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

Abstract
Cardiovascular diseases and hypoglycemia increase mortality in insulin-treated patients with type 2 diabetes (T2D). Risk of mortality in patients with long-acting insulins detemir (IDet) or glargine (IGlar), or NPH insulin (NPH) was evaluated in a nationwide prospective register 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 for a specific patient. A propensity score matched cohort analysis was performed among 3,363 patients there were 620 deaths, most common categories were circulatory n=275, neoplasms n=183, digestive n=42, respiratory n=29.

Introduction
Type 2 diabetes (T2D) is characterized by the progressive deterioration of beta-cell function and, as a concomitant, 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. Insulin resistance in patients with T2D has been demonstrated; however, it remains unclear whether this advantage is associated with fewer cardiovascular or other serious complications.2

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 included the propensity matching of all possible confounders. 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 for a specific patient. A propensity score matched cohort analysis was performed among 3,363 patients there were 620 deaths, most common categories were circulatory n=275, neoplasms n=183, digestive n=42, respiratory n=29.

Results
The age distribution of the study population is presented in Figure 2. Mortality data were obtained from the Finnish Causes of Death Register; in the propensity score-matched cohort analysis (n=9363), 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 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. In the propensity score-matched cohort with NPH insulin as reference, the Cox proportional hazard ratio for cancer mortality was 0.39 (95% CI: 0.32;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. In the propensity score-matched cohort with NPH insulin as reference, the Cox proportional hazard ratio for cardiovascular mortality was 0.39 (95% CI: 0.30;0.50) for IDet and 0.55 (95% CI: 0.44;0.69) for IGlar.

In the propensity score-matched cohort with NPH insulin as reference, the Cox proportional hazard ratio for cancer mortality was 0.39 (95% CI: 0.32;0.50) for IDet and 0.55 (95% CI: 0.44;0.69) for IGlar (Table 1).

Research design and methods
23,751 long-acting insulin naïve T2D patients aged ≥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). 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 included the propensity matching of all possible confounders. 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 for a specific patient. A propensity score matched cohort analysis was performed among 3,363 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] 1.61; 95% CI: 1.19;2.20) lower during use of IDet, and 68% (HR 1.68; 95% CI: 1.30;2.15) lower during use of IGlar compared to NPH, and 45% (HR 0.55, 95% CI: 0.44, 0.69) lower during use of IDet, and 77% (HR 0.23, 95% CI: 0.14, 0.40) lower with the use of IGlar versus NPH. In comparison to IGlar, IDet demonstrated a significantly increased risk for total, cardiovasual and cancer-related mortality compared with NPH insulin, thus supporting the validity of the findings.

Mortality data were obtained from the Finnish Causes of Death Register; in the propensity score-matched cohort analysis (n=9363), 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).

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Figure 2 Age distribution of the study population.

1. Sari Mäkimatilla
Novo Nordisk A/S, Espoo, Finland
2. Jari Haukka
ERD Research Ltd, Espoo, Finland
3. Sophi-Christine
ERD Research Ltd, Espoo, Finland
4. Peri Saukkonen
Novo Nordisk A/S, Espoo, Finland
5. Tero Saukkonen
Novo Nordisk A/S, Espoo, Finland

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