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Clinical Research Article



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# Relationship Between Time in Range, Glycemic Variability, HbA1c, and Complications in Adults With Type 1 Diabetes Mellitus

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**Abbreviations:** BMI, body mass index; CGM, continuous glucose monitoring; CV, coefficient of variation; DKA, diabetic ketoacidosis; GV, glycemic variability; OR, odds ratio; RT-CGM, real-time continuous glucose monitoring; SAP, sensor-augmented pump; SMBG, self-monitoring of blood glucose; T1D, type 1 diabetes; T2D, type 2 diabetes; TIR, time in range.

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## Abstract

**Purpose:** Real-time continuous glucose monitoring (RT-CGM) provides information on glycemic variability (GV), time in range (TIR), and guidance to avoid hypoglycemia, thereby complimenting HbA1c for diabetes management. We investigated whether GV and TIR were independently associated with chronic and acute diabetes complications.
**Methods:** Between September 2014 and January 2017, 515 subjects with type 1 diabetes using sensor-augmented pump therapy were followed for 24 months. The link between baseline HbA1c and CGM-derived glucometrics (TIR [70-180 mg/dL], coefficient

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of variation [CV], and SD) obtained from the first 2 weeks of RT-CGM use and the presence of complications was investigated. Complications were defined as: composite microvascular complications (presence of neuropathy, retinopathy, or nephropathy), macrovascular complications, and hospitalization for hypoglycemia and/or ketoacidosis.
**Results:** Individuals with microvascular complications were older ($P < 0.001$), had a longer diabetes duration ($P < 0.001$), a higher HbA1c (7.8 ± 0.9 vs 7.5 ± 0.9%, $P < 0.001$), and spent less time in range (60.4 ± 12.2 vs 63.9 ± 13.8%, $P = 0.022$) compared with those without microvascular complication. Diabetes duration (odds ratio [OR] = 1.12 [1.09-1.15], $P < 0.001$) and TIR (OR = 0.97 [0.95-0.99], $P = 0.005$) were independent risk factors for composite microvascular complications, whereas SD and CV were not. Age (OR = 1.08 [1.03-1.14], $P = 0.003$) and HbA1c (OR = 1.80 [1.02-3.14], $P = 0.044$) were risk factors for macrovascular complications. TIR (OR = 0.97 [0.95-0.99], $P = 0.021$) was the only independent risk factor for hospitalizations for hypoglycemia or ketoacidosis.
**Conclusions:** Lower TIR was associated with the presence of composite microvascular complications and with hospitalization for hypoglycemia or ketoacidosis. TIR, SD, and CV were not associated with macrovascular complications.

**Key Words:** type 1 diabetes, continuous glucose monitoring, complications, hypoglycemia, time in range, glucose variability

Managing type 1 diabetes (T1D) is challenging and requires intensive glucose monitoring and titration of insulin to reduce the risk of both acute and chronic complications. HbA1c has been accepted as the gold standard to assess overall glycemic control and, in general, a value of ≤7% (53 mmol/mol) is targeted (1). Until recently, self-monitoring of blood glucose (SMBG) was done by 4 to 7 capillary glucose measurements per day. However, SMBG does not show a complete picture on glucose control (usually including no postprandial or nocturnal data). The advent of continuous glucose monitoring (CGM) has substantially changed management of T1D. CGM systems provide a comprehensive view of glucose profiles identifying patterns, areas of glucose variability (GV), and times spent in range (TIR: 70-180 mg/dL [3.9-10.0 mmol/L]), below or above target range, thereby allowing patients to make therapeutic adjustments to improve metabolic control. Despite the limitations of CGM (costs, measurement of glucose in the interstitial fluid, time lag of ~10 minutes), a growing body of evidence supports the use of CGM because it has the potential to improve HbA1c, TIR, GV, and quality of life (2-10).

So far, HbA1c is the only metric of glucose control showing a strong association with chronic complications; however, it is unreliable in situations as anemia, transfusion, hemodialysis, cirrhosis and certain hemoglobinopathies. It is also 0.2% to 0.4% higher in US African Americans and Hispanics than in Caucasians for the same mean glucose (11). HbA1c does not inform about intraday or day-to-day glucose variability nor captures number and timing of hypo- or hyperglycemic episodes and does not provide guidance to decrease the risk of hypoglycemia. With the use of CGM, an International Consensus on Time in Range was recently published with the recommendation to spend >70% of time in range (70-180 mg/dL or 3.9-10 mmol/L) because this level corresponds to an HbA1c level of 7.0% (53 mmol/mol) (12, 13). The TIR target for older or high-risk individuals is modified to >50% because of a potential elevated risk for hypoglycemia in these populations.

Evidence linking high GV and low TIR to diabetes complications is beginning to emerge. HbA1c variability, indicating long-term GV, shows a positive association with micro- and macrovascular complications and mortality independent of the HbA1c level (14-16). A role for short-term GV in the development of chronic complications seems less obvious (17-25). The link between TIR, derived using 7-point SMBG data collected 1 day every 3 months, and chronic complications in T1D was recently suggested by a new analysis of the Diabetes Control and Complications Trial (26). Similar associations between microvascular complications and TIR have been reported, but most studies had a cross-sectional design, were based on retrospective data, or were limited by using a snapshot of only 4 to 7 SMBG measurements or by short time use of CGM, and were performed in people with type 2 diabetes (T2D) (27-34).

In this study, the association between baseline HbA1c and CGM-derived glucometrics (TIR, coefficient of variation [CV], SD) and the presence of chronic and acute complications was investigated in a large group of adults with T1D using sensor-augmented pump (SAP) therapy.

