidosis risk in young people with type 1 diabetes on insulin therapy. Continuous glucose monitoring metrics might help to identify those at risk for acute diabetes complications.

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Introduction

Blood glucose monitoring or sensor-based continuous glucose monitoring is mandatory to optimise insulin therapy and inform other management decisions in type 1 diabetes to achieve glycaemic targets.[1] Clinical trials involving children and adults with type 1 diabetes have shown that continuous glucose monitoring, compared with blood glucose monitoring, is associated with decreased HbA_{1c}.[2] However, the effect of continuous glucose monitoring on the uncommon events of severe hypoglycaemia and diabetic ketoacidosis remain unclear. Continuous glucose monitoring had no effect on the number of severe events in randomised controlled trials,[2] whereas two smaller observational studies reported reduced rates of severe events after initiation of continuous glucose monitoring.[3,4]

Research in context

Evidence before this study

We searched PubMed for articles published between Aug 1, 2017, and Aug 31, 2022, using the search terms "continuous glucose monitoring" AND "type 1 diabetes" AND "severe hypoglycemia" AND "diabetic ketoacidosis", with no language restrictions. We retrieved 57 papers, including 14 clinical trials and three meta-analyses. After reviewing all of the studies, no prospective study was identified that directly compared the occurrence of severe hypoglycaemia, hypoglycaemic coma, diabetic ketoacidosis, and severe ketoacidosis between patients with type 1 diabetes using continuous glucose monitoring and those using blood glucose monitoring, and that investigated the association of continuous glucose monitoring metrics with these acute diabetes complications. Two small observational studies analysing the event rates of severe hypoglycaemia and diabetic ketoacidosis at 12 months in one study and 24 months in the other study after starting continuous glucose monitoring revealed reduced rates of severe hypoglycaemia in one study and reduced rates of ketoacidosis in the other study. Three registry-based studies in populations with type 1 diabetes analysed the incidence of severe hypoglycaemia and diabetic ketoacidosis associated with use of continuous glucose monitoring. However, these studies showed contradictory results. Of the three meta-analyses, two reported a reduced number of severe hypoglycaemia events with continuous glucose monitoring, whereas continuous glucose monitoring had no effect on the number of ketoacidosis events. These studies were not sufficiently powered to assess these uncommon, but clinically relevant, acute complications of diabetes therapy or did not adjust event rates for known confounders. Taken together, to the best of our knowledge, no data are yet available to confirm the effect of continuous glucose monitoring on the reduction of severe hypoglycaemia and diabetic ketoacidosis in young people with type 1 diabetes.

Added value of this study

To the best of our knowledge, this study is the first prospective multicentre study of its kind to analyse the effect of continuous glucose monitoring on the risk of severe hypoglycaemia and diabetic ketoacidosis in a large cohort of more than 30 000 young people with type 1 diabetes. Our study is sufficiently powered to provide a valid statement regarding the question of whether the rates of severe hypoglycaemia and diabetic ketoacidosis are lower in patients using continuous glucose monitoring compared with patients using blood glucose monitoring, and which continuous glucose monitoring metrics are associated with these acute diabetes complications. We used consistent methods throughout to minimise confounding and reverse causality. We showed evidence of lower rates of severe hypoglycaemia and diabetic ketoacidosis in patients with type 1 diabetes using continuous glucose monitoring than in those using blood glucose monitoring, and, even more importantly, of lower rates of hypoglycaemic coma and severe ketoacidosis. The continuous glucose monitoring metrics associated with lower rates of severe hypoglycaemia (ie, percentage of time below target glucose range [<3·9 mmol/L] <4% and coefficient of variation <36%) and lower rates of ketoacidosis (ie, mean sensor glucose <10·0 mmol/L, percentage of time in target glucose range [3·9–10·0 mmol/L] ≥50%, and percentage of time above target glucose range [>10·0 mmol/L] <50%) might help to reduce risks of acute diabetes complications in young people with type 1 diabetes.

Implications of all the available evidence

Our study might influence future decisions regarding continuous glucose monitoring use in patients on insulin therapy, identifying individual risk to predict and prevent acute diabetes complications, and defining determinants of treatment success.

Continuous glucose monitoring offers dense time series of glucose measurements that enable determination of new aspects of glycaemia and glycaemic variability.[5,6] Despite increasing use of continuous glucose monitoring,[7] continuous glucose monitoring metrics have not yet been established as predictors of severe metabolic events. The formerly strong association of low HbA_{1c} with severe hypoglycaemia in people with type 1 diabetes has decreased,[8] and, therefore, low HbA_{1c} has become a minor predictor for severe hypoglycaemia in these patients. Now, the validation of continuous glucose monitoring data as an outcome measure for diabetes complications is required,[9–11] but it is unclear whether continuous glucose monitoring metrics can serve as a tool to predict short-term outcomes.

We aimed to determine whether the rates of severe hypoglycaemia and diabetic ketoacidosis are lower with continuous glucose monitoring, compared with blood glucose monitoring, in people younger than 25 years with type 1 diabetes, and to investigate which continuous glucose monitoring metrics are informative for these uncommon but clinically relevant acute diabetes complications.

