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Day-to-day Fasting Self-monitored Blood Glucose Variability is Associated with Risk of Hypoglycaemia in Insulin-Treated Patients with Type 1 and Type 2 Diabetes: A *Post Hoc* Analysis of the SWITCH Trials

Short running title: Fasting SMBG variability and hypoglycaemia

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Abstract

Aims

To investigate the association between day-to-day fasting self-monitored blood glucose (SMBG) variability and risk of hypoglycaemia in type 1 (T1D) and type 2 diabetes (T2D), and compare day-to-day fasting SMBG variability between treatments with insulin degludec (degludec) and insulin glargine 100 units/mL (glargine U100).

Materials and methods

Data were retrieved from two double-blind, randomised, treat-to-target, two-period (32 weeks each) crossover trials of degludec versus glargine U100 in T1D (SWITCH 1, n=501) and T2D (SWITCH 2, n=720). Available fasting SMBGs were used to determine the standard deviation (SD) of day-to-day fasting SMBG variability for each patient and treatment combination. The association between day-to-day fasting SMBG variability and overall symptomatic, nocturnal symptomatic and severe hypoglycaemia was analysed for the pooled population using linear regression, and with fasting SMBG variability included as a three-level factor defined by population tertiles. Finally, day-to-day fasting SMBG variability was compared between treatments.

Results

Linear regression showed that day-to-day fasting SMBG variability was significantly associated with overall symptomatic, nocturnal symptomatic, and severe hypoglycaemia risk in T1D and T2D (p<0.05). Day-to-day fasting SMBG variability was significantly associated (p<0.01) with all categories of hypoglycaemia risk, except for severe hypoglycaemia in T2D when analysed within tertiles. Degludec was associated with 4% lower day-to-day fasting SMBG variability than glargine U100 in T1D (p=0.0082) and 10% lower in T2D (p<0.0001).

Conclusions

Higher day-to-day fasting SMBG variability is associated with an increased risk of overall symptomatic, nocturnal symptomatic and severe hypoglycaemia. Degludec has significantly lower day-to-day fasting SMBG variability versus glargine U100.

ClinicalTrials.gov numbers: NCT02034513 (SWITCH 1) and NCT02030600 (SWITCH 2).

Introduction

Diabetes, both type 1 (T1D) and type 2 (T2D), results in chronic hyperglycaemia placing patients at risk of diabetes-related complications,[1-3] requiring treatment with glucose-lowering therapies. However, with tighter glycaemic control comes an elevated risk of hypoglycaemia and its associated problems.[4] Hypoglycaemia is a major concern for patients and physicians,[5] has significant negative effects on patients' health and quality of life, and potentially increases risk of adverse cardiovascular (CV) events.[5-7] The physical and psychological effects of hypoglycaemia make it a primary barrier to establishing glycaemic control.[4]

Traditionally, management of diabetes has focused on HbA1c.[8,9] As an average measure of glycaemia, HbA1c does not reflect the fluctuations in blood glucose (glycaemic variability) that more directly indicate a patient's risk of hypoglycaemia or hyperglycaemia.[9]

Glycaemic variability is determined by a multitude of interconnected factors, some inherent to the patient (physiology and behaviour) and their diabetes (remaining endogenous insulin secretion and insulin sensitivity), but also reflecting the pharmacodynamic glucose-lowering variability of treatment.[9,10] Several studies have investigated the role of glycaemic variability on risk of complications; an association with microvascular complications has been demonstrated in patients with T2D, while conflicting results have been found in patients with T1D.[11,12] Furthermore, in patients

with T2D, variability in fasting self-monitored blood glucose (SMBG) has been linked to an increased risk of mortality.[13-15]

High day-to-day glycaemic variability exposes patients to risk of hypoglycaemia and is a frustrating issue for patients particularly in patients treated with insulin.[16] Although there may be debate about the most accurate metric of measuring glycaemic variability,[9] one can expect that improved and simpler techniques will become more widely adopted when continuous glucose monitoring is more widely applied in research and clinical practice. Nonetheless, the consolidated evidence to-date supports the importance of both the magnitude and duration of glucose variability,[9] with respect to increased risk of hypoglycaemia, regardless of the method of variability measurement.[15,18-22]

However, in many cases, studies of glucose variability have limitations in terms of the applicability of their findings to clinical practice. For example, many of these studies were limited by the relatively small numbers of patients studied.[20-22] In addition, there is heterogeneity in the definition of hypoglycaemia used across studies, with some focused on symptomatic hypoglycaemia or episodes with blood glucose (BG) ≤70 mg/dL (3.9 mmol/L),[18] and others investigating episodes of severe[15,19]and nocturnal hypoglycaemia.[19,23]

A *post hoc* analysis of the two double-blind crossover trials of insulin degludec (degludec) versus insulin glargine 100 units/mL (glargine U100), in patients with T1D (SWITCH 1)[24] and those with T2D (SWITCH 2)[25] provided an opportunity to further

study the association between day-to-day fasting SMBG variability and the risk of hypoglycaemia and to analyse the difference in day-to-day fasting SMBG variability between degludec and glargine U100. The SWITCH trials allowed the investigation of a broader range of definitions of hypoglycaemia, including previously studied severe[15,19] and nocturnal hypoglycaemia,[19,23] but also non-severe hypoglycaemia. Furthermore, the double-blind, crossover design adds to the validity of the data obtained in the SWITCH trials[24,25] as it reduces the influence of inter-individual variability and investigator or patient bias on study outcomes.

