Hypoglycaemia, irrespective of the definition used, is reduced when switching to insulin degludec from other basal insulins in routine clinical care: the ReFLeCT study

Michael D. Feher[1,2]; Gian Paolo Fadini[3]; Troels Krarup Hansen[4]; Johan Jendle[5]; Ángel Merchante[6,7]; Mette Marie Koefoed[8]; Ehsan Parvaresh Rizi[8]; Esther Zimmermann[8]; Harold W. de Valk[9]

[1]Beta Cell Diabetes Centre, Chelsea and Westminster Hospital, London, UK; [2]University of Surrey, Guildford, UK; [3]Department of Medicine, Division of Metabolic Diseases, University of Padova, Padova, Italy; [4]Steno Diabetes Center Aarhus, Aarhus University Hospital, Aarhus, Denmark; [5]Faculty of Medicine and Health, School of Medical Sciences, Örebro University, Örebro, Sweden; [6]University General Hospital of Castellón, Castellón de la Plana, Spain; [7]Jaume I University, Castellón de la Plana, Spain; [8]Novo Nordisk A/S, Søborg, Denmark; [9]Department of Internal Medicine, University Medical Center Utrecht, Utrecht, The Netherlands

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Background

- Hypoglycaemia is a frequent event in patients with diabetes treated with insulin and has been linked to impaired glycaemic control.[1,2]
- Randomised controlled trials have demonstrated that degludec is associated with less hypoglycaemia than with other basal insulins at equivalent glycaemic control, across a broad spectrum of patients with diabetes.[3–7]
- ReFLeCT (Results From Real-World Clinical Treatment with Tresiba®) was a multicentre, prospective, observational study that evaluated the safety and effectiveness of switching from other basal insulins to degludec, as part of routine clinical care, in patients with type 1 (T1D) or type 2 diabetes (T2D).[8,9]
- As different hypoglycaemia definitions can impact study outcomes, the present analysis of the ReFLeCT study analysed previous (pre-specified) and updated (*post hoc*) American Diabetes Association (ADA) hypoglycaemia definitions.

Aim

- The objective of this secondary analysis of the ReFLeCT study was to investigate the change in the rate of hypoglycaemia after switching to degludec from other basal insulins, according to different hypoglycaemia definitions, in patients with T1D or T2D.

Methods

ReFLeCT study

- ReFLeCT was a prospective, observational study conducted across seven European countries.[8,9]
- Patients aged ≥18 years with T1D or T2D who were already on insulin, and whose physician advised that they should switch to degludec treatment, were eligible for inclusion.[8,9]
- The study comprised a baseline period (4 weeks prior to switching to degludec) and a follow-up period (up to 12 months after switching to degludec).[8,9]
- Patients attended visits according to routine clinical practice, and could attend up to four visits during the 12-month follow-up period.
- Patients were instructed to complete 4-week study diaries prior to each visit, collecting day-by-day information on hypoglycaemic events.
- The primary endpoint was the change from the baseline period in the number of overall hypoglycaemic events during the 12-month follow-up period.[8,9]
- In ReFLeCT, switching to degludec from other basal insulins was associated with significantly reduced rates of overall hypoglycaemia in combination with improved glycaemic control in insulin-treated adults with T1D or T2D.[8,9]

Hypoglycaemia definitions

- The hypoglycaemia definitions included in this analysis consisted of:
  - Previous (pre-specified) ADA definitions
    - **Asymptomatic hypoglycaemia:** an event not accompanied by typical symptoms of hypoglycaemia but with a measured plasma glucose concentration ≤3.9 mmol/L (70 mg/dL).[10]
    - **Documented symptomatic hypoglycaemia:** an event during which typical symptoms of hypoglycaemia are accompanied by a measured plasma glucose concentration ≤3.9 mmol/L (70 mg/dL).[10]
    - **Pseudo-hypoglycaemia:** an event during which the person with diabetes reports any of the typical symptoms of hypoglycaemia with a measured plasma glucose concentration >3.9 mmol/L (70 mg/dL) but approaching that level.[10]
    - **Probable symptomatic hypoglycaemia:** an event during which symptoms typical of hypoglycaemia are not accompanied by a plasma glucose determination but that was presumably caused by a plasma glucose concentration ≤3.9 mmol/L (70 mg/dL).[10]
    - **Severe hypoglycaemia (Level 3 hypoglycaemia):** severe hypoglycaemia, denoted by severe cognitive impairment that requires external assistance for recovery.[10–12]
  - Updated (*post hoc*) ADA definitions
    - **Level 2 hypoglycaemia:** an event with a measured plasma glucose concentration <3.0 mmol/L (54 mg/dL) indicating serious, clinically important hypoglycaemia.[11,12]
    - **Level 1 hypoglycaemia:** an event with a measured plasma glucose concentration ≥3.0–<3.9 mmol/L (54–70 mg/dL).[11,12]

Statistical analysis

- The numbers of hypoglycaemic events were converted to rates per patient-year of exposure for analysis purposes.
- Rate ratios for hypoglycaemia between the 4-week baseline and 12-month follow-up periods, according to different definitions, were analysed using negative binomial regression specifying a log-transformed follow-up time offset term adjusted for baseline covariates. Baseline covariates included period (pre/post-switch to degludec), baseline HbA_{1c}, gender, body mass index, duration of diabetes, age and country, in addition to bolus insulin (Yes/No) and sulfonylureas or glinides (Yes/No) for T2D.
- All statistical tests were two-sided with a significance level of $p<0.05$.

