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# Nocturnal hypoglycemia is underdiagnosed in older people with insulin-treated type 2 diabetes: The HYPOAGE observational study

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## Abstract

**Background:** There is a lack of real-life data regarding the frequency and predictive factors of hypoglycemia in older patients with type 2 diabetes (T2D). This study aimed to determine the frequency and predictors of hypoglycemia in older patients with insulin-treated T2D.

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**Methods:** This prospective multicenter study included 155 insulin-treated T2D patients aged 75 years and older with  $\geq 2$  self-monitoring of blood glucose (SMBG) daily controls. Participants underwent a geriatric and diabetic assessment and received ambulatory blinded continuous glucose monitoring (CGM) for 28 consecutive days with FreeStyle Libre Pro<sup>®</sup> sensor. Study population ( $n = 141$ ) has  $>70\%$  CGM active time. Multivariable logistic regressions were used to identify factors associated with SMBG confirmed hypoglycemia ( $\geq 70$  mg/dL) and with nocturnal level 2 time below range (glucose concentration  $<54$  mg/dL during  $\geq 15$  consecutive min between 0.00 and 6.00 am).

**Results:** The mean age of the 141 analyzed patients was  $81.5 \pm 5.3$  years and 56.7% were male. The mean baseline HbA<sub>1c</sub> was  $7.9\% \pm 1.0\%$ . After geriatric assessment, 102 participants (72.3%) were considered as complex and 39 (27.7%) as healthy. The primary endpoint (confirmed SMBG  $<70$  mg/dL) occurred in 37.6% patients. In multivariable analysis, the risk of SMBG-confirmed hypoglycemia was positively associated with a longer duration of diabetes (OR (+1 year) = 1.04, (1.00–1.08),  $p = 0.04$ ) and glycemic variability assessed by CGM (CV %) (OR (+1%) = 1.12, [1.05–1.19],  $p = <0.001$ ). Ninety-two patients (65.2%) experienced nocturnal time in hypoglycemia (i.e.,  $<54$  mg/dL during  $\geq 15$  consecutive min between midnight and 6 a.m.). In multivariable analyses, cognitive impairment (OR: 9.31 [2.59–33.4]), heart failure (OR: 4.81 [1;48–15.6]), and depressive disorder (OR: 0.19 [0.06–0.53]) were associated with nocturnal time in hypoglycemia.

**Conclusion:** Nocturnal hypoglycemia is very common and largely underdiagnosed in older patients with insulin-treated T2D. CGM is a promising tool to better identify hypoglycemia and adapt diabetes management in this population.

**KEYWORDS**

basal insulin analogues, continuous glucose monitoring, glycemic control, hypoglycemia, older patients, type 2 diabetes

**INTRODUCTION**

Type 2 diabetes mellitus (T2D) is one of the most common and increasing chronic health conditions associated with aging, affecting up to 20% of adults aged  $\geq 75$  years.<sup>1,2</sup> Its management remains challenging in older patients because of the need to find a balance between prevention of chronic diabetic complications, complications related to acute hyperglycemia and the need to avoid the occurrence of hypoglycemia in this particularly high-risk population.<sup>3,4</sup> Hypoglycemia is independently associated with an increased risk of all-cause mortality as well as serious adverse events such as falls, seizure, dementia, and altered quality of life.<sup>5–7</sup> Its frequency varies widely according to the definition used and the study setting, ranging from 1% of self-reported severe hypoglycemia on questionnaire to 33.6% of non-severe

hypoglycemia diagnosed by self-monitoring of blood glucose (SMBG) in frail older patients.<sup>8,9</sup>

Although the detection and prevention of hypoglycemia is a priority issue for patients with diabetes, there is still a lack of real-life data regarding the frequency and predictive factors of hypoglycemia in older patients with T2D on insulin therapy. Frequency and risk factors for hypoglycemia were identified in studies that included either inpatients or outpatients able to monitor blood glucose.<sup>9–12</sup> Reliability of self-reported measures of hypoglycemia is contingent on patients' hypoglycemia awareness and willingness to report hypoglycemic events. Older subjects could have less neuroglycopenic manifestations and adrenergic manifestations of hypoglycemia resulting in absence or delayed recognition of hypoglycemia.<sup>13</sup> This remains a barrier to improve routine care, to reduce hypoglycemic episodes, and to improve quality of

life in this population. In accordance to recent international consensus recommendations, continuous glucose monitoring (CGM) technology allows to detect asymptomatic hypoglycemia by measuring the time below range (TBR) characterized by glucose concentrations between 54 and 69 mg/dL or <54 mg/dL for TBR level 1 and TBR level 2, respectively.<sup>14–16</sup> To date, there have been few studies that have used the CGM to measure the frequency of hypoglycemia in older subjects living with T2D, which also showed discrepant results. A small study performed in the nursing home with T2D patients reported a high prevalence of hypoglycemic event defined by glucose concentration <70 mg/dL (i.e., in 79% of patients).<sup>10</sup> In contrast, a larger study performed in Hong Kong demonstrated that in older patients with insulin-treated T2D, incremental frailty was associated with hyperglycemia rather than hypoglycemia, with a TBR level 1 in the recommended range (<1%).<sup>17</sup>

The aims of this analysis of the HYPOAGE multicenter study were to determine (i) the frequency of SMBG-confirmed hypoglycemia; (ii) the CGM metrics, with their distribution during the day; and (iii) the predictive factors of SMBG-confirmed hypoglycemia and nocturnal TBR level 2, including geriatric risk factors in insulin-treated T2D patients older than 75 years.