Materials and Methods

SWITCH 1 and SWITCH 2 overviews

Data were retrieved from two double-blind, randomised, two-period (32 weeks each) crossover, multicentre, treat-to-target clinical trials comparing degludec (100 units/mL, Novo Nordisk, Denmark) once daily (OD) with glargine U100 (Sanofi, France) OD in patients with T1D (SWITCH 1, n=501),[24] or in insulin-experienced patients with T2D (SWITCH 2, n=721),[25] fulfilling at least one pre-specified risk criterion for hypoglycaemia. Detailed trial designs and methods were reported previously for SWITCH 1[24] and SWITCH 2.[25] In SWITCH 1, mealtime insulin aspart (IAsp) was administered two- to four-times per day; in SWITCH 2, all pre-trial oral antidiabetic drugs (OADs, including 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.

In both trials, the 64-week trial period consisted of treatment periods 1 and 2 (32 weeks each, either with degludec or glargine U100). 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). Consistent with the pre-specified confirmatory analyses from the primary trial results,[24,25] the fasting SMBG values and hypoglycaemic episodes 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 (Supplemental Figure S1). During the maintenance periods, titration of basal insulin could be continued using the same glucose target (4.0—5.0 mmol/L [71—90 mg/dL]) and algorithm used in the titration periods.

The trial protocols were approved according to local regulations by appropriate health authorities and by institutional review boards at all participating institutions, and conducted in accordance with the Declaration of Helsinki[26] and Good Clinical Practice guidelines.[27] Written informed consent from all patients was obtained before enrolment.

Fasting SMBG

In SWITCH 1, the lowest fasting SMBG values were used for weekly titration of basal insulin, whereas in SWITCH 2, the mean of the three fasting SMBG measurements

on three consecutive days before each contact were used for weekly titration of basal insulin. Therefore, up to seven fasting SMBG measurements per week were available for patients in SWITCH 1, and up to three fasting SMBG measurements per week were available for patients in SWITCH 2. Only patients with two or more fasting SMBG values within 1 week at least once during the maintenance periods contributed to the analyses.

Statistical analyses of day-to-day fasting SMBG variability and hypoglycaemia

To analyse the association between fasting SMBG variability and risk of hypoglycaemia, data were pooled regardless of the treatment allocation, but analysed separately for patients with T1D and those with T2D. For each patient and treatment combination, the standard deviation (SD) of the fasting SMBG was determined and used as the measure of day-to-day glycaemic variability. First, the weekly variances were calculated based on the log-transformed fasting SMBG values. The day-to-day fasting SMBG SD variability (for each patient and treatment combination) was defined as the square root of the mean value of the weekly variances of fasting SMBG values across the 16 weeks during the maintenance period, thereby obtaining an efficient estimate of the SD, which is not confounded by dose adjustments.

A linear regression was initially performed to analyse the association between day-to-day fasting SMBG variability and rate of hypoglycaemia using a Poisson model with logarithm of the exposure time (100 years) as offset. This model was an

extension of the pre-specified confirmatory model used for the SWITCH trials[24,25] with the addition of adjusting for variability measure. This model included treatment, treatment period, sequence and dosing time as fixed effects, day-to-day fasting SMBG variability, as defined above, as a covariate, and patient as a random effect.

Patients were also grouped into three tertiles, based on their day-to-day fasting SMBG variability values, as done in the previously published studies to allow comparison of these data.[15,19] The rates of hypoglycaemia were analysed using the same model as that for the linear regression except that the day-to-day fasting SMBG SD variability was included as a fixed effect.

A second measure of the day-to-day fasting SMBG variability was calculated as the geometric mean of the weekly coefficient of variation (CV%). Patients were then grouped into three equally sized tertiles, based on these values. The rates of hypoglycaemia were analysed using the same Poisson model as described above, except that the day-to-day fasting SMBG variability (CV%) was only evaluated as a fixed effect defined by tertiles.