## Materials and Methods

### Study Design and Participants

A prospective multicenter observational cohort study, the Reimbursement Study of Continuous Glucose Monitoring in Belgium trial, was performed assessing the impact of nationwide reimbursement of real-time continuous glucose monitoring (RT-CGM) in 515 Belgian adults with T1D on insulin pump therapy (7, 8). Participants were consecutively recruited between September 2014 and January 2017 after giving written informed consent. All adults with T1D who entered the reimbursement program were included without exception. They needed to wear their RT-CGM >70% of the time and upload their RT-CGM and pump data on a monthly basis. Data collection ended in March 2019, after a 24-month follow-up. In Belgium, people with T1D are managed in specialist centers by multidisciplinary teams led by endocrinologists. If individuals chose to opt for sensor-augmented pump therapy, they were trained individually or in group during 2 to 3 hours by experienced diabetes educator nurses, as part of the standard of care.

The study was performed in line with the International Conference on Harmonization/Good Clinical Practice guidelines and the Declaration of Helsinki in its latest form. The study protocol was approved by the Ethics Committee of all participating centers (EC number: 15/46/482). This study is registered at ClinicalTrials.gov (NCT02601729).

### Outcomes and Data Collection

The primary outcome parameter was the independent association between TIR obtained from the first 2 weeks of RT-CGM use after start of reimbursement of SAP therapy and composite microvascular complications at initiation of this study, defined as presence of at least 1 of the following: neuropathy, retinopathy, nephropathy. Secondary outcome parameters were the association between CGM-derived glucometrics (TIR, CV, SD) and retinopathy, nephropathy, neuropathy, composite macrovascular complications, and hospitalizations for severe hypoglycemia and ketoacidosis. We hypothesized that subjects with high glucose variability were more at risk to be hospitalized for severe hypoglycemia and ketoacidosis. We also evaluated the evolution of TIR, CV, and SD over 24 months of SAP reimbursement to assess how variable these parameters of glucose variability are. CGM data were collected at 2 weeks and 4, 8, 12, and 24 months.

Presence of nephropathy was scored positive in case of 24-hour urinary albumin excretion >20 µg/min or eGFR <60 mL/min/1.73 $m^2$ or creatinine level >1.5 mg/dL. Presence of retinopathy was scored positive if fundoscopy showed preproliferative (microaneurysms, intraretinal microvascular abnormalities, exudates, venous beading) or proliferative retinopathy. Peripheral neuropathy was scored positive if monofilament tests were abnormal or abnormal nerve conduction velocities were documented by electromyography of the lower limbs. Macrovascular disease was scored positive if (1) electrocardiogram showed abnormalities suggestive of cardiac ischemia (eg, ST segment depression or elevation, intraventricular conduction block, Q waves) or (2) medical history was positive for myocardial infarction or coronary artery bypass graft or (3) clinical signs of heart failure and (4) peripheral artery disease was present as assessed by clinical examination or Doppler of the arteries of the lower limbs. Patient-reported hospitalizations for hypoglycemia and/or ketoacidosis were validated using hospital records in the individual centers.

### Statistical Analysis

All data were analyzed using SPSS (IBM SPSS Statistics version 26.0, Armonk, NY). Normality of data was tested by the Kolmogorov-Smirnov test. Parametric data are expressed as mean ± SD, nonparametric data are expressed as median (minimum-maximum), and categorical data are expressed as numbers and percentages. The *t* test, Mann-Whitney *U* test, or ANOVA were used to determine differences between groups. To compare groups with low vs high glucose variability based on CV, we used a cutoff of 36% per consensus (35, 36). For SD, we conducted a median split at 24 months (SD < 61 mg/dL vs SD ≥61 mg/dL). For TIR, we used a cutoff of 70% per consensus (12, 33). Differences in distributions of categorical data were evaluated by $\chi^2$ (with Cramer's V) or Fisher exact test. A linear mixed model with an unstructured covariance matrix was used to assess the evolution of HbA1c, time spent in different glycemic ranges, CV, and SD. By using a linear mixed model, cases with missing data still contributed to the analyses. Stepwise backward logistic regression and multiple linear regression analyses were used to assess the strength and independency of associations between CGM-derived glucometrics and the presence of chronic or acute complications. Factors that were significant in univariate analyses were included in multiple linear regression models together with the glucometrics that were part of the research question (TIR, SD, CV). Statistical significance was predetermined as a 2-sided *P* value <0.05.

## Results

### Patient Characteristics

The majority of the 515 persons with T1D were female (59%), highly educated (64%), and Caucasian (97%).

Their mean age was 42.2 ± 12.5 years. They had a long diabetes duration (22.3 ± 11.6 years) with 5.7 ± 4.6 years of continuous subcutaneous insulin infusion experience and a baseline HbA1c of 7.6 ± 0.9% (60.0 ± 9.8 mmol/mol). Self-reported impaired hypoglycemia awareness was common (47%). Thirty-five percent of patients were diagnosed with 1 or more microvascular complications (29% retinopathy, 13% neuropathy, and 10% nephropathy) and 5% already had macrovascular complications (see Table 1 of Charleer et al (7)). Data of glucose variability (SD and CV) and of TIR were available in respectively 383 and 334 subjects. Demographic and glucometric characteristics did not differ between the entire group vs the group of subjects of whom RT-CGM data were available vs those in whom baseline RT-CGM data were lacking.

## Evolution of Glucometrics

HbA1c decreased from 7.6 ± 0.9% at baseline to 7.3 ± 0.8% at 24 months ($P < 0.001$) (see Fig. 1 of Charleer et al (7)). Time in range evolved from 62.9 ± 12.9% at 2 weeks to 61.2 ± 13.5% at 4 months, 60.4 ± 12.5% at 8 months, 60.7 ± 13.7% at 12 months, and to 60.8 ± 14.0% at 24 months, demonstrating a significant time effect ($P = 0.043$), which was also the case for time below range ($P < 0.001$) and time above range ($P = 0.002$) (Fig. 1A). The CV at 2 weeks was 38.6 ± 6.1% evolving toward 37.8 ± 4.6% at 4 months, 37.6 ± 5.0% at 8 months, 37.8 ± 5.2% at 12 months, and 37.0 ± 5.1% at 24 months ($P = 0.002$) (Fig. 1B). No significant time effect on SD was found over the 24-month time course (Fig. 1C).