Methods

Study design and population

In a population-based cohort study, we included patients identified from the Diabetes Prospective Follow-up (DPV) database at Ulm University, Ulm, Germany. As of Sept 30, 2021, 511 diabetes centres in Austria, Germany, Luxembourg, and Switzerland had documented treatment and outcome of diabetes care using the DPV Diabetes Documentation Software,[12,13] covering an estimated proportion of more than 90% of all paediatric patients with diabetes in Austria, Germany, and Luxembourg. Patients were eligible for

	Continuous glucose monitoring group (n=10 883)	Blood glucose monitoring group (n=21 234)
Age, years	13·7 (10·4 to 16·4)	17·5 (15·5 to 19·1)
1·5 to 5·9	650 (6·0%)	290 (1·4%)
6·0 to 11·9	3206 (29·5%)	1963 (9·2%)
12·0 to 17·9	6045 (55·6%)	11 609 (54·7%)
18·0 to 25·0	982 (9·0%)	7372 (34·7%)
Sex		
Female	5236 (48·1%)	9825 (46·3%)
Male	5647 (51·9%)	11 409 (53·7%)
Duration of diabetes, years	5·0 (2·7 to 8·3)	7·3 (4·0 to 11·1)
1·0 to 4·9	5485 (50·4%)	6981 (32·9%)
5·0 to 9·9	3693 (33·9%)	7556 (35·6%)
≥10·0	1705 (15·7%)	6697 (31·5%)
Migration background	2798 (25·7%)	4361 (20·5%)
BMI SD score	0·58 (–0·08 to 1·23)	0·56 (–0·12 to 1·24)
HbA_{1c}		
%	7·5% (6·9 to 8·2)	8·0% (7·2 to 9·2)
mmol/mol	58·2 (51·6 to 66·3)	63·7 (54·7 to 76·8)
Insulin treatment		
Injection therapy	3707/10 853 (34·2%)	11 207/19 436 (57·7%)
Pump therapy	7146/10 853 (65·8%)	8229/19 436 (42·3%)

Data are median (IQR), n (%), or n/N (%). The BMI is reported as a SD score based on German normative data. A SD score of 0 corresponds to the 50th percentile (median), and a SD score of +2 corresponds to the 97·7th percentile of an age-specific and sex-specific reference group. The data on age, sex, diabetes duration, and migration background (defined as birthplace outside Austria, Germany, Luxembourg, or Switzerland for the patient or for one or both parents) were complete in all patients. The data for BMI SD score were available in 10 690 patients using continuous glucose monitoring versus 18 045 using blood glucose monitoring, for HbA_{1c} in 10 839 patients versus 20 421 patients, and for insulin treatment in 10 853 patients versus 19 436 patients.

Table 1: **Baseline characteristics**

inclusion in this study if they had a clinical diagnosis of type 1 diabetes. Exclusion criteria were age younger than 18 months or older than 25 years; diabetes duration of 1 year or less; no documented treatment between Jan 1, 2014, and June 30, 2021; and observation time of 120 days or less in the most recent treatment year. We divided patients into those using continuous glucose monitoring for more than 120 days per year and providing continuous glucose monitoring data (ie, raw profiles or aggregated metrics) and those not using continuous glucose monitoring and performing blood glucose monitoring. Individuals who used continuous glucose monitoring but did not provide data were excluded from this analysis.

For each participant, clinical data including BMI, HbA_{1c}, frequency of blood glucose monitoring per day, and continuous glucose monitoring metrics of the most recent treatment year were aggregated as medians for repeated measurements, and hypoglycaemic and ketoacidosis events were summed up.

HbA_{1c} values were mathematically standardised to the Diabetes Control and Complications Trial (DCCT) reference range 4·05–6·05% with the multiple-of-the-mean transformation method. BMI values, computed as weight in kilograms divided by height in metres squared, were transformed to SD scores based on German reference values.[12] From original continuous glucose monitoring profiles, we calculated mean sensor glucose values, time in target glucose range (3·9–10·0 mmol/L), time above target glucose range (>10·0 mmol/L), time below target glucose range (<3·9 mmol/L), and glycaemic variability measured as the coefficient of variation.[14] If continuous glucose monitoring profiles were not available as raw data, we used the recorded continuous glucose monitoring metric data.

Informed consent for participation in the DPV initiative was obtained from patients or their parents by verbal or written procedure, as approved by the responsible administrators for data protection of each centre. The analysis of anonymised data was approved by the Ethics Committee of Ulm University.

Outcomes

The primary outcome was the difference in event rates of severe hypoglycaemia and of diabetic ketoacidosis between patients using continuous glucose monitoring and patients using blood glucose monitoring during the most recent year of treatment. Severe hypoglycaemia was defined as an event with severe cognitive impairment (including coma or convulsions) requiring external assistance by another person to actively administer carbohydrates or glucagon, or take other corrective actions.[15] Hypoglycaemic coma was defined as a subgroup of severe hypoglycaemia, as an event with a seizure or loss of consciousness.[15] Diabetic ketoacidosis was defined as blood pH of less than 7·3, bicarbonate concentration of less than 15 mmol/L (all events), or both, and severe ketoacidosis was defined as pH of less than 7·1, bicarbonate concentration of less than 5 mmol/L, or both.[16]

Statistical analysis

Event rates for severe hypoglycaemia, hypoglycaemic coma, diabetic ketoacidosis, and severe ketoacidosis were evaluated in patients using continuous glucose monitoring and in patients using blood glucose monitoring by negative binomial regression analyses with individual time under risk as offset. These analyses were adjusted for sex, age group (1·5–5·9 years, 6·0–11·9 years, 12·0–17·9 years, and 18·0–25·0 years), diabetes duration (1·0–4·9 years, 5·0–9·9 years, and ≥10·0 years), migration background (defined as birthplace outside Austria, Germany, Luxembourg, or Switzerland for the patient or for one or both parents), insulin therapy (pump or injections), and treatment period (2014–17 or 2018–21) to account for relevant confounders. Additionally, we investigated in both groups the event rates by HbA_{1c} level comparing patients with elevated HbA_{1c} of 7·0–7·9% (53–63 mmol/mol), 8·0–8·9% (64–74 mmol/mol), and ≥9% (75 mmol/mol) versus patients with HbA_{1c} in the target range of less than 7·0% (53 mmol/mol) and, separately, with HbA_{1c} as continuous variable for trend analysis.