## METHODS

### Study design and procedures

The HYPOAGE trial ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03020264) identifier: NCT03020264) was a prospective multicenter study conducted between November 2017 and March 2020 in 6 French centers. The inclusion criteria were adults aged 75 and older, with T2D for at least 1 year and treated with insulin for at least 6 months, benefiting from at least two SMBG checks per day, carried out by the patient himself or a caregiver. Exclusion criteria are detailed in Data S1.

The study was designed in accordance with the declaration of Helsinki and approved by an independent ethical committee (CPP Ouest IV, ref 47/16). All study participants signed an informed written consent before enrolment.

At baseline, all participants underwent a geriatric assessment in addition to a medical diabetes evaluation. For blood glucose monitoring, participants or their caregivers were asked to perform and self-report on a paper-based diary at least two of three fasting SMBG value per day. They were encouraged to perform SMBG if they experienced hypoglycemic symptoms. In addition, a FreeStyle Libre Pro<sup>®</sup> (FSLP) Sensor (Abbott Diabetes Care, D-65205 Wiesbaden, Germany) was applied during site visits for two consecutive 14-day recording periods, for a total of 28 days. FSLP-CGM data remained blinded

### Key points

- Around a third of insulin-treated older patients with type 2 diabetes experienced hypoglycemia (<70 mg/dL) based on self-monitoring of blood glucose.
- When using continuous glucose monitoring (CGM), 65% of patients experienced nocturnal time below range (glucose concentration <54 mg/dL during ≥15 consecutive min).
- Cognitive impairment and heart failure were risk factors for nocturnal time below range.

### Why does this paper matter?

Preventing hypoglycemia is one of the major challenges in the management of older patients with insulin-treated type 2 diabetes patients, because hypoglycemia is associated with reduced quality of life and long-term complications. Nocturnal hypoglycemia is frequent and rarely diagnosed by self-monitoring of capillary glucose tests because many of these episodes do not waken the person who is affected. In contrast to HbA<sub>1c</sub>, the use of CGM is a powerful tool to detect a nocturnal time in hypoglycemia and to personalize patients' management especially for those with cognitive impairment.

for patients and physicians to avoid measurement bias in the estimation of the frequency of hypoglycemia and corrective actions beyond those recommended with SMBG results alone.

### Baseline data

The data of interest collected at inclusion were epidemiological and clinical data, medical history, diabetes complications, diabetes duration, current medications including antidiabetic drugs, and laboratory results including fasting plasma glucose, HbA<sub>1c</sub>, and renal function according to estimated glomerular filtration rate (CKD-EPI formulae). The comprehensive geriatric assessment (CGA) performed at baseline by a geriatrician assessed comorbidities, physical performances, functional status, cognition, major depressive disorder, and nutritional status (please see the complete definition in Data S1). This led to two different patient groups defined according to the American Diabetes Association (ADA) health status categories<sup>2</sup>:

“Healthy patients,” defined by the absence of vulnerability found in the geriatric assessment.

“Complex patients,” defined either by advanced diabetes complications, life-limiting comorbid illnesses, or any geriatric frailty such as neurocognitive disorders, undernutrition, major depressive disorder, physical or functional impairments. Definition of cognitive impairment was based on dichotomized scores. Standard cut-off points were defined according to current literature: cognitive impairment if MMSE <23 points or FAB <15 points.<sup>18,19</sup>

At the end of the evaluation, the geriatrician proposed an individualized care plan (nutritional support, physiotherapy, etc.) to the patient and the diabetologist.

## Endpoints

The primary endpoint was the percentage (with 95% confidence interval [95% CI]) of participants with at least one confirmed hypoglycemia (symptomatic or asymptomatic) defined by a SMBG < 70 mg/dL, according to the ADA definition,<sup>2</sup> during the 28 days of follow-up.

Secondary prespecified endpoints were: (i) the time spent in hypoglycemia (TBR level 2) determined if patients had at least two consecutive sensor readings at 15-min intervals below 54 mg/dL. TBR level 2 was calculated as the time interval between the first reading below the target glucose range (<54 mg/dL) and the first reading returning above the target glucose range ( $\geq$ 54 mg/dL); (ii) the frequency of nocturnal hypoglycemia (i.e. occurring between midnight and 6.00 a.m.); (iii) TBR level 2 during the night (midnight—6.00 a.m.), and (iv) subgroup analysis according to geriatric status (“healthy” vs. “complex”).

The relative recorded usage time (defined as the percentage of time with data collected, relative to device wear time) was analyzed. Adverse events and sensor-insertion or sensor-wear symptoms were monitored throughout the study.

## Statistical analysis

For baseline characteristics, quantitative variables were described as mean  $\pm$  SD if normally distributed and as median (25th–75th percentile) otherwise and were compared using Student *t*-test or Mann–Whitney *U*-test, respectively. Qualitative variables were described as number (%) and compared using Chi-squared test or Fisher's exact test. To assess the agreement between the SMBG and FSLP data, Bland Altman analysis was used by

studying the mean difference and constructing limits of agreement.

Patients were separated into groups based on the occurrence of SMBG-confirmed hypoglycemia and nocturnal TBR level 2 (sensor glucose below 54 mg/dL during  $\geq$ 15 consecutive min) on CGM (dichotomous variable). Univariate logistic regressions were used to identify factors associated with occurrence of SMBG-confirmed hypoglycemia or factors associated with nocturnal TBR level 2. All baseline variables with a *p*-value <0.20 in univariate analysis, and covariates of interest established from background knowledge were considered as candidates for entering the stepwise multivariable regression model. Variables significant with a *p*-value lower than 0.05 were retained for the final model. Given the important overall influence of age, T2D duration, and geriatric status on the occurrence of hypoglycemia, these three variables were forced in this final regression model independently of the significance of their association with hypoglycemia, as long as there was no independent variable collinearity.

