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Statin use and risk of cataract: A nested case-control study within a healthcare database

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ABSTRACT

Background and aims: We aimed to assess the association between exposure to statins and hospitalization for cataract.
Methods: A population-based, nested case-control study was performed on a cohort of 134,441 patients from Lombardy (Italy), newly treated with statins between 2005 and 2007. Cases were patients hospitalized for cataract or lens extraction surgery after initial statin prescription until December 31, 2012. For each case patient, up to 5 controls were randomly selected from the cohort and matched by gender, age at cohort entry, and date of index prescription. Logistic regression was used to model the outcome risk associated with low (proportion of days covered, PDC 25–49%), intermediate (PDC 50–74%), and high (PDC $\geq$ 75%) adherence compared with very-low adherence (PDC < 25%).
Results: 1334 case patients were matched to 6601 controls. Mean age (SD) of cases and controls was about 70 years (9 years) and 51% of them were men. There was a slight but continuous trend toward an increased risk of cataract as adherence to statin therapy increased in the adjusted risk models, with a significant odds ratio of 1.19 (95% CI 1.01–1.40%) for PDC 50–74% and 1.20 (95% CI 1.02–1.40) for PDC $\geq$ 75% *vs.* PDC < 25%, respectively. There was no statistical evidence that the effect of statins on cataract risk differed according to statin potency at starting therapy.
Conclusions: Statin therapy was associated with a modestly increased risk of cataract surgery. Nevertheless, in view of the overwhelming benefit of statins for reduction of CV events, clinical practice for statins therapy does not need to change.

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1. Introduction

Cataract is the world's leading cause of blindness, accounting for approximately 42% of all cases of blindness in all nations [1,2]. The aetiology of cataract, the opacification of the ocular lens of the eyes, is a multifactorial process that may be triggered by oxidative damage from oxygen radicals [1]. In most cases, cataracts are age-related [3,4]; in other cases, it may be related to eye trauma, long-term diabetes, corticosteroid medications or radiation treatments [5]. Although surgery is often effective in restoring vision [6], this intervention still remains a major healthcare cost in Europe and other Western countries [7].

The concern about statin cataractogenicity arose in the 1980s, when the Food and Drug Administration approved lovastatin with the precaution that patients should be examined with a slit-lamp before and during treatment. The agency removed this recommendation in 1991. Concern about the potential of statins to affect the lens was stimulated by a report of an animal study [8–10], in which dogs were administered high doses of different HMG-CoA

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reductase inhibitors. In addition, cataract was also detected in experimental animals treated with cholesterol synthesis inhibitors developed before the availability of statins [9,11,12].

Recently, observational studies have reported conflicting results. In a meta-analysis on both randomized control trials (RCTs) and observational studies performed by Kostis and Dobrzynski, statin use was associated with a 19% decrease in the risk of cataract [13]. After publication of this meta-analysis, Leuschen et al. published a propensity score-matched analysis that indicated an increased risk of cataract among statin users as compared to non-users [14]. Furthermore, Lai et al. conducted a retrospective cohort study using the Longitudinal Health Insurance Database of Taiwan, showing that statin therapy was associated with a modestly increased risk of cataract surgery [15], and Wise et al. showed that statin use is significantly associated with cataract requiring surgical intervention in two large North American cohorts [16].

So far, studies exploring the association between statin use and the incidence of cataract have been inconsistent and controversial; the objective of the current study was to further explore the influence of statin therapy on the development of cataracts in the general population of Northern Italy.

2. Materials and methods

2.1. Healthcare utilization database of Lombardy

Data 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 population is covered by the National Health Service (NHS), which provides universal, free-of-charge coverage for many healthcare services, including cataract surgery and statin therapy; Lombardy provides an automated system of databases to collect a variety of information, including: (1) an archive of residents who receive NHS assistance, reporting demographic and administrative data; (2) a database on outpatient drug prescriptions reimbursable by the NHS; and (3) a database on diagnosis at discharge from public or private hospitals of the region. For each patient, we linked the aforementioned databases via a single identification code. In order to preserve privacy, each identification code was automatically converted into an anonymous code; the inverse process was prevented by deletion of the conversion table. Full details of the databases and the merging procedure have been reported elsewhere [17].

2.2. Cohort selection and follow-up

The target population consists of all beneficiaries of the NHS, resident in Lombardy. Those to whom statins were prescribed from January 1, 2005 until December 31, 2007 were identified, and the first prescription was defined as the index prescription. Patients were excluded from data analysis if:

(i) they had received any lipid-lowering drugs within the 5 years before the index prescription;
(ii) they had been hospitalized for cataract in the 5 years before the index prescription;
(iii) they were hospitalized for any ocular problem other than cataracts and/or were treated with antiglaucoma preparations and miotics in the 5 years before the index prescription or during the follow-up;
(iv) they had received prescriptions of drugs known to influence risk of cataract [18] within the 5 years before the index prescription;
(v) they were hospitalized for tumours or cancer treatments in the 5 years before the index date;
(vi) they had less than one year of follow-up.

Each member of the cohort accumulated person-years of follow-up from the date of index prescription until the earliest among the dates of hospitalization for cataract (see below), death, emigration, or end of follow-up (December 31, 2012).

2.3. Selection of cases and controls

A case-control study was nested into the cohort of incident statin users. Cases were members of the cohort who during follow-up were hospitalized for cataracts (ICD-9 code 366) or lens extraction surgery (ICD-9 procedure code 13). The earliest date of hospital admission was considered as the event date.

For each case patient, up to five controls randomly selected from the cohort were matched for gender, age at cohort entry, and date of index prescription. In this way, every set constituted by the index case and the corresponding controls had the same period of observation.

2.4. Assessing exposure to statins

We identified all prescriptions dispensed to the cohort members during follow-up. The period covered by a prescription was calculated from the number of dispensed tablets, assuming a treatment schedule of one tablet per day [19]. Adherence to therapy was assessed as the cumulative number of days covered by medication divided by the number of days of follow-up, a quantity referred to as the proportion of days covered (PDC) [20]. Patients were categorized as having very-low (PDC $< 25\%$), low (PDC 25–49%), intermediate (PDC 50–74%), and high (PDC $\geq 75\%$) adherence.

Case patients and controls were also classified according to whether high-potency or low-potency statins was employed at starting therapy. Treatment with high-potency statins was defined as at least 10 mg rosuvastatin, at least 20 mg atorvastatin, or at least 40 mg simvastatin; all other statin treatments were defined as low-potency [21].

2.5. Covariates

Information additionally included: 1) use of blood-pressure lowering agents during the 5-year time-window before the index prescription; 2) use of antidiabetic drugs during the 5-year time-window before the index prescription; 3) drugs known to influence risk of cataract during the follow-up (e.g. corticosteroids for systemic use, allopurinol, hormone replacement therapy); 4) the Charlson comorbidity index score [22] calculated using diagnostic information available from inpatient charts in the five years prior the date of the index prescription.

2.6. Data analysis

Chi-square, or its version for the trend, was used when appropriate to test the differences between cases and controls. Conditional logistic regression models were fitted to estimate the odds ratio (OR), as well as its 95% confidence interval (CI), of cataract in relation to exposure to statins. The predictor variables of interest were the factors constructed according to the categories of PDC, using the very low adherence category as reference. Adjustments were made for the above reported covariates. Trends in ORs were tested, when feasible, according to the statistical significance of the regression coefficient of the recorded variables obtained by scoring the corresponding categories.

All analyses were performed using the Statistical Analysis System Software (version 9.2; SAS Institute, Cary, NC, USA). Statistical

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