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Original Article

Are generic and brand-name statins clinically equivalent? Evidence from a real data-base

Giovanni Corrao [a,*], Davide Soranna [a,b], Andrea Arfè [a], Manuela Casula [c], Elena Tragni [c], Luca Merlino [d], Giuseppe Mancia [b,e], Alberico L. Catapano [c,f]

[a] Department of Statistics and Quantitative Methods, Division of Biostatistics, Epidemiology and Public Health, Laboratory of Healthcare Research and Pharmacoepidemiology, University of Milano-Bicocca, Milan, Italy
[b] IRCSS Istituto Auxologico Italiano, Milan, Italy
[c] Department of Pharmacological and Biomolecular Sciences, Centre of Epidemiology and Preventive Pharmacology (SEFAP), University of Milano, Milan, Italy
[d] Operative Unit of Territorial Health Services, Region Lombardia, Milan, Italy
[e] Department of Health Science, University of Milano-Bicocca, Milan, Italy
[f] IRCSS Multimedica, Sesto San Giovanni, Milan, Italy

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ABSTRACT

Background: Use of generic drugs can help contain drug spending. However, there is concern among patients and physicians that generic drugs may be clinically inferior to brand-name ones. This study aimed to compare patients treated with generic and brand-name statins in terms of therapeutic interruption and cardiovascular (CV) outcomes.

Methods: 13,799 beneficiaries of the health care system of Lombardy, Italy, aged 40 years or older who were newly treated with generic or brand-name simvastatin during 2008, were followed until 2011 for the occurrence of two outcomes: 1) therapeutic discontinuation and 2) hospitalization for CV events. Hazard ratios (HR) associated with use of generic or brand-name at starting therapy (intention-to-treat analysis) and during follow-up (as-treated analysis) were estimated by fitting proportional hazard Cox models. A Monte-Carlo sensitivity analysis was performed to account for unmeasured confounders.

Results: Patients who started on generic did not experience a different risk of discontinuation (HR: 0.98; 95% CI 0.94 to 1.02) nor of CV outcomes (HR: 0.98; 95% CI 0.79 to 1.22) from those starting on brand-name. Patients who spent >75% of time of follow-up with statin available on generics did not experience a different risk of discontinuation (HR: 0.94; 95% CI 0.87 to 1.01), nor of CV outcomes (HR: 1.06; 95% CI 0.83 to 1.34), compared with those who mainly or only used brand-name statin.

Conclusions: Our findings do not support the notion that in the real world clinical practice brand-name statins are superior to generics for keeping therapy and preventing CV outcomes.

1. Introduction

Because of its lower costs, use of generic drugs is supported by health care systems by recommending physicians to prefer them whenever available over brand-name drugs [1–4]. However, whether generic drugs are as therapeutically effective as their brand-name counterparts is still a matter of debate [5–7]. European regulations accept generics with a bioavailability that can be considerably different from the brand-name reference drugs [8,9]. It has been argued that, while the lower cost of generics may favor treatment persistence, the widespread skepticism about their safety and effectiveness may have an opposite effect [10].

Conflicting results exist on the effects of generic statins on treatment adherence [11–14]. Similar uncertainty concerns clinical equivalence of generics and brand-name products used for cardiovascular (CV) diseases. A recent literature systematic review reported that most studies included small populations and were only powered to assess differences in pharmacokinetic parameters, rather than clinical outcomes [15]. Furthermore, most investigations included young and healthy subjects, which make available evidence of questionable relevance for diseased patients [16].

In Italy, generic statins have been made available a few years ago, the first agent being simvastatin followed by pravastatin, fluvastatin and atorvastatin. We took advantage of these circumstances to evaluate whether patients on treatment with generic statins showed different risks of experiencing both discontinuation from therapy with statins,

* Corresponding author at: Dipartimento di Statistica e Metodi Quantitativi, Sezione di Biostatistica, Epidemiologia e Sanità Pubblica, Università degli Studi di Milano-Bicocca, Via Bicocca degli Arcimboldi, 8, Edificio U7, 20126 Milano, Italy. Tel.: +39 02 64485854; fax: +39 02 64485899.
E-mail address: giovanni.corrao@unimib.it (G. Corrao).

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and onset of major CV events, with respect to patients on treatment with brand-name statins. The present study reports data from a large population-based cohort study aimed at comparing, over a long follow-up, persistence and effectiveness of generic and brand-name statins dispensed in the setting of prevention of coronary and cerebrovascular events.

2. Methods

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 a 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 [17].

2.1. Cohort selection and follow-up

Lombardy residents aged 40 years or older who were beneficiaries of NHS represented the target population. According to the 2011 Italian Census, this population comprised 4,708,097 individuals. Of these, patients prescribed brand-name or generic simvastatin formulations during 2008 were identified, and the first identified dispensation was defined as the index prescription.

