# Non-interventional study report

# Study ID: *NN304-4528*

# *Retrospective Cohort study of all-Cause and Cardiovascular Mortality in Type 2 Diabetes Patients Using Insulin Detemir or Insulin Glargine*

# PASS information

| | |
|---|---|
| **Title** | Retrospective Cohort Study of All-Cause and Cardiovascular Mortality in Type 2 Diabetes Patients Using Insulin Detemir or Insulin Glargine |
| **Version identifier of the final study report** | Version 1.0 |
| **Date of last version of the final study report** | 18 May 2020 |
| **EU PAS Register number** | EUPASS 29708 |
| **EU PAS Register link** | http://www.encepp.eu/encepp/viewResource.htm?id=35055 |
| **Active substance** | Insulin detemir ([redacted]), Insulin glargine ([redacted]) |
| **Medicinal product(s)** | Levemir®, Lantus®, Toujeo® |
| **Marketing authorisation holder(s)** | Novo Nordisk A/S |
| **Joint PASS** | No |
| **Research question and objectives** | The overall objective is to estimate the differences in all-cause and cardiovascular mortality rates between new users of basal insulin detemir or insulin glargine in a population-based study of type 2 diabetes patients. The hypothesis is that use of insulin detemir is associated with a lower all-cause and cardiovascular mortality than use of insulin glargine. |
| **Country(-ies) of study** | United Kingdom (UK) |
| **Author** | [redacted] |
| **UTN** | U1111-1233-0930 |
| **ClinicalTrials.gov identifier** | NCT03960814 |
| **IND number** | Not applicable |
| **Generic name** | Insulin detemir, Insulin glargine |
| **Indication** | Diabetes mellitus |
| **Physician(s)** | Not applicable |
| **Study site(s)** | The study was based on data from the Clinical Practice Research Datalink (CPRD) GOLD national database, United Kingdom (UK).<br><br>Clinical Practice Research Datalink<br>The Medicines and Healthcare products Regulatory Agency<br>10th Floor |

| | |
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| | 10 South Colonnade<br>Canary Wharf<br>London E14 4PU<br>United Kingdom |
| **Study initiated** | 21 May 2019 |
| **Study completed** | 07 June 2019 |

# Marketing authorisation holder(s)

| | |
|---|---|
| **Marketing authorisation holder(s) (MAH(s))** | Novo Nordisk A/S, Novo Alle, DK-2880 Bagsværd, Denmark |
| **MAH contact person** | [redacted] |

This study was conducted in accordance with the Declaration of Helsinki, World Medical Association (WMA) – Ethical Principles for Medical Research Involving Human Subjects, 7th revision, October 2013, and the Guidelines for Good Pharmacoepidemiology Practices, ISPE (International Society for Pharmacoepidemiology) - Guideline for Good Pharmacoepidemiology Practices (GPP). Revision 3, June, 2015 (available on the ISPE website).

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# 1 Abstract

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# 2 List of abbreviations and definitions of terms

| | |
|---|---|
| BMI | body mass index |
| CPRD | Clinical Practice Research Datalink |
| crd | current registration date |
| CKD | chronic kidney disease |
| CVD | cardiovascular disease |
| eGFR | estimated glomerular filtration rate |
| EU | European Union |
| EU PAS | The EU electronic register of post-authorisation studies maintained by the European Medicines Agency |
| GLP1-RA | glucagon like peptide-1 receptor agonists |
| GPP | Guidelines for Good Pharmacoepidemiology Practices |
| HbA1c | Haemoglobin A1c |
| HDL | high-density lipoprotein |
| HR | hazard ratio |
| ICD | International Classification of Diseases |
| ICSR | Individual Case Safety Reports |
| IMD | index of multiple deprivation |
| IQR | inter quartile range |
| ISAC | Independent Scientific Advisory Committee |
| ISPE | International Society for Pharmacoepidemiology |
| lcd | latest collection date |
| LDL | low-density lipoprotein |
| NSR | non-interventional study report |
| NPH | Neutral Protamine Hagedorn |
| ONS | Office for National Statistics |
| PY | person-years |
| RCT | randomised controlled trial |
| SGLT2i | sodium-glucose cotransporter 2 inhibitor |
| T1D | type 1 diabetes |
| T2D | type 2 diabetes |
| trd | transfer out date |
| UTS | up to standard |
| UK | United Kingdom |
| UTN | Universal Trial Number |
| WMA | World Medical Association |

# 3 Physicians

Not applicable.