Hypoglycaemia episodes in the SWITCH trials were classified as follows: overall symptomatic, nocturnal symptomatic and severe hypoglycaemia. Overall symptomatic hypoglycaemia was defined as severe or BG-confirmed (<3.1 mmol/L [56 mg/dL]) symptomatic episodes; nocturnal symptomatic hypoglycaemia was defined as severe or BG-confirmed episodes in the time interval of 00:01–05:59 am, both inclusive; severe hypoglycaemia was defined as events requiring third-party

assistance (based on the ADA definition).[28] All severe episodes reported by investigators or identified via a predefined Medical Dictionary for Regulatory Activities version 18.1 search of safety data were adjudicated prospectively by an external Event Adjudication Committee; only those confirmed by adjudication were included in the analysis.

Day-to-day fasting SMBG variability and hypoglycaemia with degludec versus glargine U100

The available fasting SMBG values during the maintenance period were also used to calculate the day-to-day fasting SMBG SD variability in the two treatment arms separately. The weekly day-to-day fasting SMBG variability estimates (SDs) were subsequently compared between degludec and glargine U100 using a linear mixed effect model with treatment, treatment period, sex, region (only in SWITCH 1), antidiabetic therapy at screening, visit and dosing time as fixed effects, age as a covariate, and patient as a random effect. A similar treatment comparison was also conducted using the day-to-day fasting SMBG variability based on the CV% values.

The rates of hypoglycaemia with degludec versus glargine U100 for each tertile were analysed using a Poison model with logarithm of the exposure time (100 years) as offset, with treatment, period, sequence, dosing time, fasting SMBG variability tertiles and its interaction with treatment as fixed effects and with patient as a random effect. In addition, the interaction between fasting SMBG variability and treatment was

investigated using a similar Poison model but with fasting SMBG variability on log scale as a linear regressor.

Results

In the SWITCH 1 and 2 trials, 16 and 6 patient and treatment combinations were excluded respectively from the statistical analysis due to too few reported SMBGs. Patients included in the analysis had sufficient data to calculate the SMBG SD values for at least 1 week for one period. Available SMBG variabilities were calculated on an average of 84 and 45 SMBG measurements per patient in SWITCH 1 and 2, respectively. Baseline characteristics of the patients in each day-to-day fasting SMBG variability tertile are shown in Table 1. In patients with T1D, those in the higher day-to-day fasting SMBG variability tertile had longer durations of diabetes, were younger and had higher HbA1c values. In patients with T2D, a similar trend was observed for duration of diabetes and HbA1c values, but there was no link between day-to-day fasting SMBG variability and mean age or age groups.

Day-to-day fasting SMBG variability and hypoglycaemia

In patients with T1D, the rates of overall symptomatic, nocturnal symptomatic and severe hypoglycaemia all increased significantly with higher day-to-day fasting SMBG variability (SD values) in the linear regression analysis (Figure 1). In patients with T2D, the same significant association was seen across all hypoglycaemia categories (Figure 1). With a doubling of the day-to-day fasting SMBG variability (SD

values) , the risks of overall, nocturnal symptomatic and severe hypoglycaemia increased by 2.1-, 2.7-, and 2.0-fold for T1D, and 3.3-, 3.5-, and 1.9-fold for T2D, respectively (Supplemental Figure S2).

In patients with T1D, the cumulative number of hypoglycaemic episodes per patient in the high tertile was higher than those for the patients in the low or medium tertiles during the maintenance period (Figure 2). Patients in the high day-to-day fasting SMBG variability tertile had a higher number of overall symptomatic, nocturnal symptomatic and severe hypoglycaemic episodes per 100 patient-years of exposure (PYE), compared with patients in the low or medium tertiles (Supplemental Figure S3). In patients with T1D, the day-to-day fasting SMBG variability was significantly associated with the rates of overall symptomatic (p<0.0001), nocturnal symptomatic (p<0.0001) and severe hypoglycaemia (p=0.0053, Table 2 and Supplemental Figure S3).

In patients with T2D, similarly, patients in the high day-to-day fasting SMBG variability tertile had a higher cumulative number of hypoglycaemic episodes than those in the low or medium tertiles during the maintenance period (Figure 2). The lowest number of overall symptomatic, nocturnal symptomatic and severe hypoglycaemic episodes per 100 PYE were observed for the patients in the low day-to-day fasting SMBG variability tertile (Supplemental Figure S3). Day-to-day fasting SMBG variability was significantly associated with overall and nocturnal symptomatic hypoglycaemia in patients with T2D (both p<0.0001, Table 2 and Supplemental

Figure S3). For severe hypoglycaemia, a similar pattern of an increased number of hypoglycaemic episodes per 100 PYE with higher day-to-day fasting SMBG variability was observed; however, it did not reach statistical significance in patients with T2D (*p*=0.1140, Table 2 and Supplemental Figure S3).

In patients with T1D or T2D, a larger proportion in the high day-to-day fasting SMBG variability tertile had overall symptomatic, nocturnal symptomatic and severe hypoglycaemia than those in the low day-to-day fasting SMBG variability tertile (Supplemental Figure S3).

