Research: Complications

A meta-analysis of rate ratios for nocturnal confirmed hypoglycaemia with insulin degludec vs. insulin glargine using different definitions for hypoglycaemia

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Abstract

Aims A prospective meta-analysis of phase 3 trials showed lower rates of nocturnal hypoglycaemia with insulin degludec vs. insulin glargine. We investigated the consistency of the results across different definitions of hypoglycaemia.

Methods This post-hoc, patient-level meta-analysis included six randomized, controlled, 26- or 52-week phase 3a trials in insulin-naïve participants with Type 2 diabetes mellitus (Type 2 diabetes$_{insulin\ naïve}$), participants with Type 2 diabetes mellitus using basal−bolus therapy (Type 2 diabetes$_{BB}$) and those with Type 1 diabetes mellitus. We used three definitions of hypoglycaemia and different timescales for the nocturnal period. Rates were analysed for the entire core trial period, the 'maintenance period' only, and the extension trial set population. Analyses utilized a negative binomial regression model.

Results In Type 2 diabetes$_{insulin\ naïve}$ participants, risk of nocturnal hypoglycaemia was significantly lower with insulin degludec vs. insulin glargine for all hypoglycaemia definitions and trial periods. Risk was also lower for the timescale 21.59–05.59, but not 00.01–07.59. For Type 2 diabetes$_{BB}$, nocturnal hypoglycaemia rates were lower with insulin degludec vs. insulin glargine across all definitions, timescales and trial periods, with one exception. For individuals with Type 1 diabetes mellitus, nocturnal hypoglycaemia risk was significantly lower with insulin degludec during the maintenance period for the original definition (plasma glucose < 3.1 mmol/l, timescale 00.01–05.59) and in the extension trial set population for all hypoglycaemia definitions except for the nocturnal timescale 00.01–07.59.

Conclusions Compared with insulin glargine, insulin degludec is associated with lower rates of nocturnal hypoglycaemia in people with Type 2 diabetes mellitus, and similar or lower rates in Type 1 diabetes mellitus, across different definitions.

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Introduction

Insulin degludec is a recently developed basal insulin analogue with an ultra-long duration of action and a flatter and more stable pharmacokinetic and pharmacodynamic profile, with less variability in glucose-lowering activity, compared with insulin glargine [1,2]. The efficacy and safety of insulin degludec have been examined in an extensive phase 3a programme (BEGIN). This included seven treat-to-target clinical trials in which insulin degludec was compared with insulin glargine [3–9], showing similar glycaemic control when titrated to the same targets. A prospectively planned meta-analysis of the seven trials showed that rates of overall and nocturnal hypoglycaemia were significantly lower with insulin degludec compared with insulin glargine in participants with Type 2 diabetes mellitus [10]. This meta-analysis was made possible because a consistent definition of hypoglycaemia was used in all the trials: self-reported confirmed events with plasma glucose < 3.1 mmol/l (56 mg/dl), or severe events requiring assistance. Nocturnal events were defined as those occurring between 00.01 and 05.59, inclusive [10].

Lower rates of nocturnal hypoglycaemia may have specific benefits, as even non-severe nocturnal hypoglycaemic events have been shown to have a greater negative impact on

What's new?

· This meta-analysis investigated the rate of nocturnal hypoglycaemia using different definitions of hypoglycaemia and of the nocturnal timescale in participants treated with insulin glargine or insulin degludec from phase 3a trials.

· Insulin degludec was associated with lower rates of nocturnal hypoglycaemia in participants with Type 2 diabetes mellitus, and lower or similar rates in participants with Type 1 diabetes mellitus across all definitions.

· Insulin degludec may help patients reach and maintain glucose targets, and reduce the frequency of nocturnal hypoglycaemia and its negative impact on patients' daily lives.

patients than previously believed, affecting their sleep and their functioning and productivity the next day [11,12]. The development of nocturnal hypoglycaemia is particularly problematic because basal insulins have traditionally been titrated to ambitious fasting plasma glucose targets with evening dosing.

The threshold value of 3.1 mmol/l for defining hypoglycaemia was chosen because it represented a degree of hypoglycaemia at which patients typically report symptoms [10,13] and was in line with the guidelines of the European Medicines Agency at the time [14]. For physicians who are deciding on the best choice of therapy for patients with problematic hypoglycaemia, it is important to know whether the benefit seen with insulin degludec is consistent across different definitions. Therefore, in the analyses reported here, we investigated how robust the estimated rate differences are when the sensitivity or specificity of the hypoglycaemia definition is changed. The sensitivity of the definition was increased by considering the American Diabetes Association (ADA) cut-off for defining hypoglycaemia [blood glucose < 3.9 mmol/l (70 mg/dl)] [15], whereas the specificity was increased by restricting the definition to cover only hypoglycaemic events that were reported with symptoms. Furthermore, we also expanded the time interval for nocturnal hypoglycaemia by 2 h either in the late evening or in the early morning. Additionally, we investigated whether the titration of the insulin preparation influenced the treatment difference, by considering rate ratios in the maintenance period, and finally whether the treatment difference was sustained in the long term, by including finalized extension trials in the analysis.