# 4 Other responsible parties

Not applicable.

# 5 Milestones

**Table 5-1 Milestones**

| Milestone | Planned date | Actual date | Comments |
|---|---|---|---|
| Start of data collection | 01 Apr 2019 | 21 May 2019 | |
| End of data collection | 01 Apr 2019 | 07 Jun 2019 | |
| Registration in the EU PAS Register | 01 Apr 2019 | 16 May 2019 | |
| ISAC approval | 01 Apr 2019 | 26 Mar 2019 | |
| Final report of study results | 30 Sep 2019 | 18 May 2020 | |

# 6 Rationale and background

Insulin detemir and insulin glargine are long-acting basal insulins, which are commonly initiated in patients with type 2 diabetes. Most RCTs are not adequately designed to assess treatment effects on long-term outcomes such as death. A previous observational study investigated differences in survival among patients with type 2 diabetes treated with insulin detemir versus insulin glargine and found a lower risk of mortality with insulin detemir versus insulin glargine [1] indicating a difference in mortality risk. However, the mortality risk associated with long-term insulin use has not been extensively examined in clinical practice, and hence additional well-designed studies assessing insulin detemir versus insulin glargine and risk of death are needed to further examine the potential differences in mortality risk.

This study was conducted in accordance with the Declaration of Helsinki, World Medical Association (WMA) – Ethical Principles for Medical Research Involving Human Subjects, 7th revision, October 2013, and the Guidelines for Good Pharmacoepidemiology Practices, ISPE (International Society for Pharmacoepidemiology) - Guideline for Good Pharmacoepidemiology Practices (GPP). Revision 3, June, 2015 (available on the ISPE website).

The study was initiated voluntarily. Prior to study initiation, the study protocol (protocol number:19_058) was approved by the Independent Scientific Advisory Committee (ISAC) (Medicine and Healthcare Products Regulatory Agency).

# 7 Research question and objectives

The aim of this UK register-based cohort study is to investigate the potential differences in risk of death in users of insulin detemir or insulin glargine in terms of all-cause and cardiovascular mortality among patients with type 2 diabetes in real-life clinical practice

As stated in the protocol, the objectives of the study were as follows:

**Primary objectives:**

The overall objective is to estimate the differences in all-cause and cardiovascular mortality rates between new users of basal insulin detemir or insulin glargine in a population-based study of type 2 diabetes patients 40 years or older in UK in the years 2004-2019.

The hypothesis is that use of insulin detemir is associated with a lower all-cause and cardiovascular mortality than use of insulin glargine.

In this cohort of new users of basal insulins, the specific aims are to asses:

- Rates of all-cause mortality
- Rates of cardiovascular mortality

# 8 Amendments and updates

None.

# 9 Research methods

## 9.1 Study design

The study is a retrospective cohort study comparing all-cause and cardiovascular mortality rates (hazard rates) in new users (type 2 diabetes (T2D), ≥ 40 years at initiation) of basal insulins detemir or insulin glargine identified through national UK registers.

## 9.2 Setting

UK primary care (UK Clinical Practice Research Datalink (CPRD) GOLD national database). Study period was set to 2004-2019.

## 9.3 Patients

The study population comprised insulin-naïve patients with T2D, aged 40 years or above initiating therapy with basal insulins detemir or insulin glargine between 24 June 2004 and 10 May 2019.

### 9.3.1 Inclusion criteria

T2D patients were defined as a record of a read code for T2D, without any record of a read code for type 1 diabetes (T1D) ever in the database. New users of insulin detemir or insulin glargine was defined as a record of a prescription of one of these treatments at or after 24 June 2004, as this was the date where both drugs occurred in the database, and thus were available for prescription in the UK. Only insulin-naïve patients without history of prescription of any type of insulin were included. Moreover, only patients with acceptable research quality data from one year prior to initiation of insulin detemir or insulin glargine were included in the study (i.e. only patients flagged as *acceptable patients* in the database were included and moreover the latest of the CPRD variables *up to standard date (uts)* and *current registration date (crd)* should be at least one year prior to initiation).

### 9.3.2 Exclusion criteria

See section 9.3.1 above.

