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Long-term use of statins reduces the risk of hospitalization for dementia

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ABSTRACT

Background: Dementia is a major public health problem because of its high prevalence in elderly individuals, particularly in the growing category of subjects aged 80 years or more. There is accumulating evidence that cholesterol may be implicated in the pathogenesis of dementia, and this has led us to assess the relationship between time spent with statins available and the risk of hospitalization for dementia.
Methods: A population-based, nested case-control study was carried out by including the cohort of 152,729 patients from Lombardy (Italy) aged 40 years or older who were newly treated with statins between 2003 and 2004. Cases were the 1380 patients who experienced hospitalization for dementia disease from initial prescription until 2010. Up to twenty controls were randomly selected for each case. Logistic regression was used to model the risk of dementia associated with the cumulative time during which statins were available. Monte-Carlo and rule-out sensitivity analyses were performed to account for unmeasured confounders.
Results: Compared with patients who had very short statins coverage (less than 6 months), those on 7–24, 25–48, and >48 months of coverage respectively had risk reductions of 15% (OR: 0.85; 95% CI: 0.74 to 0.98), 28% (OR: 0.72; 95% CI: 0.61 to 0.85), and 25% (OR: 0.75; 95% CI: 0.61 to 0.94). Simvastatin and atorvastatin were both associated with a reduced risk of dementia, while no similar evidence was observed for fluvastatin and pravastatin.
Conclusions: Long-term use of statins seems effective for the prevention of dementia.

1. Introduction

Dementia is a major public health problem because of its high prevalence in elderly individuals, particularly in subjects aged 80 years or more [1]. Epidemiological studies suggest that cardiovascular (CV) disease, hypercholesterolemia, hypertension, and diabetes are important risk factors for vascular dementia [1,2].

The hydroxy-methyl-glutaryl-CoA reductase inhibitors, known as statins, are principally used in the treatment of hypercholesterolemia [3]. Large randomized clinical trials (RCTs) have shown that statins reduce cardiovascular morbidity and mortality in patients with dyslipidaemia [3], even in those without established cardiovascular disease [4]. Evidence exists for the potential benefits from statins in a variety of other diseases [5]. Among these, biological mechanisms for a beneficial effect of statins on dementia have been suggested [6], but conflicting results have been reported. For example, a meta-analysis of the first seven published studies reported a significant 57% reduction in the risk of later cognitive impairment in patients under treatment with statins [7]. However, a cohort study failed to confirm this association [8] and a recent meta-analysis of both cohort and case-control studies concluded

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that the positive effect of statins on mild cognitive impairment and dementia may be less than expected [9]. Finally, two double-blind, randomized, placebo-controlled clinical trials, did not show a reduction in incident dementia associated with statin use [10,11].

Both observational studies and randomized trials are not immune from limitations. Confounding by indication and other sources of undetected bias may have affected the findings of observational studies. Concerns can also be raised about the use of an add-on design and the statistical power to detect the effect of statins on dementia in clinical trials. To address this issue we used the data provided by the healthcare utilization databases of Lombardy, a region of Italy with more than 10 million inhabitants. A nested case-control study investigating the effect of the duration of statin use on the risk of hospitalization for dementia was performed. The differential effect of different statins was also tested and data were subjected to a variety of procedures to account for unmeasured confounders.

2. Methods

2.1. Setting

The data used for the present study were retrieved from the healthcare utilization databases of the Italian Lombardy region. In Italy, the population is covered by the National Health Service (NHS), and Lombardy provides an automated system of databases to collect a variety of information. Full details of the databases and the merging procedure have been reported elsewhere [12].