In patients using continuous glucose monitoring, the rates of severe hypoglycaemia, hypoglycaemic coma, diabetic ketoacidosis, and severe ketoacidosis were evaluated by several continuous glucose monitoring metrics: mean sensor glucose, percentage of time in the target glucose range, percentage time above the target glucose range, percentage time below the target glucose range, and the coefficient of variation. We compared event rates for mean sensor glucose (8·3–9·9 mmol/L, 10·0–11·6 mmol/L, and ≥11·7 mmol/L *vs* <8·3 mmol/L); percentage of time in the target glucose range (50–69%, 25–49%, and <25% vs ≥70%); percentage of time above the target glucose range (25–49%, 50–69%, and ≥70% *vs* <25%); percentage of time below the target glucose range (4–7·9% and ≥8% *vs* <4%); and coefficient of variation (≥36% *vs* <36%).[17] Separately, we investigated event rates in relation to mean sensor glucose, time in target glucose range, time above target glucose range, and time below target glucose range as continuous variables using trend analyses.

Baseline characteristics of the study population are presented as medians with IQR or as numbers with percentages. Results from regression analyses are presented as adjusted least-squares mean, event rates per 100 patient-years, absolute between-group differences, and incidence rate ratios, all with 95% CIs. CIs and p values were adjusted for multiple group comparisons using the Sidak method. Because the percentage of missing data was small (0–6%), no imputation was performed. p values of less than 0·05 (two-sided) were considered significant. All analyses were performed using SAS for Windows (version 9.4, build TS1M7) on a Window server 2019 mainframe.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Of the 511 diabetes centres, 412 treated 32 117 individuals with type 1 diabetes (17 056 [53·1%] males, median age 16·8 years [IQR 13·3–18·1], median age at onset of type 1 diabetes 8·5 years [4·9–11·9], and median diabetes duration 6·4 years [3·4–10·2]) meeting the inclusion criteria (appendix pp 3, 6), with a median number of four (3–5) visits per patient during the most recent treatment year. 10 883 patients used continuous glucose monitoring for a mean of 289 days (95% CI 284–294) per year. In these patients, median mean sensor glucose was 9·8 mmol/L (IQR 8·7–11·1), median percentage of time in the target glucose range was 52% (41–63), median percentage of time above the target glucose range was 44% (33–56), median percentage of time below the target glucose range was 3% (2–6), and the coefficient of variation was 36% (32–40). The median completeness of continuous glucose monitoring profiles was 95% (IQR 86–98) in 4561 patients, with a median of 15 294 (7931–25 364) glucose measurements per patient and year every 15 min (5–15). 21 234 individuals used blood glucose monitoring, with a median frequency of four (IQR 3–6) measurements per day. Baseline characteristics of the study population are shown in table 1.

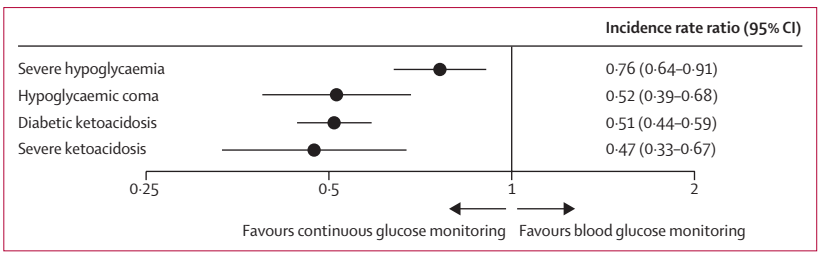

Figure 1: **Incidence rate ratio of severe hypoglycaemia and of diabetic ketoacidosis with continuous glucose monitoring versus blood glucose monitoring**

Values are estimated from negative binomial regression analyses adjusted for sex, age, diabetes duration, migration background, insulin therapy (pump or injections), and period of treatment (2014–17 or 2018–21).

In the entire study population, 2821 events of severe hypoglycaemia were observed in 1512 (4·7%) patients, including 597 events of hypoglycaemic coma in 503 (1·6%) patients during the most recent treatment year. Event rates for severe hypoglycaemia were significantly lower in patients using continuous glucose monitoring than in those using blood glucose monitoring (6·74 [95% CI 5·90 to 7·69] per 100 patient-years *vs* 8·84 [8·09 to 9·66] per 100 patient-years; difference per 100 patient-years of –2·10 [95% CI –3·42 to –0·79]; incidence rate ratio 0·76 [95% CI 0·64 to 0·91], p=0·0017) in adjusted analyses (figure 1; table 2). Event rates for hypoglycaemic coma were also significantly lower with continuous glucose monitoring than with blood glucose monitoring (1·01 [95% CI 0·80 to 1·27] per 100 patient-years *vs* 1·96 [1·73 to 2·23] per 100 patient-years; difference per 100 patient-years of – 0·95 [95% CI –1·32 to –0·58]; incidence rate ratio 0·52 [95% CI 0·39 to 0·68], p<0·0001; figure 1; table 2).