The second measure of the day-to-day fasting SMBG variability using CV% values indicated the same effect on the risk of hypoglycaemia (Table 3).

When adjusting for diabetes duration and eGFR at baseline, the significant association between fasting SMBG variability and overall and nocturnal symptomatic hypoglycaemia persisted.

Day-to-day fasting SMBG variability and hypoglycaemia with degludec versus glargine U100

In both trials, degludec was associated with significantly lower day-to-day fasting SMBG SD variability (T1D, variability ratio: 0.96 $[0.93; 0.99]_{95\% CI}$, *p*=0.0082; T2D, variability ratio: 0.90 $[0.86; 0.93]_{95\% CI}$, *p*<0.0001), compared with glargine U100. When using the CV% values as the measure of the day-to-day fasting SMBG variability, similar results were observed (T1D, variability ratio: 0.99 $[0.97; 1.00]_{95\% CI}$,

p=0.0783; T2D, variability ratio: 0.95 [0.93; 0.97]$_{95\%\ CI}$, *p*<0.0001) with degludec, compared with glargine U100. During the treatment with degludec, there were 31% patients with T1D and 30% patients with T2D in the high day-to-day fasting SMBG variability tertile; whereas during the treatment with glargine U100, there were 35% patients with T1D and 37% patients with T2D in the high day-to-day fasting SMBG variability tertile (Supplemental Figure S4). Day-to-day fasting SMBG variability was significantly associated with hypoglycaemia for all definitions, except for severe hypoglycaemia in T2D when analysed in variability tertiles. The non-significant interaction between fasting SMBG variability and treatment in most cases (Table S5) indicated that the fasting SMBG variability had the same effect for the two treatments, and its overall association with the risk of hypoglycaemia remained significant. There were comparable or lower rates of hypoglycaemia with degludec versus glargine U100 within all variability tertiles (Table S5).

Discussion

In these *post hoc* analyses, fasting SMBG values were used to quantify day-to-day fasting SMBG variability and evaluate its association with the risk of hypoglycaemia in patients with T1D and those with T2D.

In the present analyses, day-to-day fasting SMBG variability was investigated as an indicator of basal insulin action, which is not influenced by food intake or medications, such as bolus insulins. The methods of statistical analyses used in this study were consistent with those used in the previous investigations of within-subject

day-to-day PK/PD variability of degludec and glargine U100 under clamp conditions.[29]

A higher day-to-day fasting SMBG variability was significantly associated with an increased risk of overall symptomatic, nocturnal symptomatic and severe hypoglycaemia in patients with T1D and those with T2D. When day-to-day fasting SMBG variability tertiles were considered, similar results were seen, except for severe hypoglycaemia in patients with T2D where event rates were relatively low and this association was not significant, although a trend was observed. Findings in the current study are supported by a previous retrospective analysis of the Diabetes Control and Complications Trial (DCCT) data in patients in T1D,[19] and a study assessing the association between glycaemic variability and risk of hypoglycaemia (glucose level <3.9 mmol/L [70 mg/dL]) using CGM data in patients with T1D or T2D,[20] although these studies did not specifically investigate the variability of fasting glucose. While these other studies focused on mean glycaemic variability, in the present analysis fasting SMBG measurements were utilised as a measure of day-to-day fasting glycaemic variability relating primarily to basal insulin effects.

Prior to the publication of the results from the DEVOTE study,[15] it was unknown whether fasting blood glucose variability confers additional risk for adverse events beyond those associated with chronic hyperglycaemia. Similar to the present study, DEVOTE demonstrated in patients with T2D at high CV risk, a significant association between risk of severe hypoglycaemia and the day-to-day glycaemic variability in

fasting SMBG.[15] In this secondary analysis based on DEVOTE, it was also demonstrated that a higher day-to-day fasting glycaemic variability is associated with a higher risk of all-cause mortality.

It is worth noting that the effect of fasting SMBG variability on the risk of hypoglycaemia appears to be the same for the two treatments, as indicated by the lack of interaction between treatment and fasting SMBG for most cases. The significantly lower day-to-day fasting SMBG variability of degludec compared with glargine U100 is consistent, both with the results from the PK/PD clamp trial in patients with T1D,[29] and those from a previous prospective observational study in patients with T1D.[30] In the clamp study, degludec had four-times lower day-to-day variability for the parameter of area under the glucose infusion rate curve during one dosing interval ($AUC_{GIR0-24}$; CV 20%) than glargine U100 (CV 82%) under steady-state conditions.[29] The observation of lower fasting SMBG variability with degludec in the present analyses is probably explained by its lower day-to-day PD variability versus glargine U100.[29,31] The lower rate of hypoglycaemia with degludec, reported in the original SWITCH (and other) trials,[24,25,32,33] is also likely to be a consequence of its flatter and less variable action profile versus glargine U100.[29] The reduced risk of hypoglycaemia due to the more stable PD of degludec may itself contribute to lower glycaemic variability by reducing the likelihood of patients over-treating hypoglycaemia and experiencing rebound post-hypoglycaemia hyperglycaemia. Thus, the PD profile of degludec may reduce both glycaemic variability and hypoglycaemia.

