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 diabetesinsulin naïve), participants with Type 2 diabetes mellitus using basal–bolus therapy (Type 2 diabetesBB) 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 diabetesinsulin 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 diabetesBB, 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.

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 diabetesbag); 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 diabetesinsulin naïve, one trial in Type 2 diabetesbb 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 diabetesbag group, trial was not
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-naive people with Type 2 diabetes mellitus**

From Table 3(a) it can be seen that for the Type 2 diabetes 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 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. 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 diabetesBB 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
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 naive, Type 2 diabetes basal–bolus, Type 1 diabetes mellitus), the treatment differences for nocturnal hypoglycaemia were similar for different definitions and for 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 naive population, the rate ratio was no longer significantly in favour of insulin degludec. For this definition.

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

| Category | Type 2 diabetes mellitus (insulin naive) | Type 2 diabetes mellitus (basal–bolus) | Type 1 diabetes mellitus |
|----------|----------------------------------------|--------------------------------------|-------------------------|
| Trial    | BEGIN Once Long                        | BEGIN Once Volume                    | BEGIN BB T1 Long        |
| Core trial [ref] | 3579 [8] IDeg OD or IGlar OD + met ± DPP-4i | 3586 [7] IDeg OD or IGlar OD + OAD except DPP-4i | 3582 [3] IDeg OD or IGlar OD + IAsp TID ± met ± PIO |
| Treatment |                                       |                                       |                         |
| Duration of core trial (weeks) | 52                                      | 26                                    | 52                      |
| Randomization ratio N in full analysis set: | 3:1                                     | 2:1                                   | 3:1                     |
| IDeg     | 773                                     | 289                                   | 744                     |
| IGlar    | 257                                     | 146                                   | 248                     |
| n (%) completing core trial: |                                       |                                       |                         |
| IDeg     | 607 (79)                                | 258 (89)                              | 618 (82)                |
| IGlar    | 197 (77)                                | 136 (93)                              | 211 (84)                |
| n analysed in the meta-analysis: |                                       |                                       |                         |
| IDeg     | 1290                                    | 248                                   | 744                     |
| IGlar    | 632                                     |                                       | 637                     |
| Extension trial [ref] | 3643 [18] IDeg OD or IGlar OD + met ± DPP-4i | –                                    | 3667 [16] IAsp TID ± met ± PIO |
| Duration of extension period (weeks) | 52                                      | –                                     | 26                      |
| Total duration (weeks) | 104                                     | –                                     | 78                      |
| n entering extension trial (% of core trial): |                                       |                                       |                         |
| IDeg     | 551 (71)                                | –                                     | 566 (76)                |
| IGlar    | 174 (68)                                |                                       | 191 (77)                |
| n completing extension trial (% of core trial): |                                       |                                       |                         |
| IDeg     | 505 (65)                                | –                                     | 539 (71)                |
| IGlar    | 154 (60)                                |                                       | 183 (73)                |
| 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.

1Patients 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.

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| Category | Type 2 diabetes mellitus (insulin naive) | Type 2 diabetes mellitus (basal-bolus) | Type 1 diabetes mellitus |
|----------|----------------------------------------|----------------------------------------|-------------------------|
| Core trial [ref] | | | |
| 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 | 157 | 165 | 164 |
| Sex, N (%), male | | | | | | | | | | | | | |
| 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) | 11.6 (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 only | 322 (43.3) | 105 (42.3) | 336 (71.2) | 108 (68.8) | 107 (64.8) | 104 (61.0) | 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* | IDeg* | IGlar* |
| No. subjects | 551 | 174 | 566 | 191 | 351 | 118 | 239 | 133 | 317 | 100 |
| 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) | 58.9 (8.6) | 58.4 (9.9) |
| Age, years, mean (sd) | 59.7 (9.3) | 59.3 (9.2) | 38.9 (13.3) | 43.6 (13.5) | 44.6 (13.1) | 43.9 (13.3) | 44.8 (12.7) | 59.7 (9.3) | 59.3 (9.2) | 58.9 (8.6) | 58.4 (9.9) |
| Diabetes duration, years, mean (sd) | 9.7 (6.3) | 9.0 (5.6) | 9.7 (6.3) | 9.0 (5.6) | 9.7 (6.3) | 9.0 (5.6) | 9.7 (6.3) | 9.0 (5.6) | 9.7 (6.3) | 9.0 (5.6) | 9.7 (6.3) | 9.0 (5.6) |
| BMI, kg/m², mean (sd) | 30.9 (4.7) | 31.8 (4.3) | 32.4 (4.6) | 31.9 (4.3) | 32.4 (4.6) | 31.9 (4.3) | 32.4 (4.6) | 31.9 (4.3) | 32.4 (4.6) | 31.9 (4.3) | 32.4 (4.6) | 31.9 (4.3) |

*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.
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

Table 3: Estimated rates of hypoglycaemia

| Type of Hypoglycaemia | Entire Period | Maintenance Period | Extension Period |
|-----------------------|--------------|--------------------|------------------|
|                       | IDeg         | IGlar              | IDeg             | IGlar             |
| Nocturnal confirmed hypoglycaemia (original definition)* (00.01−05.59) | 24.3 | 38.0 | 26.8 | 52.6 |
|                       | Extension set |                   | IDeg             | IGlar             |
|                       |             |                    | 24.2 | 41.7 |
| Nocturnal confirmed symptomatic hypoglycaemia† (00.01−05.59) | 15.7 | 28.1 | 17.2 | 40.4 |
| Nocturnal ADA documented symptomatic hypoglycaemia‡ (00.01−05.59) | 14.8 | 29.4 | 73.8 | 100.5 |
| Nocturnal confirmed hypoglycaemia (21.59−05.59)§ | 25.8 | 42.8 | 29.5 | 60.1 |
| Nocturnal confirmed hypoglycaemia (00.01−07.59)§ | 75.1 | 101.5 | 77.3 | 105.8 |
| Nocturnal confirmed hypoglycaemia (extension)¶ | 25.1 | 45.1 | 75.1 | 105.9 |

*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.
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 HbA1c < 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\textsubscript{naive} and Type 1 diabetes populations. In the extension study in Type 2 diabetes\textsubscript{naive} [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-naive 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.

### (a) Type 2 diabetes Insulin-naive

| Nocturnal confirmed hypoglycaemia | Rate Ratio (95% CI) |
|-----------------------------------|--------------------|
| (original definition) (0.01–5.59) |                    |
| I.                               |                    |
| II.                              |                    |
| III.                             |                    |
| IV.                              |                    |
| V.                               |                    |

### (b) Type 2 diabetes Basal–bolus

| Nocturnal confirmed hypoglycaemia | Rate Ratio (95% CI) |
|-----------------------------------|--------------------|
| (original definition) (0.01–5.59) |                    |
| I.                               |                    |
| II.                              |                    |
| III.                             |                    |
| IV.                              |                    |
| V.                               |                    |

### (c) Type 1 diabetes

| Nocturnal confirmed hypoglycaemia | Rate Ratio (95% CI) |
|-----------------------------------|--------------------|
| (original definition) (0.01–5.59) |                    |
| I.                               |                    |
| II.                              |                    |
| III.                             |                    |
| IV.                              |                    |
| V.                               |                    |
[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.

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**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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