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BRIEF REPORT

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Duration of type 2 diabetes does not appear to moderate hypoglycaemia rate with insulin degludec versus insulin glargine U100

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Abstract

In the DEVOTE and SWITCH 2 trials, insulin degludec 100 units/mL (degludec) was superior to insulin glargine 100 units/mL (glargine U100) with respect to the rates of severe (DEVOTE; across trial) and overall symptomatic (SWITCH 2; during the maintenance period of the trial) hypoglycaemia in individuals with type 2 diabetes. In this post hoc analysis, data from 7635 individuals from DEVOTE and 720 individuals from SWITCH 2 were analysed by subgroups of diabetes duration at baseline (<10, ≥10–<15, ≥15–<20 and ≥20 years) using prespecified models from both trials. There was a trend towards lower rates of hypoglycaemia with degludec versus glargine U100 across all diabetes duration subgroups in both trials, with the difference being statistically significant in some subgroups in DEVOTE and SWITCH 2. Overall, however, no significant interaction was observed between diabetes duration and treatment (DEVOTE interaction, $P = .496$; SWITCH 2 interaction, $P = .144$). Therefore, in this post hoc analysis of DEVOTE and SWITCH 2, diabetes duration did not appear to affect the reduction in rates of hypoglycaemia observed with degludec compared with glargine U100.

KEYWORDS
basal insulin, hypoglycaemia, type 2 diabetes

1 | INTRODUCTION

Tight glycaemic control is essential in individuals with type 2 diabetes (T2D), to prevent diabetes-related complications.[1,2] For some individuals, however, achieving good glycaemic control will necessitate the use of exogenous insulin therapy, and this (or use of insulin secretagogues) places the patient at risk of hypoglycaemia, which is associated with significant morbidity.[3,4] Recurrent hypoglycaemia is associated with cardiovascular complications and poor health-related quality-of-life outcomes.[3,4] Mild to moderate hypoglycaemia directly impacts upon patient well-being and daily functioning,[3,5] and is associated with all-cause mortality.[6] In addition, individuals tend to lower their own insulin doses after a hypoglycaemic event, and this can lead to a decline in glycaemic control and increase the risk of associated complications.[3,5,7] Hypoglycaemia therefore has a considerable health-economic impact. Managing the risk of hypoglycaemia remains a priority in diabetes care, and should be a key factor for healthcare professionals and individuals with T2D when deciding on treatment approaches.[5,8]

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Insulin degludec and insulin glargine 100 units/mL (glargine U100) are basal insulins used for the management of diabetes, and the relative efficacy and safety of these treatments have been investigated.[9] DEVOTE was a randomized trial of 7637 individuals with T2D at high risk of cardiovascular events, and was designed to assess the cardiovascular safety of insulin degludec 100 units/mL (degludec) versus glargine U100.[10] As a notable secondary endpoint, the trial showed a significant difference in the rate of severe hypoglycaemia between degludec and glargine, in favour of degludec (3.70 vs. 6.25 events/100 patient-years of observation; rate ratio: 0.60; $P < .001$).[10] In SWITCH 2, a randomized crossover trial in which 721 individuals with T2D having at least one hypoglycaemic risk factor were included, degludec compared with glargine U100 was associated with a significantly reduced rate of overall symptomatic hypoglycaemia during the maintenance phase of the study, i.e. after initial titration (185.6 vs. 265.4 episodes/100 patient-years of exposure; estimated rate ratio 0.70; $P < .001$).[11]

Evidence suggests an association between risk of hypoglycaemia and diabetes duration[7,12–16]; individuals with longer diabetes duration tend to be at a higher risk of severe hypoglycaemia,[7,13,15] particularly if their HbA1c is <8%.[7] This may be a result of a declining counter-regulatory response and hypoglycaemia-associated autonomic failure with progression of diabetes, as well as the choice of treatment (which is more likely to include insulin).[7,12] In a pooled analysis of 24-week patient-level data from randomized controlled studies in individuals with T2D, the rates of daytime hypoglycaemia were similar for glargine U100 and neutral protamine Hagedorn (NPH) insulin, irrespective of disease duration.[17] However, for symptomatic nocturnal hypoglycaemia, the rates were significantly lower with glargine U100 than with NPH insulin in individuals with longer durations of diabetes.[17]

In an effort to investigate methods to reduce the rate of hypoglycaemia with increasing diabetes duration, we assessed the difference in hypoglycaemia rate reduction with degludec versus glargine U100 according to baseline diabetes duration using data from DEVOTE and SWITCH 2.

