Day-to-day variability of fasting self-measured blood glucose associates with risk of hypoglycaemia in adults with type 1 and type 2 diabetes

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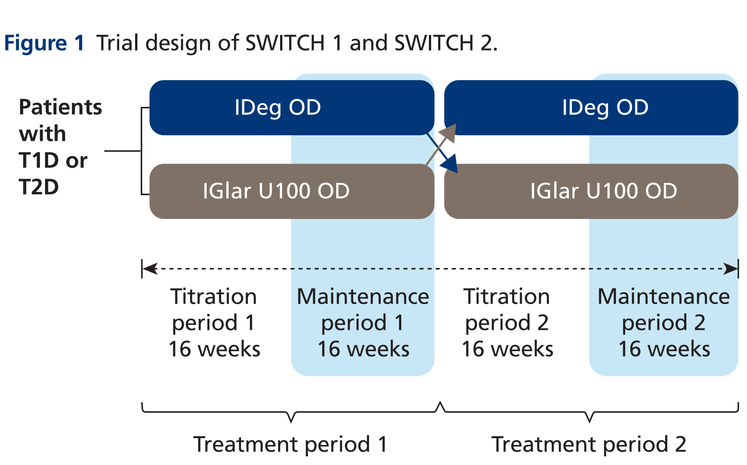
Background

- The relationship between glycaemic variability and the risk of hypoglycaemia has not yet been well established.
- Hypoglycaemia has significant negative effects on patient health and quality of life,[1] and is a major concern to both patients and physicians.[2]
- Day-to-day variability can be assessed as the variation in glucose level at a given time-point over a series of days, as a measure of glycaemic variability.
- This *post hoc* analysis aimed to investigate the association between the day-to-day variability of fasting self-measured blood glucose (SMBG) values and risk of hypoglycaemia in patients with type 1 (T1D) or type 2 diabetes (T2D).

Methods

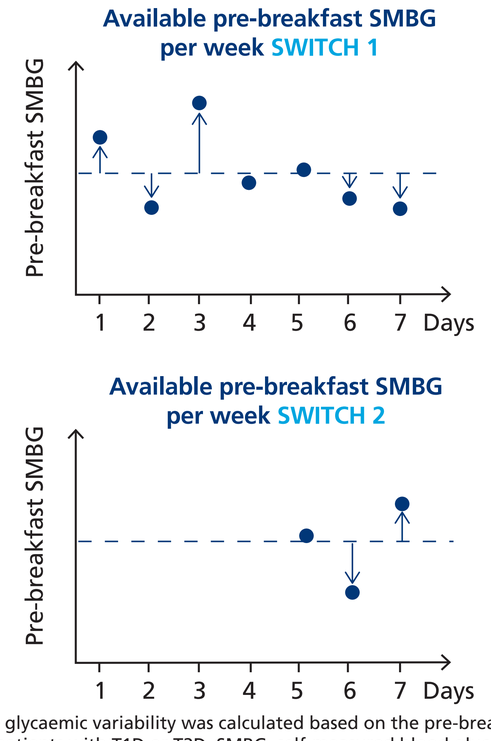
- A *post hoc* analysis was performed to investigate the association between day-to-day variability of fasting SMBG with hypoglycaemic rates using data from two 64-week, randomised, multicentre, controlled, double-blind, treat-to-target, two-period crossover trials with insulin degludec (IDeg) once daily (OD) and insulin glargine 100 units/mL (IGlar U100) OD. One trial comprised adult patients with T1D (SWITCH 1 [NCT02034513], n=501), the other insulin-experienced patients with T2D (SWITCH 2 [NCT02030600], n=721).
- The trial design used for both SWITCH 1 and SWITCH 2 is shown in Figure 1. In both studies, the 64-week trial period consisted of two 32-week treatment periods, one on each of the comparator basal insulins. Each treatment period consisted of a 16-week titration period (Weeks 1–16 and Weeks 32–48) and a 16-week maintenance period (Weeks 16–32 and Weeks 48–64). The fasting pre-breakfast SMBG values in this *post hoc* analysis were retrieved from the two 16-week maintenance periods of both treatments (Weeks 16–32 and Weeks 48–64) in both trials (Figure 1). The data were pooled for the two treatment arms, but analysed separately for T1D and T2D.
- A schematic illustration of the data collection for day-to-day glycaemic variability of fasting SMBG values is shown in Figure 2.

Figure 1 Trial design of SWITCH 1 and SWITCH 2.



