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ORIGINAL ARTICLE

Cardiovascular safety and lower severe hypoglycaemia of insulin degludec versus insulin glargine U100 in patients with type 2 diabetes aged 65 years or older: Results from DEVOTE (DEVOTE 7)

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Aims: The aim of this study was to describe the risks of cardiovascular (CV) events and severe hypoglycaemia with insulin degludec (degludec) vs insulin glargine 100 units/mL (glargine U100) in patients with type 2 diabetes (T2D) aged 65 years or older.

Materials and methods: A total of 7637 patients in the DEVOTE trial, a treat-to-target, randomized, double-blind trial evaluating the CV safety of degludec vs glargine U100, were divided into three age groups (50-64 years, *n* = 3682; 65-74 years, *n* = 3136; ≥75 years, *n* = 819). Outcomes by overall age group and randomized treatment differences were analysed for major adverse cardiovascular events (MACE), all-cause mortality, severe hypoglycaemia and serious adverse events (SAEs).

Results: Patients with increasing age had higher risks of CV death, all-cause mortality and SAEs, and there were non-significant trends towards higher risks of MACE and severe hypoglycaemia. Treatment effects on the risk of MACE, all-cause mortality, severe hypoglycaemia and SAEs were consistent across age groups, based on the non-significant interactions between treatment and age with regard to these outcomes.

Conclusions: There were higher risks of CV death, all-cause mortality and SAEs, and trends towards higher risks of MACE and severe hypoglycaemia with increasing age after adjusting for baseline differences. The effects across age groups of degludec vs glargine U100 on MACE, all-cause mortality and severe hypoglycaemia were comparable, suggesting that the risk of MACE, as well as all-cause mortality, is similar and the risk of severe hypoglycaemia is lower with degludec regardless of age. Evidence is conclusive only until 74 years of age.

KEYWORDS

basal insulin, cardiovascular disease, hypoglycaemia, type 2 diabetes

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Peer Review
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1 | INTRODUCTION

The global burden of type 2 diabetes (T2D) in patients aged 65 years or older is projected to increase substantially during the next few decades, as patients with diabetes live longer and the incidence of diabetes continues to rise.[1] Thus, the growing problem of diabetes and its consequences in patients aged 65 years or older is an important public health concern.

The management of diabetes in patients aged 65 years or older presents unique challenges. Differences in drug metabolism as the result of deteriorating kidney and liver function and the challenges of polypharmacy related to the treatment of multiple co-morbidities lead to a higher risk of drug-drug interactions and adverse events in this population.[2,3] Cardiovascular disease (CVD), in particular, is a common complication and co-morbidity among many older individuals with diabetes is the leading cause of mortality in this population.[4] Further complicating treatment, patients aged 65 years or older are more susceptible to severe hypoglycaemic events than younger patients, in part because of a reduced ability to recognize and respond to symptoms.[5,6] Severe hypoglycaemia has been shown to be associated with a higher risk of adverse cardiovascular (CV) events and mortality.[7,8] In addition, severe hypoglycaemic episodes can increase utilization of healthcare resources.[9] Several organizations have published guidelines for managing T2D in patients aged 65 years or older; however, most of these are based on expert opinion only, as there is a lack of high-quality evidence from randomized clinical trials in this population.[10–13] Although most guidelines support the use of insulin as one of several treatment options, data suggest that it is under-utilized in patients aged 65 years or older,[14] and there are few long-term studies in this population that demonstrate the efficacy and safety of basal insulins.[15–17] Possible reasons for under-utilization of insulin in this population include lack of clinical evidence, less stringent glycaemic targets suggested in recent recommendations, and the potential elevated risk of and concern about hypoglycaemia in these individuals.[5,11–14,17]

CV safety and the lower risk of severe hypoglycaemia with insulin degludec (degludec) compared with insulin glargine 100 units/mL (glargine U100) was demonstrated in a double-blind trial in patients with T2D who were at high risk of CV events (DEVOTE).[16,18] Given the mean age (65 years) of the study population,[16] DEVOTE provides a unique opportunity to investigate CV safety and the risk of severe hypoglycaemia with degludec vs glargine U100 in patients with T2D aged 65 years or older who are at high risk of CV events.

2 | METHODS

2.1 | DEVOTE trial overview

DEVOTE was a multicentre, treat-to-target, randomized, double-blind, active-comparator trial that evaluated the CV safety of degludec vs glargine U100, in addition to standard of care, in patients with T2D who were at high risk of CV events. This trial was designed to continue until the occurrence of at least 633 MACEs, as confirmed by a central, blinded event adjudication committee (EAC).[16,18] The detailed trial design, trial protocol and primary results have been published previously.[16,18]

DEVOTE (ClinicalTrials.gov NCT01959529) was conducted in accordance with the Declaration of Helsinki and ICH Good Clinical Practice Guideline.[19,20] The protocol was approved by independent ethics committees or institutional review boards for each centre. Written informed consent was obtained from each participant.