Results

- Baseline characteristics from the overall ReFLeCT study are presented in Table 1.
- Seventy (12.6%) patients in the T1D group and 67 (11.0%) in the T2D group withdrew from the study during the follow-up period.
- In total, 481 patients with T1D and 516 patients with T2D contributed to the present analysis with diary data and complete covariate information.

T1D

- Estimated rate ratios (ERRs) demonstrated significantly lower rates of hypoglycaemia across the previous ADA hypoglycaemia definitions during the 12-month follow-up versus the 4-week baseline period, except for asymptomatic hypoglycaemia in patients with T1D (Figure 1a).
- ERRs also demonstrated significantly lower rates of hypoglycaemia for the updated ADA definitions during the 12-month follow-up versus the baseline period (Figure 1a).

T2D

- ERRs demonstrated significantly lower rates of hypoglycaemia across all previous ADA hypoglycaemia definitions during the 12-month follow-up versus the 4-week baseline period in patients with T2D (Figure 1b). The number of Level 3 hypoglycaemic events in patients with T2D was insufficient to allow for statistical comparison.
- ERRs also demonstrated significantly lower rates of hypoglycaemia for the updated ADA definitions for hypoglycaemia during the 12-month follow-up versus the baseline period (Figure 1b).

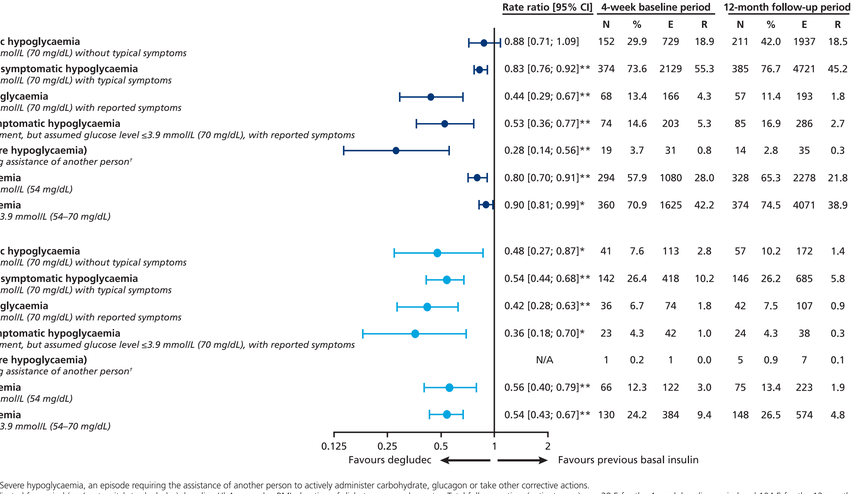
Table 1: Baseline characteristics of patients

	T1D	T2D
Full analysis set, n	556	611
Age, years	47.4 (15.7)	65.2 (9.6)
Female/male, %	44.2/55.8	40.4/59.6
Duration of diabetes, years	21.4 (13.5)	18.0 (9.5)
BMI, kg/m²	26.1 (4.7)	31.1 (6.3)
Body weight, kg	76.4 (15.6)	87.6 (19.6)
HbA_{1c}, %	8.1 (1.3)	8.2 (1.4)
FPG, mmol/L mg/dL	8.8 (3.9) 159 (70)	9.0 (3.1) 162 (56)
Antidiabetic therapies at baseline, n (%) Proportion on basal insulin Proportion on bolus insulin Proportion on ≥1 non-insulin antidiabetic therapy	 556 (100.0) 508 (91.4) 54 (9.7)	 611 (100.0) 384 (62.8) 379 (62.0)

Data are mean (SD), unless otherwise specified.
BMI, body mass index; FPG, fasting plasma glucose; SD, standard deviation; T1D, type 1 diabetes; T2D, type 2 diabetes.

Figure 1: Rate ratios of hypoglycaemia according to different hypoglycaemia definitions in patients with (a) T1D and (b) T2D

Key result



*$p<0.05$; **$p<0.001$. †Severe hypoglycaemia, an episode requiring the assistance of another person to actively administer carbohydrate, glucagon or take other corrective actions.
Fig 1a: Models were adjusted for period (pre/post-switch to degludec), baseline HbA_{1c}, gender, BMI, duration of diabetes, age and country. Total follow-up time (patient years) was 38.5 for the 4-week baseline period and 104.5 for the 12-month follow-up period.
Fig 1b: Models were adjusted for period (pre/post-switch to degludec), baseline HbA_{1c}, gender, BMI, duration of diabetes, bolus insulin (Yes/No), sulfonylureas or glinides (Yes/No), age and country. Total follow-up time (patient years) was 40.8 for the 4-week baseline period and 118.8 for the 12-month follow-up period.
%, percentage of patients with an event; ADA, American Diabetes Association; BMI, body mass index; CI, confidence interval; E, number of events; R, rate of events per patient-year of exposure; N, number of patients with an event; T1D, type 1 diabetes; T2D, type 2 diabetes.

Conclusions

- Switching to degludec from other basal insulins in routine clinical practice was generally associated with lower rates of hypoglycaemia when using different hypoglycaemia definitions in patients with diabetes.
- Definitions for Level 1, 2 and 3 hypoglycaemia were well represented in the rate of events and for the change between the baseline and follow-up periods (except for Level 3 hypoglycaemia for T2D), strengthening the generalisability of the results from this study.
- This analysis of ReFLeCT corroborates the findings of the primary study that switching to degludec from other basal insulins is associated with reduced rates of overall hypoglycaemia in patients with T1D and T2D in routine clinical care.

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