Based on the frequency of hypoglycemia in older patients and on the frequency of frail older patients, we calculated the sample size with a precision between 5% and 10% for a 95%CI and a total of 250 patients was required.<sup>20,21</sup> *p*-values <0.05 were considered to indicate statistical significance. Adjustment for multiple comparisons was not performed due to the exploratory nature of the HYPOAGE study. All statistics were performed without imputation, with SAS version 9.4 software (SAS Institute, Cary, NC).

## RESULTS

### Participant characteristics

A total of 155 patients with T2D were included in the study across 6 centers. Two participants died during the evaluation period (not related to hypoglycemic events), three withdrew their consent, one was lost to follow-up and eight were excluded from the full analysis set due to insufficient (<70%) CGM data collected during the 28-day study period. Finally, 141 patients were analyzed with both available SMBG and CGM data (see the Flow Chart, Figure S1).

Participants (43% women) had a mean age of  $81.5 \pm 5.3$  years, a mean T2D duration of  $25.0 \pm 11.5$  years, and a mean HbA<sub>1c</sub> of  $7.9\% \pm 1.0\%$  (Table 1). As expected from the duration of diabetes and older age, the participants had numerous comorbidities including 60.9% cardiovascular disease, 50.0% chronic kidney disease, and 33.6% retinopathy. Regarding insulin therapy

TABLE 1 Baseline characteristics of the overall study population and according to geriatric status: healthy or complex.

	All population N = 141	Geriatric status		p-value
		Complex patients N = 102	Healthy patients N = 39	
Age (years)	81.5 ± 5.3	82.7 ± 5.4	78.3 ± 3.3	<0.001
Male	80 (56.7%)	55 (53.9%)	25 (64.1%)	0.27
BMI (kg/m <sup>2</sup> )	30.3 ± 6.1	30.7 ± 6.6	29.4 ± 4.7	0.17
Baseline HbA <sub>1c</sub> (%)	7.9 ± 1.0	8.0 ± 1.1	7.6 ± 0.5	0.02
Fasting plasma glucose (mg/dL)	154.5 ± 54.4	155.5 ± 55.2	152.2 ± 53.1	0.77
Mean SMBG measures per day per patient	2.6 ± 1.2	2.5 ± 1.3	2.8 ± 1.0	0.25
eGFR (mL/min/1.73m <sup>2</sup> )	60.8 ± 22.4	58.2 ± 23.2	67.3 ± 18.8	0.03
Comorbidities				
Arterial hypertension	128 (90.8%)	92 (90.2%)	36 (92.3%)	0.99
Dyslipidemia	106 (77.9%)	73 (74.5%)	33 (86.8%)	0.12
Macrovascular disease	84 (60.9%)	66 (66.7%)	18 (46.2%)	0.03
Heart failure	41 (30.1%)	37 (36.6%)	4 (11.4%)	0.005
Chronic kidney disease	69 (50.0%)	54 (54.0%)	15 (39.5%)	0.13
Retinopathy	41 (33.6%)	29 (34.1%)	12 (32.4%)	0.85
Peripheral neuropathy	68 (51.5%)	54 (57.4%)	14 (36.8%)	0.03
T2D duration (years)	25.0 ± 11.5	25.1 ± 12.1	24.7 ± 10.2	0.85
History of severe hypoglycemia	9 (6.4%)	7 (6.9%)	2 (5.1%)	0.99
Insulin use				
Insulin regimen: 1 injection/day	66 (46.8%)	47 (46.1%)	19 (48.7%)	0.96
Insulin regimen: 2 or 3 injections/day	30 (21.3%)	22 (21.6%)	8 (20.5%)	
Insulin regimen: basal-bolus or CSII	45 (31.9%)	33 (32.4%)	12 (30.8%)	
Self-inject insulin	71 (50.7%)	36 (35.3%)	35 (92.1%)	<0.001
Insulin injection by caregiver	7 (5.0%)	7 (6.9%)	0 (0.0%)	
Insulin injection by nurse	62 (44.3%)	59 (57.8%)	3 (7.9%)	
Non-insulin antidiabetics drugs				
Metformin	62 (44.0%)	35 (34.3%)	27 (69.2%)	<0.001
DPP4-inhibitors	32 (22.7%)	23 (22.5%)	9 (23.1%)	0.94
GLP-1 RAs	12 (8.5%)	10 (9.8%)	2 (5.1%)	0.51
SUs/repaglinide	22 (15.6%)	8 (7.8%)	14 (35.9%)	<0.001
Geriatric status				
ADL	5.5 (4.0; 6.0)	5.0 (3.0; 5.5)	6.0 (6.0; 6.0)	<0.001
Living in Nursing home	29 (20.6%)	29 (28.4%)	0 (0.00%)	<0.001
Frail defined by Fried criteria	71 (55.0%)	66 (73.3%)	5 (12.8%)	<0.001
CIRS-G score	12.4 ± 4.9	13.5 ± 4.6	9.5 ± 4.5	<0.001
Low physical performances	63 (49.2%)	57 (64.0%)	6 (15.4%)	<0.001
MMSE	23.4 ± 5.3	22.4 ± 5.6	25.8 ± 3.3	<0.001
Cognitive impairment	112 (81.8%)	87 (88.8%)	25 (64.1%)	<0.001
Risk of depression	65 (48.1%)	52 (54.2%)	13 (33.3%)	0.03
Risk or presence of malnutrition on MNA	61 (45.9%)	54 (56.3%)	7 (18.9%)	<0.001

(Continues)

TABLE 1 (Continued)