In the entire study population, 2203 events of diabetic ketoacidosis were observed in 1822 (5·7%) patients, including 273 events of severe ketoacidosis in 255 (0·8%) patients during the most recent treatment year. Patients using continuous glucose monitoring had significantly lower event rates for diabetic ketoacidosis than those using blood glucose monitoring (3·72 [95% CI 3·32 to 4·18] per 100 patient-years *vs* 7·29 [6·83 to 7·78] per 100 patient-years; difference per 100 patient-years of –3·57 [95% CI –4·26 to –2·88]; incidence rate ratio 0·51 [95% CI 0·44 to 0·59], p<0·0001) in adjusted analyses (figure 1; table 2). Event rates for severe ketoacidosis were also significantly lower with continuous glucose monitoring than with blood glucose monitoring (0·44 [95% CI 0·33 to 0·59] per 100 patient-years *vs* 0·93 [0·79 to 1·10] per 100 patient-years; difference per 100 patient-years of –0·49 [95% CI –0·70 to –0·28]; incidence rate ratio 0·47 [95% CI 0·33 to 0·67], p<0·0001; figure 1; table 2).

See Online for appendix

	Continuous glucose monitoring group (n=10 883)	Blood glucose monitoring group (n=21 234)	Between-group difference (95% CI)*	p value
Severe hypoglycaemia				
Number of events	705	2116	..	..
Number of patients with events (%)	363 (3·3%)	1149 (5·4%)	..	..
Rate per 100 patient-years (95% CI)	6·74 (5·90 to 7·69)	8·84 (8·09 to 9·66)	−2·10 (−3·42 to −0·79)	0·0017
Hypoglycaemic coma				
Number of events	97	500	..	..
Number of patients with events (%)	81 (0·7%)	422 (2·0%)	..	..
Rate per 100 patient-years (95% CI)	1·01 (0·80 to 1·27)	1·96 (1·73 to 2·23)	−0·95 (−1·32 to −0·58)	<0·0001
Diabetic ketoacidosis pH <7·3				
Number of events	393	1810	..	..
Number of patients with events (%)	338 (3·1%)	1484 (7·0%)	..	..
Rate per 100 patient-years (95% CI)	3·72 (3·32 to 4·18)	7·29 (6·83 to 7·78)	−3·57 (−4·26 to −2·88)	<0·0001
Severe ketoacidosis pH <7·1				
Number of events	58	215	..	..
Number of patients with events (%)	58 (0·5%)	197 (0·9%)	..	..
Rate per 100 patient-years (95% CI)	0·44 (0·33 to 0·59)	0·93 (0·79 to 1·10)	−0·49 (−0·70 to −0·28)	<0·0001

Values are estimated from negative binomial regression analysis adjusted for sex, age, diabetes duration, migration background, insulin therapy (pump or injections), and period of treatment (2014–17 or 2018–21). *Absolute difference between continuous glucose monitoring and blood glucose monitoring.

Table 2: **Severe hypoglycaemia and diabetic ketoacidosis with continuous glucose monitoring versus blood glucose monitoring**

In patients with continuous glucose monitoring, event rates for severe hypoglycaemia did not differ by HbA_{1c} level (p_{trend}=0·15, all p≥0·31 between categories; appendix pp 4, 6). In patients with blood glucose monitoring, severe hypoglycaemia rates were lower with HbA_{1c} level of 9·0% (75 mmol/mol) or higher than with less than 7·0% (53 mmol/mol; p=0·0071; p_{trend}=0·0011; appendix pp 4, 6). Hypoglycaemic coma rates did not differ by HbA_{1c} level with continuous glucose monitoring (p_{trend}=0·62, all p≥0·97 between categories) and with blood glucose monitoring (p_{trend}=0·79, all p≥0·54 between categories; appendix pp 4, 6).

Event rates for diabetic ketoacidosis rose with increasing HbA_{1c} level in patients with continuous glucose monitoring and in patients with blood glucose monitoring (both p_{trend}<0·0001; appendix pp 4, 6). The risk of diabetic ketoacidosis in patients using continuous glucose monitoring increased with HbA_{1c} levels of 7·0–7·9% (53–63 mmol/mol) versus less than 7·0% (incidence rate ratio 2·44 [95% CI 1·47–4·04], p<0·0001), 8·0–8·9% (64–74 mmol/mol) versus less than 7·0% (4·81 [2·89–7·99], p<0·0001), and 9·0% (75 mmol/mol) or higher versus less than 7·0% (13·74 [8·25–22·87], p<0·0001). In patients using blood glucose monitoring, the risk of diabetic ketoacidosis did not increase with HbA_{1c} levels of 7·0–7·9% (53–63 mmol/mol) versus less than 7·0% (incidence rate ratio 1·36 [95% CI, 0·95–1·96], p=0·12) but did increase with 8·0–8·9% (64–74 mmol/mol) versus less than 7·0% (3·66 [2·62–5·11], p<0·0001) and 9·0% (75 mmol/mol) or higher versus less than 7·0% (13·94 [10·24–18·98], p<0·0001). The number of severe ketoacidosis events was low in patients using continuous glucose monitoring and did not differ by HbA_{1c} level (p_{trend}=0·86, all p=1·0 between categories; appendix pp 4, 6). Patients using blood glucose monitoring had an increasing risk of severe ketoacidosis with HbA_{1c} levels of 8·0–8·9% (64–74 mmol/mol) versus less than 7·0% (incidence rate ratio 3·01 [95% CI 1·13–7·99], p=0·021) and 9·0% (75 mmol/mol) or higher versus less than 7·0% (15·78 [6·55–38·01], p<0·0001; p_{trend}<0·0001; appendix pp 4, 6).