In SWITCH 1, insulin aspart was administered 2- to 4-times a day as part of a full basal–bolus regimen.
In SWITCH 2, all pre-trial OADs (any combination of metformin, dipeptidyl peptidase-4 inhibitor, alpha-glucosidase inhibitor, thiazolidinediones, and sodium glucose cotransporter-2 inhibitor) were continued at the pre-trial dose throughout the trial.
IDeg, insulin degludec; IGlar U100, insulin glargine 100 units/mL; OAD, oral antidiabetic drug; OD, once daily; RCT, randomised controlled trial; T1D, type 1 diabetes; T2D, type 2 diabetes; TTT, treat-to-target.

Figure 2 Schematic illustration of the data used to assess the day-to-day glycaemic variability of fasting SMBG values in SWITCH 1 and SWITCH 2.



Day-to-day glycaemic variability was calculated based on the pre-breakfast SMBG values for patients with T1D or T2D. SMBG, self-measured blood glucose; T1D, type 1 diabetes; T2D, type 2 diabetes.

- For patients with T1D, the fasting pre-breakfast SMBG measurements were used for weekly titration of basal insulin and also daily glycaemic control. For patients with T2D, three fasting pre-breakfast SMBG measurements were used for weekly titration of basal insulin. Therefore, up to seven SMBG measurements were available for patients with T1D and up to three SMBG measurements were available for patients with T2D.
- The available pre-breakfast SMBG values in each week of the 16-week maintenance period were used to determine a log-transformed weekly standard deviation for each patient and treatment combination; the day-to-day variability (for each patient and treatment combination) was defined as the geometric mean value of these data. The day-to-day variability data were then grouped into equally sized tertiles for the analyses. This method of grouping patients by tertiles was based on a previous study.[3]
- The number of hypoglycaemic events was analysed using the pre-specified primary model[4,5] with the fasting SMBG as an additional factor.
- Hypoglycaemic episodes were defined as:
  - Overall symptomatic: severe or blood glucose (BG)-confirmed (<3.1 mmol/L [56 mg/dL]) symptomatic hypoglycaemia.
  - Nocturnal symptomatic: severe or BG-confirmed (<3.1 mmol/L [56 mg/dL]) symptomatic hypoglycaemia, 00:01–05:59 (both inclusive).
  - Severe: hypoglycaemic events requiring third-party assistance (based on the ADA definition[6]) and confirmed by a blinded independent adjudication committee.

Table 1 Baseline characteristics in SWITCH 1 and SWITCH 2 trials.

Characteristic	SWITCH 1	SWITCH 2
n (%)	501 (100.0%)	720 (100.0%)*
Male (%)	269 (53.7%)	382 (53.1%)
Country of residence, n (%)		
United States	458 (91.4%)	720 (100.0%)
Poland	43 (8.6%)	0 (0.0%)
Race, n (%)		
White	462 (92.2%)	578 (80.3%)
Black	32 (6.4%)	106 (14.7%)
Asian	2 (0.4%)	22 (3.1%)
Other	5 (1.0%)	14 (1.9%)
Ethnicity: Hispanic or Latino, n (%)	51 (10.2%)	262 (36.4%)
Age, years	45.9 (14.2)	61.4 (10.5)
Body weight, kg	80.5 (17.4)	91.7 (19.5)
BMI, kg/m^2	27.5 (4.8)	32.2 (5.6)
Duration of diabetes, years	23.4 (13.4)	14.1 (8.1)
HbA_{1c}, %	7.6 (1.0)	7.6 (1.1)
HbA_{1c}, mmol/mol	59.3 (11.1)	59.4 (11.9)
FPG, mmol/L	9.4 (4.4)	7.6 (2.9)
FPG, mg/dL	169.8 (79.6)	137.0 (52.6)

*One patient was excluded because of an unsigned casebook.
Data are mean ± standard deviation unless otherwise stated.
BMI, body mass index; FPG, fasting plasma glucose.

Table 2 Effect of day-to-day fasting SMBG variability on hypoglycaemia by tertiles of low, medium and high variability in SWITCH 1 and SWITCH 2.

Hypoglycaemia	Variability tertiles	SWITCH 1 Estimate [95% CI]	SWITCH 1 *p*-value	SWITCH 2 Estimate [95% CI]	SWITCH 2 *p*-value
Overall	Low	0.71 [0.62; 0.81]		0.32 [0.23; 0.45]	
	Medium	Reference	*p*<0.0001	Reference	*p*<0.0001
	High	1.17 [1.05; 1.29]		2.25 [1.81; 2.81]	
Nocturnal	Low	0.40 [0.30; 0.54]		0.27 [0.15; 0.48]	
	Medium	Reference	*p*<0.0001	Reference	*p*<0.0001
	High	1.31 [1.04; 1.64]		2.15 [1.55; 2.98]	
Severe	Low	1.16 [0.68; 1.98]		0.74 [0.23; 2.35]	
	Medium	Reference	*p*<0.0001	Reference	*p*=0.1835
	High	2.52 [1.60; 3.96]		1.85 [0.74; 4.61]	

CI, confidence interval; SMBG, self-measured blood glucose.

