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Risk of major cardiovascular events, severe hypoglycaemia, and all-cause mortality for users of insulin degludec versus insulin glargine U100-A Danish cohort study

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Risk of major cardiovascular events, severe hypoglycemia and all-cause mortality for users of insulin degludec versus insulin glargine U100 – a Danish cohort study

Running title: Safety of insulin degludec vs glargine

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Abstract

Aims: Real-world evidence of the safety of insulin degludec compared to insulin glargine U100 is sparse. This study sought to investigate the risk of major cardiovascular events, severe hypoglycemia and all-cause mortality after initiation of degludec or glargine U100 in the population of Denmark.

Materials and Methods: All Danish people with diabetes initiating treatment on degludec (*n*=5,159) or glargine (*n*=4,041) in 2016-17 were included in the study. The effect of insulin treatment on the endpoints of major cardiovascular events, severe hypoglycemia and all-cause mortality was analysed with Cox proportional hazard models. The models were adjusted for age, sex, diabetes duration, diabetes type, highest completed education and annual income. The model of severe hypoglycemia was also adjusted for severe hypoglycemia prior to baseline. The model of mortality was also adjusted for history of alcohol abuse, use of antidepressants, use of opioids and use of anxiolytics. Lastly, the models of major cardiovascular events and mortality were also adjusted for Charlson comorbidity index.

Results: Use of degludec resulted in an almost 2-fold decrease in risk of death (HR: 0.54, 95% CI: 0.44-0.65) compared to use of glargine. No statistically significant risk changes were found for major cardiovascular events (HR: 0.86, 95% CI: 0.62-1.19) and severe hypoglycemia (HR: 1.13, 95% CI: 0.66-1.93). The proportion of cause of death due to malignant neoplasm of pancreas was almost doubled for glargine compared to degludec.

Conclusions: These results indicate that insulin degludec has a safer profile with respect to all-cause mortality as compared to insulin glargine U100.

Introduction

Insulin degludec is an ultra-long acting insulin producing a flat glucose-lowering profile to improve the imitation of the pancreatic basal insulin secretion[1]. An indication for clinicians to recommend patients to switch from other long acting insulins to insulin degludec is among others issues with hypoglycemia[2]. In the DEVOTE study[3], Pratley et al. investigated 7,637 people with type 2 diabetes and found a comparable risk of major cardiovascular events (MACE) and all-cause mortality for users of insulin degludec compared to glargine U100 with a slight statistically insignificant favoring towards degludec. However, the risk of severe hypoglycemia was statistically significantly lower for users of insulin degludec. In a meta-analysis of 4,330 people with both type 1 diabetes and type 2 diabetes, Ratner et al.[4] found that users of degludec experienced significant lower rates of particularly nocturnal

hypoglycemic events as compared to users of glargine. In another meta-analysis by Zhang et al.[5] investigating 16,791 people with type 1 diabetes and type 2 diabetes, similar outcomes were observed: Risk reduction in confirmed and nocturnal hypoglycemia for users of degludec compared to glargine U100, but no statistically significant difference in cardiovascular events and all-cause mortality.

Evidence of the safety of insulin degludec vs glargine U100 is rich with respect to controlled settings and sometimes unnatural population selections in randomized controlled trials (RCTs). For example, an exclusion criterion of previous malignant neoplasm[6] is unnatural in the sense that strong evidence for a positive association between diabetes and cancer exists[7], thereby making cancer a natural part of the diabetes population. Another example is the exclusion criterion of hypoglycemia unawareness in a basal-bolus study of people with type 1 diabetes[8], which is unnatural because around one fifth of the type 1 diabetes population suffers from impaired awareness[9]. On the other hand, real-world evidence of the safety is sparse. In a small real-world study of degludec vs glargine U100 in a previous insulin-naïve population in India, Ghosal et al.[10] found less patient-recorded hypoglycemic episodes for degludec compared to glargine U100 users. In a prospective cohort study of 80 people with type 1 diabetes and type 2 diabetes switched to degludec from another basal insulin, Kobuke et al.[11] found that degludec can maintain glucose control at a lower insulin dose and frequency of hypoglycemia in type 1 diabetes, and improve glycemic control at an equal insulin dose in type 2 diabetes.