To make data relevant to the study aim, four patient categories were excluded: (i) individuals who received any lipid-lowering agent within the eight years before the index prescription, to ensure inclusion only of newly treated individuals [18]; (ii) patients with CV hospitalization or prescription of drugs for coronary disease or heart failure during the 8 years preceding the index prescription, to ensure inclusion only of incident CV outcomes during follow-up; (iii) patients who did not reach at least one year of follow-up, to ensure at least 1 year of potential exposure to the drugs of interest; and (iv) patients who received only one dispensation of statins during the first year after the index prescription, based on the assumption that continuous drug treatment might not have been indicated for these individuals. The remaining patients represented the study cohort.

Each member of the cohort accumulated person-years of follow-up from the date of index prescription until the earliest date among outcome onset (see below) or censoring, i.e., death, emigration, or December 31st, 2011.

2.2. Outcome identification

Two outcomes were assessed during follow-up: the first episode of statin therapy discontinuation and the first hospitalization for major CV events, i.e., coronary or cerebrovascular events. Treatment discontinuation was defined as failure to renew a statin prescription for ≥90 days after expiration of the previous dispensation. Hospitalizations for coronary or cerebrovascular events were extracted from the regional hospital discharge database and, according with the recorded ICD-9 diagnostic codes, they were defined by the WHO MONICA criteria [19,20]. Coronary events included acute myocardial infarction, acute or subacute types of ischemic heart disease, and interventions for coronary revascularization. Cerebrovascular events included subarachnoid hemorrhage, intracerebral hemorrhage, and unspecified intracranial hemorrhage, occlusion of cerebral arteries, acute cerebrovascular disease, and surgical interventions on intracranial, extracranial or neck vessels. The expiration date of the last prescription preceding discontinuation or the date of hospital admission was considered as the outcome onset time.

2.3. Measuring statin use

Statin use was considered both at therapy start and during follow-up. Since simvastatin is the only lipid-lowering agent available in both generic and brand-name formulations during 2008, and since patients entered the cohort because they started lipid-lowering therapy with simvastatin in that year, we classified patients according to whether they started therapy with generic or brand-name simvastatin.

Because in the following years pravastatin, fluvastatin and atorvastatin were made available with generic formulations, all statin prescriptions dispensed to each cohort member were evaluated during follow-up. The time covered by each prescription was calculated from the number of tablets in the dispensed canister, assuming a treatment schedule of one tablet per day [21]. For overlapping prescriptions, an individual was assumed to have made entire use of the first canister before starting the second. The ratio between the cumulative number of days in which any statin was available and the days of the overall follow-up was assessed as a measure of adherence with statin therapy, and termed as the proportion of days covered by statin therapy [22].

With the aim of measuring the relative exposure to generic and brand-name statins during follow-up, the proportion of days covered by generic statins over the total amount of days covered by therapy with any statin was calculated. This measure was termed "generic coverage" and patients were categorized as having a <25%, 25% to 49%, 50% to 74%, and ≥75% generic coverage (respectively corresponding to ≥75%, 50% to 74%, 25% to 49%, and <25%, brand-name coverage).

Finally, we also calculated whether patients switched between classes (e.g., from simvastatin to atorvastatin) or formulations (e.g., from generic to brand-name) during follow-up, and whether they increased the dose of the dispensed statin.

The commercial names of statin available in the Italian market classified in the generics and brand-name formulations are provided as supplemental material.

2.4. Covariates

Additional information included 1) gender and age at index date; 2) co-treatment with antihypertensive, antidiabetic and antidepressant agents during follow-up; and 3) the Charlson comorbidity index score [23]. The latter was calculated via the information available from inpatient charts in the eight years prior and one year after the date of the index prescription.

2.5. Data analysis

Several statistical tests (chi-square, its version for the trend, and *t*-test) were used when appropriate to test differences in demographic and clinical features between patients starting on generic or brand-name simvastatin.

Intention-to-treat analyses and time-to-event techniques were used to compare patients on initial generic or brand-name simvastatin. The curves representing the proportion of patients experiencing the considered outcomes were separately built according to the Kaplan–Meier approach. For either outcome, the log-rank test was used to test differences between generic and brand-name simvastatin groups. This was done also for the hazard ratio (HR) assessed, together with its 95% confidence interval, using Cox proportional hazard models.

As-treated analyses were used to evaluate generic or brand-name statins dispensed during follow-up, again using Cox proportional hazard regression models to estimate the HR (and its 95% confidence interval) of each outcome according to the categories of generic coverage.

Adjustments were made for the covariates mentioned above. Because the covariates measured during follow-up could change over time, they were included in the Cox models as time-dependent covariates. Linear trends in HRs associated with generic coverage were tested by including a continuous variable obtained by scoring the categories of generic coverage in the model and testing the statistical significance of the resulting regression coefficients.

Finally, because relevant clinical features were not available in our databases, we addressed the potential bias generated by unmeasured confounders. As a motivating example, we considered severity of