Methods

This post-hoc, patient-level meta-analysis included six randomized, controlled, open-label, multicentre, phase 3a,

treat-to-target trials of 26 or 52 weeks' duration in participants with diabetes. Trials were categorized as in the original prospectively planned meta-analysis; for Type 2 diabetes mellitus, analysis was restricted to trials in which participants were either insulin-naïve or using a basal–bolus regimen [10]. Three trials were in insulin-naïve participants with Type 2 diabetes mellitus (Type 2 diabetes$_{insulin\ naïve}$); one trial was in participants with Type 2 diabetes mellitus treated with a basal–bolus regimen (Type 2 diabetes$_{BB}$); and two trials were in participants with Type 1 diabetes mellitus. The BEGIN FLEX trial, which enrolled both insulin-naïve participants and those already on basal insulin [6], was therefore excluded. All trials were registered at Clinicaltrials.gov as follows: BEGIN Once Long and BEGIN Once Long extension: NCT00982644; BEGIN Once Asia: NCT01059799; BEGIN Low Volume: NCT01068665; BEGIN BB: NCT00972283; BEGIN BB extension: NCT01190956; BEGIN BB T1 Long: NCT00982228; BEGIN BB T1 Long extension: NCT01193322; BEGIN Flex T1 and BEGIN FLEX T1 Extension: NCT01079234.

In all the trials, confirmed hypoglycaemia was defined as episodes with a measured plasma glucose concentration of < 3.1 mmol/l or severe episodes necessitating assistance, and the nocturnal period was defined as 00.01–05.59 inclusive. In addition to this original definition, we performed sensitivity analyses using two further definitions for reporting hypoglycaemia: only confirmed hypoglycaemic episodes that were accompanied by symptoms (i.e. a more specific definition) and the ADA definition (symptomatic event and plasma glucose ≤3.9 mmol/l, i.e. a more sensitive definition). To test the robustness of the results, we also performed analyses in which 2 h were added to either end of the nocturnal period (Fig. 1).

Furthermore, we analysed rates of nocturnal hypoglycaemia for different trial periods: the entire core trial period, the 'maintenance period' only and the extension period (Table 1). In the BEGIN trial programme, separate analysis of the maintenance period (week 16 onwards, after stable glycaemic control and stable insulin dose had usually been achieved following active titration) was included at the specific request of the regulatory authorities. The extension period applied to the four trials that were continued for a longer duration (one trial in Type 2 diabetes$_{insulin\ naïve}$, one trial in Type 2 diabetes$_{BB}$ and two trials in Type 1 diabetes mellitus) (Table 1) [9,16–18]. In the analyses reported here, the term 'extension set' refers to the full duration of the trials concerned (core trial plus extension period).

The number of episodes was analysed using the same model that was employed in the previous meta-analysis – a negative binomial regression model using a log link and the logarithm of the exposure time (100 years) as offset. The model included treatment, sex, region, anti-diabetic treatment at screening and trial as fixed effects and age as covariate. For the Type 2 diabetes$_{BB}$ group, trial was not

	Analysis	Description
Definition of hypoglycaemia	I. Nocturnal confirmed hypoglycaemia (original)	Episodes confirmed by a plasma glucose of <3.1 mmol/L (56 mg/dL) and severe episodes, occurring between 00:01 and 05:59 (both inclusive)
	II. Nocturnal confirmed symptomatic hypoglycaemia	Episodes confirmed by a plasma glucose of <3.1 mmol/L (56 mg/dL) accompanied by reported symptoms, and severe episodes, occurring between 00:01 and 05:59 (both inclusive)
	III. Nocturnal ADA documented symptomatic hypoglycaemia	Symptomatic episodes confirmed by a plasma glucose of <3.9 mmol/L (70 mg/dL) and severe episodes, occurring between 00:01 and 05:59 (both inclusive)
Timescales for nocturnal period	IV. Nocturnal confirmed hypoglycaemia (21:59–5:59)	Episodes confirmed by a plasma glucose of <3.1 mmol/L (56 mg/dL) and severe episodes, occurring between 21:59 and 05:59 (both inclusive)
	V. Nocturnal confirmed hypoglycaemia (00:01–7:59)	Episodes confirmed by a plasma glucose of <3.1 mmol/L (56 mg/dL) and severe episodes, occurring between 00:01 and 07:59 (both inclusive)