These small real-world studies add to the evidence shown in the larger RCTs that degludec reduces the risk of hypoglycemia as compared to glargine U100. However, investigation of major cardiovascular events and all-cause mortality in real-world studies remain sparse.

This study sought to investigate the hypothesis that risk of major cardiovascular events, severe hypoglycemia and all-cause mortality is lower after initiation of insulin degludec compared to insulin glargine U100 in the population of Denmark.

Materials and Methods

Study design

This study was carried out using a cohort of all adult people in Denmark initiating basal insulin treatment on either insulin degludec (Novo Nordisk A/S, Bagsvaerd, Denmark) or insulin glargine (Sanofi, Paris,

France) from 2016 to 2017. A general reimbursement of insulin degludec was approved in Denmark with effect from January 4th, 2016[12], and a significant use of degludec thus started in 2016. Data were extracted from the Danish National Patient Registry (DNPR). Date of initiation of insulin degludec or insulin glargine defined baseline for each person. The follow-up period was terminated at the dispense of another insulin product after baseline. People with dispensed bolus insulin in the year before basal insulin initiation were excluded. Dispenses of degludec and glargine were extracted from The National Pharmacological Database using the Anatomical Therapeutical Chemical (ATC) classification code of A10AE (Insulins and analogues for injection, long-acting) and the product names of Tresiba (insulin degludec) and Lantus (insulin glargine). Bolus insulins were found in the same database from the ATC code A10AB (Insulins and analogues for injection, fast-acting). From all Danish adult citizens in 2016-17, 313,690 people were diagnosed with diabetes. 5,159 people initiated treatment on insulin degludec, whereas 4,041 initiated treatment on insulin glargine U100.

Endpoints

Three endpoints were defined in this study: 1) Major cardiovascular event (MACE), 2) severe hypoglycemia and 3) death. The endpoints were found via the International Classification of Diseases 10 (ICD-10) system. MACE is a composite endpoint consisting of nonfatal acute myocardial infarctions, nonfatal ischemic strokes and cardiovascular deaths. Nonfatal acute myocardial infarctions were found from the ICD-10 code DI21 (Acute myocardial infarction) and nonfatal ischemic strokes from DI61 (Nontraumatic intracerebral hemorrhage). Cardiovascular deaths were extracted from the Danish Register of Causes of Death via the ICD-10 codes of DI00-DI99 (Diseases of the circulatory system). Hypoglycemic episodes were identified via the ICD-10 codes DE160 (drug-induced hypoglycemia without coma), DE161 (other hypoglycemia) and DE162 (Hypoglycemia, unspecified). They were characterized as severe because they were related to hospital admissions. The last endpoint of death was defined as all-cause deaths extracted from the Danish Register of Causes of Death.

Source of data

Diagnoses used for endpoints and covariates came from The Danish National Patient Register (DNPR)[13]. DNPR was established in 1977 and initially covered information on inpatient in somatic wards. Since then it has been expanded and now includes information on all patients in Danish

hospitals[13]. The validity of registrations is high[14,15], especially, registrations related to MACE[16,17].

Information about drug use came from The National Pharmacological Database by the Danish Medicines Agency, which is a nationwide register of medicines sold after 1996. Information about mortality came from the Danish Register of Causes of Death, which is a register of all deaths since 1875 and is managed by the National Board of Health[18].

