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Self-reported hypoglycemia in insulin-treated patients with diabetes: Results from an international survey on 7289 patients from nine countries

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ABSTRACT

Aims: Hypoglycemia constitutes a significant barrier to achieving glycemic control with insulin in both type 1 and type 2 diabetes. Historically, it has been difficult to accurately verify the rates of hypoglycemia within a clinical setting and there is a need for high-quality, real-world data to ascertain the true rates of hypoglycemia in clinical practice. The global Hypoglycemia Assessment Tool (HAT) study was designed to assess the global incidence of hypoglycemia in patients with insulin-treated diabetes, and the results have indicated that the overall incidence of hypoglycemia is high, with large variations between geographical regions.

Methods: The International Operations HAT (IO HAT) study retrospectively and prospectively assessed the incidence of hypoglycemia in patients with insulin-treated diabetes in Bangladesh, Colombia, Egypt, Indonesia, Philippines, Singapore, South Africa, Turkey, and United Arab Emirates.

Results: During the prospective period, hypoglycemic events were reported by 97.4% of patients with type 1 diabetes and 95.3% of those with type 2 diabetes, with an estimated rate of 6.86 events

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per patient per month (PPPM) for patients with type 1 diabetes and 2.37 events PPPM for patients with type 2 diabetes.

Conclusions: These results represent the first patient-reported dataset on hypoglycemia in the participating countries and confirm that hypoglycemia is under-reported and more widespread than previously believed. Although the incidence of hypoglycemia was variable among patients on different treatment regimens, there were substantial impacts on both productivity and healthcare utilization following an episode of hypoglycemia.

This trial is registered at clinicaltrials.gov: NCT02306681.

1. Introduction

Insulin is the most common treatment for type 1 diabetes (T1D), and is also often needed for patients with type 2 diabetes (T2D). Hypoglycemia, and particularly the fear of hypoglycemia, constitutes a significant barrier to achieving glycemic control with insulin [1]. The recent multinational Global Attitude of Patients and Physicians (GAPP2) survey demonstrated that around a quarter of patients with T2D intentionally miss, mistime or reduce their basal insulin dose, primarily due to the perceived risk of hypoglycemia [2]. These issues are well recognized and recent diabetes treatment guidelines recommend personalized targets that seek to balance the achievement of good glucose control with no or little hypoglycemia [3].

Historically, it has been difficult to accurately verify the rates of hypoglycemic events within a real-world clinical setting. Randomized controlled trials (RCTs) remain the most common data source and are the gold standard for demonstrating clinical efficacy and safety of antidiabetic drugs. However, the constraints of a clinical trial setting and exclusion of patients who are more likely to experience hypoglycemic events may limit their transposition to routine clinical practice [4]. A recent comparison of real-world data (RWD) and data from RCTs in populations of patients with insulin-treated diabetes revealed higher rates of hypoglycemia in real-world settings compared with clinical trial settings [4]. The study highlights that RWD on the incidence of hypoglycemia are limited, particularly in non-Western countries [4]. These results further demonstrate the need for RWD to ascertain the true rates of hypoglycemia occurring in real-world clinical practice [4].

Previous observational studies and surveys of hypoglycemia in T1D and T2D were primarily retrospective or cross-sectional studies (leading to potential recall bias), conducted online (restricting participation to those who have access and ability to use the internet, a potential source of selection bias), and most of the large studies have thus far been limited to North America and Europe [2,5–9]. Large-scale, real-world studies of hypoglycemia may therefore aid clinical practice by helping to ascertain the real-life magnitude and impact of hypoglycemia, particularly outside Europe and North America.

The global Hypoglycemia Assessment Tool (HAT) study was designed to assess the global incidence of hypoglycemia in patients with T1D or T2D treated with insulin (pre-mix, short-acting, long-acting, and insulin pump [sensor-augmented pump therapy]) [10]. The non-interventional, multicenter, 6-month retrospective and 4-week prospective HAT study used self-assessment questionnaires (SAQs) and patient diaries and comprised 27,585 adult patients with T1D ($n = 8022$) or T2D ($n = 19{,}563$) treated with insulin for >12 months, at 2004 sites in 24 countries worldwide, including countries for which data on hypoglycemia rates had not previously been available [10]. The results indicated that the overall incidence of hypoglycemia is high, with large geographical variations. Prospective rates (events per patient per month [PPPM]) of any, nocturnal, and severe hypoglycemia were 6.11 (95% CI 6.05–6.17), 0.94 (95% CI 0.92–0.97), and 0.41 (95% CI 0.39–0.42) for T1D and 1.61 (95% CI 1.59–1.63), 0.31 (95% CI 0.30–0.31), and 0.21 (95% CI 0.20–0.21) for T2D, respectively. The highest rates of any hypoglycemia were observed in Latin America for T1D and Russia for T2D [10].

The International Operations (IO) HAT (IO-HAT) study builds on the information gathered as part of the global HAT study and can be considered the next wave of the HAT study. It was designed to assess the incidence of hypoglycemia in patients with T1D or T2D, treated with insulin (pre-mix, short-acting, long-acting, or insulin pump) in Bangladesh, Colombia, Egypt, Indonesia, Philippines, Singapore, South Africa, Turkey, and United Arab Emirates.

2. Subjects

2.1. *Study population*

Consecutive patients were enrolled during a routinely scheduled clinical consultation with their healthcare provider. Eligible patients were aged ≥ 18 years at baseline, with T1D or T2D treated with insulin (pre-mix, short-acting, long-acting, or insulin pump) for >12 months, who had given informed consent to participate in the study. Exclusion criteria included non-ambulatory status and illiteracy or other issues resulting in an inability to complete a written questionnaire. Patients were not paid for their participation in the study, but travel costs were reimbursed in some countries.

3. Materials and methods

3.1. Study design

This study was a non-interventional, multicenter, 6-month retrospective and 4-week prospective study of hypoglycemic events across 300 sites in nine countries (Bangladesh, Colombia, Egypt, Indonesia, Philippines, Singapore, South Africa, Turkey and United Arab Emirates) using a two-part SAQ (Part 1 SAQ and Part 2 SAQ) and patient diaries. The study design is described in Fig. 1. The study protocol and assessments were conducted in accordance with the Declaration of Helsinki (2013) and the Guidelines for Good Pharmacoepidemiology Practices (2007), and approved by country-specific regulatory and ethics agencies, as applicable. Where required, all study materials were translated into local languages, and data obtained were translated back into English for analysis.