## Glucometrics vs Chronic Complications

### Time in range

Subjects who spent >70% of time in range (n = 97/334 or 29.0%) had a better HbA1c (7.1 ± 0.8 vs 7.9 ± 0.8%, $P < 0.001$), a shorter duration of pump therapy ($P = 0.042$), a lower SD (48.5 ± 8.5 vs 66.0 ± 10.6 mg/dl, $P < 0.001$), and a lower CV (35.6 ± 4.9 vs 39.7 ± 6.2%, $P < 0.001$) compared with individuals who spent ≤70% TIR. Age, diabetes duration, and body mass index (BMI) were similar (Table 1).

Subjects who spent ≤70% TIR had a higher prevalence of composite microvascular complications ($P = 0.044$), retinopathy (32.9% vs 21.6%, $P = 0.041$), and peripheral neuropathy (16.0 vs 7.2%, $P = 0.032$) and, importantly, were 2.85 times more prone to be hospitalized for hypoglycemia or diabetic ketoacidosis (DKA; 18.1 vs 7.2%, $P = 0.011$) than those with a TIR >70%.

With decreasing time spent in range, the frequency of composite microvascular complications increased, being present in 26.8% of subjects spending >70% TIR, in 35.3% of those spending 60% to 70% TIR, in 39.7% of those with 50% to 59% TIR, and in 44.4% of those with <50% TIR (Fig. 2). For retinopathy, the same pattern was seen: 21.6% (for those with >70% TIR), 29.1% (for those with 60%-70% TIR), 32.5% (for those with 50%-59% TIR), and 42.6% (for those with <50% TIR).

**Table 1.** Comparison of subjects spending ≤70% vs >70% TIR

| | TIR ≤ 70% | TIR > 70% | OR (95% CI) | *P* value |
|---|---|---|---|---|
| Total number (men/women) | 237 (92/145) | 97 (41/56) | | NS |
| Age (y) | 42.4 ± 12.6 | 42.4 ± 13.1 | | NS |
| Diabetes duration (y) | 22.7 ± 11.3 | 22.3 ± 13.1 | | NS |
| BMI (kg/m²) | 25.5 ± 3.8 | 24.8 ± 3.7 | | NS |
| Duration of pump therapy (y) | 5.6 (0.0-31.3) | 4.1 (0.1-18.4) | | 0.042 |
| HbA1c at start (%) | 7.9 ± 0.8 | 7.1 ± 0.8 | | <0.001 |
| HbA1c at start (mmol/mol) | 63 ± 9 | 54 ± 9 | | <0.001 |
| Standard deviation after 2 wk (mg/dL) | 66.0 ± 10.6 | 48.5 ± 8.5 | | <0.001 |
| Coefficient of variation after 2 wk (%) | 39.7 ± 6.2 | 35.6 ±4.9 | | <0.001 |
| Any microvascular complication (n, %) | 91 (38.4) | 26 (26.8) | 1.70 (1.01-2.86) | 0.044 |
| Nephropathy (n, %) | 30 (12.7) | 7 (7.2) | NS | NS |
| Retinopathy (n, %) | 78 (32.9) | 21 (21.6) | 1.78 (1.02-3.09) | 0.041 |
| Total neuropathy (n, %) | 45 (19.0) | 9 (9.3) | 2.29 (1.07-4.89) | 0.029 |
| Peripheral neuropathy (n, %) | 38 (16.0) | 7 (7.2) | 2.46 (1.06-5.71) | 0.032 |
| Autonomic neuropathy (n, %) | 23 (9.7) | 4 (4.1) | NS | NS |
| Any macrovascular complication (n, %) | 13 (5.5) | 3 (3.1) | NS | NS |
| Hospitalization for hypoglycemia or DKA in the last year (n, %) | 43 (18.1) | 7 (7.2) | 2.85 (1.23-6.58) | 0.01 |

Data are expressed as mean ± SD, or as median (minimum-maximum), categorical data are expressed as number (n) with percentages (%).
Abbreviations: BMI, body mass index; DKA, diabetic ketoacidosis; NS, not significant; OR, odds ratio; TIR, time in range.