Patients were considered for the trial if they had been diagnosed with T2D and were undergoing treatment with at least one antihyperglycaemic agent, if they had an HbA1c value of at least 7.0% (53 mmol/mol) or were undergoing treatment with at least 20 units/day of basal insulin. Criteria for eligibility for the trial were: at least 50 years of age with a history of prior CVD or moderate chronic kidney disease (CKD); or were at least 60 years of age with one or more pre-specified CV risk factors.[16]

Primary adjudicated outcome was the time from randomization to first occurrence of a three-component MACE: CV death, non-fatal myocardial infarction (MI) or non-fatal stroke. Secondary confirmatory outcome was the number of EAC-confirmed events of severe hypoglycaemia, defined according to American Diabetes Association guidelines as an episode requiring assistance of another person to actively administer carbohydrate or glucagon, or to take other corrective actions.[8]

2.2 | Statistical analysis

In these secondary analyses, all randomized patients (n = 7637, full analysis set [FAS]) were categorized into three age groups: 50 to 64 years (n = 3682), 65 to 74 years (n = 3136) and ≥75 years (n = 819). These age groups and statistical analyses of all endpoints were pre-specified, with the exception of analyses of serious adverse events (SAEs). Comparisons across age groups, treatment differences within each age group, and interaction between treatment and age groups were investigated for all endpoints. Analyses were based on FAS and followed previous analyses of the DEVOTE data,[16] with the exception of adjustment for the following pre-specified baseline variables: sex, region, diabetes duration, CV risk, insulin-naïve, smoking status and kidney function. It was of particular importance to adjust for baseline CV risk, as patients between 50 and less than 60 years of age were required to have established CVD in order to be included in the trial, whereas those 60 years of age or older could have either CV risk factors or established CVD.

As details of the analyses have been described previously,[7,16] only a brief summary is provided here. Time-to-first event were analysed using Cox proportional hazard regression models. The numbers of severe and nocturnal severe (00:01 AM-05:59 AM, both

inclusive) hypoglycaemic events and SAEs were analysed using a negative binomial-regression model. Associations between severe hypoglycaemia and subsequent accidents and injuries (within one day, defined according to standardized Medical Dictionary for Regulatory Activities query), time to first MACE and time to all-cause mortality (any time after a severe hypoglycaemic event) were analysed using a Cox regression model with treatment and previous severe hypoglycaemia (Yes/No) as time-varying covariates, and were adjusted for the baseline covariates listed above, similar to those in DEVOTE 3.[7]

Interactions with age group, pooled across treatments for insulin dose (U/kg), HbA1c and fasting plasma glucose (FPG), were analysed using a mixed model for repeated measures (MMRM) within patients using an unstructured residual covariance matrix among visits. *P* values were not multiplicity adjusted and a *P* value less than 0.05 was considered significant.

3 | RESULTS

3.1 | Baseline characteristics

The lowest proportion of patients with established CVD/CKD, compared with the other age groups (50-64 years or ≥75 years) was in the 65 to 74 years age group (Table 1), in part the result of the inclusion criteria. Compared with the 50 to 64 years age group, the 65 to 74 and ≥75 years age groups had a longer duration of diabetes and had lower body weight, body mass index (BMI), pulse, HbA1c, FPG, estimated glomerular filtration rate (eGFR), total cholesterol and triglycerides, and a lower proportion of patients in these groups were identified as smokers. Differences in the above baseline characteristics and demographic variables between age groups were significant (all $P < 0.001$).

3.2 | Cardiovascular and mortality outcomes

There was a trend towards higher risks of MACE and non-fatal stroke across the age groups and a significantly higher risk of CV death in the ≥75 years age group, as compared with the 50 to 64 years age group (Figure 1). Compared with the 50 to 64 years and the 65 to 74 years age groups, the risk of all-cause mortality was significantly higher in the ≥75 years age group (Figure 1). There was no evidence of heterogeneity of the effects of degludec vs glargine U100 on MACE, on all-cause mortality (Figures 2 and S1) or on individual MACE components (CV death, non-fatal MI and non-fatal stroke) (Figures 2 and S2) among age groups (Figure 2).