Event rates for severe hypoglycaemia and for hypoglycaemic coma were not associated with mean sensor glucose (p_{trend}=0·86 and p_{trend}=0·29, respectively; figure 2A). Risk of severe hypoglycaemia was similar with a mean sensor glucose of 8·3–9·9 mmol/L versus less than 8·3 mmol/L, 10·0–11·6 mmol/L versus less than 8·3 mmol/L, and 11·7 mmol/L or higher versus mean sensor glucose of <8·3 mmol/L (figure 3A). Risk of hypoglycaemic coma was also similar with a mean sensor glucose of 8·3–9·9 mmol/L versus less than 8·3 mmol/L (incidence rate ratio 0·56 [95% CI 0·23–1·37], p=0·32), 10·0–11·6 mmol/L versus less than 8·3 mmol/L (0·68 [0·27–1·69], p=0·67), and 11·7 mmol/L or higher versus less than 8·3 mmol/L (0·54 [0·19–1·55], p=0·42). Similarly, event rates for severe hypoglycaemia and for hypoglycaemic coma were not associated with the percentage of time in target glucose range (p_{trend}=0·28 and p_{trend}=0·34, respectively; figure 2C). Patients with a percentage of time in target glucose range of 50–69% versus 70% or more, 25–49% versus 70% or more, and less than 25% versus 70% or more had similar risk of severe hypoglycaemia (figure 3A). Risk of hypoglycaemic coma was also similar with a percentage of time in target glucose