	All population N = 141	Geriatric status		p-value
		Complex patients N = 102	Healthy patients N = 39	
Hypoglycemic outcomes				
At least one SMBG-confirmed hypoglycemia (<70 mg/dL)	53 (37.6%)	33 (32.4%)	20 (51.3%)	<b>0.04</b>
Severe hypoglycemia	6 (4.3%)	5 (4.9%)	1 (2.6%)	0.99
Symptomatic hypoglycemia	18 (12.8%)	10 (9.8%)	8 (20.5%)	0.10

Note: Based on independent samples t-test or chi-square test as appropriate, with significant,  $p < 0.05$ ; Significant  $p$ -values are indicated in bold. Macrovascular disease = myocardial infarction, angina, stroke, and/or peripheral arterial disease. Chronic kidney disease = eGFR  $< 60$  mL/min/1.73 m<sup>2</sup>. Two different patients' groups were defined after geriatric assessment as in the American Diabetes Association-defined health status categories (2): (1) Healthy patients defined by the absence of vulnerability found in the geriatric assessment. (2) Complex patients, defined either by a patient with advanced diabetes complications, life-limiting comorbid illnesses, or a patient with any geriatric frailty as neurocognitive disorders, undernutrition, major depressive disorder, physical or functional impairments.

Abbreviations: ADL, activities of daily living; BMI, body mass index; CIRS-G score, cumulative illness rating scale-geriatric; DPP4i: dipeptidyl peptidase 4 inhibitors; eGFR: estimated glomerular filtration rate (using CKD-EPI formulae); FPG, fasting plasma glucose; GLP-1 RAs, glucagon-like peptide 1 receptor agonists; MMSE, mini mental state examination; MNA, Mini-nutritional assessment; SMBG, self-monitored blood glucose; SUs, sulfonylureas; T2D, type 2 diabetes.

regimen, 46.8% of patients were on a single insulin injection while 31.9% were on basal-bolus. Nine patients (6.4%) had a history of severe hypoglycemia. The mean MMSE score was 23.4 ( $\pm 5.3$ ) and the mean CIRS-G score was 12.6 ( $\pm 5.1$ ). Patients had good functional status (median ADL: 5.5 [4.0–6.0]). According to the geriatric assessment, 39 patients (27.7%) were described as “healthy” and 102 as “complex” patients (72.3%). Baseline characteristics of these two groups are shown on Table 1.

### Hypoglycemia and predictors of hypoglycemia assessed with self-systematic monitoring of blood glucose

Mean SMBG measures reported on paper-based diary was of 2.6 per patients per day. Fifty-three patients (37.6%, 95% CI [30.4–46.7]) experienced at least one hypoglycemia (SMBG  $< 70$  mg/dL) during the study period (median of 2.0 [1–4] hypoglycemia/patient). Hypoglycemias were self-reported to be symptomatic by 12.8% of the patients. There were six severe hypoglycemia requiring external assistance for recovery, of which two led to hospitalization (Table 1).

Of note, SMBG-confirmed hypoglycemia occurred more frequently in healthy vs complex older subjects (51.3% vs. 32.4%,  $p = 0.04$ ). The participants' characteristics according to the occurrence of hypoglycemic episodes are shown in Table S1, as well as a univariate analysis performed to identify predictive factors of hypoglycemia. In multivariable analysis, the risk of SMBG-confirmed

hypoglycemia was positively associated with a longer duration of diabetes (OR (+1 year) = 1.04, [1.00–1.08],  $p = 0.04$ ) and glycemic variability assessed by CGM (CV %) (OR (+1%) = 1.12, [1.05–1.19],  $p = < 0.001$ ) (Table 3).

### Time spent in hypoglycemia assessed with CGM

In addition to the conventional SMBG method, we used FSLP device in order to capture CGM data and detect asymptomatic hypoglycemia. The FSLP sensor was worn between 14 and 30 days, with a median at 28 days (26–28). The main reason for early discontinuation was sensor detachment (30 patients, 20%). Overall, the median percentage of sensor data obtained was 99.8% (99.6; 100.0). The concordance between SMBG and the corresponding CGM was determined by a Bland-Altman plot on 2977 paired-glycemic pre-breakfast measures and a correlation analysis (Figure S2). The average discrepancy between the two methods was of +5.21 mg/dL for the CGM with limits of agreement (–143.9; 133.5).

By analyzing the CGM data, the median coefficient of variation (CV) was of 33.7% (29.7; 39.8). Patients experienced a median of 2.9% (0.9; 8.4) of TBR level 1 (glucose concentration 54–69 mg/dL), while the median TBR level 2 (glucose concentration  $< 54$  mg/dL) was 0.7%. The median time in range (glucose concentration 70–180 mg/dL) was 70.4% (53.7; 81.4) showing a glycemic control within the recommended targets<sup>15</sup> (Table 2). The