## 9.4 Variables

*Outcomes:* All-cause mortality, defined as death from any cause, was based on registration of a death date in the CPRD GOLD database. CVD mortality, defined as death from CVD, was obtained by linkage to the Office for National Statistics (ONS) death registration data, which includes information on the official date and causes of death. Death from CVD was defined as a record of selected ICD-10 codes I00-I99 noted as the underlying cause of death. Linkage was not available for the full cohort, but only for practices in England and Wales who consented to participate in the linkage scheme.

*Follow-up time:* The index date was defined as the date of the first ever prescription of insulin detemir or insulin glargine, respectively. Total follow-up time was calculated as time (in years) from index date until death, end of follow-up in CPRD GOLD (the earliest of transfer out date (trd) and latest collection date (lcd), or the end of ONS coverage, whichever came first.

*Baseline characteristics/confounders:* Information on socioeconomic data was obtained by linking to small area-level databases (patient and practice level of index of multiple deprivation (IMD2015). Information on all other baseline characteristics was obtained from the CPRD GOLD database. These included age, sex (male, female), calendar year of index date (2004–2019), diabetes duration, smoking status (current, former, never), and glycated haemoglobin ($HbA_{1c}$). Body mass index (BMI) was calculated from weight and height (at age ≥18 years). Dyslipidaemia was defined as total cholesterol >6.2 mmol/L, or low-density lipoprotein (LDL) cholesterol >6.2 mmol/L, or high-density (HDL) cholesterol ≤1 mmol/L for men, or HDL cholesterol ≤1.2 mmol/L for women, or triglyceride ≥1.7 mmol/L. Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg. Kidney function was "measured" by estimated glomerular filtration rate (eGFR) calculated according to the Cockcroft-Gault formula: eGFR in mL/min = (140–age in years) * weight in Kg * 1.23 for men, 1.03 for women) / serum creatinine in µmol/L. The latest values prior to index date were used for weight, height, $HbA_{1c}$, dyslipidaemia, systolic and diastolic blood pressure. History of CVD, prior hypoglycaemia, nephropathy, retinopathy, neuropathy, chronic kidney disease (CKD), and cancer were defined as a record of selected read codes prior to index date. Bolus insulin, non-insulin glucose-lowering medication, and CVD preventive medication, were defined as records of selected product codes within 1 year prior to index. They were further categorised as "bolus insulin" (yes/no), "sodium-glucose cotransporter 2 inhibitor (SGLT2i) and/or glucagon like peptide-1 receptor agonists (GLP-1 RA)" (yes/no), "other glucose-lowering drugs" (yes/no), "anti-hypertensive medication" (yes/no), "lipid-lowering medication" (yes/no), and "other CVD preventive medication" (yes/no).

## 9.5 Data sources and measurement

Patients were identified from the CPRD GOLD national database, a large, primary care database that includes data from patients registered at general practices in the United Kingdom (England, Wales, Scotland and Northern Ireland). The database has information on individual patients' demographics, medical diagnoses and symptoms, prescribing information and lifestyle factors, including alcohol consumption and smoking. All-cause mortality, defined as death from any cause, was based on registration of a death date in the CPRD GOLD database. Individual patients can be linked to secondary care and other health datasets, enabling a wider view of patient care. CVD mortality, defined as death from CVD, was obtained by linkage to the ONS death registration data, which includes information on the official date and causes of death.

## 9.6 Bias

This study has several limitations including that it may not be able to account completely for confounding by indication. There may have been misclassification due to the assumption that "no

information" in the register indicates "no exposure" for some of the variables, and this may not always have been true. The information in primary care records can be incomplete. Insulin detemir may have been chosen for patients who have concerns about hypoglycaemia or weight gain, therefore the results may underestimate the benefits. Only prescriptions are recorded and it is not known if the patients adhered to the medication or collected the medication from the pharmacy.

## 9.7 Study size

A recent study by Strandberg et al. of a cohort of T2D patients from Finland [1] used a similar study design and definitions of study population as the current study. This study followed 10,467 new users of insulin glargine and 4,749 patients initiating insulin detemir. Median follow-up time was 1.7 years in the study and 705 deaths were identified among insulin glargine users and insulin detemir users during this time. The reported hazard ratio (HR) for all-cause mortality was 0.71 (95% confidence interval (CI), 0.54-0.93) for insulin detemir users compared with users of insulin glargine.

In the present cohort study, 9,816 new users of insulin glargine and 3,031 new users treated with insulin detemir was identified. Median follow-up time was 3.86 vs 3.59 years for the detemir and glargine groups, respectively. This is more than two times longer time of follow-up of the patients than what was available in the study by Strandberg et al. [1] Consequently, more deaths (n=3231) are observed among insulin detemir and insulin glargine users included in the current study. Therefore, a better precision in the risk estimates is reported.