Strengths of these *post hoc* analyses based on the SWITCH trials include the crossover design of these trials, which reduces the influence of inter-individual variability on the obtained outcomes, and the double-blind design, which would reduce investigator and patient bias. Furthermore, the inclusion criteria of the SWITCH trials allowed for a broader patient population more closely resembling that encountered in clinical practice, than the cohorts typical of Phase 3 parallel-group trials. In addition, the number of patients included in these analyses were much larger than some of the previous studies in this area.[20-22] In the SWITCH trials, the threshold for hypoglycaemic episodes was BG <3.1 mmol/L (56 mg/dL). This is consistent with the recent recommendations made by the International Hypoglycaemia Study Group whereby hypoglycaemic episodes with BG <3.0 mmol/L (54 mg/dL) are considered clinically important.[34] Furthermore, all severe hypoglycaemic episodes in these two trials were adjudicated by an external Event Adjudication Committee; only those confirmed by adjudication were included in these analyses.

There are limitations to this study adding to the inherent limitation of a *post hoc* analysis, which is not pre-specified. Firstly, glycaemic variability was related solely to fasting SMBG, not allowing for analysis of the patients' blood glucose levels throughout the day. Secondly, as mentioned in the Results, in the SWITCH 1 and 2 trials, 16 and 6 patient and treatment combinations were excluded respectively due to too few reported SMBGs; however, given the large number of patients included and the number of SMBG measurements available per patient, it is believed that

sufficient data were used to calculate the SMBG SD values. Finally, other factors that may affect the fasting SMBG variability, such as exercise, food intake and stress, have not been investigated in the current study.

In conclusion, these two *post hoc* analyses of SWITCH 1 and SWITCH 2 further establish the association between day-to-day fasting SMBG variability and risk of hypoglycaemia, showing that lower day-to-day fasting SMBG variability is significantly associated with lower risk of hypoglycaemia in patients with T1D or T2D. Clearly, treatment choices that reduce day-to-day fasting SMBG variability could contribute to a reduced risk of hypoglycaemia. For this reason, reducing glycaemic variability might be a useful additional clinical goal in the management of diabetes.

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Conflict of interest

JHD: *Advisory Panel;* Novo Nordisk A/S, Sanofi. *Research Support;* Sanofi. *Speaker's Bureau;* Novo Nordisk A/S.

TSB: *Consultant*: Abbott, Astra Zeneca, Ascensia, BD Medical Diabetes Care, Calibra, Capillary Biomedical, Eli Lilly, Intarcia, Medtronic, Novo Nordisk, Sanofi; *Research Support*: Abbott, Ambra, Ascensia, BD Medical Diabetes Care, Boehringer Ingelheim, Calibra Medical, Companion Medical, Dance Biopharm, Dexcom, Eli Lilly, Glooko, Glysens, Kowa, Lexicon Pharmaceuticals, Inc., MannKind, Medtronic, Novo

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AB: *Advisory Panel;* Abbott, Janssen Pharmaceuticals, Inc., Sanofi. *Research Support; Author*; Boehringer Ingelheim Pharmaceuticals, Inc., Bristol-Myers Squibb Company, Novo Nordisk A/S, Eli Lilly and Company, Dexcom, Inc., Medtronic, Sanofi, Mylan, Duke Clinical Research Institute, Janssen Pharmaceuticals, Inc., Jaeb Center for Health Research, GlaxoSmithKline, Orexogen Therapeutics, Inc., Hygieia, University of Oxford, AbbVie Inc. *Speaker's Bureau;* Abbott, Sanofi, AstraZeneca.

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SH: *Advisory Panel;* Eli Lilly and Company, Novo Nordisk A/S, Takeda, Sanofi Aventis, Merck, Boehringer Ingelheim. *Consultant;* Eli Lilly. *Research support;*

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BZ: *Consultant;* Novo Nordisk A/S, Boehringer Ingelheim, AstraZeneca, Eli Lilly, Janssen, Sanofi, Merck.

BAB: *Employee;* Novo Nordisk A/S.

EHN: *Employee;* Novo Nordisk A/S.

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Figure legends

Figure 1. Linear regression analysis on the effect of day-to-day fasting SMBG variability (SDs) on rate of hypoglycaemia

Data were based on the full analysis set during the maintenance period.