3.3 | Severe and nocturnal severe hypoglycaemia

The risks of severe and nocturnal severe hypoglycaemia in patients aged ≥75 years, compared with those aged 50 to 64 and 65 to 74 years (Figure 1) were numerically higher. There was a lower risk of severe hypoglycaemia with degludec vs glargine U100 across age groups, although a non-significant trend was demonstrated in patients aged ≥75 years (Figures 2 and S3). This lower risk with degludec vs glargine U100 was also observed for nocturnal severe hypoglycaemia in patients aged 50 to 64 and 65 to 74 years but was not evident in the 16 events observed among patients aged ≥75 years (Figure 2). There was no evidence of interaction between randomized treatment and age group for severe or nocturnal severe hypoglycaemia (Figure 2).

3.4 | Association between severe hypoglycaemia and time to first MACE and time to all-cause mortality by age group

The risk of MACE after a severe hypoglycaemic event in the two older age groups was higher compared with before an event; this was significant in the 65 to 74 years age group (hazard ratio [HR], 1.69; 95% CI, 1.03-2.77) and not significant in the ≥75 years age group (HR, 1.58; 95% CI, 0.71-3.51) (Figure S4). Concerning time to all-cause mortality, there was a significantly higher risk following a severe hypoglycaemic event in all age groups (≥75 years: HR, 2.20; 95% CI, 1.11-4.33; 65-74 years: HR, 2.36; 95% CI, 1.42-3.92; 50-64 years: HR, 1.95; 95% CI, 1.01-3.75) (Figure S4).

3.5 | Glycaemic control

Both total and basal insulin dose (U/kg) were significantly lower in the two older age groups after 24 months of treatment, compared with the younger age group (Figures S5 and S6A). However, there was no evidence of an association between randomized treatment and age group for total, basal and bolus insulin doses (*P* interaction = 0.63, 0.41 and 0.38, respectively) (Figure S6B).

Concerning change in HbA1c from baseline to Month 24, there was no significant difference between age groups, with the exception of the 65 to 74 years age group, which had a significantly greater reduction in HbA1c compared with the 50 to 64 years age group (Figure S7). Similarly, concerning change in FPG from baseline to Month 24, there was no significant difference across age groups; degludec achieved a significantly greater reduction in FPG during the same period compared with glargine U100 in all age groups (Figure S8). There was no evidence of an association between randomized treatment and age group for HbA1c and FPG (HbA1c: *P* interaction = 0.62; FPG: *P* interaction = 0.58).

Across the three age groups, there were no significant differences in day-to-day fasting self-measured blood glucose (SMBG) variability (pooled treatments). In addition, there was a consistently lower day-to-day fasting SMBG variability with degludec compared with glargine U100 across age groups [$P < 0.05$].

3.6 | Serious adverse events

The most frequent SAEs were cardiac disorders, which occurred in 15.0% of patients aged 50 to 64 years, in 15.5% of patients aged 65 to 74 years and in 19.0% of patients aged ≥75 years of age (Table S1). The oldest age group (≥75 years) had significantly higher rates of SAEs compared with the 50 to 64 years and 65 to 74 years age groups (Figure 1). The proportion of patients in the ≥75 years age group who had accidents and injuries was 6.2% (rate, 4.19/100 patient-years of observation [PYO]), whereas, in the 50 to 64 years and 65 to 74 years age groups, the proportions were 3.7% (rate, 2.29/100 PYO) and 3.5%