3.2. Endpoints

The primary endpoint of the study was the percentage of patients experiencing at least one hypoglycemic event during the 4-week prospective follow-up period. Secondary endpoints included the difference in the reported incidence of overall and nocturnal hypoglycemia between the 4 weeks before baseline and the 4 weeks after baseline; the reported incidence of severe hypoglycemia and hypoglycemia requiring hospitalization in the 6-month retrospective and 4-week prospective assessment; the incidence of hypoglycemia associated with a blood glucose (BG) measurement < 3.1 mmol/L (56 mg/dL) irrespective of symptoms, in the 4 weeks following the baseline visit; the relationship between hypoglycemic events and insulin regimen; the impact of hypoglycemia on work/school; the incidence of hypoglycemia unawareness and fear of hypoglycemia; patient response and impact on the medical system; and the association between hypoglycemia and factors such as HbA_{1c}, age, and hypoglycemia unawareness.

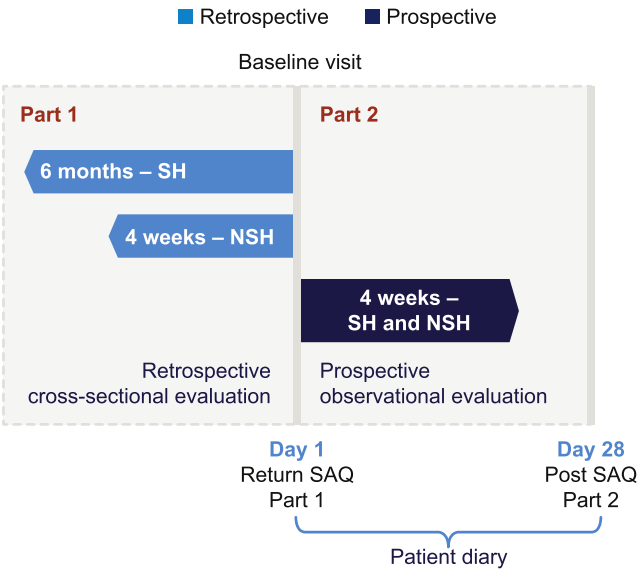

Fig. 1 – Study design. Non-severe hypoglycemia: documented symptomatic (symptoms and blood glucose measurement ≤ 3.9 mmol/L [70 mg/dL]) and probable symptomatic (symptoms only) hypoglycemia. NSH, non-severe hypoglycemia; SAQ, self-assessment questionnaire; SH, severe hypoglycemia.

3.3. Assessments

The study comprised two SAQs. The SAQs used for the IO HAT study were similar to those used in global HAT, with modifications to collect additional data on variables such as comorbidities, type of diabetes treatment used, loss of productivity (absence from work/school or arriving late/leaving early to/from work/school), and quality of life. The Part 1 SAQ was a cross-sectional assessment used to record baseline demographic and treatment information, as well as the history of severe hypoglycemia over the past 6 months and symptomatic hypoglycemia over the previous 4 weeks in the lead-up to baseline study entry. In addition, the Part 1 SAQ evaluated patients' knowledge of hypoglycemia, hypoglycemia unawareness, and perception of hypoglycemia. The Part 2 SAQ, completed 4 weeks later, evaluated the occurrence of severe and symptomatic hypoglycemia over the 4 weeks following baseline study entry as well as the effect of hypoglycemia on productivity and healthcare utilization during this time frame. To assist recall, patients were provided with a diary at their baseline visit, which was also used to record hypoglycemic events. If a patient recorded more hypoglycemic events using the patient diary than the Part 2 SAQ, the patient diary value was used to calculate prevalence of hypoglycemia in the 4 weeks after baseline, to compensate for potential underestimates due to recall bias.

Patient knowledge of hypoglycemia was evaluated by assessing if their definition was consistent with the American Diabetes Association (ADA) definition of hypoglycemia [11], and if they knew what hypoglycemia was before they read the introduction provided in the informed consent form.

Hypoglycemia unawareness was evaluated with the incorporation of the previously validated question, 'Do you have symptoms when you have a low sugar level?', where the responses 'always', 'usually', 'occasionally' and 'never' represent degrees of hypoglycemia awareness [12].

The Diabetes-Specific Quality-of-Life Scale (DSQOLS) was used to measure the impact of diabetes on quality of life [13,14], with lower scores indicating worse quality of life. The DSQOLS is sensitive to differences between various insulin regimens and includes 13 items that are specific to hypoglycemia. The DSQOLS was included in the Part 2 SAQ and comprised 57 diabetes-specific burden items assessing social aspects, dietary questions, physical complaints, daily hassles and anxiety about the future. Patients answered these questions using a 6-point Likert scale, with responses corresponding to agreement with each item statement and ranging from "very strongly agree" (score = 5) to "do not agree at all" (score = 0).

3.4. Hypoglycemia classification

Categories of hypoglycemia recorded in the questionnaire and patient diary included severe hypoglycemia (defined, based on the American Diabetes Association definition, as any hypoglycemic event requiring assistance of another person to administer carbohydrate, glucagon or other resuscitative actions [11]), any hypoglycemia (the sum of non-severe hypoglycemia [any event managed by the patient alone] and severe hypoglycemia), nocturnal hypoglycemia (any event occurring between midnight and 06:00 am) and BG-confirmed hypoglycemia (any event accompanied by BG < 3.1 mmol/L or <56 mg/dL).

3.5. Sample size

Target sample size was determined assuming a worst-case scenario proportion of patients (=50%) reporting at least one hypoglycemic event during the observation period, and assuming that the range of the 95% confidence intervals (95% CI) should be <3 percentage points for the total cohort (n = 6000).

3.6. Statistical analyses

Statistical tests were two-sided and regarded as exploratory, with the threshold for statistical significance set at $P < 0.05$. There was no adjustment for multiple comparisons, but p-values were interpreted conservatively (i.e. P-values from 0.01 to 0.05 were taken to indicate a modest evidence of a difference, and P-values of <0.01 were taken to indicate moderate evidence).

Baseline refers to data collected using the Part 1 SAQ; follow-up refers to data collected using the Part 2 SAQ and, where applicable, patient diaries.

The percentage of patients experiencing at least one hypoglycemic event was calculated together with the 95% CI for this percentage, assuming a binomial distribution.

4. Results

4.1. Patient characteristics

Overall, 7289 patients (1016 with T1D and 6273 with T2D) enrolled and completed the Part 1 SAQ and were included in the full analysis set (FAS). Of these, 6728 patients (92%; 912 with T1D and 5816 with T2D) completed the Part 2 SAQ in the prospective period of the study (i.e. 4 weeks from baseline and were included in the completers analysis set).