**TABLE 2** Comparison of CGM metrics according to geriatric status.

	All population, N = 141	Geriatric status		p-value*
		Complex patients, N = 102	Healthy patients, N = 39	
Percentage of sensor data obtained	99.8 (99.6; 100.0)	99.8 (99.6; 100.0)	99.8 (99.6; 100.0)	0.66
Times in ranges				
Level 2 TAR (Glucose concentration >250 mg/dL)	3.5% (0.6; 13.0)	4.8% (0.5; 15.7)	1.7% (0.6; 6.4)	0.19
Level 1 TAR (Glucose concentration between 181–250 mg/dL)	19.8% (10.6; 26.7)	21.0% (11.4; 27.4)	16.6% (9.6; 23.9)	0.16
Time above range (Glucose concentration >180 mg/dL)	23.8% (12.0; 42.5)	26.1% (13.3; 44.4)	19.7% (10.6; 30.5)	0.15
Time in range (Glucose concentration between 70 and 180 mg/dL)	70.4% (53.7; 81.4)	66.5% (50.0; 80.9)	75.0% (61.9; 81.7)	0.16
Time below range (Glucose concentration <70 mg/dL)	2.9% (0.9; 8.4)	2.7% (0.9; 7.6)	3.8% (1.3; 9.6)	0.24
Level 1 TBR (Glucose concentration between 54 and 69 mg/dL)	2.1% (0.6; 4.7)	1.9% (0.4; 4.5)	2.6% (1.1; 6.9)	0.07
Level 2 TBR (Glucose concentration <54 mg/dL)	0.7% (0.1; 2.9)	0.6% (0.1; 3.0)	0.8% (0.0; 2.7)	0.79
Mean sensor glucose, mg/dL	149.0 (126.2; 174.8)	152.9 (126.4; 176.6)	137.9 (125.1; 159.3)	0.07
Glucose Management Indicator, %	6.9% (6.3; 7.5)	7.0% (6.3; 7.5)	6.6% (6.3; 7.1)	0.07
Glycemic variability (%CV), %	33.7% (29.7; 39.8)	32.7% (29.0; 40.0)	34.9% (31.5; 38.3)	0.30

Note: Data are median (25th–75th).

Abbreviations: CGM, continuous glucose monitor; CV, coefficient of variation; TAR, time above range; TBR, time below range; TIR, time in range.

\*Based on Wilcoxon test, with significant,  $p < 0.05$ .

**TABLE 3** Factors associated with at least one SMBG confirmed hypoglycemia (<70 mg/dL) in multivariable analysis.

Variable	OR	95% CI	p-value
Age (years)	0.95	(0.86; 1.05)	0.36
T2D duration (years)	1.04	(1.00; 1.08)	<b>0.04</b>
Geriatric status « Healthy »	0.60	(0.25; 1.45)	0.26
Glycemic variability (%CV)	1.12	(1.05; 1.19)	<b>&lt;0.001</b>

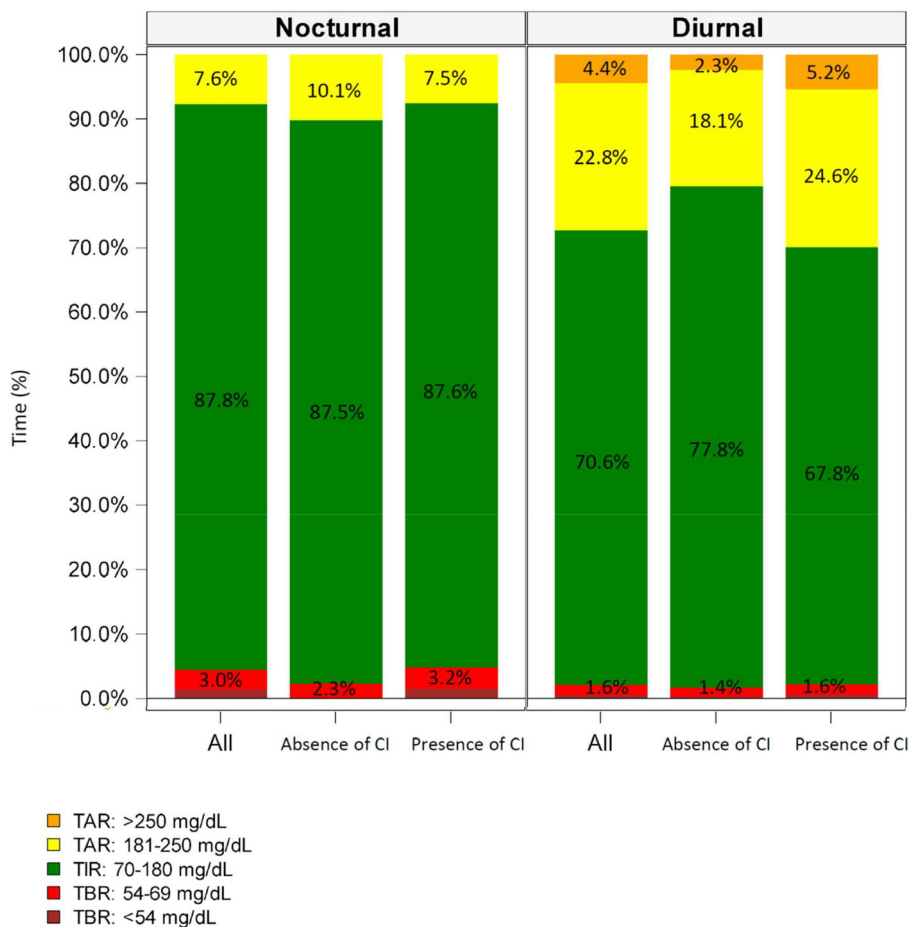
Note: All baseline variables with a  $p$ -value <0.20 in univariate analysis (glycemic variability, T2D duration, insulin regimen  $\geq 2$  injections, DDP4 inhibitors, anticoagulant therapy, and geriatric status) and covariates of interest established from background knowledge were considered as candidates for entering the model. Age and geriatric status were forced in this final regression model independently of the significance of their association with hypoglycemia; Significant  $p$ -values are indicated in bold. Abbreviations: 95% CI, 95% confidence interval; CV, coefficient of variation; OR, odds ratio calculated using multivariable logistic regression; SMBG, self-monitoring blood glucose; T2D, type 2 diabetes.

comparison of CGM metrics between healthy and complex subjects are shown in Table 2. Interestingly, Figure S3. clearly shows that in older patients, hypoglycemia detected by the FSLP occurred mainly during the night, with approximately 2/3 of patients (92 patients, 65.2%) who experienced a TBR between midnight and

6.00 a.m. Overall, the CGM metrics for the night and day-time periods for the whole population are detailed in Figure 1.