2 | METHODS

The study design, methods and statistical analysis of DEVOTE (NCT01959529) and SWITCH 2 (NCT02030600) have been described previously.[10,11] Briefly, DEVOTE was conducted at 438 sites in 20 countries and was a treat-to-target, double-blind, active-comparator-controlled cardiovascular outcomes trial.[10] Individuals at a high risk of cardiovascular events were randomized 1:1 to either degludec (insulin degludec 100 U/mL; Novo Nordisk, Bagsvaerd, Denmark) or glargine U100 (insulin glargine 100 U/mL; Sanofi, Paris, France), administered once daily alongside standard care.[10] SWITCH 2 was conducted across 152 sites in the United States and was a double-blind, two-period crossover, multicentre, treat-to-target trial.[11] Individuals were randomized 1:1 to one of the treatment sequences: either degludec (insulin degludec 100 U/mL) for 32 weeks followed by crossover to glargine U100 (insulin glargine 100 U/mL) for 32 weeks, or glargine U100 for 32 weeks followed by crossover to degludec for another 32 weeks.[11]

In this post hoc subgroup analysis, data from DEVOTE and SWITCH 2 were analysed by diabetes duration at baseline (<10, ≥10–<15, ≥15–<20 and ≥20 years). Categories for diabetes duration were selected based on distribution of these data in each trial, with an aim to achieve a high level of granularity while maintaining a sufficient number of patients in each subgroup to allow for statistical analysis. In DEVOTE, severe hypoglycaemia was defined (as per the American Diabetes Association) as a hypoglycaemic event requiring the assistance of another person for corrective action[18]; it was an externally adjudicated outcome. Non-severe hypoglycaemic events were not systematically collected in the DEVOTE trial. In SWITCH 2, overall symptomatic hypoglycaemia was defined as severe hypoglycaemia or hypoglycaemia confirmed with a blood glucose level of <56 mg/dL accompanied by hypoglycaemic symptoms. Severe events were also externally adjudicated in SWITCH 2. Given the differences between the DEVOTE and SWITCH 2 trials in study design, categorization of hypoglycaemia and statistical models used for hypoglycaemia, the post hoc analyses were performed separately for each trial.

The prespecified model from the DEVOTE trial was used to investigate the rate of severe hypoglycaemia, i.e. a negative binomial model with treatment, diabetes duration, treatment*diabetes duration (test: type-3 likelihood ratio) and log-observation time as offset.[10] Similarly, in SWITCH 2, rates of overall symptomatic hypoglycaemia (during the maintenance period) were analysed with the prespecified confirmatory model from the trial protocol, i.e. a Poisson model with individuals as random effect, and treatment, diabetes duration, period, sequence, dosing time, treatment*diabetes duration (test: type-3 F-test) and log-observation time as offset.[11] Statistical analysis of age between subgroups of diabetes duration was not carried out and age was not adjusted for in either model. This was because in the DEVOTE trial, mean age was similar for degludec and glargine U100 groups in each of the four diabetes duration subgroups (Table 1A), and, as SWITCH 2 was a crossover study, age was identical between the degludec and glargine U100 arms. Severe hypoglycaemic episodes from SWITCH 2 were included in the overall symptomatic event assessment, but they were not assessed separately by diabetes duration in the current post hoc analysis because of a low event number. Statistical analysis of the rates of hypoglycaemia between the diabetes duration subgroups was not carried out.

3 | RESULTS

For the analysis of data from DEVOTE, a total of 7635 participants were included: 1890 participants (25%) with a diabetes duration <10 years, 1850 (24%) with a diabetes duration ≥10–<15 years, 1574 (21%) with a diabetes duration ≥15–<20, and 2321 (30%) with a diabetes duration ≥20 years (Table 1A). From SWITCH 2, a total of

TABLE 1 Baseline characteristics in A, the DEVOTE trial by diabetes duration and treatment, and in B, the SWITCH 2 trial[a] by diabetes duration

