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Dynamics of HbA1c, BMI and rates of severe hypoglycemia in 4,434 adults with type 1 or type 2 diabetes after initiation of continuous glucose monitoring

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Running title: Beneficial effects of CGM in adults with T1D/T2D

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Abstract

Background: Continuous glucose monitoring (CGM) might have beneficial effects on glycemic control and body-mass-index (BMI) in adults with type 1 (T1D) or type 2 diabetes (T2D).

Methods: The diabetes prospective follow-up registry was used to identify individuals with T1D or T2D ≥18 years starting CGM management in 2015 or later and follow-up information available. HbA1c, BMI and event rates of severe hypoglycemia in the year prior to CGM start were compared to two follow-up periods: 1) CGM use for 3-6 months and 2) CGM use for >6 months. Repeated measurements linear and negative binomial regression were used (adjustment for sex, age at diabetes onset and baseline parameters) and stratified by diabetes type.

Results: Mean follow-up time was 1.8 years in T1D (n=2,994) and 1.9 years in T2D (n=1,440). In T1D, adjusted mean HbA1c decreased significantly from 7.65% (95%-confidence interval: 7.62-7.68) at baseline to 7.54% (7.51-7.57) during follow-up. BMI increased slightly (baseline: 25.4 kg/m^2 (25.3-25.5), follow-up >6 months: 25.8 kg/m^2 (25.7-25.9)), whereas event rates of severe hypoglycemia were significantly lower after >6 months with CGM (9.0 events/100 PY (8.0-10.1)) compared to baseline (11.3 events/100 PY (10.4-12.2)) in adults with T1D. In T2D, HbA1c decreased from 7.21% (7.17-7.25) to 7.00% (6.95-7.04%) and BMI did not change after CGM initiation.

Conclusion: Our results provide real world evidence on CGM management in adult individuals with T1D or T2D. We suggest to strengthen patients' and physicians' readiness towards diabetes technology in T2D and more openness of health insurance to cover cost based on proven benefits.

Introduction

The use of continuous glucose monitoring (CGM) systems has increased over the past years [1, 2] and new devices are introduced every year [3]. The proportion of CGM users in adult individuals with diabetes is significantly lower compared to the pediatric population[1, 2]. Results on type 2 diabetes, especially from observational studies in real-world settings, are rare so far [3, 4]. Randomized controlled trials comparing CGM use to self-monitoring blood glucose management have shown beneficial effects of CGM management on HbA1c and episodes of hypoglycemia in adult individuals with type 1 diabetes [5-7]. However, a reduction in event rates of severe hypoglycemia has been observed in some [6, 7] but not all studies [3, 5] as clinical trials did not have enough power to detect these effects due to rare events and low sample size.

The DIAMOND study on 158 adult individuals with type 2 diabetes with multiple daily insulin injections and a baseline mean HbA1c of 8.5% (SD 0.6%) reported an HbA1c improvement of 0.8% (95%-confidence interval (CI): -1.0; -0.7) in CGM users compared to 0.5% (-0.7; -0.3) in a control group with traditional blood glucose monitoring after 24 weeks [8].

Moreover, Martens et al (2021), evaluated the effectiveness of CGM in adult individuals with type 2 diabetes using less-intensive insulin regimens managed by primary care clinicians [9]. HbA1c mean was 9.1% (SD 1.0%) at randomization and a stronger HbA1c improvement with CGM (-1.1% (SD 1.5)) compared to traditional blood glucose monitoring (-0.6% (SD 1.2)) was found after 8 months [9]. A retrospective cohort study from Northern California including 41,753 adult individuals with insulin-treated diabetes (5,673 type 1 diabetes, 36,080 type 2 diabetes) reported significant decreases in HbA1c and in hospitalizations for severe hypoglycemia in association with CGM initiation [4].