All analysed for the following trial periods:

Entire core trial period	Week 0 to end of trial (up to 52 weeks)
Maintenance period only	Week 16 to end of trial (up to 52 weeks)
Extension set	Week 0 to end of extension period (up to 104 weeks for type 2 DM$_{insulin-naïve}$ and type 1 DM, 78 weeks for type 2 DM$_{BB}$)

FIGURE 1 Description of the different analyses that were conducted.

included as a covariate. The results are shown as estimated treatment rate ratios with their two-sided 95% confidence intervals (CIs).

Results

Trial characteristics and study participants

Demographic characteristics for the groups in each trial are shown in Table 2. In each trial, baseline characteristics and demographics and withdrawal rates were similar between treatment groups.

For all the patient populations, the estimated number of episodes per 100 patient-years of exposure (PYE) are shown in Table 3.

Insulin-naïve people with Type 2 diabetes mellitus

From Table 3(a) it can be seen that for the Type 2 diabetes$_{insulin\ naïve}$ population, estimated rates of nocturnal hypoglycaemia were consistently lower with insulin degludec vs. insulin glargine, with the difference ranging between 5 and 44 episodes per 100 PYE, depending on definition of hypoglycaemia and nocturnal period. For this population, treatment with insulin degludec was associated with significantly lower rates of nocturnal hypoglycaemia using all three definitions for reporting hypoglycaemia, and for all trial periods (Fig. 2a).

With different defined times for the nocturnal period, these participants still had a lower risk of nocturnal hypoglycaemia with insulin degludec compared with insulin glargine for the period between 21.59 and 05.59 (Fig. 2a). For the

extended timescale of 0.01–07.59, however, the risk was lower only during the maintenance period. It is notable that adding these two morning hours to the definition resulted in a two- to threefold increase in the number of episodes per 100 PYE (e.g. from 24.3 to 75.1 with insulin degludec, and from 38.0 to 80.7 with insulin glargine, for the entire period) (Table 3a).

Participants with Type 2 diabetes mellitus using basal−bolus therapy

For the Type 2 diabetes$_{BB}$ participants, estimated rates of nocturnal hypoglycaemia were lower with insulin degludec vs. insulin glargine by between 37 and 74 episodes per 100 PYE across the different definitions (Table 3b). Treatment with insulin degludec was associated with significantly lower rates of nocturnal hypoglycaemia across all definitions, all nocturnal timescales and all trial periods, compared with insulin glargine, with one exception: in the original definition, the 95% CI upper limit reached 1 for the maintenance period (Fig. 2b).

Participants with Type 1 diabetes mellitus

For participants with Type 1 diabetes mellitus, estimated rates of nocturnal hypoglycaemia were lower with insulin degludec vs. insulin glargine by between 97 and 203 episodes per 100 PYE, depending on the definition used, with one exception: the nocturnal hypoglycaemia rate was 2 episodes per 100 PYE higher with insulin degludec for the core trial period when the nocturnal period was defined as 0.01–07.59 (Table 3c). The risk of nocturnal hypoglycaemia did not

Table 1 Summary of phase 3a trials comparing insulin degludec with insulin glargine included in the current analysis

Category	Type 2 diabetes mellitus (insulin naïve)			Type 2 diabetes mellitus (basal–bolus)	Type 1 diabetes mellitus	
Trial	BEGIN Once Long	BEGIN Once Asia	BEGIN Low Volume	BEGIN BB	BEGIN BB T1 Long	BEGIN Flex T1
Core trial [ref]	3579 [8]	3586 [7]	3672 [4]	3582 [3]	3583 [5]	3770* [9]
Treatment	IDeg OD or IGlar OD + met ± DPP–4i	IDeg OD or IGlar OD + OAD except DPP–4i	IDeg 200 U/mL OD or IGlar OD + met ± DPP–4i	IDeg OD or IGlar OD + IAsp TID ± met ± PIO	IDeg OD or IGlar OD + IAsp TID	IDeg OD or IGlar OD + IAsp TID
Duration of core trial (weeks)	52	26	26	52	52	26
Randomization ratio	3:1	2:1	1:1	3:1	3:1	1:1
N in full analysis set:						
IDeg	773	289	228	744	472	165
IGlar	257	146	229	248	157	164
n (%) completing core trial:						
IDeg	607 (79)	258 (89)	200 (87)	618 (82)	404 (86)	139 (84)
IGlar	197 (77)	136 (93)	201 (87)	211 (84)	137 (87)	152 (93)
n analysed in the meta-analysis:						
IDeg		1290		744		637
IGlar		632		248		321
Extension trial [ref]	3643 [18]	–	–	3667 [16]	3644 [17]	3770-Ext [9]
Duration of extension period (weeks)	52	–	–	26	52	26
Total duration (weeks)	104	–	–	78	104	52
n entering extension trial (% of core trial)[†]:						
IDeg	551 (71)	–	–	566 (76)	351 (74)	239 (73)[‡]
IGlar	174 (68)			191 (77)	118 (75)	133 (81)
n completing extension trial (% of core trial)[†]:						
IDeg	505 (65)	–	–	539 (71)	330 (70)	223 (68)[†]
IGlar	154 (60)			183 (73)	113 (72)	122 (74)
n analysed in the meta-analysis:						
IDeg		1290		744		801
IGlar		632		248		321