Statistical analysis

Descriptive statistics are presented with mean and standard deviation (SD) or percentage of people. Unpaired T-tests, Chi-square tests and Mann-Whitney U tests will be used to present statistical differences in person characteristics. Age was calculated as years from date of birth to baseline. Diabetes duration was calculated as years from date of diagnosis to baseline. Insulin dose was calculated by dividing each dose (in international units – IU) with the duration to the next dispense to get daily dose per dispense. Median of all dose dispenses per person was then calculated. Finally, grand median per treatment was calculated and is presented with interquartile ranges (IQR). as the median dose for each patientEnrolled people were stratified into type 1 diabetes or type 2 diabetes based on codes from the Anatomical Therapeutical Chemical (ATC) classification system. They were classified as type 2 diabetes (*n*=8,618) if they had at least one A10B (blood glucose lowering drugs, excl. insulins) ATC code; otherwise they were classified as type 1 diabetes (*n*=582). Kaplan-Meier curves were applied to illustrate unadjusted time to each of the three endpoints, whereas Cox proportional hazards models were applied to analyse adjusted and unadjusted effect of treatment on each of the three endpoints. People enrolled were considered censored at the first date of emigration or end of follow-up (31st December 2017). The proportional hazards models were adjusted for age, sex, diabetes duration and diabetes type. Furthermore, they were adjusted for socioeconomic factors of highest completed education and yearly income prior to baseline. Yearly gross income per person was stratified in Low (<200,000 DKK ≈ 30,000 USD), Normal (200,000-500,000 DKK ≈ 30,000-75,000 USD) or High (>500,000 DKK ≈ 75,000 USD). Highest completed education was stratified in <High-school graduate (or equal) or >High-school graduate. The model of severe hypoglycemia was adjusted for occurrence of at least one severe hypoglycemia prior to baseline. The model of mortality was adjusted for history of alcohol abuse (ICD-10: DF10, DZ721), use of antidepressants (ATC: N06AA),

use of opioids (ATC: N02A) and use of anxiolytics (ATC: N05B) prior to baseline. The models of MACE and mortality were adjusted for Charlson comorbidity index[19]. Comorbidities related to MACE were excluded from the index, and the comorbidities searched for prior to baseline and associated scores were Cardiac insufficiency (1, ICD-10: DI50, DI110, DI130, DI132), Cardiovascular disease (1, ICD-10: DI70, DI71, DI72, DI73, DI74, DI77), Cerebrovascular disease (1, ICD-10: DI60, DI61-9, DG45, DG46), Dementia (1, ICD-10: DF00-DF03, DF051, DG30), Chronic pulmonary disease (1, ICD-10: DJ40-DJ47, DJ60-DJ67, DJ684, DJ701, DJ703, DJ841, DJ920, DJ961, DJ982, DJ983), Connective tissue disease (1, ICD-10: DM05, DM06, DM08, DM09, DM30, DM31, DM32, DM33, DM34, DM35, DM36, DD86), Peptic Ulcer (1, ICD-10: DK221, DK25-DK28), Mild liver disease (1, ICD-10: DB18, DK700-DK703, DK709, DK71, DK73, DK74, DK760), Diabetes mellitus (1, ICD-10: DE100, DE101, DE109, DE110, DE111, DE119), Hemiplegia (1, ICD-10: DG81, DG82), Nephrological disease (2, ICD-10: DI12, DI13, DN00-DN05, DN07, DN11, DN14, DN17-DN19, DQ61), Late-diabetic complications (2, ICD-10: DE102-DE108, DE112-DE118), Solid cancers (2, ICD-10: DC00-DC75), Leukemia (2, ICD-10: DC91-DC95), Lymphoma (2, ICD-10: DC81-DC85, DC88, DC90, C96), Moderate to severe liver disease (3, ICD-10: DB150, DB160, DB162, DB190, DK704, DK72, DK766, DI85), Metastatic cancer (6, ICD-10: DC76-DC80), AIDS (6, ICD-10: DB21-DB24). Finally, the five most frequent causes of death were found and the distribution across treatments are summarized.