## 9.8 Data transformation

See section 9.4 Variables

## 9.9 Statistical methods

### 9.9.1 Main summary measures

Baseline characteristics were examined by standard descriptive characteristics.

Crude mortality rates were calculated as number of deaths divided by total follow-up time, and reported as rates per 100 person-years (PY).

Cox proportional hazards models were used to calculate crude and adjusted HRs with 95% CIs.

### 9.9.2 Main statistical methods

Cox proportional hazards models were used to calculate crude and adjusted HRs with 95% CIs. for all-cause and CVD mortality, respectively, associated with insulin detemir relative to insulin glargine. Patients were allocated to the treatment group of their first prescription during the entire follow-up. Age was used as the underlying timescale in Cox's regression model. Both the crude and adjusted models included calendar year of index date (2004–2019). Furthermore, the following pre-

specified covariates that were expected to be the most likely potential confounders were included in the adjusted models: sex, diabetes duration, body mass index (BMI), history of CVD, CVD medication, and non-insulin glucose-lowering medications (time-varying), bolus insulin (time-varying). In addition, the fully adjusted models included socioeconomic status, smoking status, $HbA_{1c}$, prior hypoglycaemia, nephropathy, retinopathy, neuropathy, chronic kidney disease, dyslipidaemia, hypertension, serum creatinine (eGFR), history of cancer, if the hazard ratio of insulin detemir versus insulin glargine changed by more than 10% on the natural log-scale. Results from the crude and fully adjusted model are presented in the results section.

Separate analyses, including the selection of covariates included in the fully adjusted model, of the following subgroups were performed on: only obese patients (BMI $\geq$30 kg/m$^2$); only patients with duration of diabetes $\geq$5 years; only patients treated with CVD medication and/or with prior CVD at index date, and only patients with $HbA_{1c}$ above median at index date.

### 9.9.3 Missing values

Patients with missing covariate data were excluded from the analyses (complete cases analyses).

### 9.9.4 Sensitivity analyses

In order to investigate the sensitivity of assumptions in the statistical models, four additional analyses were conducted. 1) Patients with prescription data that indicated that they were switched to another type of basal insulin were censored at the time of the switch. 2) All patients were censored after 8 years of follow-up. 3) Included only patients with an index date post 2006 in the analysis and 4) a time-varying exposure model, where deaths occurring in exposure time periods with and without evidence of continuous prescriptions, respectively, were examined. In the time-varying model, exposure was set to "continuous prescriptions" if the patient had one or more prescriptions of their first basal insulin within the last year, if not, the exposure was set to "Unknown".

### 9.9.5 Amendments to the statistical analysis plan

For calculation of drug exposure, the duration of a drug prescription was set to 1 year instead of the 80% quantile of distribution of the prescription renewal times for prevalent users. The latter turned out to be unnecessarily complicated.

Originally a sensitivity analysis including multiple imputation on missing values was planned. As only limited missing data was observed, it was decided not to impute any values.

## 9.10 Quality control

Not Applicable.

# 10 Results

## 10.1 Participants

The CPRD GOLD database consisted of 16,945,866 acceptable patients (database release: May 2019). Between 24 June 2004 and 5 April 2019, 12,847 insulin-naïve patients were identified, who were aged 40 years or over, had T2D, and who initiated use of insulin detemir (N=3,031) or insulin glargine (N=9,816) (Table 10-1)). Of the total cohort, 53.7% (6,897 patients) were eligible for linkage to the ONS for cardiovascular death data (insulin detemir; N=1,833 and insulin glargine; N=5,064).

**Table 10-1 Patient disposition**

| | **Total N** | **Insulin detemir N** | **Insulin glargine N** |
|---|---|---|---|
| **Patients in the CPRD GOLD database (May 2019 build)** | 16,945,866 | | |
| **Patients fulfilling inclusion criteria**<br>• Diagnosis (ever) of T2D, but not T1D<br>• Prescription (ever) of insulin detemir or insulin glargine<br>• Index date at 24 June 2004 or later<br>• Insulin- naïve (one-year observation time of research quality prior to index date)<br>• Age ≥40 years at index date | 12,847 | 3,031 | 9,816 |
| **Patients linkable to the ONS death registration data** | 6,897 | 1,833 | 5,064 |