*Trial 3770 included a third dosing arm with 'forced-flexible' dosing intervals of 8 and 40 h (*n* = 164). This dosing arm was excluded from this meta-analysis as the extreme forced-flexible dosing regimen does not represent the recommended use of insulin degludec in clinical practice.
[†]Numbers shown are those entering/completing the extension trial, as a percentage of the number randomized at baseline in the core trial.
[‡]Patients from the 'forced-flexible' arm entered the 'free-flexible' extension phase together with patients who had received IDeg OD in the core trial. The percentage is thus based on all patients who received IDeg in the core trial (IDeg OD 165, IDeg forced-flexible 164, total *n* = 329). The analysis for the extension set covered all the patients over the whole period regardless of their initial treatment.
BB, basal–bolus; DPP–4i, dipeptidyl peptidase–4 inhibitor; IAsp, insulin aspart; IDeg, insulin degludec; IGlar, insulin glargine; met, metformin; OAD, oral antidiabetic drug; OD, once daily; PIO, pioglitazone; TID, three times daily.

differ significantly between the treatment groups for any of the definitions or nocturnal timescales, during the entire core trial period (Fig. 2c). During the maintenance period, the risk was significantly lower with insulin degludec only when using the original definition for reporting hypoglycaemia. In the extension set, the risk of nocturnal hypoglycaemia was significantly lower with insulin degludec for all the definitions and for the nocturnal timescale 21.59–05.59.

Discussion

These post-hoc analyses are relevant to practising clinicians because they confirm that differences previously reported between insulin degludec and insulin glargine in rates of

nocturnal hypoglycaemia are not dependent on the definition used in the BEGIN trial programme. In general, in each population analysed (Type 2 diabetes$_{insulin\ naïve}$, Type 2 diabetes$_{BB}$, Type 1 diabetes mellitus), the treatment differences for nocturnal hypoglycaemia were similar for different definitions of hypoglycaemia and different trial periods. The results also show that the lower risk of nocturnal hypoglycaemia seen with insulin degludec vs. insulin glargine in Type 2 diabetes mellitus is maintained across different definitions.

One exception to the pattern was seen when the nocturnal timescale was extended to 0.01–07.59. In the Type 2 diabetes$_{insulin\ naïve}$ population, the rate ratio was no longer significantly in favour of insulin degludec. For this definition

