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Lower incidence of macrovascular complications in patients on insulin glargine versus those on basal human insulins: A population-based cohort study in Italy

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Abstract *Background and aim:* The aim of this study was to compare the use of insulin glargine and intermediate/long-acting human insulin (HI) in relation to the incidence of complications in diabetic patients.
Methods and results: A population-based cohort study was conducted using administrative data from four local health authorities in the Abruzzo Region (900,000 inhabitants). Diabetic patients without macrovascular diseases and treated with either intermediate/long-acting HI or glargine were followed for 3-years; the incidence of diabetic (macrovascular, microvascular and metabolic) complications was ascertained by hospital discharge claims and estimated using Cox proportional hazard models. Propensity score (PS) matching was also used to adjust for significant differences in the baseline characteristics between the two groups.
Results: Overall, 1921 diabetic patients were included: 744 intermediate/long-acting HI and 1177 glargine users. During the 3-year follow-up, 209 (28.1%) incident events of any diabetic

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complication occurred in the intermediate/long-acting HI and 159 (13.5%) in the glargine group. After adjustment for covariates, glargine users had an HR (95% CI) of 0.57 (0.44—0.74) for any diabetic complication and HRs of 0.61 (0.44—0.84), 0.58 (0.33—1.04) and 0.35 (0.18—0.70) for macrovascular, microvascular and metabolic complications, respectively, compared to intermediate/long-acting HI users. PS analyses supported these findings.
Conclusions: The use of glargine is associated with a lower risk of macrovascular complications compared with traditional basal insulins. However, limitations inherent to the study design including the short length of observation and the lack of data on metabolic control or diabetes duration, do not allow us to consider this association as a proof of causality.

Introduction

The burden of diabetes mellitus on longevity and quality of life is largely due to the development of its devastating long-term complications [1]. Among these, cardiovascular diseases cause up to 65% of all deaths in people with diabetes in the Western countries, accounting for 85% of all costs related to diabetic complications [1—3]. It is particularly important for health care providers to recognize the risk markers for the development of these complications in order to attempt appropriate preventing measures.

Optimal blood glucose (BG) control has been consistently indicated as the major driver for prevention of microvascular complications in people with diabetes; whereas its role on reducing macrovascular events is more controversial [4]. A recent meta-analysis has shown that glucose lowering is able to decrease the incidence of events in patients without a history of cardiovascular episodes [5]; conversely it has no demonstrable effect in people with previous macrovascular diseases.

The introduction of insulin analogues may help to achieve better glycemic control and less hypoglycemic episodes than with the traditional human insulin (HI) formulations [6]. This might have a beneficial impact on the cardiovascular risk of type 2 diabetic patients as suggested by the study of Juhaeri et al. [7], in which the use of glargine was associated with a lower risk of myocardial infarction compared with the other intermediate/long-acting insulins.

Aim of this study was to compare the use of insulin glargine and intermediate/long-acting HI in relation to the incidence of complications in a cohort of diabetic patients without macrovascular disease.

Methods

We conducted a 3-year longitudinal, retrospective cohort study using administrative data from four local health authorities in the Abruzzo Region (Central Italy), which comprise about 900,000 inhabitants (68% of the overall regional population).

Our data were obtained from outpatient drug prescriptions, hospital discharges and prescriptions for laboratory tests, services use and specialistic consultations collected from January 1, 2005 to December 31, 2008 (study period). Details regarding data sources have been published previously [8]. All data sources were matched by record-linkage analysis through a unique encrypted personal identification code and linked to the civil registry in order to collect demographic information (i.e. age, gender, date of death or emigration).

Because this automated system is anonymous, neither ethical committee approval nor informed consent was required for this study.

Study population

A patient selection flowchart is shown in Fig. 1. From the source population, we identified individuals with at least four prescriptions of insulin agents between January 1, 2005 and December 31, 2005 (baseline year).

At baseline, we excluded patients if they had at least one of the following conditions: (i) prescription of antiplatelets (excluding low-dose aspirin), pentoxifylline or nitrates [8], or a diagnosis of macrovascular disease in hospital discharge or procedure codes reported on prescriptions for services use (Supplementary Table 1) [8—11]; (ii) prescription of insulin detemir; (iii) no prescription of either intermediate/long-acting HI or glargine; iv) prescriptions of both intermediate/long-acting HI and glargine during the whole study period.

Individuals were finally divided into two mutually exclusive groups (study cohorts): those treated with intermediate/long-acting HI and those treated with glargine throughout the entire follow-up. In both groups basal insulin was used alone or in combination with other types of insulin or oral hypoglycemic drugs, or both.

Each individual accumulated person—years of follow-up from January 1, 2006 until the date of hospital admission for any diabetic complications, censoring (death or emigration), or December 31, 2008, whichever occurred first.

Covariates

For each patient, the following variables were assessed at baseline: age, gender, metabolic and microvascular complications and concomitant drugs.

To identify diabetic complications we developed an algorithm by using all hospital discharges (ordinary and day hospital admissions) and prescriptions for laboratory tests, services use and specialistic consultations in the 2005 year that listed in any position a ICD-9 code indicative of either microvascular or metabolic complications (Supplementary Table 1) [8—11]. Microvascular and metabolic complications at baseline were included as a reasonable proxy measure of severity and duration of diabetes [12—14].