Results

Table 1 shows the baseline characteristics of people enrolled in this study. Less users of glargine than degludec were found. Age, sex and socioeconomic factors were fairly equally distributed between the two treatments. Degludec users had a longer diabetes duration. More type 1 diabetes people were users of glargine and more type 2 diabetes people were users of degludec. Degludec users had in general a higher insulin dose. The Charlson comorbidity index was slightly higher for glargine users. Furthermore, a larger proportion of glargine users had a history of alcohol abuse. On the other hand, a larger proportion of degludec users were on opioids and anxiolytics before baseline. Time-to-event curves derived from Kaplan-Meier analyses are presented in Figure 1. A separation of the treatments from time zero favoring degludec can be observed for time to MACE and time to death. Time to severe hypoglycemia shows inconclusive results but an indication of a favoring of glargine half a year after

initiation of treatment may be observed. However, only about half of the population is present in the last half year. In Table 2, unadjusted and adjusted hazard rate ratios (HR) and 95% confidence intervals (CI) are shown for degludec/glargine. Unadjusted HRs and CIs are similar to the adjusted versions, and the indications are similar to those of the time-to-event curves. Risk of MACE is reduced for degludec compared to glargine, but the results are not statistically significant. Risk of severe hypoglycemia is increased for degludec compared to glargine, but the results are not statistically significant. Risk of all-cause mortality is statistically significantly decreased for degludec compared to glargine. Being female reduced the risk of MACE (HR: 0.64, CI 95%: 0.45-0.90), severe hypoglycemia (HR: 0.84, CI 95%: 0.49-1.44) and all-cause mortality (HR: 0.83, CI 95%: 0.69-1.01), but only the former was statistically significant. In Table 3 the five most frequent causes of death are summarized across treatments. The excessive deaths among people using glargine is from the top five death causes mainly driven by pancreatic malignancy.

Discussion

In this study, we investigated risk of major cardiovascular events (MACE), severe hypoglycemia and all-cause mortality after initiation of insulin degludec or insulin glargine U100 in the population of Denmark in 2016-17. Risk of MACE and severe hypoglycemia was decreased and increased, respectively, for degludec compared to glargine, but the results were not statistically significant. Furthermore, a statistically significant approximately 2-fold risk reduction of all-cause mortality could be observed for degludec compared to glargine.

In several randomized controlled trials (RCTs), a risk reduction with respect to hypoglycemia has been observed for degludec compared to glargine[3–5]. In this study, we were unable to demonstrate this link. In the first half year of initiation of degludec or glargine, a small favoring of degludec was observed, but in the next half year, glargine is favored leading to a statistically insignificant 1-year risk increase for degludec compared to glargine. It should be noted that the number of episodes is low (59). Furthermore, the episodes investigated in this study are all related to hospital admission. In other studies, e.g. the DEVOTE study[3], the American Diabetes Association's definition of an episode requiring assistance of another person to actively administer carbohydrate or glucagon, or to take other corrective actions[20] is typically used. This different definition and the number of episodes might explain the results and the

statistically insignificance with respect to hypoglycemia. A protective effect of degludec compared to glargine with respect to MACE was observed in this study, but the effect was not statistically significant. These results are comparable with findings from the DEVOTE study by Pratley et al.[3] and a meta-analysis by Zhang et al.[5]. In the DEVOTE study, a MACE risk reduction of 12% for people with type 2 diabetes aged 65-74 was shown, which is comparable with the 14% risk reduction shown in this study. Both results were not statistically significant though.