Our objectives were to investigate potential beneficial effects of CGM initiation in individuals ≥18 years with type 1 or type 2 diabetes on HbA1c, body-mass-index (BMI) and event rates of severe hypoglycemia using data of the diabetes prospective follow-up registry (DPV). DPV captures data from diabetes specialist care and enables to study treatment and outcomes of people with diabetes in a multicenter, real-world setting.

Methods

Study population and covariates

The multicenter, diabetes prospective follow-up registry (DPV) comprises pediatric as well as adult health care facilities [10, 11]. Among 507 collaborators, 456 centers are located in Germany, 46 in Austria, four in Switzerland and one center in Luxembourg. In total 618,903 individuals with diabetes of all age groups are documented in the DPV initiative. Semi-annually, locally documented data are transmitted to Ulm University (Germany) in pseudonymized form and in encrypted archives. After validation, data are aggregated into an anonymized, cumulative database. Data collection and analysis for benchmarking and diabetes research were approved by the ethics committee of Ulm University (Number 314/21) and by local review boards of the participating centers. Individuals with type 1 or type 2 diabetes ≥ 18 years of age with CGM initiation in 2015 or later were included in the underlying study.

Demographic and clinical data included sex, current age, age at diabetes onset, BMI (kg/m^2), HbA1c (% or mmol/mol), diabetes treatment (conventional insulin therapy (CT, ≤3 injection time-points per day), intensive insulin therapy (ICT, 4-8 injection time-points per day), insulin pump, oral antidiabetic medication), daily insulin dose (IU/kg), systolic and diastolic blood pressure (mmHg). The multiple of the mean transformation method was used to standardize HbA1c values to the Diabetes Control and Complications Trial (DCCT) reference range of 4.05–6.05% (20.7–42.6 mmol/mol) [12]. Severe hypoglycemia was defined as an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions [13]. Events of hypoglycemia were actively enquired and recorded at each visit using the DPV documentation software [10]. The year prior to CGM initiation was defined as the baseline period. HbA1c, BMI and event rates of severe hypoglycemia at baseline were compared to two follow-up periods: 1) CGM use for 3 to 6 months and 2) CGM use for more than 6 months. Only individuals with documented information on the respective outcomes at baseline and during the two follow-up periods were included.

Statistical analysis

Continuous variables are presented as median with lower and upper quartiles. Binary variables are presented as percentages in the descriptive analyses. To study changes in outcome parameters during follow-up, repeated measurements analyses were conducted with a banded autoregressive covariance (Toeplitz) structure [14]. Linear regression was used to investigate changes in HbA1c and BMI and negative binomial regression were used for event rates of severe hypoglycemia. All models were adjusted for sex, age at diabetes onset and respective baseline parameters. Analyses were stratified by diabetes type. We conducted additional analyses stratifying by HbA1c at baseline categorized as <7%, 7-<8% and ≥8% for each diabetes type separately. For individuals with type 2 diabetes we implemented a further sensitivity analysis including only individuals with insulin therapy at baseline. Regression results are presented as adjusted least square means or event rates per 100 patient years (PY) together with 95%-confidence intervals. Statistical analyses were conducted using SAS version 9.4 (build TS1M7, SAS Institute Inc, Cary, NC) and a two-sided p-value <0.05 was considered statistically significant.

Results

Of the 618,908 documented individuals with diabetes in DPV, 579,346 had type 1 or type 2 diabetes and of these 509,337 were ≥18 years of age (Figure 1). In 2015 or later, 9,851 individuals started CGM management. Information on the year prior to CGM initiation (baseline period) and on the two follow-up periods was available for 4,434 individuals with type 1 (n = 2,994) or type 2 (n = 1,440) diabetes. Baseline characteristics of the included individuals with type 1 and type 2 diabetes are presented in table 1. Median age in individuals with type 1 diabetes was 19.9 years (Q1: 18.2, Q3: 45.8) and median HbA1c was 7.4% (6.8, 8.3). Fifty-three percent of the individuals with type 1 diabetes were males and half of them used an insulin pump. Individuals with type 2 diabetes had a median age of 67.5 years (58.8, 76.2) at baseline and HbA1c was 7.0% (6.4, 7.8). Proportion of people with type 2 diabetes treated with insulin was 46% and 56% were males.