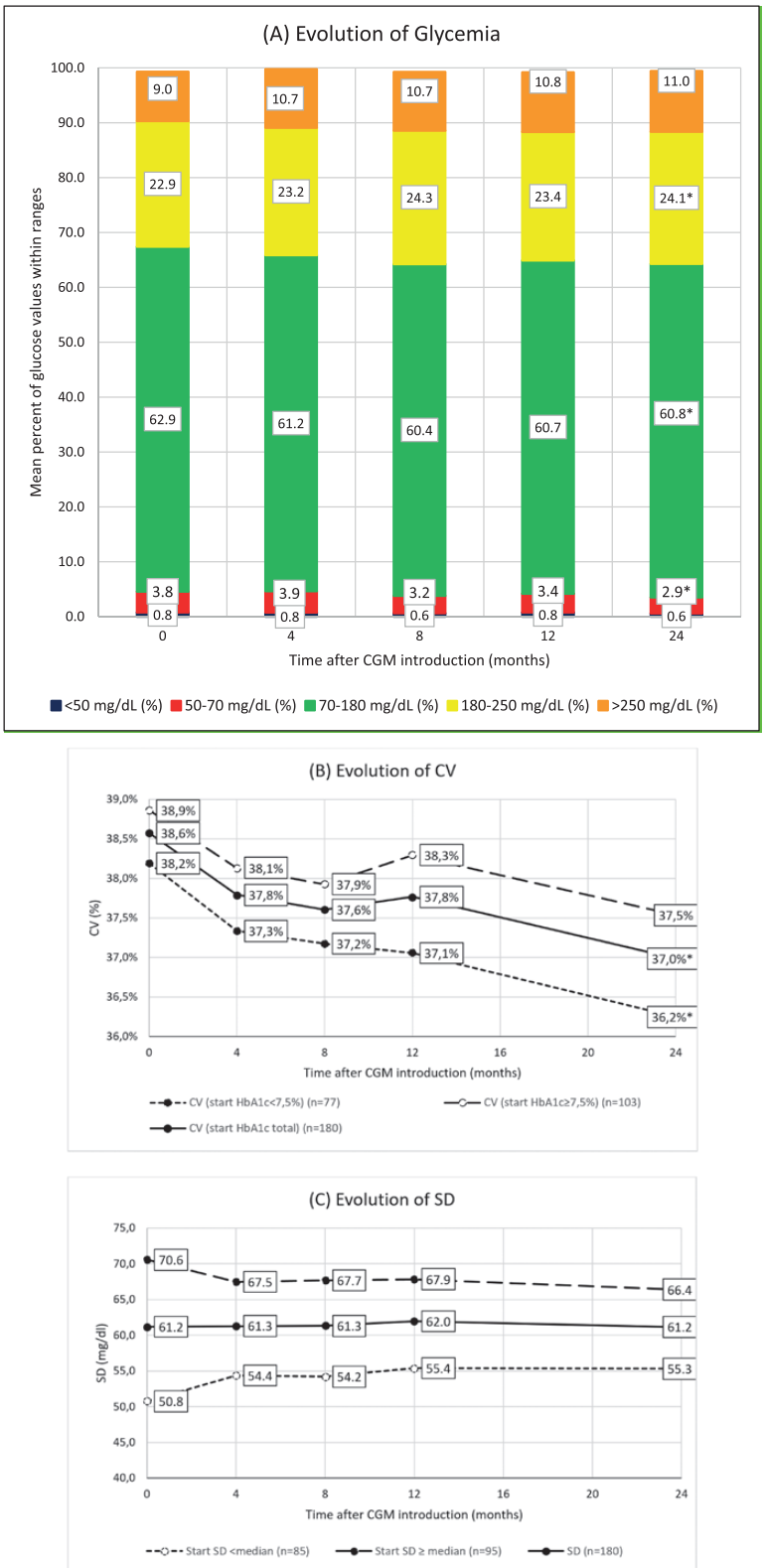


**Figure 1.** Evolution of (A) percentage of time spent in different glycemic ranges, (B) coefficient of variation, and (C) standard deviation from the start of CGM introduction until 24 months. *Statistically significant difference compared with baseline ($P < 0.05$). CGM, continuous glucose monitoring.

Nephropathy was present in 10.3% of the total cohort, ranging from 7.2% in those spending >70% of TIR to 14.8% in those with TIR <50%. There was no clear relationship between TIR and macrovascular complications (3.1% for those with >70% TIR vs 7.4% for those with <50% TIR) (Fig. 2).

### Coefficient of variation

Individuals with more variable diabetes (CV > 36%) (n = 257 or 67%) were younger (41.3 ± 12.7 vs 44.3 ± 12.2 years, $P = 0.027$), had a longer experience with pump therapy (5.6 [0-31.3] vs 3.5 [0.2-19.0] years, $P = 0.004$), a higher HbA1c (7.7 ± 0.9 vs 7.4 ± 1.0%, $P = 0.001$), and a lower TIR (61.1 ± 10.4 vs 65.8 ± 17.5%, $P = 0.011$). No differences in BMI, presence of chronic micro- or macrovascular complications or hospitalization for hypoglycemia, or DKA were observed.

### Standard deviation

A median split was performed for SD because there is no recommended cutoff in the literature. Subjects with a SD ≥ 61 mg/dL had a higher HbA1c (7.9 ± 0.8 vs 7.3 ± 0.9%, $P < 0.001$), had a longer experience with pump therapy (5.6 [0-31.3] vs 4.0 [0-20.3], $P = 0.012$), and a lower TIR (55.3 ± 9.9 vs 70.2 ± 12.1%, $P < 0.001$) compared with those with a lower SD. Subjects with a SD ≥ 61 mg/dL were more frequently affected by macrovascular complications (6.9 vs 2.6%, odds ratio [OR] = 2.80, 95% CI = 1.002-8.91, $P = 0.046$). All other characteristics were similar. No differences were observed in hospitalization for hypoglycemia or DKA.

## Comparing Subjects With vs Without Complications

### Microvascular complications

Individuals with microvascular complications (n = 180 or 35%) were older ($P < 0.001$), had a longer diabetes duration ($P < 0.001$), a longer duration of pump therapy ($P = 0.040$), a higher HbA1c (7.8 ± 0.9 vs 7.5 ± 0.9%, $P < 0.001$), and spent less time in range (60.4 ± 12.2 vs 63.9 ± 13.8%, $P = 0.022$) than those without any microvascular complication. The SD also tended to be larger in subjects with microvascular complications, but CV was similar (Table 2).

Logistic regression analysis showed that diabetes duration (OR = 1.12, $P < 0.001$) and TIR (OR = 0.97, $P = 0.005$) were independent risk factors for composite microvascular complications, but age, duration of pump therapy, HbA1c, SD, and CV were not (Table 3). For nephropathy, diabetes duration (OR = 1.08, $P < 0.001$) and HbA1c (OR = 1.65, $P = 0.012$) were independently associated. For retinopathy, it was diabetes duration (OR = 1.14, $P < 0.001$) and TIR (OR = 0.96, $P < 0.001$) and for neuropathy diabetes, duration (OR = 1.09, $P < 0.001$) and SD (OR = 1.03, $P = 0.026$) were independent risk factors (Table 3).