(A)								
Diabetes duration (DEVOTE)	**<10 y**		**≥10-<15 y**		**≥15-<20 y**		**≥20 y**	
	Degludec n = 905	**Glargine U100 n = 985**	**Degludec n = 912**	**Glargine U100 n = 938**	**Degludec n = 805**	**Glargine U100 n = 769**	**Degludec n = 1195**	**Glargine U100 n = 1126**
Age (y, mean)	63.1	63.1	64.0	64.2	65.3	65.4	66.8	67.3
Gender (%, female)	34.6	36.1	37.4	36.8	36.4	37.3	39.7	39.8
BMI (kg/m^2, mean)	33.5	33.4	33.6	33.9	33.7	33.9	33.5	33.5
HbA1c (% mean)	8.4	8.5	8.5	8.5	8.5	8.5	8.4	8.3
Established CV disease (%)	84.1	83.2	83.8	84.2	87.6	86.0	86.6	86.4
Insulin-naïve (%)	26.3	24.9	17.5	18.0	13.3	12.5	8.2	10.0
Basal insulin only (%)	40.9	42.1	42.3	40.4	36.1	36.4	34.1	32.5
Basal–bolus insulin regimen (%)	32.8	33.0	40.1	41.6	50.6	51.1	57.7	57.5
eGFR (mL/min/1.73 m^2, mean)	73.1	72.2	70.9	70.6	66.5	66.6	63.3	62.5

(B)				
Diabetes duration (SWITCH 2)	**<10 y n = 222**	**≥10-<15 y n = 205**	**≥15-<20 y n = 135**	**≥20 y n = 158**
Age (y, mean)	58.6	60.6	63.2	64.8
Gender (% female)	41.9	47.3	53.3	48.1
BMI (kg/m^2, mean)	32.3	32.3	32.4	31.8
HbA1c (mean %)	7.5	7.6	7.6	7.8
eGFR (mL/min/1.73 m^2, mean)	82.3	81.9	73.6	71.8

Abbreviations: BMI, body mass index; CV, cardiovascular; degludec, insulin degludec 100 units/mL; eGFR, estimated glomerular filtration rate; glargine U100, insulin glargine 100 units/mL.

[a]SWITCH 2 was a crossover trial; baseline characteristics are therefore not presented by treatment.

720 participants were included in the analysis: 222 participants (31%) with a diabetes duration <10 years, 205 (28%) with a diabetes duration ≥10–<15 years, 135 (19%) with a diabetes duration ≥15–<20 years, and 158 (22%) with a diabetes duration ≥20 years (Table 1B).

Baseline characteristics in DEVOTE were mostly similar across treatment groups for all diabetes duration categories (Table 1A). Of note, mean age and the percentage of women increased slightly with increasing diabetes duration, while the percentage of previously insulin-naïve patients decreased markedly. Mean baseline HbA1c was remarkably constant across all groups. SWITCH 2 was a crossover trial, and baseline characteristics are therefore not divisible into treatment groups (Table 1B). In both trials, renal function declined with increasing diabetes duration (Table 1A,B). In DEVOTE, the proportions of individuals using basal–bolus insulin were larger in those with a longer diabetes duration.

There was a trend towards lower rates of hypoglycaemia with degludec versus glargine U100 across all subgroups of diabetes duration in both DEVOTE (Figure 1A, severe hypoglycaemia) and SWITCH 2 (Figure 1B, overall symptomatic hypoglycaemia during the maintenance period). There was no evidence of a significant interaction between treatment and diabetes duration in either DEVOTE ($P = .496$) or SWITCH 2 ($P = .144$), indicating that the benefit of degludec versus glargine U100 in terms of reduced hypoglycaemia rate was not dependent on a patient's diabetes duration (Figure 1A,B). However, statistical significance was observed only in certain subgroups of diabetes duration in the two trials. In DEVOTE, the rate of severe hypoglycaemia was significantly reduced with degludec compared with glargine U100 in the diabetes duration subgroups <10 years (rate ratio [RR]: 0.48; 95% confidence interval [CI]: 0.29, 0.81; $P = .006$) and ≥20 years (RR: 0.52; 95% CI: 0.35, 0.77; $P = .001$; Figure 1A). Similarly, in the SWITCH 2 trial, rates of overall symptomatic hypoglycaemia were significantly reduced when using degludec versus glargine U100 in the diabetes duration subgroups ≥10–<15 years (RR: 0.60; 95% CI: 0.46, 0.80; $P = .0004$), ≥15–<20 years (RR: 0.69; 95% CI: 0.52, 0.91; $P = .0085$), and ≥20 years (RR: 0.62; 95% CI: 0.46, 0.82; $P = .0010$).