## Predictors of nocturnal TBR level 2 detected with CGM

Predictors associated with nocturnal TBR level 2 in univariate analysis are shown in Table S2. In multivariable analysis, factors positively associated with nocturnal TBR level 2 were the presence of at least one SMBG-confirmed hypoglycemia during the whole day (OR = 11.6 [3.1–43.0],  $p < 0.001$ ), cognitive impairment (OR = 24.0 [4.3–133.9],  $p < 0.001$ ) and heart failure (OR = 5.74 [1.53–21.5],  $p < 0.01$ ). Conversely, history of major depressive disorder (OR = 0.18 [0.06–0.56],  $p = 0.003$ ) was negatively associated with nocturnal TBR level 2 (Table 4). The impact of cognitive impairment on CGM metrics is detailed in Figure 1 and Table S3. Patients with cognitive impairment spent on average 1.5 h less in TIR ( $p = 0.04$ ), during the day-time period compared to those without cognitive impairment, with also a non-significant trend for a longer TBR.



**FIGURE 1** CGM metrics for all the population and according to the presence of cognitive impairment (CI) is shown during night-time (between midnight and 6.00 a.m.) and day-time (between 6.00 a.m. and midnight). TAR, time above range; TBR, time below range; TIR, time in range.

**TABLE 4** Factors associated with nocturnal TBR level 2 assessed by FSLP in multivariable analysis.

Variable	OR	95% CI	p-value
Age (years)	0.94	(0.85; 1.05)	0.32
Male	0.39	(0.14; 1.12)	0.08
HbA <sub>1c</sub> (increase of 1%)	0.84	(0.51; 1.40)	0.52
Heart failure	<b>4.81</b>	<b>(1.48; 15.6)</b>	<b>0.009</b>
Cognitive impairment	<b>9.31</b>	<b>(2.59; 33.4)</b>	<b>0.001</b>
Risk of depression	<b>0.19</b>	<b>(0.06; 0.53)</b>	<b>0.001</b>

*Note:* Nocturnal TBR level 2 is defined by glucose concentration <54 mg/dL measured by continuous glucose monitoring (FSLP) on at least 2 consecutive datapoints (i.e., greater than 15 min duration), between midnight and 6.00 a.m. *p*-values <0.05 are indicated in bold. All baseline variables with a *p*-value <0.20 in univariate analysis (arterial hypertension, heart failure, eGFR, insulin regimen  $\geq 2$  injections, cognitive impairment, risk of depression), and covariates of interest established from background knowledge were considered as candidates for entering the stepwise regression model. Variables significant with a *p*-value lower than 0.05 were retained for the final model. Given the important overall influence of age, sex and HbA<sub>1c</sub> on the occurrence of hypoglycemia, these three variables were forced in this final regression model independently of the significance of their association with hypoglycemia.

Abbreviations: CI, 95% confidence interval; FSLP, Free Style Libre Pro<sup>®</sup>; OR, odds ratio calculated using multivariable logistic regression; SMBG, self-monitoring blood glucose.

## DISCUSSION

HYPOAGE is one of the largest prospective studies specifically designed to determine the frequency and the predictors of hypoglycemia detected either by SBMG or by FSLP-CGM in older patients with insulin-treated T2D. Although 37.6% of patients experienced at least one confirmed hypoglycemia (SMBG < 70 mg/dL) during the 28 days of follow up, 65.2% experienced nocturnal time spent in hypoglycemia by using the FSLP-CGM. In addition, TBR in HYPOAGE participants, especially during the night, was above the recommended consensus target for older subjects (<1% for TBR level 2). This demonstrates that most of hypoglycemic episodes in older people are asymptomatic, especially during the night.

One important finding of our study was the high prevalence of confirmed hypoglycemia and the high nocturnal TBR percentage, even though included patients had HbA<sub>1c</sub> values in the recommended range for older people and were regularly followed by geriatrician and diabetologist.<sup>2</sup> The fact that HbA<sub>1c</sub> was higher in complex compared with healthy subjects confirms that physicians have considered the risk of hypoglycemia and were not too aggressive in blood glucose management. It is

important to note that HbA<sub>1C</sub> is neither a predictor of SMBG-confirmed hypoglycemia nor of nocturnal TBR level 2 in multivariable analyses. This finding is in accordance with the results from the HARE study, also conducted in older patients (mean age: 74 years) with T2D, in which HbA<sub>1C</sub> was also not associated with TBR.<sup>17</sup> Similar results were also observed in older patients with T1D in the WISDM study, in which hypoglycemia unawareness, but not HbA<sub>1C</sub>, was associated with TBR.<sup>22</sup>

Beyond HbA<sub>1C</sub>, CGM-derived CV, a marker of glucose variability, appears to be an important risk factor for hypoglycemia in older population. Indeed, it is the only parameter, along with the duration of diabetes, which remains significantly associated with SMBG-confirmed hypoglycemia in our study. Interestingly, this observation confirms previous data observed in older adults with type 1 diabetes (T1D) in whom CGM-derived CV better predict the risk of hypoglycemia than HbA<sub>1C</sub>.<sup>23</sup>