### Macrovascular complications

Patients with macrovascular complications (n = 25 or 5%) were older ($P < 0.001$), had a longer diabetes duration ($P < 0.001$), and a higher HbA1c (8.2 ± 0.8 vs 7.6 ± 0.9%, $P = 0.001$) compared with those without macrovascular complications (Table 2). Logistic regression identified age (OR = 1.08, $P = 0.003$) and HbA1c (OR = 1.80, $P = 0.044$) as independent risk factors for composite macrovascular complications, but diabetes duration, duration of pump therapy, SD, CV, and TIR were not (Table 3).

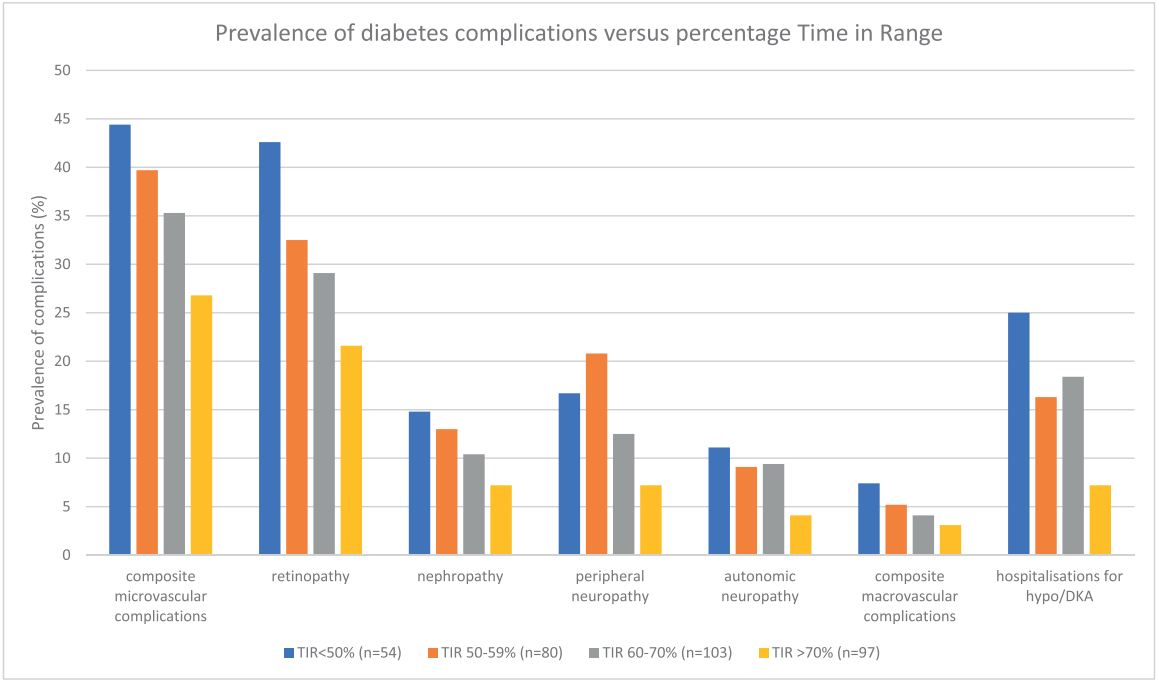


**Figure 2.** Prevalence of complications versus percentage of time spent in optimal range (70-180 mg/dL or 3.9-10.0 mmol/L).