TABLE 1 Baseline characteristics by age groups

Characteristic	50-64 years *n* = 3682	65-74 years *n* = 3136	≥75 years *n* = 819
Age (years)	58.9 ± 4.0	68.8 ± 2.8	78.2 ± 3.1
Male	2273 (61.7)	2008 (64.0)	497 (60.7)
Ethnicity			
Hispanic or Latino	591 (16.1)	438 (14.0)	108 (13.2)
Race			
White	2596 (70.5)	2510 (80.0)	669 (81.7)
Asian	452 (12.3)	283 (9.0)	41 (5.0)
Black	500 (13.6)	253 (8.1)	79 (9.6)
Other	134 (3.5)	90 (2.8)	30 (3.7)
Established CVD/CKD	3169 (86.1)	2620 (83.5)	720 (87.9)
Smoker (yes)	557 (15.1)	262 (8.4)	33 (4.0)
Diabetes duration (years)	14.5 ± 7.9	17.8 ± 9.1	19.8 ± 10.2
Body weight (kg)	97.9 ± 24.0	95.5 ± 22.2	90.4 ± 19.0
BMI (kg/m^2)	34.1 ± 7.2	33.4 ± 6.6	32.1 ± 5.8
Blood pressure			
Systolic (mmHg)	135.1 ± 18.0	135.9 ± 18.1	136.0 ± 17.8
Diastolic (mmHg)	78.6 ± 10.0	74.4 ± 10.1	72.1 ± 10.2
Heart rate (beats/min)	74.8 ± 11.2	71.8 ± 11.3	70.4 ± 10.9
HbA1c (%)	8.7 ± 1.8	8.2 ± 1.5	8.0 ± 1.4
[mmol/mol]	[71.8 ± 19.6]	[66.0 ± 16.1]	[64.1 ± 14.7]
FPG (mmol/L)	10.0 ± 4.2	9.1 ± 3.6	8.9 ± 3.5
[mg/dL]	[180.7 ± 76.2]	[164.2 ± 63.9]	[159.5 ± 62.2]
eGFR ($mL/min/1.73m^2$) based on CKD-EPI	74.9 ± 21.9	63.2 ± 19.2	54.9 ± 16.9
Total cholesterol (mmol/L) [mg/dL]	4.4 ± 1.3 [170.8 ± 50.0]	4.2 ± 1.2 [160.5 ± 44.2]	4.1 ± 1.1 [157.1 ± 40.7]
LDL-C (mmol/L) [mg/dL]	2.3 ± 1.0 [89.4 ± 38.5]	2.1 ± 0.9 [82.3 ± 34.5]	2.1 ± 0.8 [79.5 ± 32.4]
HDL-C (mmol/L) [mg/dL]	1.1 ± 0.3 [43.8 ± 12.7]	1.2 ± 0.3 [44.6 ± 12.9]	1.2 ± 0.3 [46.5 ± 13.3]
Triglycerides (mmol/L) [mg/dL]	2.3 ± 2.2 [200.7 ± 191.0]	2.0 ± 1.4 [173.2 ± 126.7]	1.8 ± 1.2 [160.0 ± 106.9]
Antihyperglycaemic medication at baseline			
Insulins			
Long acting	2101 (57.1)	1973 (62.9)	523 (63.9)
Intermediate acting[a]	602 (16.3)	384 (12.2)	88 (10.7)
Short acting	1281 (34.8)	1244 (39.7)	306 (37.4)
Premix	413 (11.2)	294 (9.4)	75 (9.2)
Other antihyperglycaemic treatment (excluding insulins)			
Metformin	2406 (65.3)	1800 (57.4)	358 (43.7)
Sulfonylurea	1050 (28.5)	921 (29.4)	258 (31.5)
Alpha glucosidase inhibitor	73 (2.0)	49 (1.6)	11 (1.3)
Thiazolidinedione	112 (3.0)	128 (4.1)	28 (3.4)
DPP-4i	438 (11.9)	379 (12.1)	126 (15.4)
GLP-1RA	292 (7.9)	271 (8.6)	41 (5.0)
SGLT-2i	83 (2.3)	67 (2.1)	18 (2.2)
Others	34 (0.9)	58 (1.8)	26 (3.2)
CV medication at baseline			
Antihypertensive therapy	3389 (92.0)	2948 (94.0)	772 (94.3)
Diuretics	1753 (47.6)	1630 (52.0)	433 (52.9)
Lipid-lowering drugs	2961 (80.4)	2623 (83.6)	690 (84.2)
Platelet aggregation inhibitors	2631 (71.5)	2267 (72.3)	592 (72.3)
Anti-thrombotic medication	185 (5.0)	296 (9.4)	116 (14.2)

Note. Full analysis set; data listed are number (proportion [%]) for discrete variables and mean ± SD for continuous variables.
Abbreviations: BMI, body mass index; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; DPP-4i, dipeptidyl peptidase-4 inhibitors; eGFR, estimated glomerular filtration rate; EPI, epidemiology collaboration formula; FPG, fasting plasma glucose; GLP-1RA, glucagon-like peptide-1 receptor agonist; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NPH, neutral protamine Hagedorn; SGLT-2i, sodium-glucose co-transporter-2 inhibitor.
[a]Intermediate-acting insulins include human insulins, neutral protamine Hagedorn and unknown types of insulins.

