Insulin degludec and insulin glargine have similar frequency of exercise-related hypoglycaemia

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Introduction

- Insulin degludec (IDeg) is a new basal insulin that forms long chains of soluble multi-hexamers upon subcutaneous injection resulting in a flat and stable profile with an ultra-long duration of action lasting more than 42 hours.
- In the IDeg clinical development programme, significantly lower rates of overall confirmed hypoglycaemic episodes were reported with IDeg compared with insulin glargine (IGlar) in the type 2 diabetes (T2D) population, with significantly lower nocturnal confirmed episodes in both T2D and type 1 diabetes (T1D) populations.[1]
- During exercise, increased glucose requirements as well as increased insulin sensitivity can lead to an increased risk for hypoglycaemia in patients with diabetes. Exercise intensity, dose timing and the individual pharmacodynamic properties of insulin can affect the risk of hypoglycaemia.
- The aim of this study was to evaluate if there was a difference between IDeg and IGlar for reporting of exercise-related hypoglycaemic episodes in the Phase 3a clinical program.

Methods

- All seven trials (five T2D and two T1D) in this *post-hoc* analysis were randomised, open-label, treat-to-target trials of 26 or 52 weeks' duration with IDeg or IGlar administered once daily.[2–8]
- Patients reported hypoglycaemic episodes in their subject diaries and were instructed to note any relation to exercise (based on their own judgment).
- The numbers of patients reporting exercise-related hypoglycaemic episodes are presented as percentages of the total number of patients with confirmed hypoglycaemia in each group.

Methods – Definitions

- Confirmed hypoglycaemia was defined as plasma glucose <3.1 mmol/L (56 mg/dL) or severe episodes requiring assistance.
- Nocturnal hypoglycaemia was defined as confirmed episodes occurring between 00:01 and 05:59.

Results – Baseline characteristics

- This meta-analysis analysed 4,714 patients (3,288 for IDeg vs. 1,426 for IGlar, reflecting the unequal randomisation in different trials [2:1 or 3:1]).
- Baseline characteristics of all patients who reported ≥1 confirmed hypoglycaemic episode are presented in Table 1. There were no differences in age, BMI, or duration of diabetes for the patients whose hypoglycaemia was exercise-related compared to the total populations of patients with confirmed hypoglycaemia.

Results – Exercise-related hypoglycaemic episodes

- There was no difference in exercise-related hypoglycaemia across the patient groups for IDeg *versus* IGlar.
- Of the patients with T1D who reported ≥1 confirmed hypoglycaemic episode, 79.8% (IDeg) and 79.9% (IGlar) reported an episode as related to exercise (Table 2 and Figure 1).
- Of the patients with T2D treated with basal–bolus therapy who reported ≥1 confirmed hypoglycaemic episode, 51.1% (IDeg) and 51.5% (IGlar) reported an episode as related to exercise (Table 2 and Figure 1).
- Of the patients with T2D treated with basal–oral therapy who reported ≥1 confirmed hypoglycaemic episode, 20.9% (IDeg) and 21.8% (IGlar) reported an episode as related to exercise (Table 2 and Figure 1).

Results – Exercise-related nocturnal confirmed hypoglycaemic episodes

- Few patients reported nocturnal confirmed hypoglycaemic episodes that were related to exercise.
- Exercise-related nocturnal hypoglycaemia was more commonly reported by patients with T1D compared with patients with T2D with either basal–bolus or basal–oral therapies (Table 3 and Figure 2).
- There was no difference in exercise-related hypoglycaemia across the patient groups for IDeg *versus* IGlar (Table 3 and Figure 2).

Table 1 Baseline characteristics of total patients with confirmed hypoglycaemia and who experienced ≥1 exercise-related hypoglycaemic episode.

Population	T1D		T2D basal–bolus therapy		T2D basal–oral therapy	
Type of hypoglycaemic episode	≥1 confirmed	≥1 exercise-related confirmed	≥1 confirmed	≥1 exercise-related confirmed	≥1 confirmed	≥1 exercise-related confirmed
Total patients, n	1072	856	815	417	1159	246
Sex, n (%) Female Male	 450 (42.0) 622 (58.0)	 340 (39.7) 516 (60.3)	 380 (46.6) 435 (53.4)	 188 (45.1) 229 (54.9)	 501 (43.2) 658 (56.8)	 93 (37.8) 153 (62.2)
Age, years	43.2 (13.4)	43.7 (13.2)	59.4 (9.3)	58.9 (9.4)	58.8 (9.4)	59.0 (9.1)
BMI, kg/m^2	26.5 (3.8)	26.4 (3.8)	32.2 (4.7)	32.0 (4.7)	28.9 (4.9)	28.4 (4.3)
Duration of diabetes, years	18.7 (12.1)	18.8 (12.2)	13.9 (7.2)	14.3 (7.3)	10.4 (6.7)	10.6 (6.6)

Values are mean (SD) unless otherwise stated. T1D = type 1 diabetes; T2D = type 2 diabetes; n = number of patients; BMI = body mass index; SD = standard deviation. Trials: T1D: NN1250-3770, NN1250-3583 (both basal–bolus therapy), T2D: NN1250-3586, NN1250-3668, NN1250-3672, NN1250-3579 (all basal ± oral), NN1250-3582 (basal–bolus therapy). Trials were unequally randomised (IDeg:IGlar – 2:1 or 3:1). Safety analysis set: subjects exposed to ≥1 dose of trial product.

