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High-potency statins increase the risk of acute kidney injury: Evidence from a large population-based study

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ABSTRACT

Objective: To assess the association between acute kidney injury and exposure to either high-potency statins or low-potency statins.
Design: A population-based, nested case-control study was performed on a cohort of 316,449 patients from Lombardy (Italy) newly treated with statins between 2007 and 2010 aged 40 years or older. 458 patients experienced acute kidney injury within six months after initial statin prescription. Up to four controls were randomly selected for each case. Logistic regression was used to model the outcome risk associated with high-potency contrasted with low-potency statins dispensed at starting therapy, and during follow-up.
Results: Patients at whom high-potency statins were initially dispensed were more likely to be hospitalized for acute kidney injury within six months after starting treatment than those on low-potency statins (adjusted OR 1.54, 95% confidence interval 1.25–1.91). Patients receiving high-potency statins within three weeks before the outcome onset had a significant increased risk respect to those who did not receive statins during the same time-window (adjusted OR 1.45, 95% confidence interval 1.04–2.03). When follow-up was extended from 6 months to 12 months the difference was not significant anymore (adjusted OR 1.17, 95% confidence interval 0.89–1.54).
Conclusions: Use of high-potency statins is associated with an increased risk of acute kidney injury compared with low-potency statins in the first 6 months after starting therapy.

1. Introduction

Statins (HMG-CoA-reductase inhibitors) are the most popular drugs for reducing plasma low density lipoprotein (LDL) cholesterol levels because of their cardiovascular protective effects and tolerability [1–5]. The most important adverse effects are associated with muscle and liver toxicity [6]. However, with increased use and dose of statins and their over-the-counter availability in some countries more cases of other rare side effects can be seen in clinical practice [7]. Among these, safety concerns have been recently raised regarding the suspect that statins could lead to unintended adverse renal effects [7–9]. Increased risks of acute renal failure (ARF) and doubling serum creatinine of 19% and 35% respectively have been reported from a randomized controlled trial – JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) – comparing high dose (20 mg) rosuvastatin with placebo [10,11]. A large, population based cohort study of over two million patients reported that use of statins was associated with a greater than 50% increase in risk of ARF, with evidence of raised risk within the first year of statin use, and a dose–response effect [9]. Finally, two recent population-based observational studies reported that use of statins with high cholesterol-lowering efficacy increased the risk for developing severe renal failure [12] and acute kidney injury [13].

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We carried out a large population-based case-control investigation, nested into a cohort of incident users of statins, to assess the brief-term effect of treatment with high and low-potency statins on the hospitalization for acute kidney injury.

2. Methods

2.1. Healthcare utilization database of Lombardy

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 [14].

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 to whom statins were prescribed from January 1, 2007, until December 31, 2010, were identified, and the first prescription was defined as the index prescription. Patients were excluded from data analysis if they had received lipid-lowering drugs and/or they had been hospitalized for any kidney disease within the 7 years before the index prescription. Each member of the cohort accumulated person-months of follow-up from the date of index prescription until the earliest among the dates of hospitalization for kidney injury, death, emigration, or 6 months after the date of index prescription.

2.3. Selection of cases and controls

A case-control study was nested into the cohort of incident statin users. Nested case-control design is a useful alternative to cohort design when the effect of time-dependent exposure on rare events needs to be investigated using large databases [15].

Cases were members of the cohort who during follow-up were hospitalized for acute kidney injury, defined according to the validated algorithm already used by Dormuth et al. (diagnosis code for acute kidney injury in any of the following listed ICD-9 codes 584, 584.5, 584.6, 584.7, 584.8, or 584.9) [13]. The earliest date of hospital admission for this event was considered as the event date.

For each case patient up to four 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. Assessing exposure to statins

Case patients and controls were classified according to treatment strategy with statins, that is whether high-potency contrasted with low-potency statins was employed at starting therapy, as well during follow-up. Treatment with high-potency statins was defined as at least 10 mg rosuvastatin, at least 20 mg atorvastatin, and at least 40 mg simvastatin; all other statin treatments were defined as low-potency. This categorization, already employed by *Dormuth* et al. [13], was derived from a systematic review and meta-analysis of randomized controlled trials that quantified the effects of statins on LDL cholesterol concentration [16].

2.5. Covariates

Information additionally included: 1) the statin employed at starting therapy; 2) use of other drugs such as blood-pressure lowering agents, other cardiovascular, antidiabetic and antidepressant drugs during the 7-year time-window before the index prescription; 3) use of antibiotics and non-steroidal anti-inflammatory agents (NSAIDs) during the 1-month time-window before the event date; 4) hospital discharge for heart failure in the seven years prior the date of the index prescription; 5) the Charlson comorbidity index score [17] calculated using diagnostic information available from inpatient charts in the seven 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 acute kidney injury in relation to exposure to statins. Adjustments were made for the above reported covariates.

Intention-to-treat and as-treated analyses were both performed as alternative ways for defining exposure to statins. In the intention-to-treat analysis the effect of high-potency statins dispensed at treatment starting was estimated using initial exposure to low-potency statins as reference. In the as-treated analysis, the effects of low and high-potency statins dispensed during the current time-window prior the event date were contrasted with no dispensation of statins during the same time-window. With the aim of designing a suitable current time-window at risk, two procedures were used: 1), the ORs associated with high-potency statins during increasing widths of the time-window prior the event date were calculated and the width generating a peak in OR was assumed as the current time-window at risk; 2), we verified if our estimates were affected by protopathic bias, i.e. if the use of statins among cases could have been attenuated in the current period owing to the onset of early symptoms of kidney injury [18]. To control for such a bias, a lag-time of 7 days prior the event date was used before starting the backward clock for measuring current exposure.

Finally, two types of sensitivity analysis were performed: 1) data were reanalyzed by lengthening the follow-up from six months, as we made for the main analysis, to twelve months; 2) patients hospitalized for chronic kidney injury were included as cases, rather than those with acute kidney injury as we made for the main analysis.

All analyses were performed using the Statistical Analysis System Software (version 9.2; SAS Institute, Cary, NC, USA). Statistical significance was set at the 0.05 level. All p-values were two-sided.

3. Results

The distribution of the exclusion criteria is shown in Fig. 1. The 316,449 patients included into the cohort accumulated 1,893,122 person-month of observation (on average near 6 months per patient) and generated 1622 hospital admissions either for acute ($n = 458$) or chronic ($n = 1164$) events, with incidence rates of 2.4 and 6.1 cases per 10,000 person-month, respectively. The 458 case patients were matched to 1824 controls (1812 were 1:4 matched with 453 cases).

As shown in Table 1, mean age (SD) of cases and controls was about 74 years (10 years) and 57% of them were men (matching variables). Simvastatin, atorvastatin and rosuvastatin were the lipid-lowering agents more commonly prescribed. Most patients were hypertensive, about one out of three received other cardiovascular, antidiabetic, and/or antidepressant agents, while almost one out of ten was currently exposed to antibiotics or NSAIDs. As compared to controls, case patients received more often atorvastatin and high-potency statins at index prescription, had higher