On the other hand, a statistically significant protective effect of degludec compared to glargine with respect to death was observed. The risk of death was decreased by 46% for people on degludec compared to glargine. In the DEVOTE study[3], people above 75 years or between 50 and 65 years using degludec had a reduced risk of death compared to glargine but both results were not statistically significant. In the meta-analysis by Zhang et al.[5], a 10% reduced risk of total mortality was observed for people on degludec compared to glargine, but this result was not statistically significant either. Compared to DEVOTE, the population of this study differs due to inclusion of people with type 1 diabetes. However, people with type 1 diabetes were also included in the meta-analysis by Zhang et al. In the DEVOTE study, several eligibility criteria[6] make comparison with the real-world population of this study difficult. First of all, an inclusion criterion was age above or equal to 50 years with predefined previous cardiovascular disease(s) or renal disease or age above or equal to 60 years with predefined cardiovascular risk factors. Secondly, an exclusion criterion was current or past (within the last 5 years) malignant neoplasm (except basal cell and squamous cell skin carcinoma). In the top five frequent causes of death in our study, malignant pancreatic neoplasm was more frequent among users of glargine compared to degludec, and if malignant disposed people were excluded in the DEVOTE study, this could be one of the reasons behind the discrepancy in risk of death among the studies. It should be noted that pancreas cancer is probably not induced within the follow-up period of one year, but the insulin treatment could induce progression of existing malignant dysplasia.

In the past, an association between insulin analogues and risk of cancers has been suspected[21]. Especially, insulin glargine, as the first long-acting insulin analogue produced by recombinant DNA technology, has been in focus[7]. In a study by Hemkens et al.[22], a cancer risk increase of 9-31% was found for glargine compared to human insulin. In other studies increase in risk of cancer was also linked to glargine[23–25]. However, in a follow-up study, one of the previous findings were proven to be random[26]. In an expert opinion by Rendell et al.[7], this example with a wrong conclusion led to

criticism of retrospective epidemiological studies with a conclusion pointing towards that controlled clinical trials are the only means to definitely prove hypotheses. We agree to this point, but as previously discussed, the issue with randomized controlled trials is that the included population is seldom completely generalizable, and at least a part of the mortality difference between this study and DEVOTE can be explained by this.

It can be observed that the diabetes duration is longer in the degludec group compared to glargine. One explanation could be a better mortality benefit as discussed above for degludec as compared to glargine. Another explanation could be that an indication for switching to degludec is issues with hypoglycemia, and risk of severe hypoglycemia increases with diabetes duration[27], which could explain the higher diabetes duration among degludec users. Another observation is the higher insulin dose among degludec users. In treat-to-target trials, a higher dose of degludec has been observed[6] but not with the same magnitude. The higher dose might also be related to that people initiating treatment on insulin degludec are more insulin resistant with history of severe hypoglycemia, for example, on insulin glargine where a relatively low insulin dose has been necessary. When they are then switched to insulin degludec the dose is being increased.

A limitation of our study is the lack of information about body mass index and glycemic control. Body mass index could be a confounder, and it would be valuable to know the glycemic control, for example in terms of HbA1c in the two treatment groups. If the glycemic control was known and approximately equal among treatments, it would have enabled adjustment of insulin dose. The higher degludec dose might affect degludec's better outcome with respect to severe hypoglycemia compared to glargine as seen in other studies, but without information about glycemic control in this study, it would be misleading to adjust for insulin dose. Another limitation is the definition of severe hypoglycemia. Since only 19% of severe hypoglycemic episodes lead to hospital admissions[28], the actual incidences of severe hypoglycemia are much higher than in this study, which may have led to the inconclusive result. A third limitation is definition of basal insulin use. Only dates of insulin dispense were available and these are not necessarily the dates of basal insulin initiations. An improvement to the study design could have been to match type 2 diabetes people between the two groups based on their oral antidiabetic medication. However, in this study it was not possible due to the low number of events under investigation. Finally, a limitation is the origin of causes of death. Death causes are registered in the

Danish Civil Registration System, typically, by general practitioners in everyday situations where register research is not on their mind. This means that more general causes of death might be used.

In conclusion, this study indicates a decreased risk of major cardiovascular events and an increased risk of severe hypoglycemia for people on insulin degludec compared to insulin glargine U100. However, both results were not statistically significant. On the other hand, a statistically significant approximately 2-fold reduced risk of death was found for degludec compared to glargine U100, which suggest that degludec has a safer profile than glargine with respect to all-cause mortality. These results add to the evidence that degludec has a safer profile, which should be considered when choosing treatment in clinical practice.