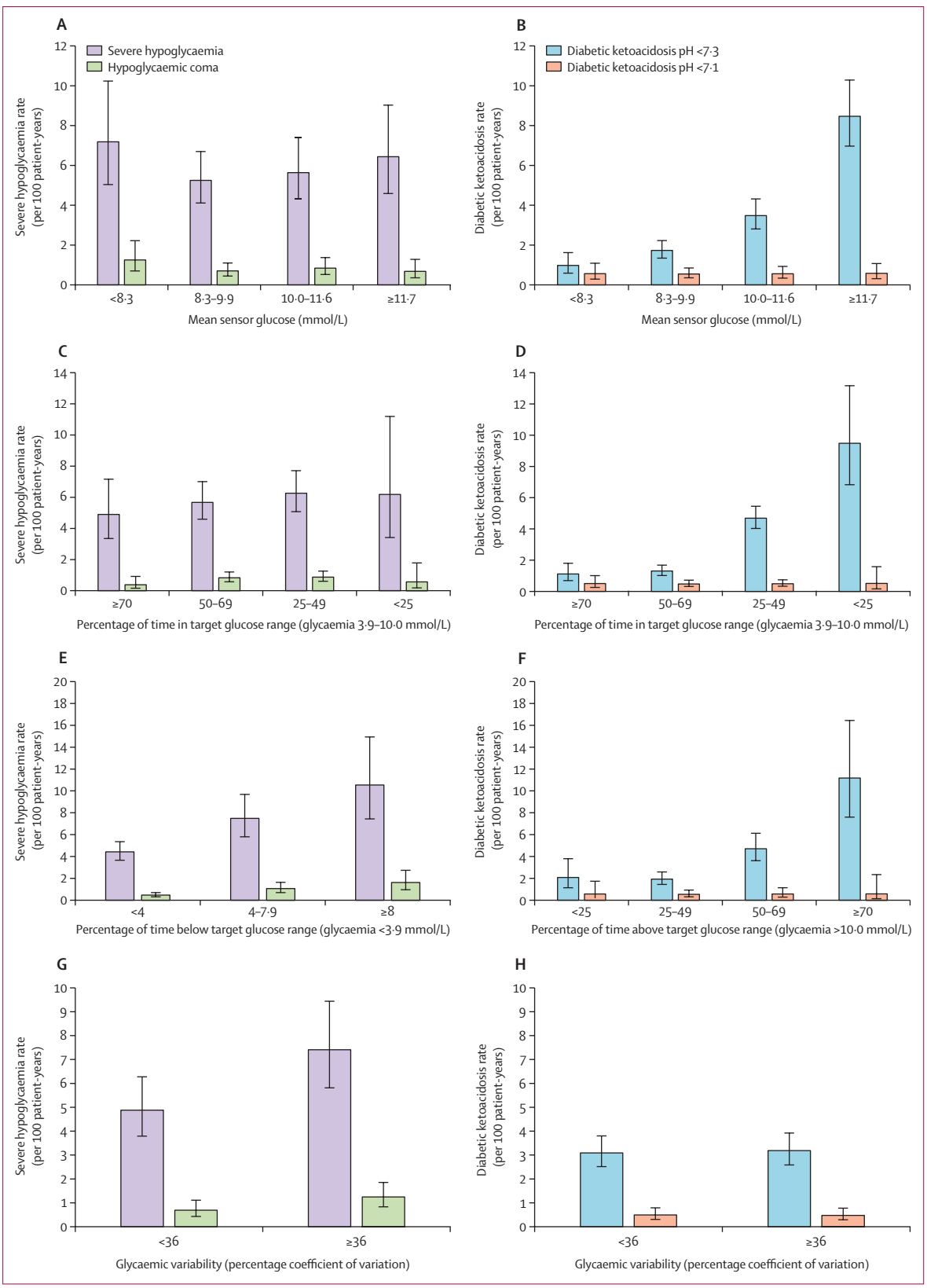

Figure 2: **Rates of severe hypoglycaemia and of diabetic ketoacidosis per continuous glucose monitoring metric**
Event rates and 95% CIs are given to show the frequency of severe hypoglycaemia, hypoglycaemic coma, diabetic ketoacidosis, and severe ketoacidosis according to mean sensor glucose (A, B), percentage of time in target glucose range (3·9–10·0 mmol/L; C, D), percentage of time below target glucose range (<3·9 mmol/L; E), percentage of time above target glucose range (>10·0 mmol/L; F), and glycaemic variability expressed as the coefficient of variation (G, H). The number of patients and percentages with each continuous glucose monitoring metric are given in the appendix (p 7). Values are estimated from negative binomial regression analyses adjusted for sex, age, diabetes duration, and migration background.

range of 50–69% versus 70% or more (incidence rate ratio 2·16 [95% CI 0·68–6·89], p=0·30), 25–49% versus 70% or more (2·28 [0·72–7·25]), p=0·24, and less than 25% versus 70% or more (1·48 [95% CI 0·25–8·58], p=0·94).

By contrast, event rates for severe hypoglycaemia and for hypoglycaemic coma increased with higher percentage of time below target glucose range (both p_{trend}<0·0001; figure 2E). A higher risk of severe hypoglycaemia was seen with percentage of time below target glucose range of 4·0–7·9% versus less than 4·0% (incidence rate ratio 1·69 [95% CI 1·18–2·43]; p=0·0024) and with a percentage of time below target glucose range of 8·0% or higher versus less than 4% (2·38 [1·51–3·76]; p<0·0001; figure 3A). A higher risk of hypoglycaemic coma was also seen with percentage of time below target glucose range of 4·0–7·9% versus less than 4·0% (incidence rate ratio 2·26 [95% CI 1·17–4·36]; p=0·012) and with a percentage of time below target glucose range of 8·0% or higher versus less than 4·0% (3·43 [1·63–7·23]; p=0·0004; figure 3A). This trend was maintained in HbA_{1c} subgroups (appendix pp 5, 6). Additionally, higher event rates for severe hypoglycaemia were observed with higher glycaemic variability comparing patients with coefficient of variation 36% or higher versus less than 36% (figure 2G; incidence rate ratio 1·52 [95% CI 1·06–2·17]; p=0·022; figure 3A). These results identify 4% or higher of time below target glucose range and 36% or higher coefficient of variation as risk markers of severe hypoglycaemia (figure 3A).

Event rates for diabetic ketoacidosis increased with higher mean sensor glucose (p_{trend}<0·0001), whereas event rates for severe ketoacidosis were low overall (p_{trend}=0·92; figure 2B). Mean sensor glucose of 8·3–9·9 mmol/L versus less than 8·3 mmol/L (incidence rate ratio 1·77 [95% CI 0·89–3·51], p=0·13), 10·0–11·6 mmol/L versus less than 8·3 mmol/L (3·56 [1·83–6·93], p<0·0001), and 11·7 mmol/L or more versus less than 8·3 mmol/L (8·66 [4·48–16·75], p<0·0001) was associated with increasing ketoacidosis risk (figure 3B). Of note, the risk of diabetic ketoacidosis already increased with mean sensor glucose of 8·3 mmol/L or more versus less than 8·3 mmol/L (p=0·047 before adjusting for multiple comparisons; appendix p 8). Although this difference was no longer significant after adjusting for multiple comparisons, it might have clinical relevance. Similarly, event rates for diabetic ketoacidosis increased with lower percentage of time in target glucose range (p_{trend}<0·0001; figure 2D). Comparing patients with percentage of time in target glucose range of 50–69%, 25–49%, and less than 25% with those who had a percentage of 70% or higher revealed an increased risk of diabetic ketoacidosis (figure 3B). Additionally, the event rate for diabetic ketoacidosis increased with higher percentage of time above target glucose range (p_{trend}<0·0001; figure 2F). Comparing patients with percentage of time above glucose range of 25–49%, 50–69%, and 70% or higher with those who had a percentage of less than 25% revealed an increased risk of diabetic ketoacidosis (figure 3B). The results identify these continuous glucose monitoring metrics as risk markers of diabetic ketoacidosis, with a progressively increasing risk at mean sensor glucose concentration of more than 10·0 mmol/L, percentage of time in target glucose range of less than 50%, and percentage of time above target glucose range of 50% or higher (figure 3B).

There was no association between the event rate for ketoacidosis and glycaemic variability (figure 2H). Patients with a coefficient of variation of 36% or higher versus less than 36% had similar risk of ketoacidosis (incidence rate ratio 1·03 [95% CI 0·78–1·37], p=0·84) and of severe ketoacidosis (0·97 [0·49–1·92], p=0·92).