## 10.2 Descriptive data

In the total cohort, the median (inter quartile range [IQR]) age was 66.77 (57.50–76.09) years (Table 10-2). Median (IQR) diabetes duration was similar for patients in both the insulin detemir and insulin glargine groups, 7.66 (4.28–11.56) vs 7.61 (4.08–11.81) years, respectively. Median (IQR) follow-up time was 3.86 (1.74–6.72) vs 3.59 (1.54–6.72) years for the insulin detemir and insulin glargine groups, respectively. After five years, the median (IQR) exposed time was 4.64 (1.93–5.00) and 5.00 (2.93–5.00) years for the insulin detemir and insulin glargine groups, respectively, assuming 1 year of exposure after each prescription date. Less than 15% of patients switched to another basal insulin during follow-up (14.4% and 9.7% with insulin detemir and insulin glargine, respectively).

**Table 10-2 Baseline characteristics**

| **Characteristic** | **Insulin detemir** | **Insulin glargine** |
|---|---|---|

| | | |
|---|---|---|
| Patients, N | 3031 | 9816 |
| Follow-up time | 3.86 (1.74–6.72) | 3.59 (1.54–6.72) |
| Age at index date | 65.1 (56.8–74.5) | 67.4 (57.7–76.5) |
| **Covariates adjusted for in crude model** | | |
| Year of index date | 2004–2019 | 2004–2019 |
| **Covariates at index date adjusted for in pre-specified model** | | |
| Diabetes duration* (years) | 7.7 (4.3–11.6) | 7.6 (4.1–11.8) |
| Sex: female, N | 1351 (44.6%) | 4387 (44.7%) |
| Prescriptions of GLP-1 RA or SGLT2i[†], % | 16.4 | 11.8 |
| Prescriptions of other glucose lowering medication[†], % | 96.6 | 95.9 |
| Prescriptions of antihypertensive medication, % | 48.9 | 41.5 |
| Prescriptions of lipid lowering medication, % | 48.8 | 40.7 |
| Prescriptions of other CVD medication, % | 33.9 | 29.7 |
| BMI[‡] ($kg/m^2$) | 30.7 (26.8–35.4) | 30.0 (26.2–34.3) |
| CVD history, % | 27.0 | 30.5 |
| **Additional confounders, included if relevant** | | |
| Hypertension, % | 36.7 | 38.3 |
| Current smoking, % | 16.1 | 16.1 |
| CKD, % | 26.0 | 24.4 |
| Dyslipidaemia, % | 79.5 | 79.3 |
| $HbA_{1c}$ in % | 9.58 (8.46–11.00) | 9.58 (8.40–11.10) |
| eGFR in $ml/min/1.73m^2$ | 80.8 (53.7–107.2) | 75.7 (50.0–102.5) |
| Cancer history, % | 8.1 | 9.3 |
| Retinopathy, % | 26.9 | 27.7 |

| | | |
|---|---|---|
| Nephropathy, % | 1.0 | 1.5 |
| Neuropathy, % | 6.33 | 6.48 |
| History of hypoglycaemia, % | 4.5 | 3.6 |
| Lowest socioeconomic status[§] (IMD2015 5), % | 18.6 | 22.0 |

***** Included as a factor in the model, grouped in approximate quintiles: [0;1], (1;2], (2;5], (5;10], >10 years.
[†] Included as time-dependent covariate
[‡] Included as a factor with levels underweight, normal weight, obesity class I, II and III.
[§] IMD2015 5 socioeconomic status included as a factor with five levels
Continuous variables are listed as median (interquartile range).
BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; GLP-1 RA glucagon-like peptide 1 receptor agonists; HbA1c, glycated haemoglobin; N, number of patients; SGLT2i, sodium-glucose transport protein 2 inhibitors

## 10.3 Outcome data

Among the 12,847 patients, there were 3,231 deaths: 635 with insulin detemir and 2,596 with insulin glargine. Of the 6,897 patients linked to the ONS, 528 patients had died from CVD, 117 of whom had been prescribed insulin detemir and 411 insulin glargine. Observed incidence rates were 5.64 and 1.88 per 100 PY for all-cause and CVD mortality, respectively.

## 10.4 Main results

### 10.4.1 All-cause mortality

The crude and fully adjusted HR (95% CI) for all-cause mortality were 0.85 (0.77; 0.92) and 0.86 (0.79; 0.95), respectively, in favour of insulin detemir.