Mean follow-up time was 1.8 years in individuals with type 1 diabetes and 1.9 years in type 2 diabetes. Results from repeated measurements analyses on changes in outcomes from baseline in type 1 diabetes are shown in figure 2. Adjusted HbA1c decreased significantly

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from 7.65% (95%-CI: 7.62-7.68) at baseline to 7.54% (7.51-7.57) after 3 to 6 months with CGM and remained stable after >6 months with CGM (Figure 2 A). BMI increased slightly in type 1 diabetes (baseline: 25.4 kg/m^2 (25.3-25.5), follow-up >6 months: 25.8 kg/m^2 (25.7-25.9)) (Figure 2 B). Moreover, we found significantly lower event rates of severe hypoglycemia (9.0 events/100 PY (8.0-10.1)) after a follow-up period of more than 6 months with CGM compared to the baseline period (11.3 events/100 PY (10.4-12.2), Figure 2 C).

CGM management was associated with a reduction in mean HbA1c in type 2 diabetes from 7.21% (7.17-7.25) at baseline to 7.00% (6.95-7.04%) after 3 to 6 months (Figure 3 A). We observed no significant change in BMI in people with type 2 diabetes (Figure 3 B). Event rates of severe hypoglycemia in type 2 diabetes were generally low and were slightly but non-significantly lower with CGM (more than 6 months use: 1.3 events/100 PY (0.9-1.7) compared to baseline (1.7 events/100 PY (1.4-2.1), Figure 3 C).

Results stratified by HbA1c baseline categories revealed that in type 1 as well as type 2 diabetes decreases in HbA1c with CGM use were strongest in individuals with a HbA1c ≥8% at baseline (Supplemental Figures 1 and 2). In individuals with type 1 diabetes with HbA1c ≥8% at baseline, HbA1c decreased from 9.2% (9.1-9.3) to 8.7% (8.6-8.8) with CGM use for more than 6 months (Supplemental Figure 1 A). BMI increased slightly with all HbA1c baseline categories and event rates of severe hypoglycemia decreased significantly in individuals with in type 1 diabetes with a baseline HbA1c <7% (12.2 events/100 PY (10.7-13.8) to 6.3 events/100 PY (5.0-8.0), Supplemental Figure 1 B and C). Individuals with type 2 diabetes with HbA1c ≥8% at baseline showed a HbA1c reduction from 9.1% (8.9-9.2) to 7.9% (7.7-8.1) (Supplemental Figure 2 A). A reduction in BMI was reported for the subgroup with a baseline HbA1c 7-<8% (32.7 kg/m^2 (32.3-33.1) to 32.5 kg/m^2 (32.1-33.0), Supplemental Figure 2 B). Due to the small number of events, severe hypoglycemia was not stratified by HbA1c baseline categories in type 2 diabetes. Including only individuals with type 2 diabetes treated with insulin did not change the results (Supplemental Figure 3).

Discussion

Results of the DPV registry indicate slight, but beneficial effects of CGM management on glycemic control in type 1 and type 2 diabetes in a real-world setting. After a mean follow-up time of 1.8 years, HbA1c and event rates of severe hypoglycemia decreased significantly in individuals with type 1 diabetes, while BMI increased slightly after CGM initiation. We also observed a significant reduction in HbA1c in individuals with type 2 diabetes with or without insulin therapy using CGM for a mean follow-up time of 1.9 years. No significant changes in BMI and event rates of severe hypoglycemia were found in type 2 diabetes.