The frequency of hypoglycemia in our study was concordant or even slightly higher than in previously published studies in older patients with T2D, including recent studies with CGM.<sup>9,10,17,24</sup> There are two potential explanations for this observation. First, the HYPOAGE population was older and under insulin therapy. Older age, comorbidities, and insulin therapy are well-established risk factors of hypoglycemia.<sup>9,11,25</sup> Second, the study period was longer than those in previous studies (i.e., 28 days vs. 5.5 days in the HARE study for instance<sup>17</sup>). It has been reported that the detection of hypoglycemic episodes increases with the duration of monitoring as in seizure or paroxysmal atrial fibrillation monitoring.<sup>26,27</sup> Thus, the results observed in HYPOAGE population are more similar to those observed in patients with T1D, with for instance a TBR level 1 of 5.0% (72 min) in the WISDM study.<sup>22</sup>

By using FSLP, we were able to have a precise idea of the cumulative duration of TBR in older patients with insulin-treated T2D. HYPOAGE participants spent on average 2.9% of 24 h-day (40 min) with glucose values <70 mg/dL (TBR 1 and 2). These results fell far short of the TBR targets of the Recommendations From the International Consensus on Time in Range.<sup>15</sup> Glycemic targets for high-risk and/or older patients are TBR <1% of readings or <15 min/day.<sup>15</sup> Our study clearly demonstrates that the majority of hypoglycemic events occurs during the night, at a time when SMBG is not performed by patients or caregivers. The occurrence of nocturnal hypoglycemic events is associated with reduced quality of life and long-term complications, as for day-time hypoglycemic episodes.<sup>28–31</sup> These nocturnal hypoglycemic events had not previously been recognized in routine care because nocturnal SMBG are not regularly performed and many of these episodes do not waken the person

who is affected.<sup>28,32</sup> Moreover, it has been previously reported that hypoglycemia unawareness is more marked in older compared with middle-aged patients with T2D,<sup>33</sup> putting them at particular risk of severe hypoglycemia. As HbA<sub>1C</sub> at baseline was in the recommended range, our results suggest that other markers of glycemic control, especially CGM metrics (TBR, CV) are needed to better assess the risk of hypoglycemia in this older population in routine clinical practice. The use of CGM in practice would help healthcare providers to reinforce patient follow-up and personalized monitoring of their blood glucose profiles. It is also a powerful tool to personalize patients' treatments such as, for instance, the use of DPP-4 inhibitors<sup>34</sup> or new basal insulin analogues which demonstrated lower nocturnal hypoglycemia incidence in patients above 75 years old.<sup>35</sup>

One of the objectives of the HYPOAGE study was to identify risk factors for hypoglycemia in older subjects. We were somewhat surprised to observe that markers of frailty were not significantly associated with the occurrence of hypoglycemia. There was no difference in nocturnal TBR between “healthy” and “complex” older patients. In contrast, “complex” patients had a greater time spent in hyperglycemia (>250 mg/dL), suggesting less aggressive glycemic management, in line with the current guidelines.<sup>2</sup> Our data are fully consistent with those of the HARE study, in which markers of frailty were associated with time above range (TAR) and not TBR.<sup>17</sup>

When we focused on the independent risk factors associated with the occurrence of nocturnal TBR, a significant relationship was found with the occurrence of hypoglycemia and/or severe hypoglycemia during the day-time. This finding is clinically relevant as the detection of nocturnal hypoglycemia by CGM would allow the identification of patients at risk of severe hypoglycemia, beyond the current use of SMBG and HbA<sub>1C</sub>, and thus allow the implementation of appropriate preventive measures. Only a randomized controlled trial could definitively validate this strategy.

Our findings highlight the positive association between cognitive impairment, and nocturnal TBR level 2. T2D increases the risk of cognitive impairment potentially through Alzheimer's disease-related and vascular disease mechanisms.<sup>36</sup> Previous studies provide evidence for a higher risk of severe hypoglycemic event in patients with reduced cognitive function, but none detailed CGM metrics and nocturnal TBR.<sup>37,38</sup> A possible explanation for our results might be that cognitive impairment, especially executive dysfunction may delay recognition of the symptoms of hypoglycemia and interfere with a patient's ability to prevent hypoglycemia or to respond with corrective measures due to compromised self-management

abilities.<sup>37,39</sup> Furthermore, patients with cognitive impairment may also be more susceptible to severe hypoglycemia, leading to a bidirectional relationship between severe hypoglycemia, T2D, and cognitive impairment.<sup>37,40</sup>

Regarding the positive association between heart failure and nocturnal hypoglycemia observed in HYPOAGE, there is accumulating evidence that severe hypoglycemia is related to both an increased risk of cardiovascular events and incident heart failure, even though mechanisms underlying this association remain unclear.<sup>41–44</sup>

At last, major depressive disorder and T2D duration were negatively associated with nocturnal TBR in our study, which is discordant with some previously published data. The association between major depressive disorder and hypoglycemic events is bidirectional.<sup>45,46</sup> Our results might be explained by the collaborative care intervention often initiated for patients with depression and long-standing diabetes and the potential implementation of a reinforced monitoring of glycemic control.<sup>47</sup> Conversely, it should be noted that we did not find an increased TAR in patients with major depressive disorder (data not shown).

Our study has some limitations that should be emphasized. First, the use of TBR level 2 instead of level 1 can be discussed. In our population, the concordance of glucose levels between the blood and interstitial fluids in patients revealed a +5.21 mg/dL difference between the two measures, even after considering the 15 min required for the diffusion of glucose from the capillaries to the subcutaneous interstitial space (Figure S2). To avoid an overestimation of hypoglycemia, we chose the minimum threshold. Furthermore, 54 mg/dL is the threshold at which neuroglycopenic symptoms begin to occur and requires immediate action to resolve the hypoglycemic event.<sup>48</sup> Second, some of the unobserved differences between healthy and complex patients might be due to the relatively small sample size, especially with the small numbers of healthy patients. The sample size was smaller than expected due to the interruption of recruitment during the COVID-19 pandemic. Another limitation of our study is that we did not accurately identify patients with hypoglycemia unawareness at inclusion, although this is a factor known to be associated with risk of severe hypoglycemia.<sup>49,50</sup> Finally, because of the exploratory approach of our study regarding the predictors of nocturnal TBR, the alpha risk was set to 5% for each test without considering multiple testing. In addition, the relatively small size of our cohort limited the statistical power. Consequently, replication cohorts should be analyzed to assess the reproducibility of our results.