**Table 2.** Comparison of individuals with or without complications

| | No microvascular complications (n = 324) | Any microvascular complication (n = 180) | *P* value |
|---|---|---|---|
| Gender (female) (%) | 60% | 57% | NS |
| Age (y) | 39.0 ± 11.9 | 47.5 ± 11.6 | <0.001 |
| Diabetes duration (y) | 17.8 ± 9.6 | 30.5 ± 10.2 | <0.001 |
| Pump therapy (y) | 4.7 (0 - 18.8) | 5.3 (0 - 31.7) | 0.040 |
| BMI at start (kg/m²) | 25.2 ± 3.7 | 25.6 ± 3.9 | NS |
| HbA1c at start (%) | 7.5 ± 0.9 | 7.8 ± 0.9 | <0.001 |
| Time in range after 2 wk (%) | 63.9 ± 13.8 | 60.4 ± 12.3 | 0.022 |
| Time < 50 mg/dL after 2 wk (%) | 0.8 ± 1.3 | 0.7 ± 1.1 | NS |
| Time < 70 mg/dL after 2 wk (%) | 4.9 ± 4.0 | 4.0 ± 3.2 | 0.058 |
| Time > 180 mg/dL after 2 wk (%) | 30.3 ± 14.2 | 34.8 ± 13.1 | 0.005 |
| Time > 250 mg/dL after 2 wk (%) | 8.7 ± 7.8 | 9.8 ± 7.0 | NS |
| Mean glucose after 2 weeks (mg/dL) | 154 ± 24 | 163 ± 22 | <0.001 |
| Coefficient of variation after 2 wk (%) | 38.6 ± 6.2 | 38.2 ± 6.2 | NS |
| SD after 2 wk (mg/dL) | 59.9 ± 12.7 | 62.4 ± 13.8 | 0.077 |
| | No macrovascular complications (n = 477) | Any macrovascular complication (n = 25) | *P* value |
| Gender (female) (%) | 59% | 48% | NS |
| Age (y) | 41.3 ± 12.2 | 54.3 ± 11.0 | <0.001 |
| Diabetes duration (y) | 21.7 ± 11.3 | 31.8 ± 11.8 | <0.001 |
| Pump therapy (y) | 4.8 (0 - 31.7) | 5.0 (0 - 15.8) | NS |
| BMI at start (kg/m²) | 25.3 ± 3.7 | 25.9 ± 4.4 | NS |
| HbA1c at start (%) | 7.6 ± 0.9 | 8.2 ± 0.8 | 0.001 |
| Time in range after 2 wk (%) | 63.0 ± 13.3 | 57.8 ± 14.3 | NS |
| Time < 50 mg/dL after 2 wk (%) | 0.8 ± 1.2 | 0.3 ± 0.6 | NS |
| Time < 70 mg/dL after 2 wk (%) | 4.7 ± 3.8 | 2.7 ± 1.8 | 0.037 |
| Time > 180 mg/dL after 2 wk (%) | 31.5 ± 13.9 | 38.4 ± 14.7 | 0.056 |
| Time > 250 mg/dL after 2 wk (%) | 8.9 ± 7.5 | 12.6 ± 7.8 | 0.053 |
| Mean glucose after 2 wk (mg/dL) | 157 ± 24 | 168 ± 21 | 0.059 |
| Coefficient of variation after 2 wk (%) | 38.4 ± 6.3 | 38.2 ± 3.8 | NS |
| SD after 2 weeks (mg/dL) | 60.5 ± 13.2 | 64.1 ± 10.3 | NS |
| | No hospitalization for hypoglycemia or DKA in the last year (n = 447) | Hospitalization for hypoglycemia or DKA in the last year (n = 57) | *P* value |
| Gender (female) (%) | 59% | 57% | NS |
| Age (y) | 42.3 ± 12.4 | 41.8 ± 13.2 | NS |
| Diabetes duration (y) | 22.1 ± 11.6 | 22.9 ± 11.5 | NS |
| Pump therapy (y) | 5.0 (0 - 20.3) | 4.4 (0 - 31.7) | NS |
| BMI at start (kg/m²) | 25.4 ± 3.8 | 25.4 ± 3.8 | NS |
| HbA1c at start (%) | 7.6 ± 0.9 | 7.8 ± 0.9 | 0.031 |
| Time in range after 2 wk (%) | 63.6 ± 13.6 | 58.9 ± 11.3 | 0.022 |
| Time < 50 mg/dL after 2 wk (%) | 0.8 ± 1.1 | 0.6 ± 1.0 | NS |
| Time < 70 mg/dL after 2 wk (%) | 4.7 ± 3.8 | 3.7 ± 3.0 | 0.072 |
| Time > 180 mg/dL after 2 wk (%) | 30.8 ± 14.0 | 36.5 ± 12.5 | 0.007 |
| Time > 250 mg/dL after 2 wk (%) | 8.6 ± 7.6 | 10.8 ± 6.8 | 0.070 |
| Mean glucose after 2 wk (mg/dL) | 155 ± 25 | 164 ± 22 | 0.013 |
| Coefficient of variation after 2 weeks (%) | 38.4 ± 6.2 | 38.7 ± 5.4 | NS |
| SD after 2 wk (mg/dL) | 59.9 ± 13.4 | 63.5 ± 11.8 | 0.054 |

Data are expressed as mean ± SD, or as median (minimum-maximum), categorical data are expressed as number (n) with percentages (%). All *P* values < 0.1 are numerically reported.

Abbreviations: BMI, body mass index; DKA, diabetic ketoacidosis; NS, not significant.

**Acute complications**

Patients with hospitalizations because of hypoglycemia or ketoacidosis (n = 57 or 11%) had a higher HbA1c (7.8 ± 0.9 vs 7.6 ± 0.9%, $P$ = 0.031) and spent less TIR (58.9 ± 11.3 vs 63.6 ± 13.6%, $P$ = 0.022) compared with those who were not hospitalized for hypoglycemia or ketoacidosis. Age, diabetes duration, and BMI were similar (Table 2). Logistic regression analysis only identified TIR (OR = 0.97, $P$ = 0.021) as an independent risk factor for hospitalization from severe hypoglycemia or ketoacidosis, but not HbA1c, SD and CV, age, diabetes duration, or duration of pump therapy (Table 3).

## Discussion

Achieving near normoglycemia over a lifetime of diabetes while also trying to avoid hypoglycemia is a real challenge for people with T1D, but probably more feasible since the introduction of RT-CGM (2-10). Besides HbA1c, GV and times in different glucose ranges are an integral part of glucose homeostasis. Individualizing care on the basis of evolution of time in different ranges and GV could be an important aspect of precision medicine, certainly if high GV and/or low TIR would prove to independently contribute to diabetes complications.

A link between TIR and chronic complications in T1D was recently suggested by a new analysis of the Diabetes Control and Complications Trial, derived from 7-point SMBG data collected 1 day every 3 months. A 10% lower TIR increased the hazard ratio for retinopathy progression by 64% and that for microalbuminuria by 40% (26). Similar associations between microvascular complications and TIR were reported in a study in which 3262 Chinese individuals with T2D were evaluated for diabetic retinopathy and used a retrospective CGM device for 3 consecutive days (28). The same group demonstrated an association between carotid intima-media thickness and TIR in 2893 people with T2D using data from 3 days of blinded CGM. After adjustments for age, sex, BMI, diabetes duration, systolic blood pressure, lipids, smoking status, and the use of aspirin and statins, a TIR with the upper limit from 140-150 to 200 mg/dL was statistically significantly related to abnormal carotid intima-media thickness and diabetic retinopathy (32). In yet another study of the same group, including 6225 Chinese adults with T2D, a link between lower TIR (data based on 3 days of blinded CGM monitoring) and increased risk of all-cause and cardiovascular disease mortality was observed (33). However, the use of statins was very low, which might influence this relationship. In a Chinese study of 740 individuals with T2D, a higher