Our results confirm reports from clinical trials showing reductions in HbA1c in adult individuals with type 1 diabetes, especially in those with poor glycemic control at baseline (HbA1c ≥8%) [5, 6]. However, a recent observational study in adult individuals with type 1 diabetes documented in the US T1D Exchange registry (T1DX) reported an increase in HbA1c levels over time despite an increase in CGM use [15]. A transatlantic comparison in metabolic control showed significant differences in HbA1c across the lifespan in individuals with type 1 diabetes between the T1DX and DPV registry, which might be an explanation for the contrasting results [16]. We observed a significant decrease in event rates of severe hypoglycemia from 11.3 events/100 PY (10.4-12.2) at baseline to 9.0 events/100 PY (8.0-10.1) with CGM use for more than 6 months in 2,994 adult individuals with type 1 diabetes. These results add to the existing literature on CGM use in adults with type 1 diabetes as clinical trials did not have enough power to detect these effects due to rare events and low sample size [3, 5, 6]. BMI increased slightly in adults with type 1 diabetes after CGM initiation. Similar results were also found in a pediatric cohort of type 1 diabetes (2 to 18 years of age) from the SWEET initiative [17]. Comparing the years 2016 and 2019, the authors reported a significantly lower HbA1c, but higher BMI z-scores in children and adolescents with type 1 diabetes switching from multiple daily injections to insulin pump with or without CGM [17]. One reason for the inverse relationship between HbA1c and BMI in type 1 diabetes might be intensified diabetes treatment and management in order to achieve HbA1c target values while preventing severe hypoglycemia [18, 19]. Nansel and colleagues examined the association between HbA1c and BMI in type 1 diabetes and

concluded that increased insulin administration might be one explanation for the inverse relationship [18].

Compared to type 1 diabetes, less research has been conducted so far on CGM use in type 2 diabetes [20] and most clinical trials included individuals with insulin-treated type 2 diabetes only [21]. In addition to the beneficial effects on glycemic control in adult individuals with type 1 diabetes, we observed a significant reduction in mean HbA1c in type 2 diabetes from 7.21% (7.17-7.25) at baseline to 7.00% (6.95-7.04%) after 3 to 6 months of CGM use with or without insulin therapy. The observed association between CGM initiation and HbA1c reduction was strongest in individuals with a baseline HbA1c ≥8% (9.06% (8.90-9.21) to 7.92% (7.76-8.08) with CGM for more than 6 months). Peek and Thomas emphasized in a recently published editorial the importance to investigate potential improvements in metabolic control in adult individuals with type 2 diabetes with less intensive insulin regimens [20]. The clinical trial conducted by Martens et al (2021) recruited individuals with type 2 diabetes on basal insulin without prandial insulin from primary care settings. HbA1c decreased from 9.1% to 8.0% in the CGM group and from 9.0% to 8.4% in the control group with traditional blood glucose monitoring after 8 months [9]. In addition to beneficial effects in HbA1c, a decrease in hospitalizations for severe hypoglycemia were observed in a retrospective cohort study on 5,673 adult individuals with type 1 diabetes and 36,080 adult individuals with type 2 diabetes [4]. The proportion of people having at least 1 hospitalization for severe hypoglycemia within 12 months declined from 4.8% to 2.9% in type 1 diabetes after CGM initiation, but increased in those without CGM initiation (3.4% to 4.0%) comparing a similar time frame as in CGM initiators [4]. An even stronger decline in hypoglycemia hospitalization rates was found for individuals with type 2 diabetes initiating CGM use (7.8% to 3.2%), while rates increased in individuals without CGM initiation (1.8% to 2.2%) [4].

Overall, results from clinical trials and selected observational studies reported improvements in glycemic control in adult individuals with type 1 as well as type 2 diabetes initiating CGM [3]. Use of CGM may be associated with improvement in treatment adherence, changes in diet, increased physical activity through CGM readings [20]. Therefore, Peek and Thomas (2021) suggested broadening access to CGM for the adult

population with 2 diabetes for example through online diabetes education programs with remote training of CGM [20, 22].