Table 2 Demographics and baseline characteristics of participants

Category	Type 2 diabetes mellitus (insulin naïve)						Type 2 diabetes mellitus (basal–bolus)				Type 1 diabetes mellitus	
Core trial [ref]	3579 [8]		3586 [7]		3672 [4]		3582 [3]		3583 [5]		3770† [9]	
Treatment	IDeg*	IGlar*	IDeg*	IGlar*	IDeg*	IGlar*	IDeg*	IGlar*	IDeg*	IGlar*	IDeg*	IGlar*
No. subjects	773	257	289	146	228	229	744	248	472	157	165	164
Sex, N (%), male	471 (60.9)	167 (65.0)	158 (54.7)	75 (51.4)	119 (52.2)	124 (54.1)	405 (54.4)	133 (53.6)	278 (58.9)	90 (57.3)	94 (57.0)	88 (53.7)
Age, years, mean (SD)	59.3 (9.7)	58.7 (9.9)	58.8 (9.8)	58.1 (10.1)	57.8 (9.0)	57.3 (9.4)	59.2 (9.1)	58.1 (10.0)	42.8 (13.7)	43.7 (13.3)	44.5 (13.1)	44.1 (12.6)
Diabetes duration, years, mean (SD)	9.4 (6.3)	8.6 (5.7)	11.8 (6.5)	11.1 (6.5)	8.4 (6.7)	8.0 (5.6)	13.6 (7.4)	13.4 (6.9)	19.1 (12.2)	18.2 (11.4)	20.0 (12.5)	18.2 (11.9)
BMI, kg/m², mean (SD)	30.9 (4.8)	31.6 (4.4)	24.6 (3.4)	25.8 (3.7)	32.2 (5.4)	32.7 (5.3)	32.3 (4.7)	31.9 (4.5)	26.3 (3.7)	26.4 (4.2)	26.4 (4.0)	26.8 (4.0)
Antidiabetic therapy, N (%)												
Insulin ± OAD	0	0	0	0	0	0	744 (100)	248 (100)	472 (100)	157 (100)	165 (100)	164 (100)
IGlar	0	0	0	0	0	0	322 (43.3)	105 (42.3)	336 (71.2)	108 (68.8)	107 (64.8)	100 (61.0)
OAD only	773 (100)	257 (100)	289 (100)	146 (100)	228 (100)	229 (100)	0	0	0	0	0	0
Extension trial [ref]	3643 [18]		–		–		3667 [16]		3644 [17]		3770-Ext† [19]	
Treatment	IDeg*	IGlar*					IDeg*	IGlar*	IDeg*	IGlar*	IDeg*	IGlar*
No. subjects	551	174					566	191	351	118	239	133
Sex, N (%), male	349 (63.3)	111 (63.8)					317 (56.0)	100 (52.4)	210 (59.8)	72 (61.0)	145 (60.7)	71 (53.4)
Age, years, mean (SD)	59.7 (9.3)	59.3 (9.2)					58.9 (8.6)	58.4 (9.9)	43.6 (13.5)	44.6 (13.1)	43.9 (13.3)	44.8 (12.7)
Diabetes duration, years, mean (SD)	9.7 (6.3)	9.0 (5.6)					13.4 (7.2)	13.7 (6.8)	18.8 (11.7)	17.8 (11.7)	18.4 (12.4)	19.0 (12.2)
BMI, kg/m², mean (SD)	30.9 (4.7)	31.8 (4.3)					32.4 (4.6)	31.9 (4.3)	26.4 (3.7)	26.6 (4.0)	26.7 (3.8)	27.0 (4.0)

*IDeg and IGlar were both injected once daily.
†Please see note in Table 1 regarding trials 3770 and 3770-Ext.
BB, basal–bolus; IDeg, insulin degludec; IGlar, insulin glargine; OAD, oral antidiabetic drug; OD, once daily.

Table 3 Estimated rates of hypoglycaemia

		Episodes per 100 PYE (least squares means estimate)	
		IDeg	IGlar
(a) Type 2 diabetes mellitus insulin naïve IDeg N **= 1279, IGlar** N **= 631**			
Nocturnal confirmed hypoglycaemia (original definition)* (00.01–05.59)	Entire period	24.3	38.0
	Maintenance period	26.8	52.6
	Extension set	24.2	41.7
Nocturnal confirmed symptomatic hypoglycaemia[†] (00.01–05.59)	Entire period	15.7	28.1
	Maintenance period	17.2	40.4
	Extension set	14.8	29.4
Nocturnal ADA documented symptomatic hypoglycaemia[‡] (00.01–05.59)	Entire period	73.8	100.5
	Maintenance period	70.6	114.7
	Extension set	73.3	105.9
Nocturnal confirmed hypoglycaemia (21.59–05.59)[§]	Entire period	25.8	42.8
	Maintenance period	29.5	60.1
	Extension set	25.1	45.1
Nocturnal confirmed hypoglycaemia (00.01–07.59)[§]	Entire period	75.1	80.7
	Maintenance period	77.3	101.5
	Extension set	75.1	82.5
(b) Type 2 diabetes mellitus basal–bolus IDeg N **= 742, IGlar** N **= 248**			
Nocturnal confirmed hypoglycaemia (original definition)* (00.01–05.59)	Entire period	112.7	149.3
	Maintenance period	101.0	141.2
	Extension set	126.6	177.4
Nocturnal confirmed symptomatic hypoglycaemia[†] (00.01–05.59)	Entire period	90.1	133.0
	Maintenance period	86.2	132.8
	Extension set	84.5	125.1
Nocturnal ADA documented symptomatic hypoglycaemia[‡] (00.01–05.59)	Entire period	167.0	233.4
	Maintenance period	148.7	211.6
	Extension set	158.8	212.6
Nocturnal confirmed hypoglycaemia (21.59–05.59)[§]	Entire period	195.8	268.3
	Maintenance period	174.4	247.6
	Extension set	178.7	238.3
Nocturnal confirmed hypoglycaemia (00.01–07.59)[§]	Entire period	168.7	220.0
	Maintenance period	133.8	192.0
	Extension set	153.2	199.5
(c) Type 1 diabetes mellitus IDeg N **= 637, IGlar** N **= 316; Extension trials**[¶] **IDeg** N **= 801, IGlar** N **= 316**			
Nocturnal confirmed hypoglycaemia (original definition)* (00.01–05.59)	Entire period	596.8	718.5
	Maintenance period	499.5	664.5
	Extension set	445.4	648.6
Nocturnal confirmed symptomatic hypoglycaemia[†] (00.01–05.59)	Entire period	507.6	577.0
	Maintenance period	434.9	535.1
	Extension set	418.1	535.5
Nocturnal ADA documented symptomatic hypoglycaemia[‡] (00.01–05.59)	Entire period	768.5	846.0
	Maintenance period	684.0	788.2
	Extension set	633.1	777.0
Nocturnal confirmed hypoglycaemia (21.59–05.59)[§]	Entire period	1103	1250
	Maintenance period	934.2	1104.0
	Extension set	957.3	1134.6
Nocturnal confirmed hypoglycaemia (00.01–07.59)[§]	Entire period	1566	1564
	Maintenance period	1309.9	1445.4
	Extension set	1292.9	1389.5