When assessing the rates of hypoglycaemia for both degludec and glargine U100 according to baseline diabetes duration, rates tended to increase with increasing diabetes duration in both DEVOTE (Figure S1A, severe hypoglycaemia) and SWITCH 2 (Figure S1B, overall symptomatic hypoglycaemia during the maintenance period).

Based on observed data, HbA1c levels appeared to decrease during the trials in all diabetes duration subgroups in DEVOTE (Figure S2A) and SWITCH 2 (Figure S2B).

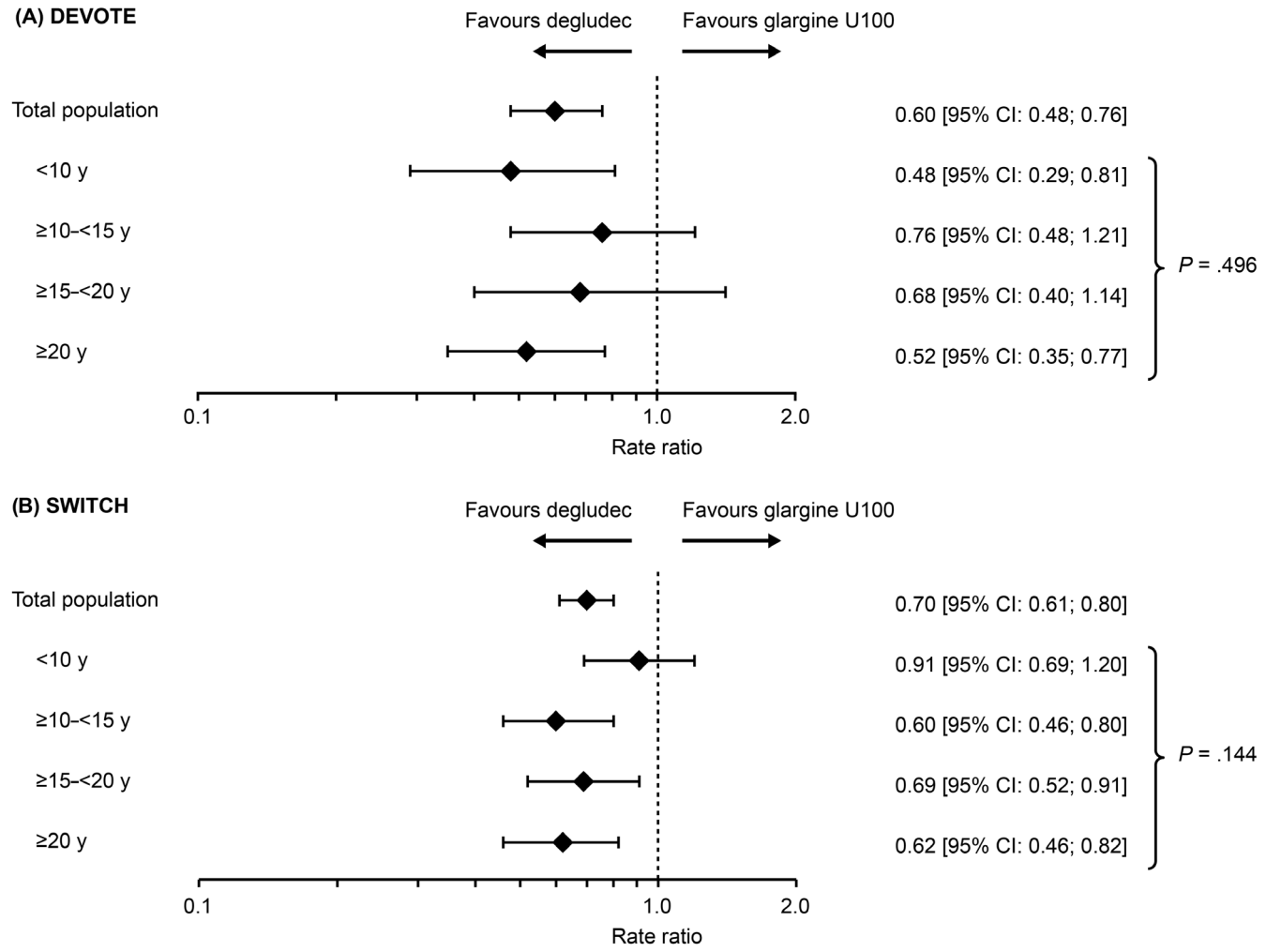

FIGURE 1 Estimated rate ratios of hypoglycaemia for degludec versus glargine U100 by diabetes duration for A, the DEVOTE trial (severe hypoglycaemia) and B, the SWITCH 2 trial (overall symptomatic hypoglycaemia). The *P* values are for assessment of interaction between treatment and diabetes duration. CI, confidence interval; degludec, insulin degludec 100 units/mL; glargine U100, insulin glargine 100 units/mL. The P-values are for assessment of interaction between treatment and diabetes duration.
Abbreviations: CI, confidence interval; degludec, insulin degludec 100 units/mL; glargine U100,insulin glargine 100 units/mL

4 | DISCUSSION

In DEVOTE, degludec was superior to glargine U100 in terms of a lower rate of severe hypoglycaemia, while in SWITCH 2 degludec was associated with a lower rate of overall symptomatic hypoglycaemia in the maintenance period (and a lower rate of overall symptomatic hypoglycaemia and severe hypoglycaemia across the full treatment period).[10,11] This post hoc analysis has shown that degludec preserved its relative benefit over glargine U100 with respect to rate of severe hypoglycaemia (DEVOTE) and overall symptomatic hypoglycaemia (SWITCH 2) regardless of previous diabetes duration.

In this post hoc analysis, overall, rates of hypoglycaemia tended to increase with longer diabetes duration in both the DEVOTE and the SWITCH 2 trials, and this was observed for both degludec and glargine U100. These findings align with other trials showing higher hypoglycaemia risk with greater diabetes duration.[13–15,17,19] There was a trend towards lower rates of hypoglycaemia with degludec versus glargine U100, however, across all subgroups of diabetes duration. In addition, a significant association between the rate of hypoglycaemia and treatment, in favour of degludec, was observed in certain subgroups, but there was no significant interaction between treatment and diabetes duration in either trial, suggesting that the advantage of degludec is independent of diabetes duration. The difference between the two trials used for this analysis is noteworthy. The DEVOTE trial population had a longer mean diabetes duration than the SWITCH 2 trial population (16.4 vs. 14.1 years).