Baseline characteristics for patients with T1D or T2D in the FAS are described in Table 1. Patients with T1D were younger than those with T2D (35.0 years vs. 57.7 years, respectively) and had a longer median duration of insulin use (12.0 years vs. 5.0 years, respectively). Mean HbA_{1c} was lower in patients with T1D (8.3% [66.6 mmol/mol]) than in those with T2D (8.6% [70.7 mmol/mol]).

Only patients in Colombia were asked specifically about insulin-pump usage; 1.7% of patients in Colombia were using an insulin pump at baseline (10.2% of those with T1D [n = 104] and 0.4% of those with T2D [n = 23]).

4.2. Frequency of hypoglycemia

4.2.1. Overall hypoglycemia

In the 4-week prospective observational follow-up period, the percentage of patients reporting at least one hypoglycemic event was 97.4% with T1D and 95.3% with T2D. In the 4-week retrospective assessment period, the percentage of patients reporting at least one hypoglycemic event was higher with T1D than T2D (72.7% vs. 48.1%), and both were lower than the respective proportions during the prospective period. In T1D, the estimated incidence rates (IRs) of overall hypoglycemia increased from 4.81 (95% CI: 4.66–4.95) events PPPM in the 4-week retrospective period, to 6.86 (95% CI: 6.68–7.04) events PPPM in the 4-week prospective period (Fig. 2A). In T2D, the estimated IR of overall hypoglycemia increased from 1.59 (95% CI: 1.56–1.62) events PPPM in the 4-week retrospective period, to 2.37 (95% CI: 2.33–2.41) events PPPM in the 4-week prospective period (Fig. 3A).

4.2.2. Nocturnal hypoglycemia

The percentage of patients with nocturnal hypoglycemia was higher with T1D versus T2D, and decreased from the 4-week retrospective to the 4-week prospective period (44.9% [95% CI: 41.8–48.2] vs. 17.3% [95% CI: 16.4–18.3] and 40.9% [95% CI: 37.7–44.3] vs. 13.5% [95% CI: 12.6–14.4], respectively). In patients with T1D, the estimated IR of nocturnal hypoglycemia decreased from 1.83 (95% CI: 1.74–1.92) events PPPM in the 4-week retrospective period to 1.20 (95% CI: 1.13–1.28) events PPPM in the 4-week prospective period (Fig. 2B). In T2D, the estimated IR of nocturnal hypoglycemia decreased from 0.46 (95% CI: 0.44–0.47) events PPPM in the 4-week retrospective period to 0.28 (95% CI: 0.27–0.30) events PPPM in the 4-week prospective period (Fig. 3B). The incidence of nocturnal hypoglycemia increased with each quartile for duration of diabetes, duration of insulin therapy and frequency of glucose monitoring (Supplementary Table 1).

4.2.3. BG-confirmed hypoglycemia (<3.1 mmol/L [<56 mg/dL])

In the 4-week prospective observational follow-up period, the percentage of patients reporting at least one hypoglycemic event associated with a BG measurement < 3.1 mmol/L (56 mg/dL) was 48.0% (95% CI: 44.7–51.4) and 12.6% (95% CI: 11.7–13.5) with T1D and T2D respectively. The estimated IR was 2.10 (95% CI: 2.00–2.20) events PPPM for patients with T1D and 0.25 (95% CI: 0.24–0.26) for patients with T2D.

4.2.4. Severe hypoglycemia

In the 6-month retrospective assessment period, 50.6% (95% CI: 47.4–53.8) of patients with T1D and 49.0% (95% CI: 47.7–50.2) of patients with T2D experienced a severe hypoglycemic event. The estimated IR was 0.58 (95% CI: 0.56–0.60) events PPPM for patients with T1D and 0.25 (95% CI: 0.24–0.25) for patients with T2D. In the 4-week prospective assessment period, 48.6% (95% CI: 45.3–51.9) of patients with T1D and 66.7% (95% CI: 65.4–67.9) of patients with T2D experienced a severe hypoglycemic event. The estimated IR was 1.21 (95% CI: 1.14–1.29) events PPPM for patients with T1D and 0.92 (95% CI: 0.90–0.95) for patients with T2D. The incidence of severe

Table 1 – Baseline characteristics.

	T1D (*n* = 1016)	T2D (*n* = 6273)
Age, (years)	**35.0 (13.0)**	**57.7 (10.9)**
Median	32.0	58.0
Upper quartile, Lower quartile	42.5, 25.0	65.0, 51.0
Male/female (%)	**42.6/56.6**	**43.9/55.2**
Duration of diabetes (years)	**14.5 (9.8)**	**13.2 (7.7)**
Median	13.0	12.0
Upper quartile, Lower quartile	20.0, 7.0	18.0, 7.0
Duration of insulin use (years)	**13.5 (9.8)**	**6.1 (5.1)**
Median	12.0	5.0
Upper quartile, Lower quartile	19.0, 6.0	8.0, 2.0
HbA_{1c}		
%	8.3% (1.7)	8.6% (1.8)
mmol/mol	66.7 (18.1)	70.7 (20.1)
FBG		
mmol/L	8.7 (4.2)	8.9 (3.6)
mg/dL	156.6 (75.6)	160.2 (64.8)
PPG		
mmol/L	10.3 (4.7)	11.6 (4.4)
mg/dL	185.4 (84.6)	208.8 (79.2)
Weight (kg)	**68.8 (15.8)**	**77.5 (17.3)**
Median	66.0	75.0
Upper quartile, Lower quartile	78.0, 58.0	88.0, 65.0
Height (cm)	**165.7 (10.3)**	**162.7 (9.4)**
Median	165.0	162.0
Upper quartile, Lower quartile	173.0, 158.0	169.0, 156.0
BMI (kg/m^2)	**25.0 (4.8)**	**29.2 (5.9)**
Median	24.3	28.4
Upper quartile, Lower quartile	27.4, 21.7	32.4, 25.2
Previous medical illnesses (%)		
Neuropathy	28.0	46.3
Retinopathy	22.8	35.9
Peripheral vascular disease	11.8	18.1
Nephropathy	10.3	7.8
Myocardial infarction	2.1	11.7
Angina	5.6	13.9
None	53.8	30.8
Symptoms of diabetes-related complications (%)		
Any	98.4	91.6
Tremors	76.7	65.1
Sweating	85.8	71.9
Weakness	78.3	66.3
Inability to concentrate	78.1	49.1
Blurred vision	60.3	51.1
Diabetes treatment regimen (%)		
Short-acting insulin/insulin pump	17.5	4.8
Long-acting insulin	4.8	19.9
Pre-mix	14.1	38.8
Both short- and long-acting	59.3	32.7
Both short-acting and pre-mix	1.7	1.9
Both long-acting and pre-mix	1.3	1.2
Short- and long-acting and pre-mix	0.1	0.1
Missing	1.3	0.7

Data are presented as mean (SD) unless otherwise stated.