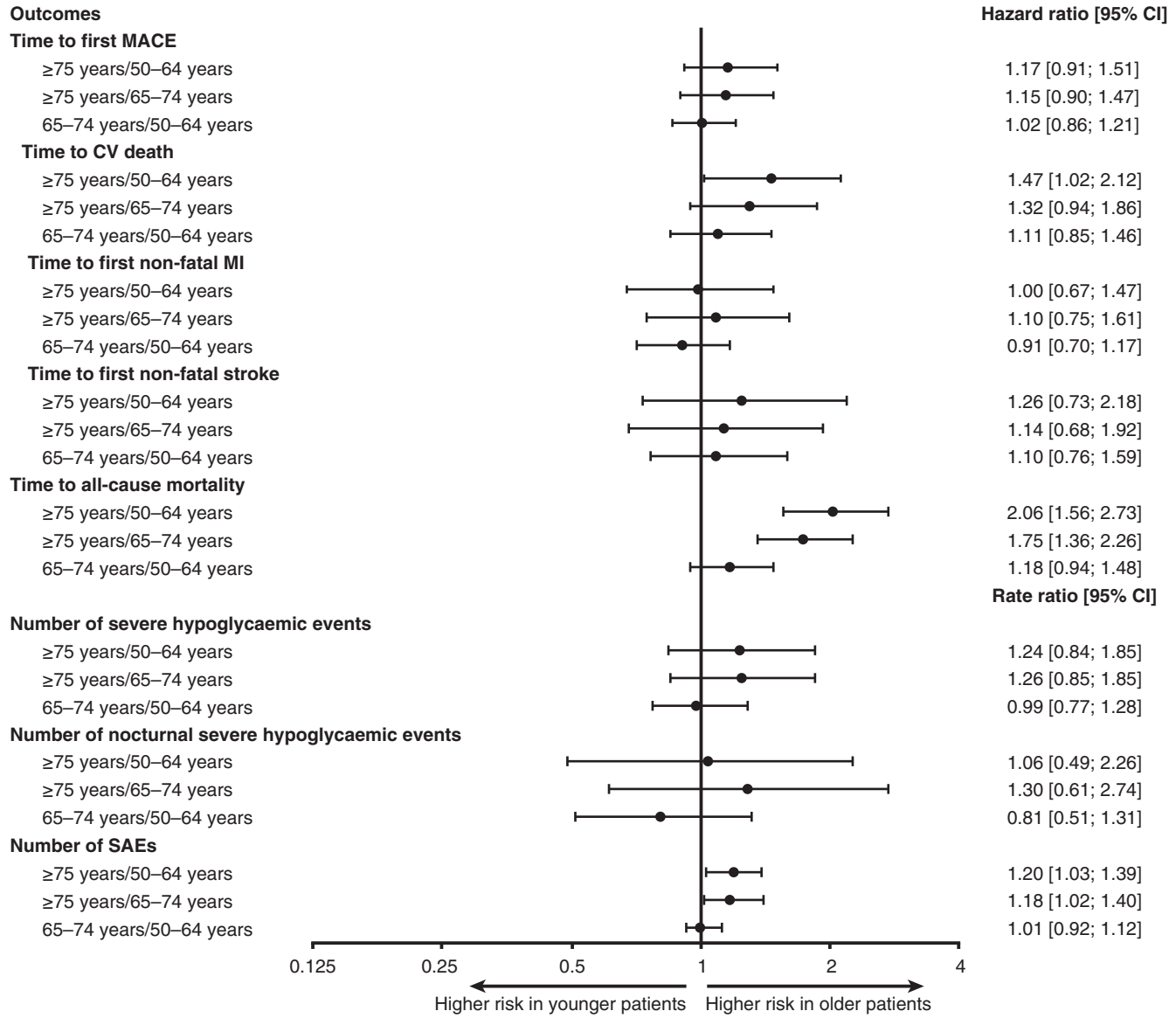
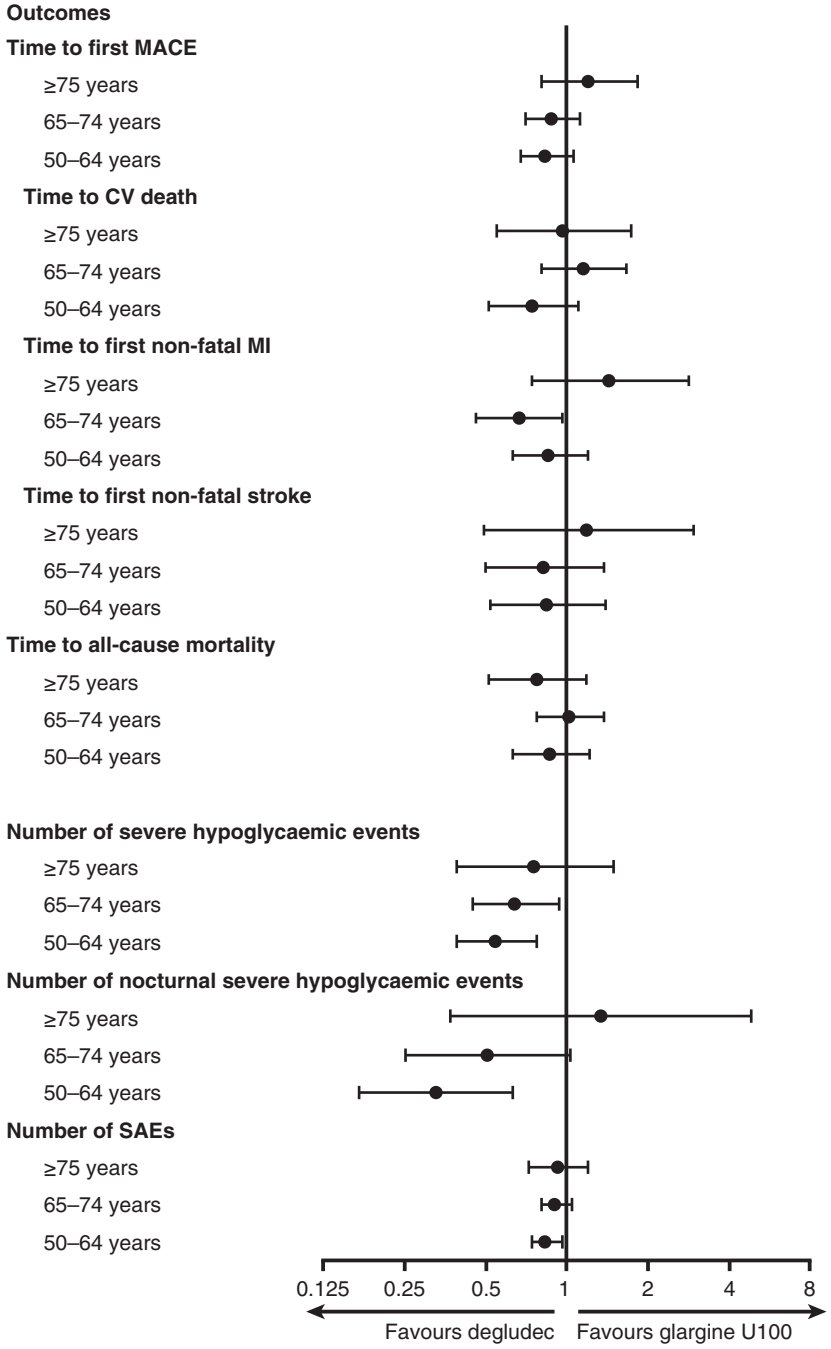