*PG < 3.1 mmol/l (56 mg/dl) or severe hypoglycaemia requiring assistance.
[†]Confirmed hypoglycaemia with symptoms.
[‡]ADA definition [symptoms + PG < 3.9 mmol/l (70 mg/dl)].
[§]Original definition with time of 'nocturnal' varied.
[¶]The extension of trial 3770 included patients from the forced-flexible dosing arm of the main trial. Forced-flexible dosing was stopped during the extension and all patients treated with IDeg followed a free-flexible dosing regimen, administering IDeg at any time of day provided they maintained a minimum of 8 and a maximum of 40 hours between doses.
IDeg, insulin degludec; IGlar, insulin glargine; PYE, patient-year of exposure.

events increased threefold, suggesting that this expansion was driven not by nocturnal hypoglycaemia, but by morning events. This might be the result of a later waking time, or

diabetes therapies taken at breakfast. One possible contributing factor may have been that pre-breakfast plasma glucose testing was prescribed by the study protocols for

insulin titration decisions, and that asymptomatic hypoglycaemia, which would have gone unrecorded, was therefore detected. It is also possible that, unlike insulin glargine where plasma insulin levels may have begun to fall, the effect of insulin degludec, which has a flat pharmacokinetic profile, may have combined with other breakfast glucose-lowering medication, and so caused a shift in the relative risk.

Extending the definition of nocturnal timescale also affected data in the Type 1 diabetes mellitus population. Rates increased 2.5-fold in this group when the nocturnal period was defined as 0.01–07.59; this increase may represent the effects of mealtime bolus insulin therapy in combination with the sustained concentration of insulin degludec. The rate ratio remained numerically in favour of insulin degludec in the majority of analyses performed.

The separate analysis of the maintenance period (week 16 onwards), which was suggested by the regulatory authorities for the BEGIN trial programme, was intended to exclude possible differences due to the titration process arising from physicians' and patients' greater familiarity with insulin glargine. The maintenance period was also where participants were most likely to be for a significant portion of their therapy and is hence clinically relevant. In the current analyses, a greater benefit was seen with insulin degludec in the maintenance period compared with the core trial period across all definitions. This difference could partially be explained by the fact that for participants treated with pre-trial doses of twice-daily basal insulin in the BEGIN trials, there was a 1:1 switch to insulin degludec but a 20–30% reduction for insulin glargine, in line with its prescribing information. In fact, absolute event rates were low, and final total insulin doses were similar for both insulins or greater with insulin glargine. This suggests that, in accordance with the prescribing information, physicians may want to consider dose reduction of insulin degludec when switching people with Type 1 diabetes mellitus who are using twice-daily basal insulin or whose $HbA_{1c} < 64$ mmol/mol (8.0%) at the time of transfer.

Compared with the core trial sets, the risk ratios for the extension sets appeared to be more favourable for insulin degludec in the Type 2 diabetes$_{insulin\ naïve}$ and Type 1 diabetes populations. In the extension study in Type 2 diabetes$_{insulin\ naïve}$ [18] and one of the extension studies in Type 1 diabetes [17], the hypoglycaemia curves did indeed show increased between-group differences in the risk of nocturnal hypoglycaemia over time. This suggests that the risk reduction with insulin degludec is a sustained effect and may improve as patients learn to optimize the use of this new insulin – although these promising results need to be balanced against the limitations of extension studies in which those who perceive little benefit from insulin degludec may be less likely to participate.

