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Original Article

Good adherence to therapy with statins reduces the risk of adverse clinical outcomes even among very elderly. Evidence from an Italian real-life investigation

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ABSTRACT

Aim: To assess whether in individuals aged 80 years or older adherence to statins is accompanied by a reduced risk of all-cause mortality and major cardiovascular events.
Methods: A nested case–control study was carried out on a cohort of patients aged 80 years or older (very elderly individuals), who were under treatment with statins between 2008 and 2009, using the database available for all citizenship (about 10 million) of Lombardy (Italy). Cases were the cohort members who experienced death or hospitalization for stroke, myocardial infarction or heart failure from the initial prescription until 2012. Up to five controls were randomly selected for each case. Logistic regression was used to model the outcome risk associated with the adherence to therapy with statins. Two younger patient cohorts aged 60 to 69 years and 70 to 79 years were taken for comparison. A set of sensitivity analyses was performed in order to account for sources of systematic uncertainty.
Results: Among very elderly individuals, those who had high adherence to statins showed significant risk reductions of death (56%; 95% Confidence Interval, 54% to 59%), myocardial infarction (15%; 5% to 24%), stroke (13%; 0% to 24%) and heart failure (30%; 23% to 36%) with respect to those at very low adherence. Adherence-related risk reductions were only slightly better for younger cohort members.
Conclusions: Adherence to therapy with statins reduced the risk of both death and cardiovascular morbidity in patients aged 80 years or older.

1. Introduction

Statins are to date the most effective drugs for the treatment of hypercholesterolemia [1], and their important protective role in primary and secondary prevention of cardiovascular (CV) morbidity and mortality is well-established [2]. Because people aged between 60 and 79 years were well represented in many trials [3,4] this applies also to elderly patients, in whom statin-dependant reductions of elevated serum total and LDL-cholesterol can reduce CV diseases and death as in the younger fraction of the population [5,6]. However, it does not apply to patients aged 80 years or more, because (i) none or few octo- and nonagenarians have been included in outcome-based trials and (ii) evidence of the protective effects of statins among them is limited to only few observational studies with inconsistent results [7–9]. This represents an important limitation because the progressive increase of life expectancy makes octogenarians the fastest growing subgroup of the population [10,11]. Furthermore, this highly advanced age accounts for a considerable portion of the overall CV events, hospitalizations and deaths [12–14]. Finally, and most importantly, the relationship between dyslipidemia and outcomes observed in younger patients may not be entirely applicable to the very elderly. A meta-analysis of 61 prospective observational studies including almost 900,000 adults, has reported that the positive association between total serum cholesterol and CV mortality decreases with the increasing age and becomes minimal after the age of 80 years [15].

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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It is also possible that statins do not have sufficient time to exert beneficial effects in individuals with limited life expectancy and advanced atherosclerotic disease [16].

To gain further information on this issue, we performed a population-based study which included a large and unselected cohort of patients aged 80 years or more who were on treatment with statins, the aim being to determine whether adherence to statin treatment was associated with a reduced risk of fatal and non-fatal outcomes, thereby implying that, at an advanced age, these drugs maintain their protective effect. Two large cohorts of younger individuals aged 60–69 and 70–79 years (i.e., ages in which the ability of statins to reduce CV risk and death is established [17,18]) were taken for comparison. All-cause mortality and CV outcomes (hospitalization for myocardial infarction, stroke and heart failure, combined and separated) were both considered primary endpoints, whereas the rate of discontinuation of statin treatment was taken as secondary endpoint.

2. Materials and methods

2.1. Data source

The data used for the present study were retrieved from the healthcare utilization databases of Lombardy, a region of Italy that accounts for about 16% (almost 10 million) of its population. In Italy, the population is covered by the National Health Service (NHS), which provides generalized free-of-charge coverage for many healthcare services, including treatment of hypercholesterolemia. In Lombardy, the NHS management has been associated since 1997 with an automated system of databases collecting a variety of information, including ICD-9 diagnostic codes of admissions to public or private hospitals and Anatomical Therapeutic Chemical (ATC) codes of NHS-reimbursable drugs dispensed from regional pharmacies or administered directly in healthcare services, including Day Hospital. Details of the healthcare utilization databases of the Lombardy Region and of their use in the field of real-life practice and effects of statins have been reported in details elsewhere [19–22].