BMI, body mass index; FBG, fasting blood glucose; HbA_{1c}, glycated hemoglobin; N, total number of subjects participating; n, total number of subjects; PPG, postprandial glucose; SD, standard deviation; T1D, type 1 diabetes; T2D, type 2 diabetes.

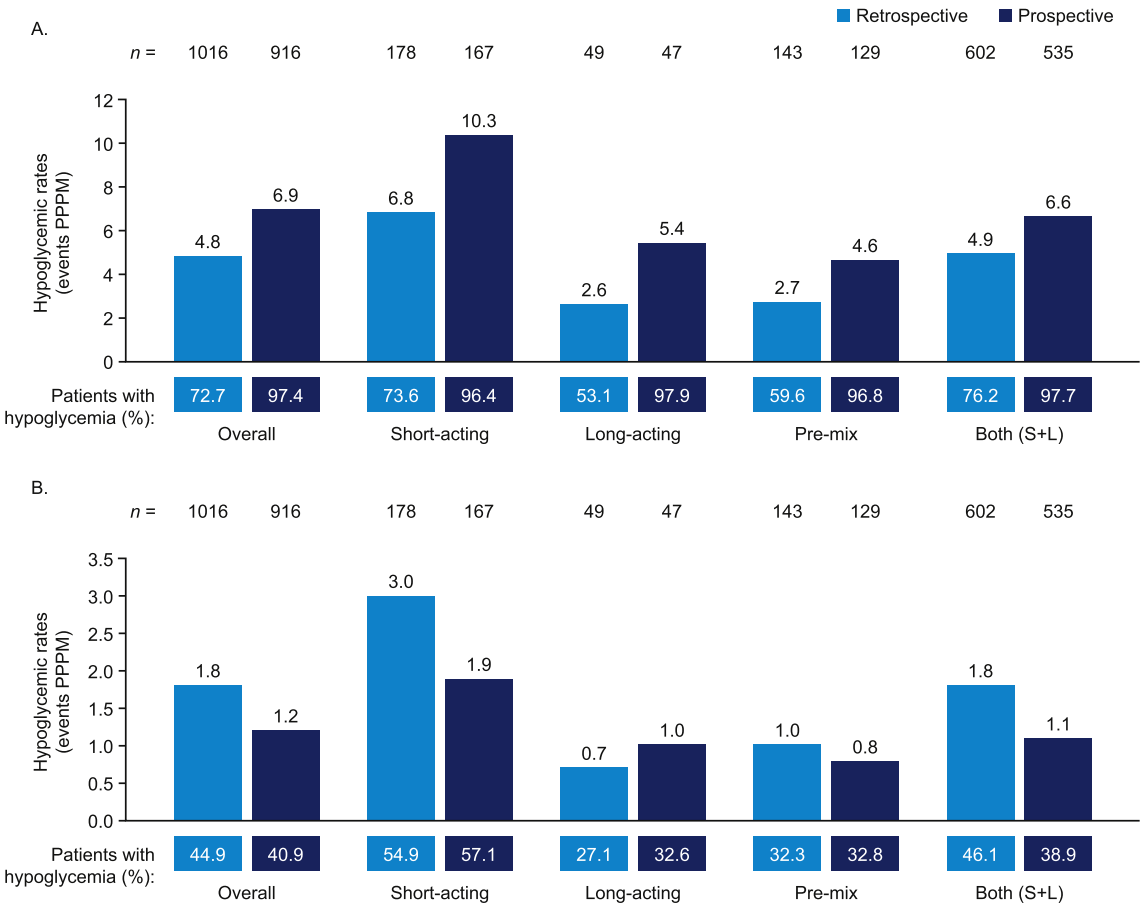

Fig. 2 – Estimated rate of (A) any hypoglycemic event, or (B) nocturnal hypoglycemic events, by insulin regimen in T1D. *n*, number of subjects; PPPM, per patient per month; S+L, short- plus long-acting; T1D, type 1 diabetes.

hypoglycemia showed no clear trend when stratified by frequency of BG monitoring (Supplementary Table 2).

4.2.5. *Hypoglycemia requiring hospital admission*

In the 6-month retrospective assessment period, 9.6% (95% CI: 7.8–11.6) of patients with T1D and 5.2% (95% CI: 4.7–5.8) of patients with T2D had hypoglycemic events requiring hospital admission. The estimated IR was 0.037 (95% CI: 0.032–0.042) events PPPM for patients with T1D, and 0.015 (95% CI: 0.014–0.017) events PPPM for patients with T2D. In the 4-week prospective period, 3.1% (95% CI: 2.0–4.4) of patients with T1D and 1.7% (95% CI: 1.3–2.0) of patients with T2D had hypoglycemic events requiring hospital admission. The estimated IR was 0.049 (95% CI: 0.035–0.067) events PPPM for patients with T1D and 0.026 (95% CI: 0.021–0.030) events PPPM for patients with T2D. Overall, the incidence of hypoglycemia requiring hospitalization was similar regardless of insulin regimen, duration of diabetes, duration of insulin therapy, and frequency of BG monitoring (Supplementary Table 3).

4.3. *Hypoglycemia by insulin regimen*

Incidence rates of overall and nocturnal hypoglycemia in T1D and T2D in the 4-week retrospective and 4-week prospective assessment periods by insulin regimen (short-acting, long-acting, pre-mix, and short- plus long-acting) are shown in Figs. 2 and 3. Estimated IRs of overall hypoglycemia increased whilst estimated IRs of nocturnal hypoglycemia generally decreased in the 4-week prospective period versus the 4-week retrospective period in patients with T1D and T2D.

The estimated IRs of any hypoglycemic events in the 4-week retrospective and 4-week prospective assessment periods were highest in patients with T1D using short-acting insulin/insulin pump (Fig.2A) and lowest in patients with T2D using long-acting insulin (Fig. 3A).

In the pooled T1D and T2D population, the rate ratios (RRs) for overall hypoglycemia were significantly lower in patients using pre-mix, long-acting and short- plus long-acting insulin compared with those using short-acting insulin/insulin pump (0.57 [95% CI: 0.50–0.64], 0.39 [0.34–0.45], and 0.70 [0.62–0.79]; $P < 0.001$ all comparisons vs. short-acting insulin/insulin pump as reference).