FIGURE 1 Age group comparisons concerning time to first MACE and its components (CV death, non-fatal MI and non-fatal stroke), time to all-cause mortality, number of severe and nocturnal severe hypoglycaemic events and SAEs (pooled treatments; adjusted for baseline covariates). All comparisons accounted for age group, treatment, interactions between age group and treatment, sex, region, diabetes duration, CV risk, insulin-naïve status, smoking status and kidney function at baseline. Severe hypoglycaemia was defined, according to the American Diabetes Association, as an episode requiring the assistance of another person to actively administer carbohydrate or glucagon, or to take other corrective actions.[8] Nocturnal severe hypoglycaemia was defined as an episode with an investigator-reported onset between 00:01 AM and 5:59 AM. Abbreviations: CI, confidence interval; CV, cardiovascular; MACE, major adverse cardiovascular event; MI, myocardial infarction; SAE, serious adverse event

(rate, 2.53/100 PYO), respectively. Furthermore, there was a significantly higher risk of accidents and injuries following, within one day, a severe hypoglycaemic event, regardless of age (229 times higher risk in the 50 to 64 years age group [$P < 0.0001$], 60 times higher risk in the 65 to 74 years age group [$P < 0.0001$] and 619 times higher risk in the ≥75 years age group [$P < 0.0001$]). However, there were no significant differences between treatments in the risk of accidents and injuries. There were trends towards a lower risk of SAEs with degludec in the 65 to 74 years and ≥75 years age groups, and a significantly lower risk of SAEs in the 50 to 64 years age group as compared with glargine U100 (Figure 2). In addition, similar to what was observed with primary outcomes, concerning SAEs, there were no significant interactions between randomized treatment and age group (Figure 2).

4 | DISCUSSION

Results from these secondary analyses demonstrated that there was a trend towards higher risks of MACE and severe hypoglycaemia, and significantly higher risks of CV death, all-cause mortality and SAEs with increasing age. There was no evidence for heterogeneity of the effects of degludec vs glargine U100 with regard to the risk of MACE, all-cause mortality and SAEs at similar levels of glycaemic control in patients with T2D who are aged 65 years or older compared with younger patients. The results suggest that the CV safety and lower severe hypoglycaemia of degludec versus glargine U100 in patients with T2D observed in the overall results of the DEVOTE trial[16] were similar for participants below or above 65 years of age. However,