**Table 3.** Logistic regression analysis for chronic and acute complications

| Logistic regression analyses | | B | OR (95% CI) | $P$ value |
|---|---|---|---|---|
| Composite microvascular complications | Diabetes duration | 0.11 | 1.12 (1.09-1.15) | <0.001 |
| | TIR | -0.03 | 0.97 (0.95-0.99) | 0.005 |
| | age, duration of pump therapy, HbA1c, SD, and CV | | | NS |
| Nephropathy | Diabetes duration | 0.08 | 1.08 (1.05-1.12) | <0.001 |
| | HbA1c | 0.5 | 1.65 (1.12-2.45) | 0.012 |
| | Age, duration of pump therapy, TIR, SD, and CV | | | NS |
| Retinopathy | Diabetes duration | 0.13 | 1.14 (1.11-1.18) | <0.001 |
| | TIR | -0.04 | 0.96 (0.94-0.98) | <0.001 |
| | Age, duration of pump therapy, HbA1c, SD, and CV | | | NS |
| Neuropathy | Diabetes duration | 0.09 | 1.09 (1.06-1.13) | <0.001 |
| | SD | 0.03 | 1.03 (1.004-1.06) | 0.026 |
| | Age, duration of pump therapy, HbA1c, TIR, and CV | | | NS |
| Composite macrovascular disease | Age | 0.08 | 1.08 (1.03-1.14) | 0.003 |
| | HbA1c | 0.58 | 1.80 (1.02-3.14) | 0.044 |
| | Diabetes duration, duration of pump therapy, TIR, SD and CV | | | NS |
| Hospitalization for severe hypoglycemia or DKA | TIR | -0.03 | 0.97 (0.95-0.99) | 0.021 |
| | Age, diabetes duration, duration of pump therapy, HbA1c, SD, and CV | | | NS |

Abbreviations: CV, coefficient of variation; NS, not significant; TIR, time in range.

TIR tertile was independently associated with better peripheral nerve function (34). However, these were all cross-sectional studies and the glucose profiles obtained in 3 days in an in-hospital setting may not necessarily reflect those experienced by the patient in the longer term and at home. In the study by Yoo et al studying 866 subjects with T2D using 3 to 6 days of CGM, multiple logistic regression analysis revealed that the OR of having albuminuria was 0.94 per 10% increase in TIR of 70 to 180 mg/dL after adjusting for multiple factors including glycemic variability, but it failed to stay significant after further adjustment for HbA1c (27). In another study of 105 people with T2D wearing a CGM for two 6-day periods, an association between TIR and distal peripheral neuropathy was noted (30). Data in people with T1D are scarce, but in a small study of 26 persons with T1D with albuminuria who were switched from multiple daily injection therapy to sensor augmented pump therapy improved TIR over 1 year was associated with reduced albuminuria, independent of HbA1c, blood pressure, and BMI (31).

In our study, individuals spending >70% TIR had a lower prevalence of retinopathy, neuropathy, and hospitalizations of hypoglycemia or DKA compared with those spending ≤70% TIR. We did not observe a link between TIR and nephropathy in contrast to the study of Ranjan et al (31), maybe because of differences in baseline HbA1c (9.0% vs 7.6%), age (51 vs 42 years) and diabetes duration (32 vs 22 years), differences in duration of CGM monitoring, and in number of people with microalbuminuria/nephropathy and/or using renin-angiotensin-aldosterone system blockers (100% vs 10%).

More solid statistics such as logistic regression analyses point toward the importance of not only HbA1c and diabetes duration as independent risk markers for microvascular complications, but also to TIR and SD. For macrovascular complications, age and HbA1c were independent risk factors, but TIR, SD, and CV were not, probably because of the low number of people with macrovascular disease, although a trend was seen. However, for hospitalizations from hypoglycemia or ketoacidosis, TIR was the most important factor. Indeed, TIR offers more information than HbA1c to guide diabetes management by improving insulin titration, thereby reducing both time below and above range. Furthermore, acutely deteriorating TIR points toward an underlying problem (less attention, illness, purposively underdosing insulin) and poses an imminent risk. Thus, TIR and HbA1c provide different kinds of information that is most evident in the context of hypoglycemia and high glycemic variability.

Glycemic variability, certainly long-term GV, as assessed by HbA1c variability, has been linked to microvascular complications (15-17). In a study of 1706 adolescents, the standard deviation of HbA1c since onset of diabetes was associated with risk of retinopathy, early nephropathy, and cardiac autonomic neuropathy, in addition to established risk factors such as duration of diabetes, HbA1c, blood pressure, and lipids (15). A meta-analysis showed that HbA1c variability was positively associated with micro- and macrovascular complications and mortality independently of the HbA1c level (16). The underlying mechanisms for the observed associations between chronic complications and GV, irrespective of any sustained hyperglycemia, are not clear. By triggering oxidative stress, inducing inflammation, and evoking epigenetic changes short-lived hyperglycemic spikes may contribute to the development and progression of chronic complications (37).

HbA1c shows a strong association with incidence and progression of diabetic nephropathy despite that its accuracy can be compromised by variables affecting red blood cell survival and other factors. CGM technology, in comparison, has the potential to use full glucose profiles, enabling a more definitive understanding of glucose variability and its role in diabetic kidney disease. Glycemic variability may be a contributing factor in the development of diabetic kidney disease, but definite evidence is lacking (38).