The IRs of nocturnal hypoglycemia in the 4-week retrospective and 4-week prospective periods were highest in patients with T1D using short-acting insulin/insulin pump (2.97 events PPPM [95% CI: 2.70–3.26] and 1.91 events PPPM [95% CI: 1.69–2.15], respectively; Fig. 2B), and lowest in patients with T2D using long-acting insulin (0.35 events PPPM [95% CI: 0.32–0.39] and 0.21 events PPPM [95% CI: 0.18–0.24], respectively; Fig. 3B).

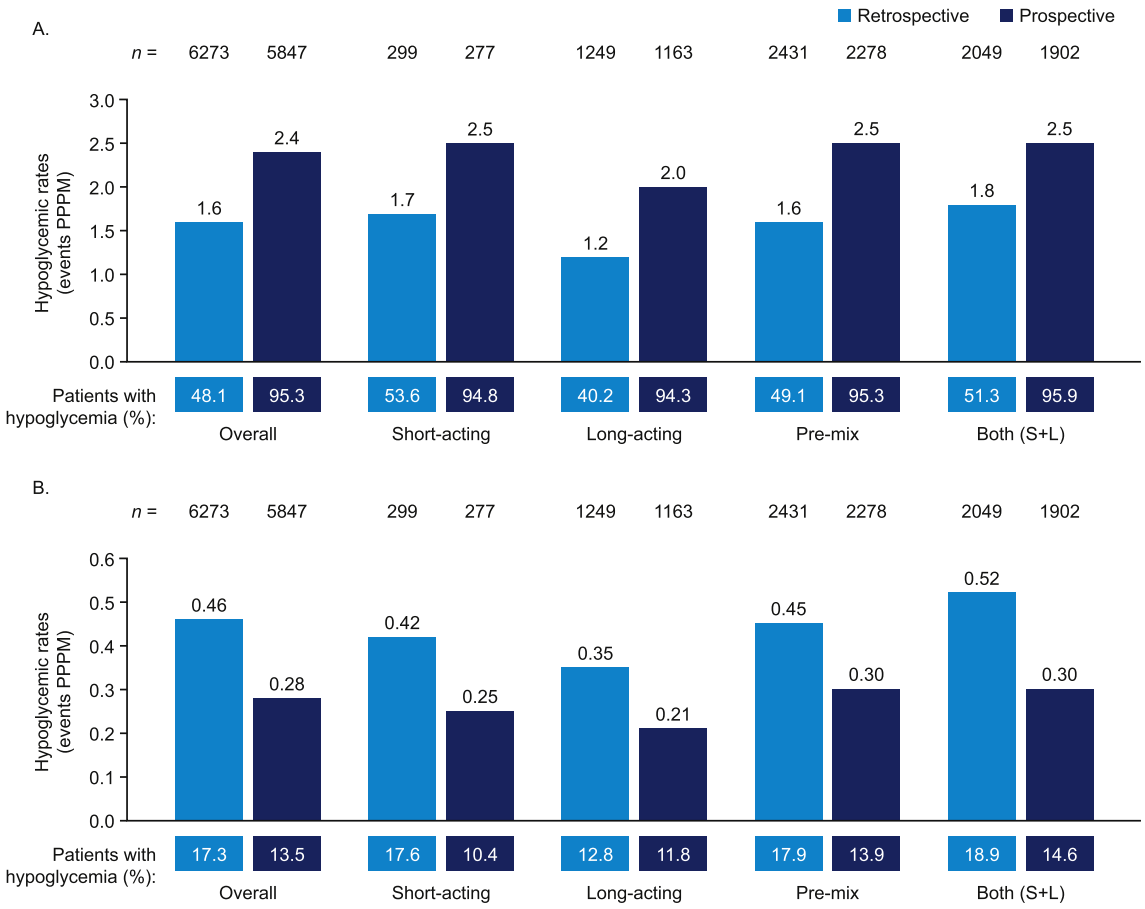

Fig. 3 – Estimated rate of (A) any hypoglycemic event, or (B) nocturnal hypoglycemic, by insulin regimen in T2D. *n*, number of subjects; PPPM, per patient per month; S+L, short- plus long-acting; T2D, type 2 diabetes.

4.4. *Impact of hypoglycemia on work/school*

Retrospective data demonstrated that hypoglycemia had a greater impact on work/school in patients with T1D compared with T2D (20.8% vs. 10.9% of patients had taken leave from work/school and 25.2% vs. 8.1% of patients had arrived late/left early from work/school, respectively). Of those patients who had taken leave or arrived late to/left early from work or studies, the mean number of days in the year before baseline assessment that the patients had taken off as a result of hypoglycemia was slightly higher in patients with T1D than those with T2D (1.5 days vs. 0.5 days). The mean was similar in the 4 weeks after baseline.

4.5. *Quality of life*

In the 4-week prospective period, patients with T1D had similar DSQOLS scores (59.2 ± 22.0) compared with those with T2D (55.1 ± 22.0) (Supplementary Table 4). Of relevance, the subscale scores for 'fear of hypoglycemia' were similar when comparing patients with T1D (56.2 ± 26.7) and T2D (55.2 ± 26.6). The lowest DSQOLS subscale scores were noted for 'dietary restrictions' (T1D: 51.6 ± 28.3; T2D: 44.5 ± 26.2), 'anxiety about future' (T1D: 46.7 ± 27.3; T2D: 46.2 ± 26.8) and 'daily hassles' (T1D: 54.5 ± 27.1; T2D: 50.7 ± 26.1).

4.6. *Patient perspectives*

Patient perspectives, including hypoglycemia awareness, fear of hypoglycemia, response to hypoglycemia and impact on the medical system, are described in Table 2.

More patients with T1D than with T2D had knowledge of hypoglycemia before reading the definition in the Part 1 SAQ (90.3% and 73.8%, respectively) and had slightly more hypoglycemia awareness. There were no notable differences between patients with T1D or T2D with respect to fear of hypoglycemia, with a mean (standard deviation) score of 5.5 (3.33) for patients with T1D and 4.5 (3.34) for patients with T2D.

More patients with T1D than with T2D were likely to consult their doctor/nurse and increase their glucose monitoring. The impact of hypoglycemia on the medical system (hospital admissions, additional clinic appointments, and telephone contacts) in the 6-month retrospective period was slightly higher than in the 4-week prospective period (both T1D and T2D).

4.7. *Associations between hypoglycemia and continuous or predictor variables*

Overall, fully adjusted negative binomial modeling showed that HbA_{1c} (%) and age were weakly correlated with the rate

Table 2 – Patient perspectives on hypoglycemia.

