# Lower Risk of Mortality in Patients with Type 2 Diabetes Using Insulins Detemir or Glargine Compared to NPH: A Propensity Score-Matched Nationwide Register Study in Finland


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## Abstract

Cardiovascular diseases and hypoglycemia increase mortality in insulin treated patients with type 2 diabetes (T2D). Risk of mortality in patients using long-acting insulins detemir (IDet), glargine (IGlar), or NPH insulin (NPH) was evaluated in a nationwide retrospective database study 2006–2009. Date and cause of death were obtained from the Finnish Causes of Death Register. Data on insulin usage were obtained from the Finnish Prescription Register. Prescription bias is minimized by government-funded reimbursement of all insulins, and by lack of preference between long-acting insulins in guidelines. There were 23,751 long-acting insulin naïve T2D patients, and 2,078 deaths in nine ICD-10 categories. Insulin exposure periods were defined based on the amount purchased and the estimated average daily dose of each drug for a specific patient. A propensity score matched cohort analysis was performed: among 9,363 patients there were 620 deaths; most common categories were circulatory n=275, neoplasms n=183, digestive n=42, respiratory n=29. The all-cause risk of mortality is greater with increasing age and male gender, and lower with the use of sulfonylurea. The adjusted risk of all-cause mortality was 61% (hazard ratio [HR] 0.39, 95% CI: 0.30, 0.50) lower during use of IDet, and 45% (HR 0.55, 95% CI: 0.44, 0.69) lower during use of IGlar vs. NPH. In comparison to IGlar, IDet had a significantly (HR 0.71, 95% CI: 0.54, 0.93) lower risk for mortality. For the deaths related to circulatory system and neoplasm, the adjusted risk during use of IDet compared to NPH were 58% (HR 0.42, 95% CI: 0.28, 0.61) and 77% (HR 0.23, 95% CI: 0.14, 0.40) lower, respectively, and during use of IGlar compared to NPH 35% (HR 0.65, 95% CI: 0.47, 0.91) and 65% (HR 0.35, 95% CI: 0.22, 0.54) lower, respectively.In conclusion, in T2D the risk of all-cause mortality and risk of death related to circulatory system or neoplasms were lower during the use of IDet or IGlar compared to NPH.

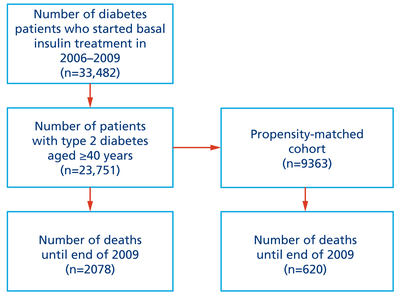

## Introduction

- Type 2 diabetes (T2D) is characterized by the progressive deterioration of beta-cell function and, as a corollary, patients will eventually require treatment intensification (insulin) to maintain good glycemic control.
- Epidemiological studies have shown an association between insulin-treated patients with T2D and worse outcomes for cardiovascular events and all-cause mortality compared with patients treated with metformin.[1]
- In insulin-naïve patients with T2D, basal insulin analogs (insulin detemir [IDet] and insulin glargine [IGlar]) are associated with less hypoglycemia compared with NPH, neutral protamine Hagedorn (NPH) insulin;[2–4] however, it remains unclear whether this advantage is associated with fewer cardiovascular or other serious complications.
- The aim of this Finnish nationwide, register-based study was to evaluate the risk of mortality in a cohort of insulin-naïve patients with T2D who initiated therapy with IDet, IGlar or NPH insulin.

## Research design and methods

- Basal insulin-naïve patients with T2D (≥40 years) who started insulin treatment with IDet, IGlar or NPH insulin between Jan 2006 and Dec 2009 were included in the study (Figure 1).

**Figure 1** Study population figures between 2006–2009.

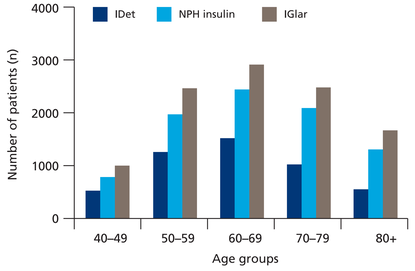



- Propensity score matching was used to form a sub-cohort to avoid potential selection bias.[5] Propensity scores were calculated based on several covariates (gender, age, use of oral diabetes medication, use of other insulin, history of hospitalization due to severe hypoglycemia, duration of diabetes, calendar year and hospital district at baseline).
- Mortality data were obtained from the Finnish Causes of Death Register; data on insulin usage were obtained from the Finnish Prescription Register; and data on hospitalization due to hypoglycemia was sourced from the Finnish Hospital Care Register.
- Insulin exposure periods were defined based on the amount purchased and the estimated average daily dose of each drug for a specific patient.
- Sensitivity analyses of all-cause mortality and cause-specific mortality were performed to address sources of potential bias and improve the validity of the findings.
- Prescription bias is minimized by government-funded full reimbursement of all insulins, and by lack of preference between long-acting insulins in national guidelines.