2.2. Cohort selection and follow-up

The target population consists of all beneficiaries of the NHS, resident in Lombardia and aged 40 years or older. Those statins to whom were prescribed from January 1, 2003, until December 31, 2004, were identified, and the first prescription was defined as the index prescription. Four categories of patients were excluded from data analysis: 1) patients who had received lipid-lowering drugs within the 3 years before the index prescription; 2) patients who had been hospitalized for dementia or to whom drugs used for Alzheimer disease (AD) (e.g., acetylcholinesterase inhibitors) had been prescribed within the 3 years before the index prescription; 3) patients who had received only one lipid-lowering drug prescription during the first year after the date of index prescription; 4) patients who did not reach 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 outcome onset (hospital admission for dementia) or censoring (death, emigration, or December 31, 2010).

2.3. Case patients and controls

Case patients were members of the cohort who during follow-up experienced at least one hospital admission with dementia as the main diagnosis. The list of ICD-9-CM codes for diagnosing dementia (Appendix A) was that of the Veteran Health Administration Dementia Registry [13]. The earliest date of hospital admission recorded with one of these codes was considered as the event date.

For each case patient up to twenty controls were randomly selected from the cohort to be matched for gender, age at cohort entry, date of index prescription and were at risk for the outcome at the time when the matched case had the event.

2.4. Assessment of statin use

For each case and control all the statin prescriptions from index prescription until event date were evaluated. The period covered by an individual prescription was calculated by the number of tablets in the dispensed canister, assuming a treatment schedule of one tablet per day [14]. For overlapping prescriptions, the individual was assumed to have refilled and completed the first canister before starting the second. Because we had no information about drug prescriptions during hospitalization the observation period was temporarily censored at the date of hospital admission for any cause, and re-established 10 days after discharge. This avoided "the immeasurable time bias" [15].

For each case and control the cumulative time during which statins were available (TSA) was calculated by summing the number of days covered by drug availability. TSA was categorized according to four increasing categories ($\leq$6, 7–24, 25–48, $>$48 months).

2.5. Covariates

For each case and control we assessed the prescription of antihypertensive and antidiabetic agents during the study period. Hospitalizations for coronary heart disease, cerebrovascular disease, and traumatic brain injury in the 3 years prior the index prescription were recorded. In addition, the Charlson comorbidity score was calculated [16] using the diagnostic information available from inpatient charts in the three years prior the index date and during the first year of follow-up. Four categories of the Charlson comorbidity score were considered, i.e. 0, 1, 2, and $\geq$3.

2.6. Conventional statistical analysis

Several statistical tests (*t*-test, chi-square test or its version for the trend) were used where appropriate to test differences or trends in distribution of some relevant characteristics between cases and controls. Conditional logistic regression models [17] were fitted to estimate the odds ratio (OR), and its 95% confidence interval (CI), of first hospitalization for dementia in relation to categories of TSA, using the first category ($\leq$6 months) as reference. Unadjusted and adjusted effects of TSA categories were estimated.

2.7. Sensitivity analyses

Although data were adjusted for a number of factors, and because in our databases some relevant clinical features were not available, we addressed the potential bias generated by unmeasured confounders. We used the Monte-Carlo sensitivity analysis [18] to correct for the severity of hypercholesterolemia as an example of unmeasured confounder. We set the prevalence of new users of statins with high serum cholesterol ($\geq$240 mg/dl) as 35% [19]. In addition, we assumed that, compared to patients with mild or moderate hypercholesterolemia ($<$200 mg/dl), those with severe hypercholesterolemia had: (i) a risk of dementia 1.5 fold greater; and (ii) an odds of experiencing the longest duration of statin therapy 1.5-, 2-, 2.5-, and 5-fold higher [20]. The Monte Carlo sensitivity analysis consists of correcting the observed ORs for the bias factor calculated from the above reported data and by taking into account random uncertainty of adjusted estimates through a Monte-Carlo sampling procedure [21].

We also addressed the possibility that unmeasured confounders might overinflate the possible protective effect of duration of statin therapy. Depression may be considered a pertinent example of such a bias since depression is a risk factor for dementia [22], and it is accompanied by reduced use of healthcare services and low compliance with chronic treatments [23]. Because of the expected direction of the bias generated by this type of confounder, we investigated it by using the rule-out method described by Schneeweiss [24]. In applying the rule-out method, we allowed the