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Conflicts of Interest

Author Vestergaard has received unrestricted grants from MSD and Servier and travel grants from

Amgen, Eli Lilly, Novartis, Sanofi Aventis, and Servier. Author Jensen is former employee at Novo

Nordisk and holds shares in Novo Nordisk.

Ethics

This was not a clinical trial, and ethics committee approval was not required.

Authors contribution

MHJ designed the study, did the statistics and drafted the article. OH came with valuable input to the

study design and the article writing. PV came with valuable input to the study design, the statistics

and the article writing. All co-authors have read and approved the final article

Data availability
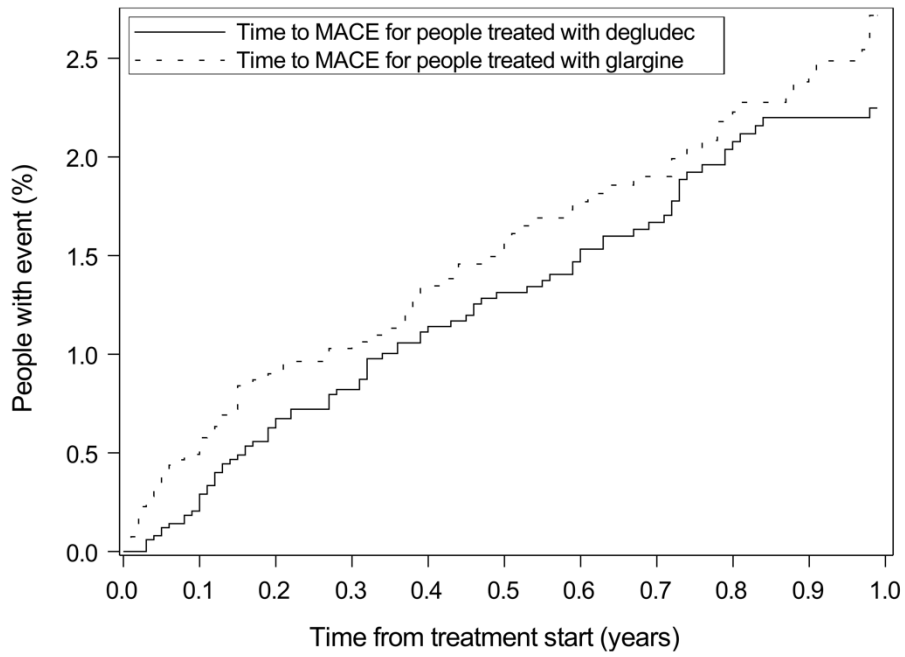
Data are available through Danmarks Statistik (http://www.dst.dk) and all authorized research

organizations can apply for access. Access for international researchers can only be gained if they

are affiliated to a Danish research organization.

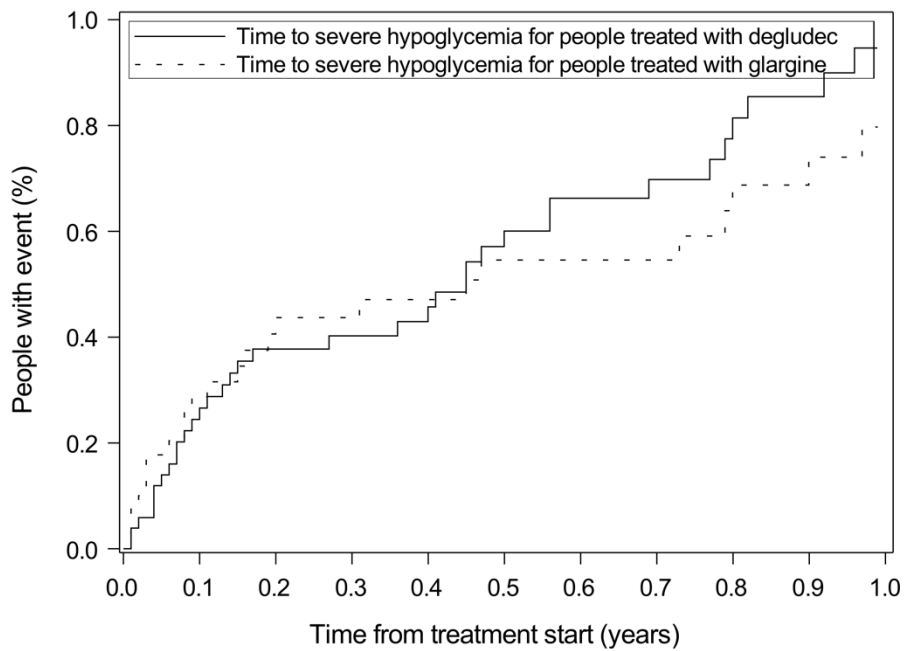*Table 1: Characteristics at baseline for people enrolled in this study.*