Even non-severe nocturnal hypoglycaemia has been shown to negatively affect patients' functioning and well-being, and may potentially lead to suboptimal glycaemic control [12]. The reported reductions in risk of nocturnal hypoglycaemia

across categories, particularly in Type 2 diabetes mellitus, are thus both statistically significant and clinically relevant. Given that rates of severe hypoglycaemia were low in all the trials over the full 24-h period [10], meta-analyses were not conducted for nocturnal severe hypoglycaemia.

In studies that enrolled participants receiving bolus as well as basal insulin, the between-treatment differences were less pronounced than in those in which participants received basal insulin only. A possible explanation is that, once people start using a bolus insulin, most hypoglycaemia will arise from the bolus insulin, confounding differences between basal insulins. Nevertheless, there may be a need for a different adaptation of bolus dosing on a background of insulin degludec, in particular in combination with exercise.

In real life, any clinical benefits observed with a new drug, such as reduction in hypoglycaemia and increased convenience of administration, have to be balanced against differences in cost. Pharmacoeconomic modelling studies based on a UK perspective suggest that insulin degludec is a cost-effective option compared with insulin glargine in selected people with Type 1 diabetes [19] and Type 2 diabetes [20]. These studies suggested that insulin degludec would be particularly cost-effective for subgroups of patients, such as those with recurrent nocturnal hypoglycaemia or impaired awareness of hypoglycaemia. This has further been confirmed by recent 'real-life' observational studies from routine clinical practice from both Sweden [21] and the UK [22], which concluded that the cost of insulin degludec compared with glargine could be considered justified in selected patients (mainly with Type 1 diabetes, but including some with Type 2 diabetes) based on the clinical benefits achieved.

A limitation of these analyses is that they were based on studies in which a different dose adjustment was used for insulin degludec and insulin glargine when switching participants who were using insulin glargine twice daily, and administration times were different (evening for insulin degludec vs. any time for insulin glargine, reflecting the licensing of insulin glargine). When interpreting the results for the extension period, it must be remembered that some participants dropped out, although the numbers doing so during the extension phase were relatively small (Table 1).