Discussion

In this contemporary cohort of young patients with type 1 diabetes, the risk of severe hypoglycaemia and diabetic ketoacidosis in patients using continuous glucose monitoring was lower than in patients using blood glucose monitoring. This study was sufficiently powered to investigate these uncommon but clinically relevant acute diabetes complications, whereas randomised clinical trials comparing continuous glucose monitoring with blood glucose monitoring have not been sufficiently powered to assess differences in the rates of severe hypoglycaemia or diabetic ketoacidosis and, even less, in the rates of severe events.[2] The results of this study are in accordance with two previous studies in smaller cohorts of patients with type 1 diabetes showing reduced rates of severe hypoglycaemia[4] and diabetic ketoacidosis[3] 1 or 2 years after initiation of continuous glucose monitoring. In this study, patients using continuous glucose monitoring, compared with patients using blood glucose monitoring, had nearly half the incidence of hypoglycaemic coma (–48%) and of severe ketoacidosis (–53%). Therefore, continuous glucose monitoring might reduce not only the occurrence of acute complications, but also their progression to severe life-threatening forms of hypoglycaemia and ketoacidosis. This might be explained by earlier recognition of impending severe hypoglycaemia with real-time glucose monitoring and alert function,[18] allowing time for counteractive measures. The higher awareness of hyperglycaemia with continuous glucose monitoring than with blood glucose monitoring might also allow timely correction of hyperglycaemia to prevent ketoacidosis. Still, current rates of severe hypoglycaemia (6·74 per 100 patient-years) and ketoacidosis (3·72 per 100 patient-years) point to the need of additional preventive measures to reduce acute complications in patients with access to continuous glucose monitoring technology.[4,18]

The continuous glucose monitoring metrics identified as risk markers of severe hypoglycaemia in this study were higher percentage of time below target glucose range (≥4%) and higher glucose variability (coefficient of variation ≥36%), in line with previous data from older adults with type 2 or type 1 diabetes.[17,19,20] The coefficient of variation and time below target glucose range emerged as suitable HbA_{1c}-independent parameters to

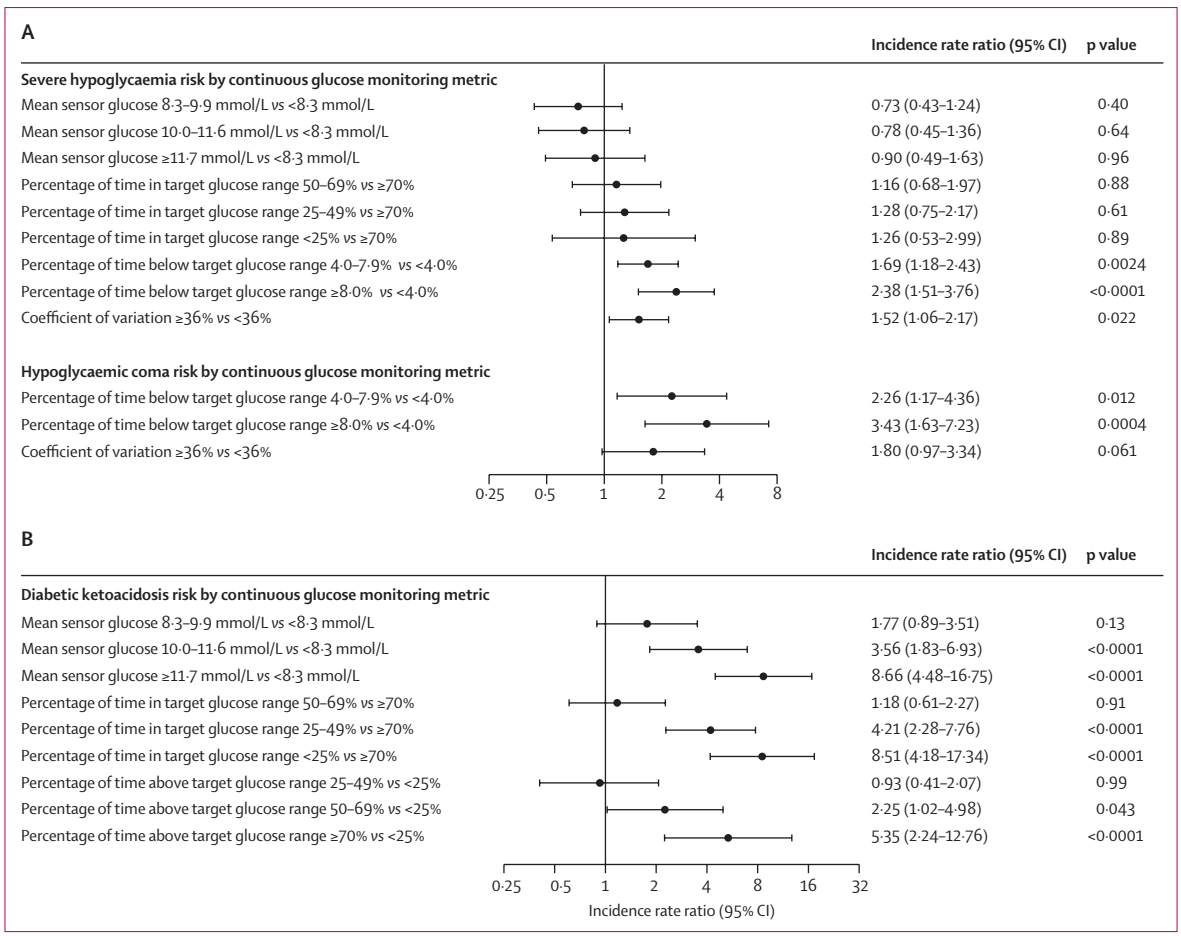

Figure 3: **Incidence rate ratio of severe hypoglycaemia and of diabetic ketoacidosis by continuous glucose monitoring metrics**
Time in target glucose range of 3·9–10·0 mmol/L, time below target glucose range of less than 3·9 mmol/L; time above target glucose range of more than 10·0 mmol/L, and coefficient of variation is a measure of glycaemic variability. Values are estimated from negative binomial regression analyses adjusted for sex, age, diabetes duration, and migration background.