ICD-9 CM and ATC codes used for drawing records and fields from databases are reported in supplementary Table S1.

2.2. Cohort selection

The target population consisted of all beneficiaries of the NHS residents in Lombardy aged 60 years or older. Of these, we identified those in whom at least one prescription of statins was dispensed during 2008 and 2009 and the first dispensation during this period was defined as the index prescription. To ensure that data reflected conditions in which lipid-lowering treatment was indicated, patients who had (i) less than three consecutive prescriptions of statins before (and including) the index one, and (ii) did not renew the index prescription in the first year of follow-up were excluded. Exclusion was also extended to patients who (iii) were beneficiaries of the NHS from less than eight years, or (iv) had less than six months of follow-up. The remaining patients represented the study cohort. Each member of the cohort accumulated person-years of follow-up from the index date (i.e., the date of the index prescription) until the earliest of the censoring dates (i.e., outcome onset (see below), death, emigration, or December 31st, 2012 (end of study period)).

2.3. Assessing exposure to statins

We identified all prescriptions dispensed to the cohort members during the follow-up. The period covered by a prescription was calculated from the number of tablets in the dispensed canister, assuming a treatment schedule of one tablet per day [23]. For overlapping prescriptions, it was assumed that the patient had entirely used the former canister before starting the second one. Because information on drug therapies dispensed during hospitalization was not available, the exposure to statins before hospital admission was assumed to be continued for the entire span of hospital stay [24]. Starting from the index date, consecutively refilled prescriptions were considered uninterrupted if the time-span between the end of one prescription and the beginning of the following one (or of censoring) was 90 days or shorter (i.e., if the between-prescription time-span was longer, treatment discontinuation was assumed). Adherence was measured by the cumulative number of days during which the medication was available divided by the number of days of follow-up, a ratio referred as "proportion of days covered" (PDC) [25]. Patients were categorized as having very low (PDC < 25%), low (PDC from 25% to 49%), intermediate (PDC from 50% to 74%) and high (PDC ≥ 75%) adherence.

2.4. Covariates

For each cohort member data included covariates measured both at and before the index prescription. At index prescription, gender, age and potency of the dispensed statins were recorded. Based on a systematic review and meta-analysis of randomized controlled trials [26], high-potency statins were defined Rosuvastatin (≥10 mg/day), Atorvastatin (≥20 mg/day) and Simvastatin (≥40 mg/day). All other statin regimes were defined as low-, medium-potency. Covariates measured in the eight-year period prior to the index prescription were hospital admissions for CV events, and the Charlson comorbidity index score [27] which was calculated via the diagnostic information available from inpatient charts. The use of other medicaments (i.e., antihypertensive, antidiabetic, antiarrhythmic, antiplatelet, antithrombotic, nitrates, digitalis, respiratory, nonsteroidal anti-inflammatory and antidepressant drugs) in the year prior to the index prescription was also recorded. A comedication score was developed by summing the number of the dispensed therapeutic agents and grading them according to a score ranging from 0 to 10. Patients were categorized as having 0, 1, 2, 3 or ≥4 comedication score.

2.5. Measuring rate and predictors of discontinuation

The rate of discontinuation (i.e., the secondary outcome of our study) was expressed as the number of patients who experienced at least one episode of discontinuation every 1000 person-years. A Cox regression model was fitted to estimate the hazard ratio (HR), with the corresponding 95% confidence interval (CI), of the first episode of discontinuation associated with the above-mentioned covariates.

2.6. Assessing the association between adherence and outcomes

A case-control study was nested into the cohort of statins users. Cases were members of the cohort who during follow-up died or were admitted in hospital for myocardial infarction, stroke or heart failure, whichever occurred first. For each case patient, up to five controls were randomly selected from the cohort to be matched for gender, age at cohort entry and date of index prescription. Controls had to be at risk of the outcome when the matched case experienced it. Conditional logistic regression models were separately fitted to estimate the odds ratio (OR), and its 95% CI, of both the primary endpoints of interest (all-cause death and CV hospital admission) in relation to the statins PDC categories, using the category with the lowest adherence (<25%) as reference. Adjustments were made for potency of the dispensed statins at index prescription, prior hospital admissions for CV events, the Charlson comorbidity index score, and the comedication score. Data analyses were separately performed in three age strata (i.e., 60–69 years, 70–79 years and ≥80 years).

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