Table 2 Confirmed hypoglycaemia related to exercise.

Population	T1D		T2D basal–bolus therapy		T2D basal–oral therapy	
Treatment	IDeg	IGlar	IDeg	IGlar	IDeg	IGlar
Total patients with ≥1 confirmed hypoglycaemic episode, n	769	303	609	206	779	380
Total patients with ≥1 exercise-related confirmed hypoglycaemic episode, n, (%)	614 (79.8)	242 (79.9)	311 (51.1)	106 (51.5)	163 (20.9)	83 (21.8)

T1D = type 1 diabetes; T2D = type 2 diabetes; IDeg = insulin degludec; IGlar = insulin glargine; n = number of patients. Trials were unequally randomised (IDeg:IGlar – 2:1 or 3:1). A modified version of this table was originally published with the abstract.

Figure 1 Proportion of patients with confirmed hypoglycaemia who reported ≥1 episode related to exercise.

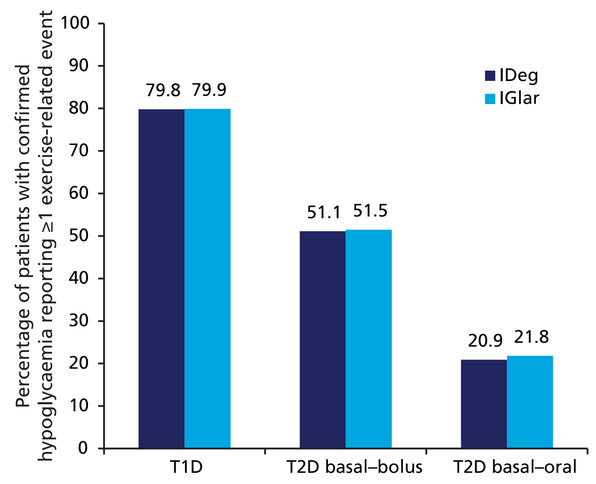
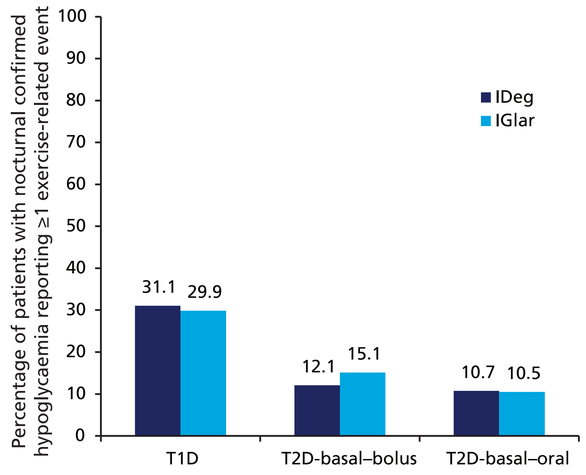


Table 3 Nocturnal confirmed hypoglycaemia related to exercise.

Population	T1D		T2D basal–bolus therapy		T2D basal–oral therapy	
Treatment	IDeg	IGlar	IDeg	IGlar	IDeg	IGlar
Total patients with ≥1 nocturnal confirmed hypoglycaemic episode, n	573	231	298	119	233	143
Total patients with ≥1 exercise-related nocturnal confirmed hypoglycaemic episode, n (%)	178 (31.1)	69 (29.9)	36 (12.1)	18 (15.1)	25 (10.7)	15 (10.5)

T1D = type 1 diabetes; T2D = type 2 diabetes; IDeg = insulin degludec; IGlar = insulin glargine; n = number of patients. Trials were unequally randomised (IDeg:IGlar – 2:1 or 3:1).

Figure 2 Proportion of patients with nocturnal confirmed hypoglycaemia who reported ≥1 episode related to exercise.



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Conclusions

- In both treatment arms, more patients with T1D reported hypoglycaemia related to exercise compared with T2D.
- Exercise-related hypoglycaemia was more common in basal–bolus treated patients (all patients with T1D and a subset of patients with T2D). Among the patients with T2D, a higher percentage of patients treated with basal–bolus therapy had exercise-related hypoglycaemia, compared with those treated with basal–oral therapy. Thus, the timing and dose of the bolus of insulin may need to be adjusted based on the intensity and duration of exercise.
- The proportions of patients reporting exercise-related hypoglycaemia, both confirmed and nocturnal, were similar between IDeg and IGlar for all patient groups. Therefore, there was no increased risk of self-reported hypoglycaemia related to exercise with IDeg compared with IGlar.

This trial was sponsored by Novo Nordisk and is registered with ClinicalTrials.gov (NCT00982228, NCT01059799, NCT01079234, NCT00972283, NCT01068665, NCT00982644, NCT01006291).
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