CI, confidence interval; RR, rate ratio; SMBG, self-monitored blood glucose; T1D, type 1 diabetes; T2D, type 2 diabetes.

Figure 2. Cumulative number of hypoglycaemic episodes for patients in the low, medium or high day-to-day fasting SMBG variability tertile

Based on the safety analysis set. The time-scale of Weeks 16–32 is included in the x-axis, as only hypoglycaemic episodes during the maintenance periods were considered. All non-withdrawn patients had the same duration of exposure.

SMBG, self-monitored blood glucose; T1D, type 1 diabetes; T2D, type 2 diabetes.

Table 1. Baseline characteristics of patients grouped by low, medium and high day-to-day fasting SMBG variability tertiles

Characteristics	Patients with T1D			Patients with T2D		
	Low day-to-day fasting SMBG variability tertile	**Medium day-to-day fasting SMBG variability tertile**	**High day-to-day fasting SMBG variability tertile**	**Low day-to-day fasting SMBG variability tertile**	**Medium day-to-day fasting SMBG variability tertile**	**High day-to-day fasting SMBG variability tertile**
Number of patients	189	217	199	288	325	292
Number of combinations of patient and treatment, n (%)	285 (100.0)	287 (100.0)	285 (100.0)	424 (100.0)	424 (100.0)	424 (100.0)
Male, n (%)	169 (59.3)	156 (54.4)	139 (48.8)	241 (56.8)	213 (50.2)	219 (51.7)
Race, n (%)						
White	270 (94.7)	258 (89.9)	266 (93.3)	344 (81.1)	340 (80.2)	342 (80.7)
Black	13 (4.6)	23 (8.0)	16 (5.6)	55 (13.0)	60 (14.2)	69 (16.3)
Asian	2 (0.7)	1 (0.3)	1 (0.4)	19 (4.5)	16 (3.8)	3 (0.7)
Other	0 (0.0)	5 (1.7)	2 (0.7)	6 (1.3)	8 (1.8)	10 (2.4)
Ethnicity: Hispanic or Latino, n (%)	35 (12.3)	22 (7.7)	28 (9.8)	212 (50.0)	136 (32.1)	107 (25.2)
Mean age, years	49.4	45.5	43.0	59.7	62.3	62.3

Age group						
18–64 years, n (%)	233 (81.8)	265 (92.3)	273 (95.8)	294 (69.3)	259 (61.1)	247 (58.3)
65–84 years, n (%)	52 (18.2)	22 (7.7)	12 (4.2)	126 (29.7)	163 (38.4)	177 (41.7)
>84 years, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.9)	2 (0.5)	0 (0.0)
Body weight, kg	81.8	81.7	78.3	93.1	92.0	90.4
BMI, kg/m^2	27.8	27.8	26.7	32.5	32.3	31.9
Duration of diabetes, years	21.0	22.9	25.3	12.7	13.8	15.6
HbA1c, %	7.2	7.6	7.8	7.4	7.5	7.8
HbA1c, mmol/mol	55.7	59.5	62.2	57.9	58.0	61.6
FPG, mmol/L	9.3	9.5	9.5	7.9	7.4	7.4
FPG, mg/dL	166.7	170.7	170.5	141.9	133.2	133.2
eGFR, mL/min/1.73 m^2	87.2	90.8	91.8	80.8	78.2	75.5
Insulin treatment at screening						
CSII	41 (14.4)	59 (20.6)	62 (21.8)	–	–	–
Basal	244 (85.6)	228 (79.4)	223 (78.2)	424 (100.0)	424 (100.0)	424 (100.0)
IDet, n (%)	185 (64.9)	172 (59.9)	171 (60.0)	111 (26.2)	92 (21.7)	83 (19.6)
NPH, n (%)	58 (20.4)	55 (19.2)	52 (18.2)	47 (11.1)	31 (7.3)	26 (6.1)
Glargine U100, n (%)	1 (0.4)	1 (0.3)	0 (0.0)	266 (62.7)	301 (71.0)	315 (74.3)

Data were summarised for the full analysis set. The baseline characteristics data were pooled for two treatment arms and two maintenance periods, and only patient and treatment combinations with two or more fasting SMBG measurements available within 1 week at least once during the maintenance periods contributed to the baseline data. C-peptide levels were not available to

determine baseline endogenous insulin production. Data are mean values.
BMI, body mass index; CSII, continuous subcutaneous insulin infusion; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; IDet, insulin detemir; n, number of combinations of patient and treatment; NPH, neutral protamine Hagedorn; SMBG, self-monitored blood glucose; T1D, type 1 diabetes; T2D, type 2 diabetes.