	Degludec	Glargine	P
Number of people	5,159	4,041	
Age (yrs), mean (SD)	66 (13)	65 (15)	0.1490
Sex			
Female (%)	39.6	40.0	0.6558
Male (%)	60.4	60.0	0.6558
Diabetes duration (yrs), mean (SD)	13 (7)	10 (7)	<.0001
Diabetes type			
Type 1 (%)	4.8	8.2	<.0001
Type 2 (%)	95.2	91.8	<.0001
Insulin dose (IU/day), median (IQR)	38 (24-58)	28 (19-43)	<0.001
MACE during follow-up, *n* (%)	81 (1.6)	76 (1.9)	0.2535
Severe hypoglycemia during follow-up, *n* (%)	35 (0.7)	24 (0.6)	0.6143
Severe hypoglycemia before baseline, *n* (%)	251 (4.9)	152 (3.8)	0.0102
Died during follow-up, *n* (%)	215 (4.2)	369 (9.1)	<.0001
Highest completed education (%)			
<High-school graduate	52.1	52.3	0.7939
>High-school graduate	47.0	46.5	0.6360
Income (%)			
Low	50.0	52.5	0.0148
Normal	34.7	31.2	0.0004
High	14.8	14.9	0.8187
Charlson comorbidity index, mean (SD)	2.9 (2.4)	3.2 (2.6)	<.0001
History of alcohol abuse (%)	6.7	8.6	0.0007
Use of antidepressants (%)	39.3	40.4	0.2737
Use of opioids (%)	14.6	13.2	0.0580
Use of anxiolytics (%)	65.3	63.5	0.0696

A

People with event (%)

(y-axis: 0.0, 0.5, 1.0, 1.5, 2.0, 2.5)

Time from treatment start (years)
(x-axis: 0.0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0)

Legend:
— Time to MACE for people treated with degludec
- - - Time to MACE for people treated with glargine

Degludec	5159	4560	4205	3812	3534	3312	3023	2722	2443	2181	2009
Glargine	4041	3480	3153	2902	2703	2513	2355	2174	1987	1808	1677

B

People with event (%)

(y-axis: 0.0, 0.2, 0.4, 0.6, 0.8, 1.0)

Time from treatment start (years)
(x-axis: 0.0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0)

Legend:
— Time to severe hypoglycemia for people treated with degludec
- - - Time to severe hypoglycemia for people treated with glargine

Degludec	5159	4561	4216	3830	3555	3335	3049	2752	2478	2213	2036
Glargine	4041	3491	3172	2921	2731	2543	2390	2210	2029	1843	1713