## Results

- There were 23,751 insulin-naïve patients with T2D aged ≥40 years who started therapy with basal insulin; 8535 (35.9%) with NPH insulin, 4749 (20%) with IDet and 10,467 (44.1%) with IGlar.
- The age distribution of the study population is presented in Figure 2.

**Figure 2** Age distribution of the study population.




IDet, insulin detemir; IGlar, insulin glargine; NPH, neutral protamine Hagedorn.

- In the total, unmatched cohort there were 2078 deaths: 681 with NPH insulin, 149 with IDet and 556 with IGlar (the type of insulin was not reported at the time of 692 deaths), during a mean follow-up time of 1.71 years.
- In the propensity score-matched cohort analysis (n=9363 patients), 620 deaths were reported. The most common causes of death were circulatory (n=275), cancer and neoplasms (n=183), gastrointestinal (n=42) and respiratory (n=29).
- In the total cohort with NPH insulin as reference, the hazard ratio for total mortality was 0.48 (95% confidence interval [CI]: 0.39;0.58) for IDet and 0.62 (95% CI: 0.55;0.70) for IGlar.
- In the propensity score-matched cohort with NPH insulin as reference, the Cox proportional hazard ratio for total mortality was 0.39 (95% CI: 0.30;0.50) for IDet and 0.55 (95% CI: 0.44;0.69) for IGlar (Table 1).
- Increasing age and male gender increase the all-cause risk of mortality. Use of sulfonylurea decreases the all-cause risk of mortality (Table 1).

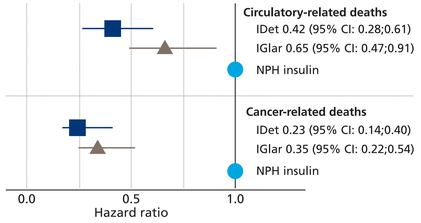
**Table 1** All-cause mortality estimated by Cox's proportional hazards model using propensity-score-matched data. NPH insulin as reference for insulins.

| Variables | Categories | Hazard ratio | 95% CI | *P*-value |
|---|---|---|---|---|
| Insulin type | IDet | 0.388 | (0.30;0.50) | <0.001 |
| | IGlar | 0.547 | (0.44;0.69) | <0.001 |
| Gender | Female | 0.727 | (0.62;0.86) | <0.001 |
| Age group, years | 50–59 | 1.173 | (0.72;1.90) | 0.516 |
| | 60–69 | 2.158 | (1.38;3.38) | <0.001 |
| | 70–79 | 4.146 | (2.66;6.47) | <0.001 |
| | ≥80 | 8.032 | (5.12;12.59) | <0.001 |
| Use of basal–bolus treatment | Yes | 0.881 | (0.70;1.11) | 0.291 |
| Use of sulfonylurea | Yes | 0.658 | (0.53;0.82) | <0.001 |
| Number of hospitalizations due to hypoglycemia | 1–2 | 1.749 | (1.03, 2.98) | 0.039 |
| | +3 | 2.512 | (1.16, 5.46) | 0.020 |
| Time from diagnosis, years | 1–2 | 1.002 | (0.66;1.53) | 0.992 |
| | 2–5 | 1.259 | (0.94;1.69) | 0.129 |
| | 5–10 | 0.829 | (0.60;1.14) | 0.249 |
| | >10 | 1.123 | (0.80;1.59) | 0.510 |

IDet, insulin detemir; IGlar, insulin glargine; NPH, neutral protamine Hagedorn.

- With regard to circulatory-related deaths, with NPH insulin as reference, the mortality hazard ratio was 0.42 (95% CI: 0.28;0.61) for IDet and 0.65 (95% CI: 0.47;0.91) for IGlar (Figure 3).
- With regard to cancer-related deaths, with NPH insulin as reference, the mortality hazard ratio was 0.23 (95% CI: 0.14;0.40) for IDet and 0.35 (95% CI: 0.22;0.54) for IGlar (Figure 3).
- Upon sensitivity analyses, the risk of all-cause mortality was 45–92% lower with IDet versus NPH insulin, and 32–87% lower with IGlar versus NPH insulin, thus supporting the validity of the findings.

**Figure 3** Mortality hazard ratios for circulatory- and cancer-related deaths. NPH insulin as reference.




IDet, insulin detemir; IGlar, insulin glargine; NPH, neutral protamine Hagedorn.

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## Conclusions

- In this real-life, register-based, nationwide study we demonstrate a significantly increased risk for total, cardiovascular and cancer-related mortality associated with the use of NPH insulin when compared with basal insulin analogues detemir and glargine in patients with type 2 diabetes.

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