A role for short-term GV in the development of chronic complications seems less obvious, with some studies reporting a link (18-20, 23) and others not (21, 22, 24), but short-term and long-term GV do not indicate the same thing. Long-term GV is based on visit-to-visit measurements of HbA1c and/or fasting plasma glucose and partially reflects ambient hyperglycemia, correlating with mean blood glucose concentrations or mean HbA1c, whereas short-term GV expresses the potential risk of episodes of either acute hypoglycemia and/or hyperglycemia. A small cross-sectional study in 35 subjects with T1D and 33 with T2D using CGM for 3 days observed a link between SD, continuous overlapping net glycemic action (2-hour intervals), and high blood glucose index and retinopathy, but its significance was lost in multivariate analysis (18). In another study of 37 people with T1D undergoing 3 days of CGM, early structural damage of neuroretina was related to GV (19). In a study including 30 T1D subjects wearing a CGM device for 5 days, increased GV was found to correlate with retinal thinning on optical coherence tomography imaging, but its significance was lost after Bonferroni correction for multiple comparisons (23). In another small cross-sectional study of 32 subjects with T1D being monitored with CGM for 12 to 14 days, those with microvascular complications (abnormal vibration perception

threshold, microalbuminuria, abnormal fundoscopy) had higher GV but comparable HbA1c compared with those without microvascular complications (20).

Short-term GV and hypoglycemia risk have not been consistently associated. In a group of 130 older subjects with T1D, those with a high CV (>36%) spent more time in hypoglycemia than those with low CV, despite the same HbA1c (29), but in another study glucose variability did not increase an individual's risk of hypoglycemia (20). In our study, although it is a bit counterintuitive, we also did not find a link between SD or CV and hypoglycemia risk. Furthermore, subjects with high glucose variability were not more at risk to be hospitalized for severe hypoglycemia and/or ketoacidosis. In our study, a higher SD was linked to neuropathy but CV did not appear to play an independent role with regard to the presence of acute or other chronic complications.

The association between short-term GV or TIR and diabetes complications is difficult to establish, however, with currently available data because of heterogeneity in study design, duration of diabetes of the cohort, and in the glucometrics used to evaluate GV. There are only a few studies in individuals with T1D, most studies had a cross-sectional design, were based on retrospective data, or were limited by using a snapshot of 4 to 7 SMBG measurements or by short time use of CGM, in contrast to the recommendation that CGM data from at least 10 to 14 days are needed (13, 33). Infrequent measurements might lead to erroneous data on TIR and GV.

We also investigated the evolution of TIR, CV, and SD over 24 months to assess how variable these parameters are. This and our previous study (8) indicate that CGM-derived glucometrics obtained from the first 2 weeks only show modest changes over a period of 24 months, suggesting that they remain quite stable in subjects treated with sensor-augmented pump therapy, who already had a quite good metabolic control at baseline. However, we cannot exclude that the greatest benefit already happened within the first 2 weeks.

Our study has some limitations. Although we collected CGM data over a period of 24 months, allowing us to draw conclusions on the evolution/stability of GV and TIR, the association between TIR and GV parameters vs complications was based on a cross-sectional analysis of CGM-derived glucometrics from the first 2 weeks of RT-CGM use after start of reimbursement, which does not allow for any assessment of the temporal/causal relationship. Long-term studies will be necessary to provide compelling evidence. However, this will take many years (at least 10 years) and be costly. It is also unethical to randomize subjects to high vs low TIR and/or GV. Nevertheless, our detailed data provide a strong hint toward the utility of TIR as a surrogate risk marker for acute and chronic complications. Based on these large observational data, we believe that an increase of time spent in range, which may become feasible for a larger population of people with T1D with the advent of hybrid closed loop and artificial pancreas systems, will result in a decrease in both acute and chronic complications.

Although we did assess the relationship between glucometrics and complications, we did not take into account confounding factors such as smoking, lipids, blood pressure, or use of cardioprotective agents and we also did not perform time-to-event analyses. These will be performed in future studies.

As per consensus, we used 70% TIR as a target but did not analyze whether these findings apply to high-risk individuals, in whom 50% TIR has been proposed (12). The incentive of lowering the target to 50% time in range is an elevated risk for hypoglycemia in a high-risk and/or older population (although evidence regarding TIR for older and/or high-risk individuals is lacking). However, because we analyzed a population using sensor-augmented pump therapy, the risk of hypoglycemia has been reduced significantly by this treatment modality, even though 47% had self-reported hypoglycemia unawareness. As shown in Figure 1, the Time < 70 mg/dL decreased from 3.8% in the first 2 weeks to 2.9% after 24 months, both achieving the target of Time < 70 mg/dL of <4%. In addition, the mean age of our population was 42.2 ± 12.5 years, and no frail person participated in this trial. For all these reasons, we did not calculate separate TIR target achievement (>50%) for a high-risk and/or older population.

The strengths of our study include the size and detailed characterization of our cohort of people with T1D and the use of RT-CGM, which allowed us to have a complete picture of glucose values in contrast to previous studies using either SMBG or only a couple of days of CGM. This increases the power of this study. Furthermore, we collected CGM data over a 2-year period, which is longer than most other studies collecting 6- or 12-month data, enabling us to interpret the long-term glucometric results.

In conclusion, in T1D subjects treated with sensor-augmented pump therapy, TIR was independently associated with the presence of composite microvascular complications, retinopathy, and with hospitalizations resulting from hypoglycemia or ketoacidosis. A higher SD was linked to neuropathy. TIR, SD, and CV did not show a link with macrovascular complications.

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***Author Contributions:*** A.E.M., M.V.E., S.C., and P.G. collected and analyzed the data, performed statistical analyses, and wrote the manuscript. A.E.M., M.V.E., and C.D.B. made figures and tables. C.D.B. designed the study, collected and analyzed and discussed the data, and wrote the manuscript. E.D., K.L., B.K., L.C., R.R., Y.T., C.V., F.N., and C.M. collected and discussed the data and edited the manuscript. A.E.M., M.V.E., S.C., P.G., and C.D.B. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

***Clinical Trial Registration:*** ClinicalTrials.gov (NCT02601729).

## Additional Information

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***Data Availability:*** Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

## Appendix: List of Reimbursement Study of Continuous Glucose Monitoring in Belgium investigators (in alphabetical order)

| | |
|---|---|
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