Results

- Baseline characteristics of the SWITCH 1 and SWITCH 2 study cohorts are shown in Table 1.
- Day-to-day glycaemic variability was significantly associated with the rates of overall and nocturnal hypoglycaemia in patients with T1D or T2D (Table 2, Figures 3 and 4).
- In patients with T1D, this significant association was also observed for severe hypoglycaemia, whereas in patients with T2D, no significant difference was found across tertiles for severe hypoglycaemia, likely due to the low number of severe hypoglycaemic events (Table 2, Figures 3 and 4).

Figure 3 Number of hypoglycaemic events by tertiles of low, medium and high day-to-day glycaemic variability in patients with type 1 diabetes (SWITCH 1).

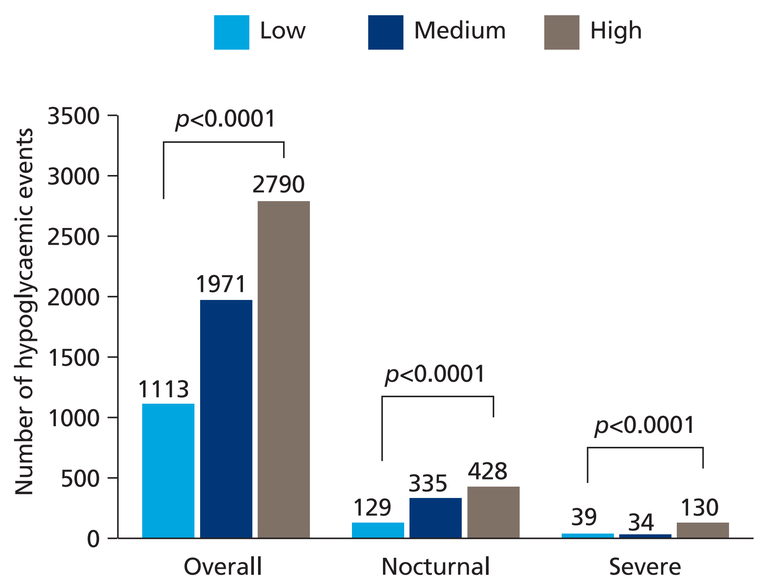
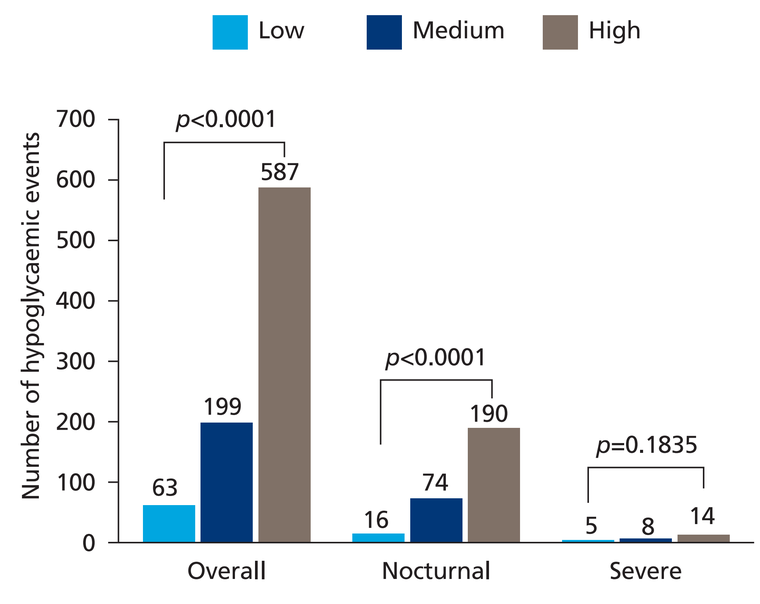


Figure 4 Number of hypoglycaemic events by tertiles of low, medium and high day-to-day glycaemic variability in insulin-experienced patients with type 2 diabetes (SWITCH 2).



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Conclusions

- Day-to-day variability in pre-breakfast SMBG values was significantly related to the risk of overall and nocturnal symptomatic hypoglycaemia in patients with T1D or T2D, and severe hypoglycaemia in patients with T1D.
- Treatment choices that reduce day-to-day glycaemic variability may contribute to a reduction in the risk of hypoglycaemia.

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