Our study is limited by the fact that we could not stratify by intermittently scanned CGM and real-time CGM due to the fact that we did not have information on the device for every individual in this study. However, it is estimated that around 90% of CGM in adult individuals with type 1 or type 2 diabetes are intermittently scanned CGM at the current stage in the countries participating in this study [23]. A further limitation is the absence of a control group of adults with type 1 or type 2 diabetes without CGM initiation. Due to selection bias we did not match CGM users with CGM non-users as unmeasured confounders like lifestyle factors and individual socioeconomic status might play an important role. However, the aim of our study was to investigate changes within the individuals after CGM initiation rather than comparing CGM users with CGM non-users. Adult individuals with diabetes treated in primary care services are underrepresented within DPV. However, the DPV registry can be regarded as representative for routine diabetes specialist care in Germany for adults with type 1 or type 2 diabetes. The main strength of our analysis is that we used real world data on a large scaled nationwide cohort of 2,994 adults with type 1 and 1,440 adults with type 2 diabetes. Therefore, our study adds to the growing body of evidence on CGM use in people with type 1 and type 2 diabetes as we show results from a multicenter, real-world setting. In addition to reductions in HbA1c with CGM management, we observed a significant decrease in event rates of severe hypoglycemia in type 1 diabetes and our results showed improved glycemic control with CGM use in people with type 2 diabetes. We suggest to strengthen patients' and physicians' readiness towards diabetes technology in type 2 diabetes which might be achieved by remote training of CGM, and more openness of health insurance to cover cost based on proven benefits. Longer follow-up periods may give further insights into adherence to CGM, persistence of metabolic changes, as well as potentially additional beneficial effects.

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Conflict of interest

The authors declare that there is no duality of interest associated with this manuscript.

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Authorship confirmation

All authors contributed to the study concept and design. SL and RWH supervised the study. SL analyzed the data. All authors participated in data interpretation. SL drafted the first version of the manuscript. The final manuscript was reviewed and approved by all. RWH is the guarantor of the study and takes full responsibility for the work as a whole, including the study design, access to data and the decision to submit and publish the manuscript.

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Figure Legends

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Dynamics of HbA1c, BMI and rates of severe hypoglycemia in 4,434 adults with type 1 or type 2 diabetes after initiation of continuous glucose monitoring (DOI: 10.1089/dia.2022.0063)