recognise the individual risk of severe hypoglycaemia, replacing HbA_{1c} level for hypoglycaemia prediction. In addition, a higher coefficient of variation was associated with vascular complications independent of HbA_{1c}.[21] These data qualify a coefficient of variation of less than 36% and percentage of time below target glucose range of less than 4% as new therapeutic targets, consistent with current recommendations.[14] The metrics mean sensor glucose of 10·0 mmol/L or higher, percentage of time in target glucose range of less than 50%, and percentage of time above glucose range of 50% or more were identified as robust risk markers of diabetic ketoacidosis, whereas an HbA_{1c} level of more than 7·0% remained a strong predictor of diabetic ketoacidosis, as noted before.[22] Continuous glucose monitoring measures reflecting hyperglycaemia are highly correlated with each other but only moderately correlated with HbA_{1c}.[23] Taken together, glucose metrics might contribute to identification of patients at particular risk of acute diabetes complications who would benefit from timely intervention.

The strengths of this study include its large database of more than 10 000 young people with type 1 diabetes providing real-world continuous glucose monitoring data to analyse its association with acute diabetes complications, directly compared with a large contemporary cohort of more than 20 000 patients using blood glucose monitoring. Sample size and data collection at the time of the adverse event allowed for further categorising the severity of hypoglycaemia and diabetic ketoacidosis, consistently showing lower event rates in patients using continuous glucose monitoring. Because of the large number of available continuous glucose monitoring profiles, we could identify continuous glucose monitoring metrics as risk factors of acute diabetes complications along with the standard parameter HbA_{1c}[8,22,24] to assess new versus established risk factors.

This study has several limitations. To account for different baseline characteristics between patients with continuous glucose monitoring and patients with blood glucose monitoring, regression analyses were adjusted for

relevant clinical and demographic confounders, but motivation, intensity of diabetes education, familial support, and mental health were not examined, and all of these factors are relevant to hypoglycaemia and ketoacidosis risk[15,16] but difficult to measure in a large population. Regional deprivation and socioeconomic disparity in use of continuous glucose monitoring might affect outcomes,[25] but patients with type 1 diabetes in the participating countries had free access to continuous glucose monitoring devices, minimising inequity. The exclusion of patients using continuous glucose monitoring but not providing continuous glucose monitoring data could have introduced a bias; however, HbA_{1c} levels were similar in those excluded for this reason and those included in the study population. Continuous glucose monitoring metrics were chosen following current standards[14] but might need modification with further experience in interpretation of continuous glucose monitoring data. Selection of treatment centres and patients participating in this study might have an effect on outcomes, but the high coverage of more than 90% of paediatric patients and more than 70% of young adult patients with type 1 diabetes in this population[26] reduces potential confounding. The results reflect treatment experience in four European countries but might not be generalisable to other regions with different health-care systems.

The findings of this study could have implications for the future care of people with type 1 diabetes. The effectiveness of continuous glucose monitoring to reduce life-threatening acute diabetes complications provides evidence to advocate its use in patients with insulin therapy. Continuous glucose monitoring metrics were the only risk marker of severe hypoglycaemia and hypoglycaemic coma and a complementary risk marker of diabetic ketoacidosis. Identification of the individual risk pattern of glucose profiling[27] might help to predict and prevent acute diabetes complications by enhancing educational measures and counselling. In addition, glucose metrics associated with improved clinical outcomes might become key determinants of treatment success[21,28] and endpoints for clinical trials.[10]

In conclusion, this study provides evidence that young people with type 1 diabetes using continuous glucose monitoring might have lower risks of severe hypoglycaemia and diabetic ketoacidosis than those using blood glucose monitoring and, more importantly, lower risks of hypoglycaemic coma and severe ketoacidosis. The continuous glucose monitoring metrics associated with lower rates of severe hypoglycaemia (ie, percentage of time below target glucose range of <4% and coefficient of variation of <36%) and lower rates of diabetic ketoacidosis (ie, mean sensor glucose <10·0 mmol/L, percentage of time in target glucose range of ≥50%, and percentage of time above target glucose range of <50%) might serve as additional tools to advance personalised treatment in children, adolescents, and young adults with type 1 diabetes.

Contributors

BK conceptualised the study, interpreted the analyses, visualised the results, searched the literature, and wrote the manuscript. RWH conceptualised the study, coordinated and supervised data collection, acquired funding for the analysis, and critically reviewed the manuscript for important intellectual content. SRT and RWH analysed the data and designed the statistical analyses. BK, AB, CF, CK, OK, ST-S, CS, CS-S, and RWH made substantial contributions to the acquisition of research data. All authors contributed intellectually to this study and critically revised the scientific content of the manuscript. All authors had access to all the data of the study, approved the final manuscript as submitted, agreed to be accountable for all aspects of the work, and had final responsibility for the decision to submit for publication. SRT and RWH are the guarantors of this work and, as such, had full access to all the data in the study, verified the data, and take responsibility for the integrity of the data and the accuracy of the data analysis.

Declaration of interests

OK received consulting fees from Dexcom and Sanofi and has stock in DreaMed. AB received support for attending meetings from Medtronic. All other authors declare no competing interests.

Data sharing

Aggregated data are available upon reasonable request via email to RWH (reinhard.holl@uni-ulm.de).

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