[10,11] Furthermore, in the DEVOTE trial, 54.8% of the patients receiving insulin at baseline were treated with basal–bolus insulin, whereas in the SWITCH 2 trial, only patients treated with basal insulin were included, indicating that the patient populations in these two trials are representative of the full disease spectrum of insulin-treated T2D.[10,11] The consistency in results across the analyses of these two studies suggests that the choice of degludec over glargine U100 can be expected to reduce

hypoglycaemia risk in all patients with T2D requiring insulin therapy, and that individuals with longstanding T2D who are at high hypoglycaemia (and cardiovascular) risk may benefit from the greatest reduction in hypoglycaemic event number. However, the post hoc nature of this analysis prevents us from drawing firm conclusions in this regard, so further studies may be needed.

Limitations that apply to post hoc analyses in general apply to the current analysis, and it is also important to note that the definitions of hypoglycaemia varied between the trials, as did the methods used to collect this information, which could have impacted the results. Furthermore, the categorization for diabetes duration used in this post hoc analysis may have influenced the results. Finally, as only individuals with T2D were included in the DEVOTE and SWITCH 2 trials, these results cannot be generalized to individuals with type 1 diabetes.

In conclusion, in this post hoc analysis, the benefits of degludec compared with glargine U100 in the DEVOTE and SWITCH 2 trials for reducing the risk of severe hypoglycaemia and overall symptomatic hypoglycaemia, respectively, were preserved across subgroups and hence are independent of diabetes duration.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

A.S.A. was involved in the conception of the study, assisted with study design, and helped to draft and edit the manuscript. A.A., A.M.D. and A.G. were involved in the interpretation of data, drafting and editing of the manuscript. J.B.B. was involved in the conception of the study, collecting the data, and helped to draft and edit the manuscript.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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