### 10.4.2 CVD mortality

The crude and fully adjusted HR (95% CI) for CVD mortality were 0.82 (0.66; 1.01) and 0.83 (0.67; 1.03), respectively, in favour of insulin detemir.

### 10.4.3 Summary of main results

Overall, the results from the present analyses indicate that prescription of insulin detemir was associated with a lower all-cause mortality when compared with insulin glargine, and a similar non-significant tendency was observed for CVD mortality. Insulin detemir was associated with a mortality risk reduction of 14%, while the adjusted risk of CVD mortality was 17% lower.

## 10.5 Other analyses

The results of the subgroup analyses are shown in Table 10-3 and Table 10-4. Overall, across all subgroups, insulin detemir was associated with numerically lower all-cause mortality when

compared with insulin glargine, although the differences were not all statistically significant. This association was especially pronounced in the BMI ≥30 kg/m$^2$ subgroup. For all-cause mortality, the crude and fully adjusted HR (95% CI) was 0.79 (0.69; 0.91) and 0.79 (0.69; 0.91), respectively. For CVD mortality, the crude and fully adjusted HR (95% CI) was 0.71 (0.52; 0.99) and 0.69 (0.50; 0.96), respectively.

Results of the sensitivity analyses are presented in Table 10-5 and Table 10-6. The point estimates for HR comparing insulin detemir with insulin glargine for mortality were not changed in any of the sensitivity analyses.

**Table 10-3 Subgroup analyses of all-cause mortality**

| All-cause mortality | HR (95%) | N | N events Insulin detemir | N events Insulin glargine | N events Total | Incidence (Events/100 PY) |
|---|---|---|---|---|---|---|
| **Overall**<br>Crude<br>Adjusted | <br>0.85 (0.77; 0.92)<br>0.86 (0.79; 0.95) | 12,847 | 635 | 2596 | 3231 | 5.64 |
| **BMI ≥30**<br>Crude<br>Adjusted | <br>0.79 (0.69; 0.91)<br>0.79 (0.69; 0.91) | 6501 | 275 | 1067 | 1342 | 4.35 |
| **Diabetes duration ≥5 years**<br>Crude<br>Adjusted | <br>0.84 (0.75; 0.93)<br>0.85 (0.76; 0.95) | 8735 | 451 | 1789 | 2240 | 6.02 |
| **CVD history/medication**<br>Crude<br>Adjusted | <br>0.83 (0.75; 0.92)<br>0.86 (0.77; 0.96) | 8357 | 459 | 1793 | 2252 | 6.52 |
| **HbA1c >median HbA1c**<br>Crude<br>Adjusted | <br>0.84 (0.73; 0.96)<br>0.86 (0.75; 0.99) | 6151 | 270 | 1149 | 1419 | 5.38 |

**Table 10-4 Subgroup analyses of CVD mortality**

| CVD mortality | HR (95%) | N | N events Insulin detemir | N events Insulin glargine | N events Total | Incidence (Events/100 PY) |
|---|---|---|---|---|---|---|
| **Overall**<br>Crude<br>Adjusted | <br>0.82 (0.66; 1.01)<br>0.83 (0.67; 1.03) | 6897 | 117 | 411 | 528 | 1.88 |
| **BMI ≥30**<br>Crude<br>Adjusted | <br>0.71 (0.52; 0.99)<br>0.70 (0.50; 0.96) | 3424 | 49 | 174 | 223 | 1.52 |
| **Diabetes duration ≥5 years**<br>Crude<br>Adjusted | <br>0.77 (0.60; 0.99)<br>0.78 (0.61; 1.01) | 4605 | 84 | 290 | 374 | 2.11 |
| **CVD history/medication**<br>Crude<br>Adjusted | <br>0.83 (0.68; 1.03)<br>0.85 (0.68; 1.05) | 6519 | 117 | 402 | 519 | 1.95 |

| | | | | | | |
|---|---|---|---|---|---|---|
| **HbA1c >median HbA1c**<br>Crude<br>Adjusted | <br>0.84 (0.62; 1.14)<br>0.89 (0.65; 1.23) | 3358 | 55 | 195 | 250 | 1.87 |