There are also some limitations with regard to the statistical analysis. It was important to use the same model as that used in the earlier pre-specified meta-analysis [10], because we wanted to test the effects of different definitions of nocturnal hypoglycaemia, without any possible confounding arising from different statistical models. For this reason, we did not model the effects of the regressors flexibly, nor did we test alternative statistical models and their fit. Furthermore, in the current study, we decided not to perform sensitivity analyses, as two sensitivity analyses that were performed for the pre-specified meta-analysis (using the pooled Type 2 and Type 1 diabetes mellitus populations) yielded results that were consistent with the main analysis
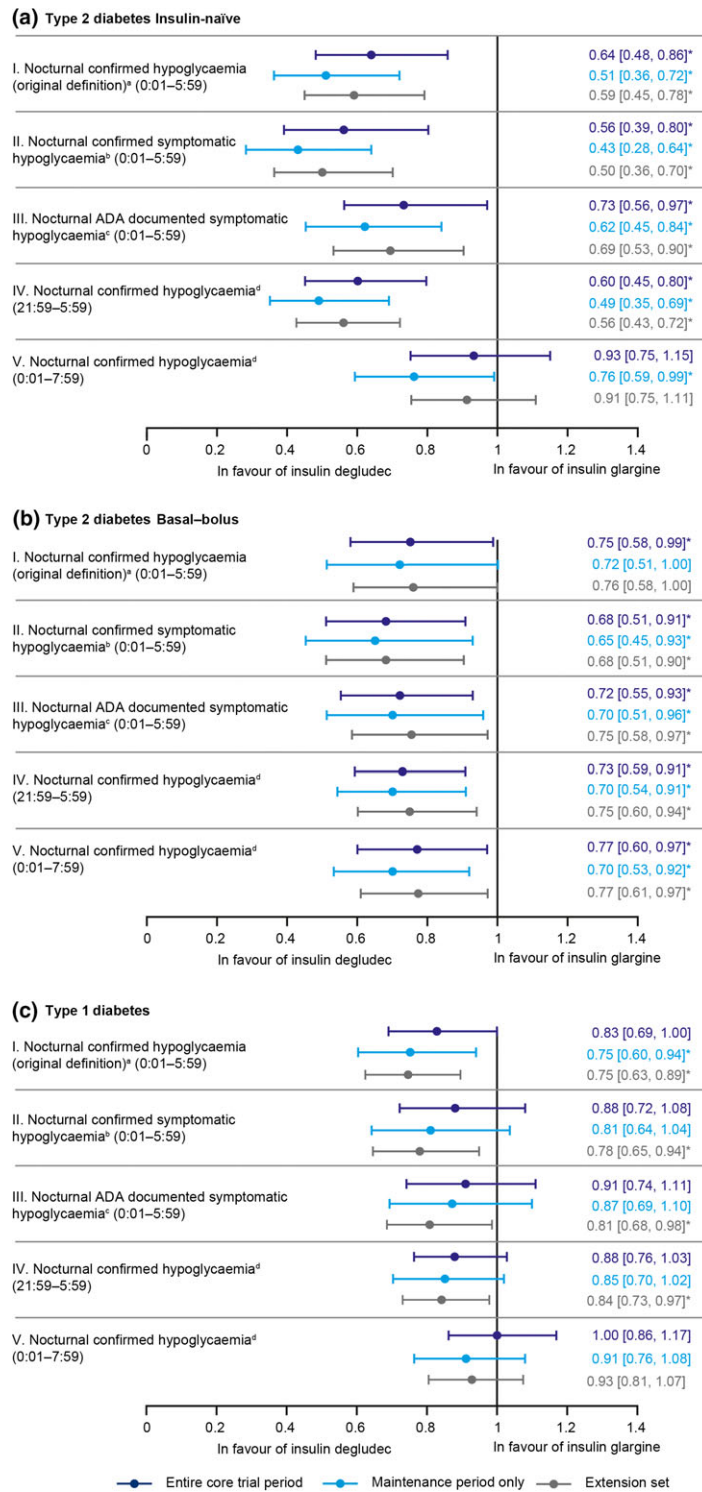
FIGURE 2 Rate ratios (insulin degludec insulin glargine) for nocturnal confirmed hypoglycaemia, using different definitions for reporting hypoglycaemia and different timescales for the nocturnal period. Results are shown for the entire core trial period, the maintenance period only and the extension set (i.e. core trials plus extension periods). (a) Insulin-naïve patients with Type 2 diabetes mellitus, (b) basal–bolus-treated patients with Type 2 diabetes mellitus, (c) patients with Type 1 diabetes mellitus. Dark blue, entire core trial period; light blue, maintenance period only (from week 16 onwards); grey, extension set (core trial plus extension period). *P < 0.05. (a) Plasma glucose < 3.1 mmol/l or severe hypoglycaemia requiring assistance. (b) Confirmed hypoglycaemia with symptoms. (c) ADA definition (symptoms + plasma glucose ≤ 3.9 mmol/l). (d) Original definition with timescale of 'nocturnal' varied.

[10]. The first sensitivity analysis used a random effects rather than a fixed effects approach; the second fitted the model without covariates other than treatment, type of diabetes and trial. Finally, participants in the BEGIN Flex T1 trial who were in an arm that used a forced-flexible regimen during the core period were excluded from the core period analysis; however, in the extension period analysis, these participants' hypoglycaemia rates were analysed over the whole trial period.

In conclusion, these data confirm previous findings, showing that compared with insulin glargine, insulin degludec is associated with significantly lower rates of nocturnal hypoglycaemia in people with Type 2 diabetes mellitus, and similar or lower rates in Type 1 diabetes mellitus. Insulin degludec may therefore help patients with nocturnal hypoglycaemia to reach and maintain tight glucose targets.

Competing interests

SH has served as a Consultant for Sanofi Aventis and Amylin; has served as an advisory board panel member for Eli Lilly & Co, Novo Nordisk A/S, Lifescan Inc. and Takeda; and has attended Speakers' Bureaux for Novo Nordisk, Abbott Diabetes Care, Eli Lilly & Co and MSD. CM has received research support from Novo Nordisk, Sanofi Aventis, MSD Ltd, Eli Lilly & Co and Novartis, and served as an advisory board panel member for Novo Nordisk, Sanofi Aventis, MSD Ltd, Eli Lilly & Co, Novartis, Bristol-Myers Squibb, Astra Zeneca LP, Pfizer, Johnson and Johnson and Mannkind. RK and MLW are employees of Novo Nordisk and hold stock in the company. BZ has received research support from Boehringer Ingelheim, Novo Nordisk and MSD, and served as an advisory board panel member for Boehringer Ingelheim, Eli Lilly & Co, Novo Nordisk, Sanofi, MSD, Takeda and Janssen.

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