Outcomes	Hazard ratio [95% CI]	Degludec N	Degludec %	Glargine U100 N	Glargine U100 %	$P_{interaction}$
Time to first MACE						0.32
≥75 years	1.21 [0.80; 1.84]	46	12.2	42	10.0	
65–74 years	0.88 [0.70; 1.12]	135	8.6	145	9.6	
50–64 years	0.84 [0.67; 1.06]	137	7.6	162	8.9	
Time to CV death						0.27
≥75 years	0.98 [0.55; 1.73]	22	5.9	25	5.9	
65–74 years	1.16 [0.81; 1.66]	67	4.3	55	3.7	
50–64 years	0.75 [0.51; 1.11]	45	2.5	60	3.3	
Time to first non-fatal MI						0.13
≥75 years	1.45 [0.74; 2.83]	20	5.3	15	3.6	
65–74 years	0.67 [0.46; 0.96]	49	3.1	70	4.6	
50–64 years	0.86 [0.63; 1.19]	70	3.9	81	4.5	
Time to first non-fatal stroke						0.77
≥75 years	1.20 [0.49; 2.95]	10	2.7	9	2.1	
65–74 years	0.83 [0.50; 1.37]	29	1.9	33	2.2	
50–64 years	0.85 [0.52; 1.39]	30	1.7	35	1.9	
Time to all-cause mortality						0.53
≥75 years	0.78 [0.51; 1.18]	38	10.1	54	12.8	
65–74 years	1.03 [0.77; 1.37]	94	6.0	87	5.8	
50–64 years	0.87 [0.63; 1.21]	68	3.8	78	4.3	
	Rate ratio [95% CI]	**E**	**R**	**E**	**R**	
Number of severe hypoglycaemic events						0.65
≥75 years	0.76 [0.39; 1.49]	38	3.13	58	4.12	
65–74 years	0.65 [0.45; 0.93]	114	2.28	181	3.53	
50–64 years	0.55 [0.39; 0.77]	113	2.11	211	3.84	
Number of nocturnal severe hypoglycaemic events						0.15
≥75 years	1.35 [0.37; 4.84]	9	0.61	7	0.45	
65–74 years	0.51 [0.25; 1.03]	17	0.29	36	0.57	
50–64 years	0.33 [0.17; 0.63]	18	0.27	62	0.82	
Number of SAEs						0.67
≥75 years	0.93 [0.72; 1.20]	440	35.66	502	38.42	
65–74 years	0.91 [0.80; 1.04]	1460	29.86	1552	32.78	
50–64 years	0.84 [0.74; 0.96]	1382	28.40	1624	33.65	

FIGURE 2 Treatment group comparisons (degludec vs glargine U100) concerning time to first MACE and its components (CV death, non-fatal MI and non-fatal stroke), time to all-cause mortality, number of severe and nocturnal severe hypoglycaemic events and SAEs adjusted for baseline covariates. All comparisons accounted for age group, treatment, interactions between age group and treatment, sex, region, diabetes duration, CV risk, insulin-naïve status, smoking status and kidney function at baseline. Severe hypoglycaemia was defined, according to the American Diabetes Association, as an episode requiring the assistance of another person to actively administer carbohydrate or glucagon, or to take other corrective actions.[8] Nocturnal severe hypoglycaemia was defined as an episode with an investigator-reported onset between 00:01 AM and 5:59 AM. Abbreviations: %, proportion of patients experiencing events; CI, confidence interval; CV, cardiovascular; E, number of events; glargine U100, insulin glargine 100 units/mL; MACE, major adverse cardiovascular event; MI, myocardial infarction; N, number of patients experiencing events; R, number of events per 100 patient-years of observation; SAE, serious adverse event

while there was strong evidence for treatment effects until the age of 74 years, there was no conclusive evidence for the group of patients who were 75 years or older, as reflected by the wide confidence intervals.

At baseline, there was a higher proportion of patients 75 years or older with established CVD/CKD, as compared with the 65 to 74 years age group, an observation that was not surprising given that these are common T2D-related complications in patients 65 years or older.[1]

The higher proportion of patients with established CVD/CKD in the 50 to 64 years age group as compared to the 65 to 74 years age group probably resulted from the pre-specified inclusion criterion that required CVD/CKD in those between 50 and less than 60 years of age. The ≥75 years age group was also characterized by a longer duration of T2D, although not to the same degree as the difference in age. To minimize the effect of differences between baseline characteristics and demographic variables, the statistical analyses in this study were adjusted for a number of baseline covariates. However, as age is probably still confounded by other baseline variables, the results can provide guidance on treatment decisions, but cannot determine the effect of age on outcomes in individuals.