### Table 10-5 Sensitivity analyses of all-cause mortality

| All-cause mortality | HR (95%) | N | N events Total |
|---|---|---|---|
| **Censor by switch**<br>Crude<br>Adjusted | <br>0.85 (0.77; 0.93)<br>0.88 (0.80; 0.97) | 12,847 | 2926 |
| **Censor at 8 years**<br>Crude<br>Adjusted | <br>0.85 (0.78; 0.93)<br>0.87 (0.79; 0.96) | 12,847 | 2926 |
| **Index date after 2006 only**<br>Crude<br>Adjusted | <br>0.84 (0.76; 0.92)<br>0.86 (0.78; 0.95) | 11,444 | 2703 |
| **Time-varying treatment**<br>Crude<br>Adjusted | <br>0.87 (0.78; 0.98)<br>0.91 (0.81; 1.02) | 12,847 | 2230 |

### Table 10-6 Sensitivity analyses of CVD mortality

| All-cause mortality | HR (95%) | N | N events Total |
|---|---|---|---|
| **Censor by switch**<br>Crude<br>Adjusted | 0.79 (0.63; 0.99)<br>0.83 (0.66; 1.04) | 6,897 | 479 |
| **Censor at 8 years**<br>Crude<br>Adjusted | <br>0.84 (0.68; 1.04)<br>0.84 (0.67; 1.05) | 6,897 | 495 |
| **Index date after 2006 only**<br>Crude<br>Adjusted | <br>0.83 (0.66; 1.03)<br>0.82 (0.65; 1.03) | 6,153 | 427 |
| **Time-varying treatment**<br>Crude<br>Adjusted | <br>0.81 (0.62; 1.05)<br>0.88 (0.67; 1.15) | 6,897 | 362 |

## 10.6 Adverse events/adverse reactions

This study was based on secondary use of data and therefore Individual Case Safety Reports (ICSR) was not be performed.

### 10.6.1 Summary of adverse events/adverse reactions

This study was based on secondary use of data and therefore Individual Case Safety Reports (ICSR) was not performed.

# 11 Discussion

## 11.1 Key results

In this UK-based cohort study, an association of lower mortality risk with insulin detemir compared with insulin glargine was found. Insulin detemir was associated with a mortality risk reduction of 14%, while the adjusted risk of CVD mortality was 17% lower. This association was especially pronounced in patients with obesity (BMI ≥30 kg/m$^2$) with adjusted risk reductions of 20% and 31% for all-cause and CVD mortality, respectively.

## 11.2 Limitations

This study has several limitations including that we may not be able to account completely for confounding by indication. There may have been misclassification due to the assumption that "no information" in the register indicates "no exposure" for some of the variables, and this may not always have been true. The information in primary care records can be incomplete. Insulin detemir may have been chosen for patients who have concerns about hypoglycaemia or weight gain, therefore the results may underestimate the benefits. Only prescriptions were recorded and it is not known, if the patients adhered to the medication or collected the medication from the pharmacy.

## 11.3 Interpretation

A recent study in Finland investigated the differences in all-cause and cause-specific mortality rates between new users of insulin detemir and insulin glargine in a population-based study [1]. The results from that study showed the HR (95% CI) for all-cause and CVD mortality for insulin detemir versus insulin glargine to be 0.71 (0.54; 0.93) and 0.64 (0.43; 0.95), respectively [1]. These findings are in alignment, although more pronounced with those in the present study.

## 11.4 Generalisability

The CPRD represents the UK population with respect to age, sex, BMI and ethnicity, however not necessarily with respect to geography and practice size [2].

# 12 Other information

Not applicable.

# 13 Conclusion

Overall, the results from the present study indicate that prescription of insulin detemir was associated with a lower all-cause mortality when compared with insulin glargine, and a similar non-significant tendency was observed for CVD mortality. The benefit was most pronounced in patients with BMI $\geq$30 kg/m$^2$ .

# 14 Tables, figures and listings

Not Applicable.

# 15 References

1. Strandberg AY, Hoti FJ, Strandberg TE, Christopher S, Haukka J, Korhonen P. All-Cause and Cause-Specific Mortality among Users of Basal Insulins NPH, Detemir, and Glargine. PLoS One. 2016 Mar 31;11(3):e0151910. doi: 10.1371/journal.pone.015191

2. Herrett, E., Gallagher, A.M., Bhaskaran, K., et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). International journal of epidemiology 2015;44(3):827-36.

# Appendices

# Annex 1. List of stand-alone documents

| Number | Document reference number | Date | Title |
|---|---|---|---|
| | 16.1.1 | 06 May 2019 | Protocol |