	T1D (n = 1016)		T2D (n = 6273)	
Knew what hypoglycemia was at baseline before Part 1 SAQ (%)	90.3		73.8	
Defined hypoglycemia based on (%):				
Symptoms only	42.9		46.9	
Blood glucose measurement only	5.0		5.5	
Either	15.6		11.7	
Both	32.6		22.0	
Hypoglycemia awareness (%)				
Normal	59.9		43.8	
Impaired	36.9		43.6	
Severely impaired	0.7		6.8	
Fear of hypoglycemia (scale of 0–10; %)				
0 = no fear	12.7		19.2	
1	4.3		5.9	
2	4.3		7.6	
3	7.1		8.2	
4	7.5		6.9	
5	13.2		13.4	
6	6.9		7.3	
7	9.5		8.1	
8	10.6		7.6	
9	6.2		4.2	
10 = absolutely terrified	17.1		10.8	
Patient response to hypoglycemia (%)	Retrospective (n = 1016)	Prospective (n = 912)	Retrospective (n = 6273)	Prospective (n = 5816)
Consulted their doctor/nurse	54.6	34.3	39.6	24.5
Required any form of medical assistance	56.0	34.9	41.0	24.8
Increased calorie intake	32.8	30.3	26.9	18.2
Avoided physical exercise	13.9	10.2	10.3	7.7
Reduced insulin dose	33.0	23.8	19.0	13.0
Skipped insulin injections	17.2	10.4	13.4	7.7
Increased blood glucose monitoring	51.6	43.8	28.0	20.0
Impact of hypoglycemic events on the medical system (%)	Retrospective (n = 917)	Prospective (n = 894)	Retrospective (n = 4987)	Prospective (n = 5591)
Events requiring hospital admission	10.5	3.0	6.5	1.7
Attended additional clinical appointments	10.8	5.8	7.5	4.3
Made additional telephone contacts	11.6	6.4	7.0	5.9

n, total number of subjects; SAQ, self-assessment questionnaire; T1D, type 1 diabetes; T2D, type 2 diabetes.

of any hypoglycemic events (incidence rate ratio [IRR] 0.96 [95% CI: 0.94–0.98] and IRR 0.99 [95% CI: 0.99–1.00], respectively; $P < 0.001$) in the pooled T1D and T2D populations. Patients with hypoglycemia unawareness (specifically, those who occasionally/never have symptoms with a low BG measurement) were less likely to report a hypoglycemic event (IRR 0.78 [95% CI 0.71–0.86]; $P < 0.001$).

5. Discussion

This multicenter, international, 6-month retrospective and 4-week prospective study with a two-part SAQ investigated the prevalence of hypoglycemia in insulin-treated adults with T1D or T2D. The primary objective of this study was to determine the percentage of patients experiencing at least one hypoglycemic event during the 4-week prospective period. The results represent the first patient-reported dataset on hypoglycemia in countries with no previously published data.

We report that the proportion of patients reporting at least one hypoglycemic event was higher during the prospective period of the study than during the retrospective period. This may reflect the fact that patient diaries were used in the prospective period to improve recall and better reflect RWD, whereas the retrospective data were based solely on SAQs that are more prone to recall bias. In contrast, the proportion of patients reporting nocturnal hypoglycemia was higher during the retrospective period of the study than during the prospective period. Several factors could have contributed to this. The definition of nocturnal hypoglycemia (midnight to 06:00 am) may have been observed more strictly by participants during the prospective study period compared with retrospective recall. Furthermore, fear of nocturnal

hypoglycemia may cause patients to believe these events are more frequent than they really are; therefore, patients may have reported more episodes of nocturnal hypoglycemia when asked to recall them retrospectively, but reported the actual number of events when they recorded them in the prospective period. In addition, the patient diary can be more difficult to complete at night, and this may have caused under-reporting of nocturnal hypoglycemia.

We further report rates of overall, nocturnal, and severe hypoglycemia in both T1D and T2D that are higher than previously reported in RCTs and observational studies, but aligned with those of the recent global HAT study [10,15–22]. The estimated IR of overall hypoglycemia in T1D within IO HAT (4.81–6.86 events PPPM) was considerably higher than previously reported in European clinical studies (0.08–0.14 events PPPM) [15–17], and somewhat higher than the rates from previous observational studies (1.82–6.35 events PPPM) [18–20]. The estimated IR of overall hypoglycemia in patients with T2D within IO HAT (1.59–2.38 events PPPM) was also considerably higher than previously reported in RCTs such as ACCORD (0.11 events PPPM) [21] and real-world epidemiological studies such as the VADT and PREDICTIVE trials (0.26–1.11 events PPPM) [18,22]. One consideration is that the study may have acted as a learning tool or reinforced the patients' knowledge about hypoglycemia, and might therefore have improved levels of reporting, particularly during the prospective period.

In addition, we reported BG-confirmed hypoglycemia (BG < 3.1 mmol/L [56 mg/dL]), which is similar to the threshold of 3.0 mmol/L [54 mg/dL] recently proposed by the International Hypoglycaemia Study Group [23], and considered sufficiently low to indicate serious, clinically important hypoglycemia. It is clear that while the incidence of hypoglycemia is lower using this threshold, i.e. when compared with the incidence of overall hypoglycemia (reported in IO HAT and other studies using a higher threshold), the incidence of hypoglycemia with a confirmed BG measurement < 3.1 mmol/L represents a considerable proportion of a patient's hypoglycemic events that are also clinically important.

Approximately 50% of patients with T1D and T2D experienced severe hypoglycemia in the 6-month retrospective assessment period, and 48.6% (T1D) and 66.7% (T2D) of patients experienced at least one severe event in the 4-week prospective period. These high frequencies may reflect the local characteristics and living conditions of people with diabetes in the non-Western developing countries included in the study. For example, patients living with family members may be more likely to receive 'assistance' by way of food or juice when they experienced hypoglycemia, and may therefore have recorded these events as severe (owing to their understanding of the ADA definition of severe hypoglycemia), regardless of the severity of their symptoms or blood sugar level. It should be noted that the high rates of severe hypoglycemic events did not result in high rates of hypoglycemia requiring hospitalization. This may further indicate that some of the 'severe' hypoglycemic events were mischaracterized, and highlights an additional need for patient education. Alternatively, this may indicate that while the frequency of severe hypoglycemia was high, patients have limited access to hospital care in some of the countries studied.

Similar to the overall incidence of any hypoglycemic event, IRs by insulin regimen for patients with T1D and T2D were higher during the prospective period than the retrospective period. Prospective IRs for patients with T1D or T2D using short-acting/insulin pump, long-acting, both short- and long-acting, pre-mix and other insulin regimens were broadly comparable with overall rates.

Taken together, these results indicate that the incidence of hypoglycemia may remain under-reported and under-estimated.