The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) demonstrated that patients with increasing age had significantly higher risks of MACE, all-cause mortality, severe hypoglycaemia and bone fractures,[21] while pre-specified subgroup analyses of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study demonstrated that increased age was significantly associated with a higher risk of hypoglycaemia that required medical assistance.[22] A similar trend was observed in our study; however, there was a lack of a significant association between MACE, severe hypoglycaemia and age. While there was a numerically greater risk of severe hypoglycaemia with increasing age groups (RR, 1.24 for ≥75 years vs 50-64 years and RR, 1.26 for ≥75 years vs 65-74 years), the trend was not statistically significant. This may be explained by the markedly smaller sample size of the oldest age group compared with the other two age groups, leading to a higher degree of imprecision in estimates of outcomes. Furthermore, the magnitude of the association may have been influenced by under-reporting of severe hypoglycaemia in patients living alone.

In the present study, there were higher risks of MACE, all-cause mortality and accidents/injuries following compared with before a severe hypoglycaemic event in patients aged 65 years or older; this was the case especially in the ≥75 years age group, in which there was a 619 times higher risk of accidents/injuries following a severe hypoglycaemic event. This observation is consistent with a post hoc analysis of data from the Veterans Affairs Diabetes Trial (VADT) (mean age, 60.5 years), in which severe hypoglycaemia within the previous three months was significantly associated with higher risks of serious CV events, CV death and total mortality.[23] Given this evidence and the vulnerability of this patient population to severe hypoglycaemia,[24,25] it is particularly important to minimize the occurrence of severe hypoglycaemia.[26]

The reduced risk of severe hypoglycaemia with degludec vs glargine U100 (24%–45% reduction across the age groups) was consistent with that revealed by a secondary analysis of the SWITCH 2 trial population stratified by age (37% reduction in patients >65 years and 48% reduction in patients ≤65 years with degludec compared with glargine U100 during the maintenance period; not significant).[27] A separate pre-planned meta-analysis of seven trials in patients with T2D ≥65 years demonstrated that degludec was associated with a significant reduction (27% for overall hypoglycaemia and 39% for nocturnal hypoglycaemia) in hypoglycaemic events during the maintenance period, compared with glargine U100.[28] This clinical benefit possibly derives from the improved pharmacokinetic/pharmacodynamic profile of degludec,[29] characterized by reduced day-to-day fasting SMBG variability with degludec compared with glargine U100 across age groups, as observed in the present study and also supported by the finding of a strong association between variability and severe hypoglycaemia in all three pooled age groups. This property may allow patients with diabetes, of all ages and all disease stages, to aim for lower glycaemic targets without increasing their risk of hypoglycaemia.[30,31] In addition, the flexibility in dosing time with degludec[32] may be beneficial in this older population that may require assistance and may not be able to administer insulin at regular daily intervals.

This study has a number of strengths, including the double-blind, active-control design, the high level of CV risk of the population, and the prospective capture and independent adjudication of CV events, mortality and severe hypoglycaemic events. The prospective design and multicentre, international nature of this trial and the high level of patient follow-up further contributed to the generalizability and robustness of the analyses. In addition, this secondary analysis was pre-specified, with the exception of statistical analyses of the SAEs. Although the DEVOTE trial was not powered to investigate confirmatory outcomes in the three age groups separately, as the only randomized, double-blind cardiovascular outcome clinical trial directly comparing two basal insulins in such large numbers, it still provides valuable information concerning these important endpoints in a population aged 65 years or older. Nevertheless, the smaller sample size leads to a higher degree of imprecision in results concerning the ≥75 years age group. Finally, there was no correction for multiplicity of comparisons in these analyses.

In conclusion, there were higher risks of CV death, all-cause mortality and SAEs, as well as a trend towards higher risks of MACE and severe hypoglycaemia, with increasing age in patients with T2D. The effects across age groups of degludec vs glargine U100 on MACE, all-cause mortality and severe hypoglycaemia were consistent with those of the overall DEVOTE population, suggesting that, regardless of age, the risk of MACE and death in patients with T2D who are at high risk of CV are comparable, and the risk of severe hypoglycaemia is lower with degludec compared with glargine U100.

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CONFLICT OF INTEREST

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C. T. H., M. V. H. and T. M. are full-time employees of, and hold stock in, Novo Nordisk A/S.

A. C. M. was a full-time employee of Novo Nordisk A/S at the time of the study and remains a consultant to Novo Nordisk, and holds stock in the company.

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AUTHOR CONTRIBUTIONS

All authors confirm that they meet the uniform requirements for authorship of the International Committee of Medical Journal Editors. Specifically, all authors made substantial contributions to the interpretation of data, drafted and critically revised the manuscript, provided final approval of the version to be published and agreed to be accountable for all aspects of the manuscript. Novo Nordisk contributed to the trial design, data collection, statistical analyses and the preparation of the clinical study report. All authors had full access to data and shared final responsibility for the content of the manuscript and the decision to submit for publication.

Subject level analysis data sets for the research presented in this publication are available from the corresponding author upon 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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