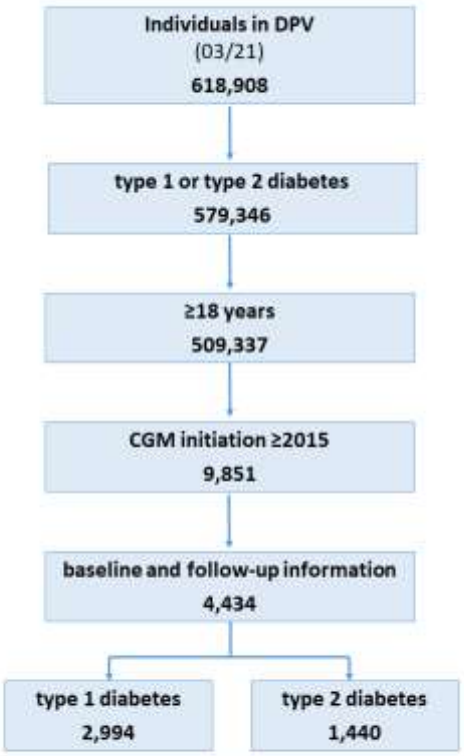

Figure 1. Flow Chart of included study participants

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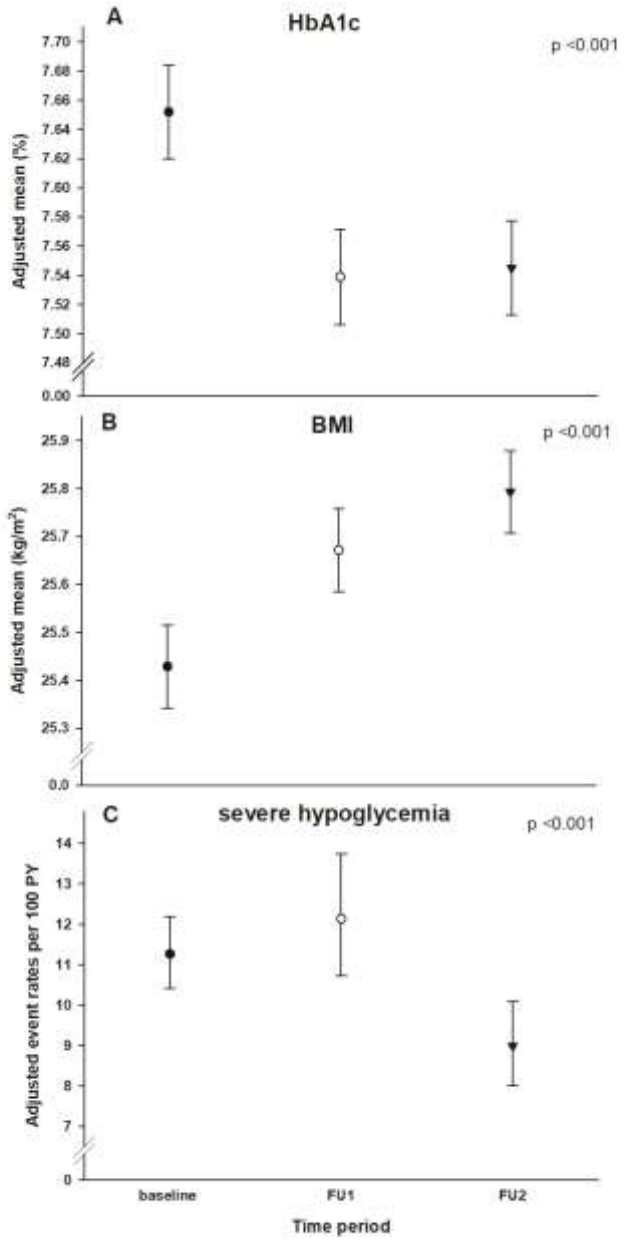

Figure 2. Changes in adjusted means of A) HbA1c, B) BMI and C) event rates of severe hypoglycemia in association with CGM use in adult individuals with type 1 diabetes.

FU1: follow-up period 1) CGM use for 3 to 6 month,

FU2: follow-up period 2) CGM use for more than 6 months.