It is now well established that hypoglycemia impacts heavily on quality of life, wellbeing and productivity of patients with diabetes, and represents a significant burden and cost to healthcare systems [6,24–27]. Our SAQ confirmed the negative impact of insulin-treated diabetes on quality of life, with the DSQOLS score in our study tending to be somewhat lower than those reported in a previous assessment of T1D patients with established diabetes-related complications [14]. Notably low subscale DSQOLS scores in our study included those concerning 'anxiety about the future' and 'fear of hypoglycemia'.

The substantial impact of hypoglycemia on work and school attendance reported here confirms these previous findings and highlights that the impact is higher in T1D than T2D, with a quarter of patients with T1D in the IO HAT study reporting an impact on work/school attendance. The IO HAT study results also demonstrate the significant impact of hypoglycemia on the healthcare system and suggest that patients with T1D experiencing hypoglycemia require a higher level of healthcare provision than those with T2D.

The patient perspectives as reported in IO HAT support previous reports that patients with insulin-treated diabetes are increasingly aware of hypoglycemia, with the majority of patients understanding the definition of hypoglycemia at baseline and around half with hypoglycemia awareness [12,28]. Unsurprisingly, patients with hypoglycemia unawareness are less likely to report incidence of any hypoglycemic event. As shown by the results of this study, many patients with diabetes fear the unpleasant symptoms and consequences of hypoglycemia; there is evidence that this fear has a negative impact on metabolic control, diabetes management, health-related quality of life, and overall mental health [2,29,30].

Many clinicians believe that the risk of hypoglycemia is inversely associated with HbA_{1c} levels, based primarily on the evidence from the DCCT [31]. However, the results presented here support recent studies that failed to demonstrate a relationship between HbA_{1c} and hypoglycemia, suggesting that hypoglycemia is common at all levels of glycemic control [21,32]. The high incidence of hypoglycemia reported by patients in this study may therefore limit treatment intensification and further HbA_{1c} reduction, regardless of baseline HbA_{1c} level.

The observational nature and short prospective duration of the IO HAT study allowed for data to be collected from a large patient pool, from which meaningful observations regarding the real-life rates and impact of hypoglycemia could be made. However, these aspects of the study design

are also limitations of the IO HAT study. Another limitation of the study design is the effect of recall bias. It has been shown that patients with T1D are able to reliably recall information regarding severe hypoglycemia episodes up to 1 year following the episode date [12]; however, information on the reliability of recall in patients with T2D, or for milder hypoglycemic episodes, has not been documented. In addition, it is difficult to verify the patients' baseline characteristics due to the data collection methods (i.e. SAQs). The IO HAT study represents an advance on previous studies in estimating the prevalence of hypoglycemia, and the simplicity of the questionnaires, although limiting the amount of additional information available for subsequent sub-analyses may have contributed to the high completion rate. Patient diaries were used in the prospective period in addition to the Part 2 SAQ to reduce recall bias, and although this may have increased the reliability of data on prevalence of hypoglycemia, it also has the potential to overestimate hypoglycemia rates.

In IO HAT, as with previous self-reporting studies, patients were permitted to record a hypoglycemic episode by either symptoms or BG testing alone, or in combination. This approach represents both a strength and a limitation of the study; both aiding the capture of events in which patients forgot or neglected to test BG, did not know the BG concentration cut-off for hypoglycemia, or were unable to test due to a lack of testing devices/materials, but also introducing the potential for confounding due to the subjective nature of the assessment. The lack of newly diagnosed/treated patients (<12 months' insulin use) in IO HAT could affect the observed rates of hypoglycemia; however, this group represents only a small proportion of the total population with diabetes and is unlikely to have a significant effect on the mean values.

While the hypoglycemia rates reported in this study are higher than those reported elsewhere, living conditions and access to care in the IO HAT countries differ from those in countries typically included in studies conducted in Europe/America, and this disparity may contribute to the different hypoglycemia rates. Increasing patient knowledge of hypoglycemia, education in the proper use of insulin, and access to home glucose-monitoring equipment are important considerations that may help to reduce the incidence of hypoglycemia.

These results are the first patient-reported dataset on hypoglycemia in Bangladesh, Colombia, Egypt, Indonesia, Philippines, Singapore, South Africa, Turkey, and United Arab Emirates, and demonstrate that hypoglycemia is underreported and more widespread than previously believed. Patients reported higher rates of hypoglycemia (especially severe) during the prospective period. This could potentially be due to recall bias during the retrospective study period, or the impact of patient education, which is important for patients with diabetes. The results of this study strengthen the evidence that hypoglycemia causes patients to have decreased work productivity, increased healthcare utilization in the form of more doctor or nurse consultations, increased calorie intake and increased frequency of home BG monitoring. The results also demonstrate that patient education on hypoglycemia and the appropriate use of insulin remains essential. It is envisaged that these observations, together with those previously reported, will aid clinicians in better tailoring insulin treatment for patients with diabetes, particularly in regions where such data were previously unavailable.

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Author contributions

Design: AJ, ZM.
Conduct/data collection: All.
Analysis: All.
Writing manuscript: All.

Declaration of Interest

Rifat Emral: speaker fees from Novo Nordisk, MSD, AstraZeneca, Boehringer, Sanofi; participation in advisory boards for Novo Nordisk, Sanofi, AstraZeneca.

Faruque Pathan: participation in advisory panels for Novo Nordisk; board member of Novo Nordisk, Sanofi and Eli Lilly; employee of BIRDEM General Hospital, Dhaka Bangladesh; received research support from Novo Nordisk, Sanofi and Novartis and has taken part in speakers' bureaus for Novo Nordisk, Sanofi, Novartis, Eli Lilly and Life-Scan.

Carlos Augusto Yepes Cortés: speaker fees from Novo Nordisk, Eli Lilly, Medtronic, Janssen; participation in advisory boards for Eli Lilly, Novo Nordisk.

M. Hesham El-Hefnawy: no conflicts of interest.

Su-Yen Goh: on the local advisory boards of, and has received speaker honorariums from, the following companies: Novo Nordisk, Sanofi Aventis, Astra Zeneca, Boehringer Ingelheim, MSD and Eli Lilly.

Ana Maria Gómez: speaker fees from Novo Nordisk, MSD, AstraZeneca, Boehringer, Abbott, Medtronic; participation in advisory boards for Eli Lilly, Novo Nordisk; research grants from Abbott and Novartis.

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Anand Jain: employee of Novo Nordisk.

Zhulin Ma: employee of Novo Nordisk at the time of this study.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.diabres.2017.07.031.

