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Clinical significance of diabetes likely induced by statins: Evidence from a large population-based cohort



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ABSTRACT

Aim: To provide information on the extent to which type 2 diabetes more likely induced by statins affects the risk of macrovascular complications compared to diabetes unlikely induced by statins.

Methods: The 84,828 residents in the Italian Lombardy Region who were newly treated with statins between 2003 and 2005 were followed from the index statin prescription until 2009 (step-1 follow-up) to identify those starting antidiabetic therapy. The proportion of days of follow-up covered by statins measured adherence with statins. Cohort members who experienced diabetes were 1:3 matched with those who did not developed diabetes for gender, age and previous adherence with statin treatment. The 3321 diabetic - non-diabetic sets, were followed from the initial antidiabetic therapy until 2012 (step-2 follow-up) to estimate the hazard ratio (HR), and 95% Confidence Interval (CI), for macrovascular complications (proportional hazard models) associated with diabetes separately in each category of adherence with statins.

Results: During the step-1 follow-up, the risk of new-onset diabetes increased progressively with increasing adherence with statins. During the step-2 follow-up, the risk of macrovascular complications associated with diabetes decreased progressively from 1.70 (1.18–2.44), 1.41 (1.17–1.70), 1.30 (1.07–1.57) until 1.10 (0.40–2.80) as adherence with statins during the step-1 follow-up increased.

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; HF, heart failure; MI, myocardial infarction; NHS, National Health Service; NSAIDs, non-steroidal anti-inflammatory drugs; PDC, proportion of days covered; HR, hazard ratio

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Conclusions: Type 2 diabetes lost its association with increasing macrovascular risk when previous adherence with statins was very high, and thus the chance of its induction by the drug greater. Statin-dependent type 2 diabetes might be prognostically less adverse than diabetes unlikely induced by statins.

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1. Introduction

A large number of studies has shown that use of statins is accompanied by an increased risk of developing type 2 diabetes [1–5], which is thus currently listed as an inconvenience of these drugs that may attenuate in some patients their protective effect. However, several aspects of the statin-induced diabetes have not been adequately clarified. For example, albeit several hypotheses have been advanced, the mechanisms through which statins favour the alteration of glucose metabolism that leads to the appearance of hyperglycaemia and diabetes remain unclear [4,6]. Furthermore, although statin-induced diabetes is generally believed not to offset the protective lipid-lowering effect of statins on the cardiovascular (CV) system [7–9], limited information exists on whether statin-induced diabetes has the same adverse prognostic significance of diabetes unlikely induced by statins, i.e., whether it is associated with a similar increasing risk of diabetes-related macrovascular complications. This information is of fundamental importance to reliably quantify the impact of statin-induced diabetes on the role played by statins on primary and secondary CV prevention [10,11].

We have previously shown that at the population level an increasing adherence with statin treatment is accompanied by a clear-cut progressive increase in the risk of new onset type 2 diabetes [12]. The purpose of the present study was to provide information on the extent to which diabetes more likely to be induced by statins affects the risk of macrovascular complications to a similar or different degree compared to diabetes unlikely induced by statins.

2. Subjects, materials and methods

2.1. Setting

The data used for this study were retrieved from the healthcare utilization databases of Lombardy, a Region of Italy which accounts for about 16% (almost ten million) of its population. In Italy, the whole population is covered by the National Health Service and in Lombardy this has been associated since 1997 with an automated system of databases to collect a variety of information. A detailed description of the healthcare utilization databases of the Lombardy Region for studying the association between lipid lowering and antidiabetic treatments is available in previous studies [12,13].

2.2. Cohort selection and follow-up – step-1

The study was designed according to the procedure shown in Fig. 1, upper part. All the 651,552 beneficiaries of the National Health Service who had their residence in Lombardy were identified, provided that their age was between 40 and 80 years and at least one prescription of statins had been dispensed between 2003 and 2005. The date of the first dispensation was considered as the step-1 index date.

Four patient categories were excluded: (i) the 372,302 patients who received one or more statin prescriptions within three years prior the step-1 index date; (ii) the 51,912 patients who received at least one antidiabetic agent, or were hospitalized with a diagnosis of diabetes, within the three years before the step-1 index date; (iii) the 70,827 patients who were hospitalized for CV disease or received prescriptions of CV drugs such as nitrates or digitalis within the three years before the step-1 index date; and (iv) the 71,683 patients who did not renew the initial prescription of statins and/or did not reach at least one year of follow-up.

The remaining 84,828 patients represented the step-1 cohort, each of its members accumulating person-years of follow-up from the step-1 index date until the earliest among the dates of starting antidiabetic drug therapy (step-1 outcome, see below) or censoring, e.g. death from any cause, emigration or step-1 phase stopping (i.e., December 31st 2009). The step-1 outcome was the appearance of diabetes as diagnosed by the prescription of antidiabetic drugs. To minimize the risk of false positive diabetic cases, three antidiabetic drug prescriptions were required for the ascertainment of step-1 outcome onset.

2.3. Cohort selection and follow-up – step-2

As shown in Fig. 1, lower part, the 4391 step-1 cohort members who experienced the step-1 outcome and the 77,893 statin-treated patients who did not have any antidiabetic drug dispensation were considered eligible for inclusion in the step-2 cohort. For each cohort members who experienced the step-1 outcome (who we assumed to be diabetics), up to three patients without signs of diabetes were randomly selected from the corresponding cohort to be matched for gender, age at cohort entry (± 1 year), step-1 index date (± 30 days) and adherence with statin therapy (see below). Patients without signs of diabetes were assumed to be at risk of diabetes when the matched patient with diabetes suffered from it. To minimize the chance of outcomes (see below) unrelated to diabetes, the 1070 sets (each formed by 1 patient

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