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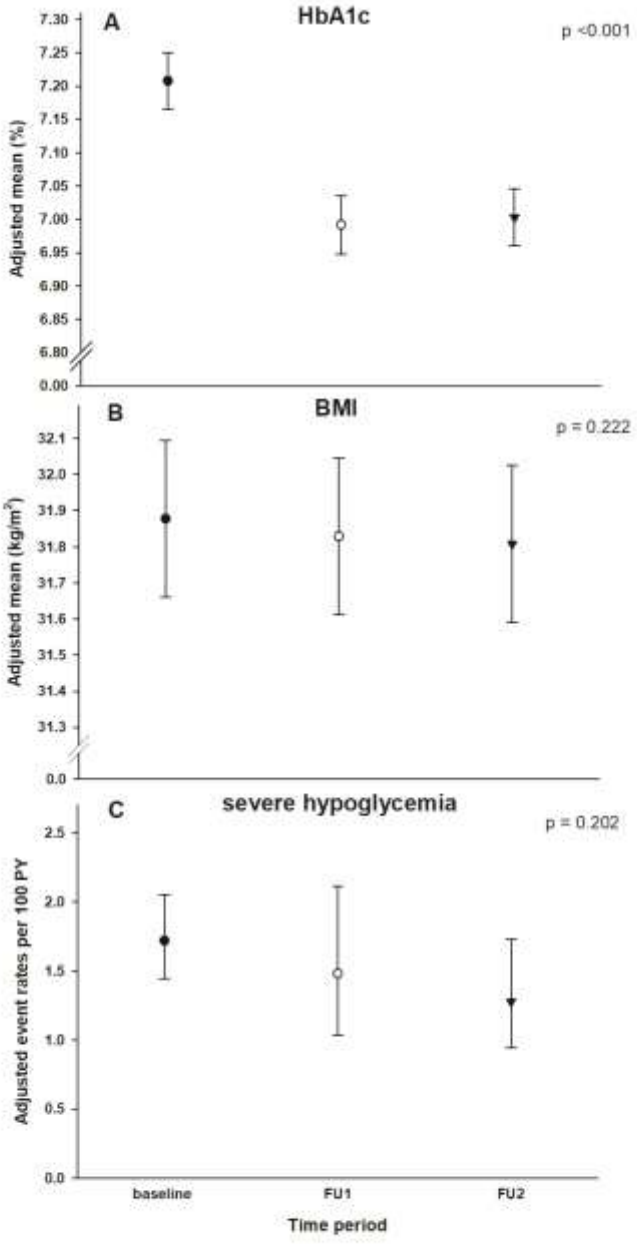

Figure 3. Changes in adjusted means of A) HbA1c, B) BMI and C) event rates of severe hypoglycemia in association with CGM use in adult individuals with type 2 diabetes.
FU1: follow-up period 1) CGM use for 3 to 6 month,
FU2: follow-up period 2) CGM use for more than 6 months.

Table 1. ***Baseline characteristics of the included individuals with type 1 (n = 2,994) and type 2 diabetes (n = 1,440)***

Patient characteristics	T1D[a] Median (Q1, Q3)	T2D[b] Median (Q1, Q3)
Age at initiation of CGM (years)	19.9 (18.2, 45.8)	67.5 (58.8, 76.2)
Age at diabetes onset (years)	13.1 (8.6, 22.5)	52.3 (43.9, 60.6)
Diabetes duration (years)	10.7 (5.9, 18.1)	13.2 (7.8, 19.6)
BMI (kg/m^2)	24.6 (22.2, 27.6)	30.8 (27.5, 35.3)
BMI-SDS	0.3 (-0.5, 1.0)	0.8 (-0.1, 1.6)
HbA1c (%)	7.4 (6.8, 8.3)	7.0 (6.4, 7.8)
HbA1c (mmol/mol)	57.6 (50.5, 66.8)	53.4 (46.7, 61.3)
daily insulin dose (IU/kg)	0.8 (0.6, 1.0)	0.5 (0.3, 0.7)
diastolic blood pressure (mmHg)	76.0 (70.0, 80.0)	80.0 (73.5, 82.5)
systolic blood pressure (mmHg)	126.0 (119.0, 135.0)	135.0 (127.5, 142.5)
% males	53.0	56.0
% insulin therapy	100.0	46.0
% CT	7.0	23.0
% ICT	44.0	22.0
% insulin pump	49.0	1.0
% OAD/GLP-1	4.0	68.0

Abbreviations: BMI, body mass index; BMI-SDS; BMI standard deviation scores; HbA1c, hemoglobin A1c;

T1D, type 1 diabetes; T2D, type 2 diabetes; CT, conventional insulin therapy; ICT intensive insulin therapy;

OAD, oral antidiabetic medication; GLP-1, glucagon-like peptide 1 receptor agonists;

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This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

[a]missing values: BMI and BMI-SDS 13, HbA1c 62, daily insulin dose 814, SBP and DPB 115;

[b]missing values: BMI and BMI-SDS 5, HbA1c 7, daily insulin dose 786, SBP and DPB 16