HYPOAGE study has several strengths. To our knowledge, it is the first study that combines complete baseline

geriatric assessment with an individual care-plan and prospective blinded CGM monitoring in older outpatients whether healthy or complex, living at home or in nursing homes. The population under study may be considered representative of the older French patients with T2D regarding the multicenter study design and the patients' geriatric characteristics.<sup>51</sup> The data quality was high for both SMBG and CGM, with a mean capture time above the recommended percentage of time of active CGM (>70% during a 28 day period).<sup>15</sup> Two patients experienced adverse events as skin reactions to the sensor which is concordant with a previous study.<sup>52</sup> Only 5 patients did not wear the CGM up to the recommended 14 days.<sup>15</sup> This study confirmed the efficacy and acceptability of the device in older and frail patients.

In conclusion, our study reports a high prevalence of hypoglycemia in older patients with insulin-treated T2D, despite an HbA<sub>1c</sub> at baseline in the recommended range. During the 28-days study period, a third of patients experienced hypoglycemia based on SMBG and two thirds experienced TBR >15 min during night-time, independently of geriatric status and frailty. Risk factors of nocturnal TBR were cognitive impairment, heart failure, and a SMBG < 70 mg/dL during the day. Therefore, new tools in addition to HbA<sub>1c</sub> are required for this population to reduce hypoglycemic events and TBR. The clinical benefit and modalities (TBR, glycemic variability) of using CGM derived parameters in older patients with T2D should be further confirmed in future randomized studies.

## AUTHOR CONTRIBUTIONS

Bertrand Cariou is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Bertrand Cariou, Anne-Sophie Boureau, and Laure de Decker designed the study. Béatrice Guyomarch performed the statistical analyses. Anne-Sophie Boureau, Pierre Gourdy, Ingrid Allix, Cédric Annweiler, Nathalie Cervantes, Guillaume Chapelet, Isabelle Delabrière, Sophie Guyonnet, Rachel Litke, Marc Paccalin, Alfred Penfornis, Pierre-Jean Saulnier, Matthieu Wargny, Samy Hadjadj, Laure de Decker and Bertrand Cariou recruited and followed study patients. Anne-Sophie Boureau and Bertrand Cariou drafted the first version of the manuscript. All co-authors critically reviewed and edited the manuscript. We are indebted to Marielle Joliveau, Pamela Hublain, and Carole Agasse for their assistance in patient screening and enrolment.

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## CONFLICT OF INTEREST

Bertrand Cariou reports grants and personal fees from Amgen, Regeneron, and Sanofi, and personal fees from AstraZeneca, Bristol Myers Squibb, Gilead, Eli Lilly and Company, LVL-Air Liquide, Novartis, Novo Nordisk, Regeneron, and Sanofi.

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The study was funded by Sanofi but Sanofi had no role in the design, methods, recruitment, data collections, nor the analysis and preparation of the paper.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

**Data S1.** Supplementary methods details.

**Figure S1.** Study flow diagram.

**Figure S2.** Concordance between the two measurements methods by Bland Altman Plot: Differences between pre-breakfast self-monitoring blood-glucose (SMBG) and continuous glucose monitoring (CGM) versus the mean of the two measurements, based on 2977 paired glycemic measures. The average discrepancy between the two methods was of +5.21 mg/dL for the CGM, limits of agreement (−143.9; 133.5).

**Figure S3.** Frequency distribution of hypoglycemia event over the 24-day across the whole analyzed population.

**Table S1.** Factors associated with at least one hypoglycemia (<70 mg/dL) on 24 h-hour daytime self-monitoring, in univariate analysis. Baseline characteristics of the overall study population, and according to the occurrence of hypoglycemia on self-monitoring blood-glucose <70 mg/dL.

**Table S2.** Predictive factors associated with nocturnal time in hypoglycemia in univariate analysis.

**Table S3.** Comparison of time in ranges (in hour) according to the presence of cognitive impairment.

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## Editor's Note

This is yet another study, one of many published in JAGS and other journals of older people in several different countries who are over-treated for diabetes and suffer adverse consequences. In this study or 155 diabetics with a mean age of 81 recruited from six centers in France, almost two-thirds had nocturnal hypoglycemia (defined as <54mg/dL) for greater than 15 minutes on at least one occasion. Two-thirds of these people were taking insulin one-three times per day. Hypoglycemia was not surprisingly associated with cognitive impairment and heart failure.

When are clinicians going to stop harming older diabetics by overtreating them? Perhaps this study will motivate more clinicians to think like I and many colleagues do—the primary goals of diabetes management, especially in older people with multimorbidity are: (1) to prevent harm from hypoglycemia; and (2) to prevent complications of symptomatic polyuria, such as urinary frequency, incontinence, and volume depletion that can lead to a hyperosmolar state. The latter complications do not occur unless the blood sugar is frequently above 250–300 mg/dL. Moreover, the time to benefit from tight blood sugar control is longer than the average life expectancy in this population.

If I had any more hair, I would pull it out! Please join me in a campaign to eliminate hypoglycemia as one of the most common and preventable iatrogenic conditions we see too often in our older diabetic population.

**-Joseph G. Ouslander, MD**