Table 2. Effect of day-to-day fasting SMBG variability (SDs) on rate of hypoglycaemia by low, medium and high tertiles

Hypoglycaemia	Day-to-day fasting SMBG variability tertile	Patients with T1D		Patients with T2D	
		Estimate [95% CI]	*p*-value	Estimate [95% CI]	*p*-value
Overall symptomatic	Low	0.68 [0.58; 0.78]	*p*<0.0001	0.28 [0.20; 0.40]	*p*<0.0001
	Medium	Reference		Reference	
	High	1.32 [1.19; 1.46]		2.23 [1.79; 2.78]	
Nocturnal symptomatic	Low	0.45 [0.33; 0.62]	*p*<0.0001	0.18 [0.09; 0.36]	*p*<0.0001
	Medium	Reference		Reference	
	High	1.59 [1.26; 2.01]		2.18 [1.56; 3.03]	
Severe	Low	0.82 [0.49; 1.38]	*p*=0.0053	0.33 [0.09; 1.22]	*p*=0.1140
	Medium	Reference		Reference	
	High	1.70 [1.11; 2.61]		1.31 [0.55; 3.09]	

Data were based on the full analysis set. The number of episodes was analysed using a Poisson Model with logarithm of the exposure time (100 years) as offset. The model included treatment, period, sequence, dosing time and SMBG as fixed effects, and participant as a random effect. SMBG was incorporated as a factor with three tertiles of the fasting SMBG variability, defined by the

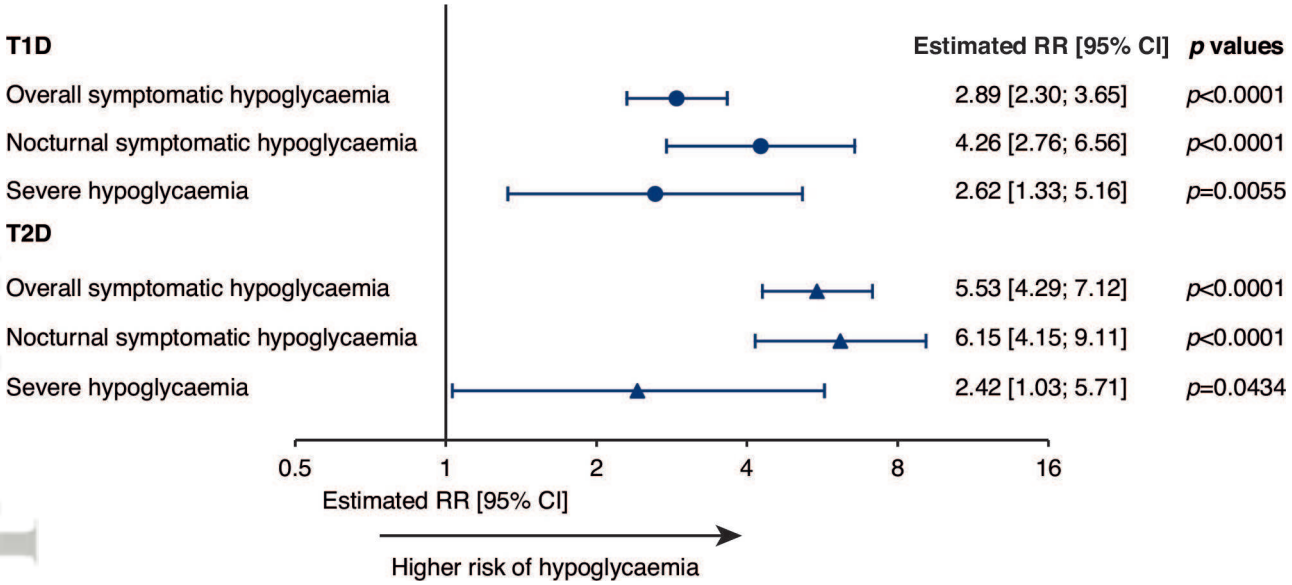
tertiles the square root of the mean value of the weekly variances of fasting SMBG values across the 16 weeks during the maintenance period.
CI, confidence interval; SMBG, self-monitored blood glucose; T1D, type 1 diabetes; T2D, type 2 diabetes.

Table 3. Effect of day-to-day fasting SMBG variability (CV%) on rate of hypoglycaemia by low, medium and high tertiles

Hypoglycaemia	Day-to-day fasting SMBG variability (CV%) tertile	Patients with T1D		Patients with T2D	
		Estimate [95% CI]	*p*-value	Estimate [95% CI]	*p*-value
Overall symptomatic	Low	0.69 [0.61; 0.78]	*p*<0.0001	0.31 [0.22; 0.44]	*p*<0.0001
	Medium	Reference		Reference	
	High	1.18 [1.07; 1.30]		2.09 [1.67; 2.61]	
Nocturnal symptomatic	Low	0.44 [0.33; 0.59]	*p*<0.0001	0.26 [0.14; 0.47]	*p*<0.0001
	Medium	Reference		Reference	
	High	1.34 [1.08; 1.67]		2.05 [1.48; 2.84]	
Severe	Low	0.59 [0.35; 0.98]	*p*=0.0106	0.68 [0.22; 2.11]	*p*=0.2705
	Medium	Reference		Reference	
	High	1.28 [0.86; 1.90]		1.59 [0.65; 3.93]	