REFERENCES

[1] Nakar S, Yitzhaki G, Rosenberg R, Vinker S. Transition to insulin in Type 2 diabetes: family physicians' misconception of patients' fears contributes to existing barriers. J Diabetes Complications 2007;21:220–6.

[2] Leiter LA, Boras D, Woo VC. Dosing irregularities and self-treated hypoglycemia in type 2 diabetes: results from the Canadian cohort of an international survey of patients and healthcare professionals. Can J Diabetes 2014;38:38–44.

[3] Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2015;38:140–9.

[4] Elliott L, Fidler C, Ditchfield A, Stissing T. Hypoglycemia event rates: a comparison between real-world data and randomized controlled trial populations in insulin-treated diabetes. Diabetes Ther 2016;7:45–60.

[5] Brod M, Wolden M, Groleau D, Bushnell DM. Understanding the economic, daily functioning, and diabetes management burden of non-severe nocturnal hypoglycemic events in Canada: differences between type 1 and type 2. J Med Econ 2014;17:11–20.

[6] Geelhoed-Duijvestijn PH, Pedersen-Bjergaard U, Weitgasser R, et al. Effects of patient-reported non-severe hypoglycemia on healthcare resource use, work-time loss, and wellbeing in insulin-treated patients with diabetes in seven European countries. J Med Econ 2013;16:1453–61.

[7] Ostenson CG, Geelhoed-Duijvestijn P, Lahtela J, et al. Self-reported non-severe hypoglycaemic events in Europe. Diabet Med 2014;31:92–101.

[8] Luddeke HJ, Sreenan S, Aczel S, et al. PREDICTIVE - a global, prospective observational study to evaluate insulin detemir treatment in types 1 and 2 diabetes: baseline characteristics and predictors of hypoglycaemia from the European cohort. Diabetes Obes Metab 2007;9:428–34.

[9] Munro N, Barnett AH. Incidence, worry and discussion about dosing irregularities and self-treated hypoglycaemia amongst HCPs and patients with type 2 diabetes: results from the UK cohort of the Global Attitudes of Patient and Physicians (GAPP2) survey. Int J Clin Pract 2014;68:692–9.

[10] Khunti K, Alsifri S, Aronson R, et al. Rates and predictors of hypoglycaemia in 27,585 people from 24 countries with insulin-treated type 1 and type 2 diabetes: the global HAT study. Diabetes Obes Metab 2016;18:907–15.

[11] Workgroup on Hypoglycemia. American Diabetes Association. Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia. Diabetes Care 2005;28:1245–9.

[12] Pedersen-Bjergaard U, Pramming S, Thorsteinsson B. Recall of severe hypoglycaemia and self-estimated state of awareness in type 1 diabetes. Diabetes Metab Res Rev 2003;19:232–40.

[13] Bott U, Muhlhauser I, Overmann H, Berger M. Validation of a diabetes-specific quality-of-life scale for patients with type 1 diabetes. Diabetes Care 1998;21:757–69.

[14] Cooke D, O'Hara MC, Beinart N, et al. Linguistic and psychometric validation of the diabetes-specific quality-of-life scale in U.K. English for adults with Type 1 diabetes. Diabetes Care 2013;36:1117–25.

[15] Pedersen-Bjergaard U, Pramming S, Heller SR, et al. Severe hypoglycaemia in 1076 adult patients with type 1 diabetes: influence of risk markers and selection. Diabetes Metab Res Rev 2004;20:479–86.

[16] MacLeod KM, Hepburn DA, Frier BM. Frequency and morbidity of severe hypoglycaemia in insulin-treated diabetic patients. Diabet Med 1993;10:238–45.

[17] ter Braak EW, Appelman AM, van de Laak M, et al. Clinical characteristics of type 1 diabetic patients with and without severe hypoglycemia. Diabetes Care 2000;23:1467–71.

[18] Dornhorst A, Luddeke HJ, Sreenan S, et al. Safety and efficacy of insulin detemir in clinical practice: 14-week follow-up data from type 1 and type 2 diabetes patients in the PREDICTIVE European cohort. Int J Clin Pract 2007;61:523–8.

[19] Agesen RM, Kristensen PL, Beck-Nielsen H, et al. Effect of insulin analogues on frequency of non-severe hypoglycaemia in patients with type 1 diabetes prone to severe hypoglycaemia: The HypoAna trial. Diabetes Metab 2016;42:249–55.

[20] UK Hypoglycaemia Study Group. Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. Diabetologia 2007;50:1140–7.

[21] Miller ME, Bonds DE, Gerstein HC, et al. The effects of baseline characteristics, glycaemia treatment approach, and glycated haemoglobin concentration on the risk of severe hypoglycaemia: post hoc epidemiological analysis of the ACCORD study. BMJ 2010;340:b5444.

[22] Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009;360:129–39.

[23] International Hypoglycaemia Study Group. Glucose concentrations of less than 3.0 mmol/L (54 mg/dL) should be reported in clinical trials: a joint position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 2017;40:155–7.

[24] Davis RE, Morrissey M, Peters JR, et al. Impact of hypoglycaemia on quality of life and productivity in type 1 and type 2 diabetes. Curr Med Res Opin 2005;21:1477–83.

[25] Brod M, Rana A, Barnett AH. Impact of self-treated hypoglycaemia in type 2 diabetes: a multinational survey in patients and physicians. Curr Med Res Opin 2012;28:1947–58.

[26] Brod M, Wolden M, Christensen T, Bushnell DM. Understanding the economic burden of nonsevere nocturnal hypoglycemic events: impact on work productivity, disease management, and resource utilization. Value Health 2013;16:1140–9.

[27] Frier BM, Jensen MM, Chubb BD. Hypoglycaemia in adults with insulin-treated diabetes in the UK: self-reported frequency and effects. Diabet Med 2016;33:1125–32.
[28] Barnett AH, Brice R, Hanif W, et al. Increasing awareness of hypoglycaemia in patients with type 2 diabetes treated with oral agents. Curr Med Res Opin 2013;29:1503–13.
[29] Shi L, Shao H, Zhao Y, Thomas NA. Is hypoglycemia fear independently associated with health-related quality of life? Health Qual Life Outcomes 2014;12:167.
[30] Wild D, von Maltzahn R, Brohan E, et al. A critical review of the literature on fear of hypoglycemia in diabetes: implications for diabetes management and patient education. Patient Educ Couns 2007;68:10–5.
[31] The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977–86.
[32] Lipska KJ, Warton EM, Huang ES, et al. HbA1c and risk of severe hypoglycemia in type 2 diabetes: the Diabetes and Aging Study. Diabetes Care 2013;36:3535–42.