C
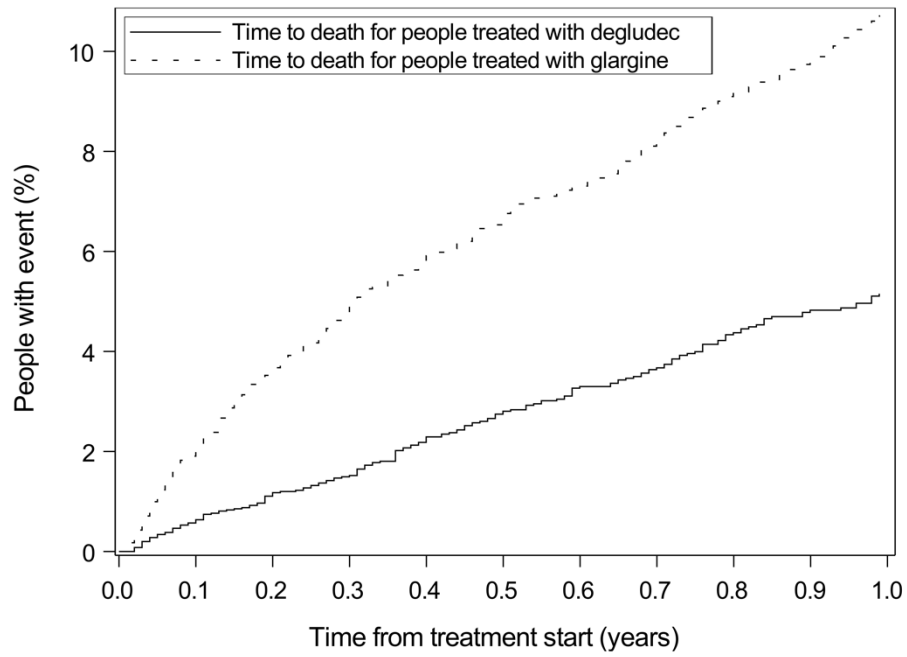
Degludec	5159	4554	4203	3806	3521	3292	3001	2699	2417	2151	1974
Glargine	4041	3469	3123	2848	2636	2434	2271	2077	1893	1708	1575

Figure 1: Time to event in a 1-year follow-up after initiation of degludec and glargine. Graph A is time to major cardiovascular event, graph B is time to severe hypoglycemia and graph C is time to death.

Table 2: Unadjusted and adjusted hazard rate ratios (HR) for degludec/glargine from the Cox proportional hazard models are shown in the table together with 95% confidence intervals (CI) and p values (p).

Models	HR (95% CI)	p
Unadjusted		
Time to major cardiovascular events	0.82 (0.60-1.13)	0.2267
Time to severe hypoglycemia	1.14 (0.68-1.91)	0.6322
Time to death	*0.44 (0.37-0.53)	<.0001
Adjusted		
Time to major cardiovascular events[a]	0.86 (0.62-1.19)	0.3687
Time to severe hypoglycemia[b]	1.13 (0.66-1.93)	0.6661
Time to death[c]	*0.54 (0.44-0.65)	<.0001

[a] Adjusted for age, sex, diabetes duration, diabetes type, education, income, Charlson comorbidity index and date of treatment initiation
[b] Adjusted for age, sex, diabetes duration, diabetes type, education, income, severe hypoglycemia before baseline and date of treatment initiation
[c] Adjusted for age, sex, diabetes duration, diabetes type, education, income, Charlson comorbidity index, history of alcohol abuse, use of antidepressants, use opioids, use of anxiolytics and date of treatment initiation
* Statistically significant result (p<0.05)

Table 3: The five most frequent causes of death in the follow-up period of the cohort. Number of people and percentage within the group is shown.

Five most frequent causes of death, *n* (%)	Degludec	Glargine
Malignant neoplasm of pancreas, unspecified (DC259)	7 (3.3)	22 (6.0)
Malignant neoplasm of unspecified part of bronchus or lung (DC349)	10 (4.7)	17 (4.6)
Malignant neoplasm of overlapping sites of pancreas (DC258)	8 (3.7)	15 (4.1)
Ill-defined and unknown cause of mortality (DR990)	7 (3.3)	12 (3.3)
Heart failure, unspecified (DI509)	7 (3.3)	7 (1.9)