Data were based on the full analysis set. The number of episodes was analysed using a Poisson Model with logarithm of the exposure time (100 years) as offset. The model included treatment, period, sequence, dosing time and SMBG as fixed effects, and

participant as a random effect. SMBG was incorporated as a factor with three tertiles of the fasting SMBG variability, defined by the tertiles the geometric mean value of the weekly CV% of fasting SMBG values across the 16 weeks during the maintenance period. CI, confidence interval; CV, coefficient of variation; SMBG, self-monitored blood glucose; T1D, type 1 diabetes; T2D, type 2 diabetes



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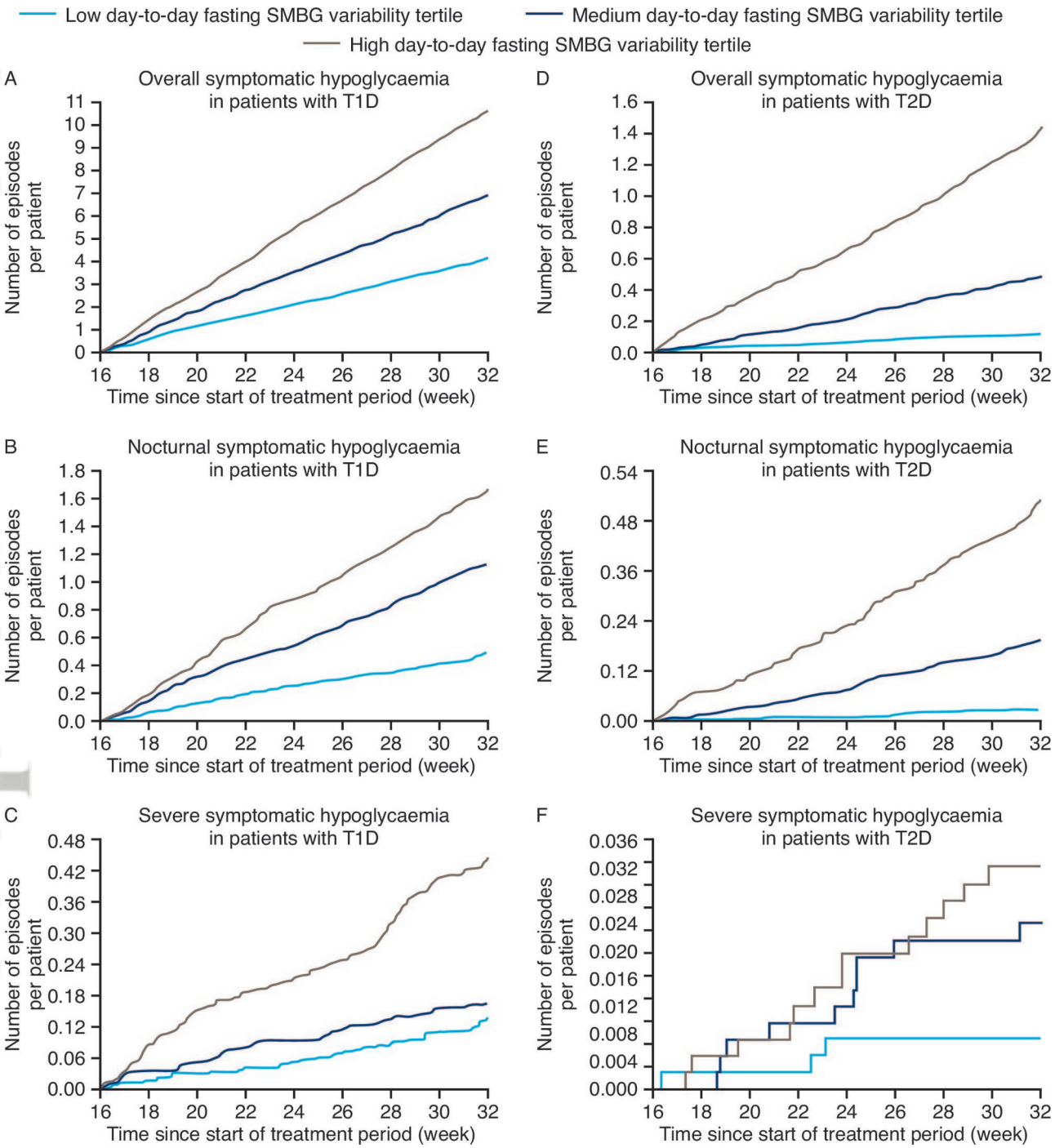

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