CLINICAL RESEARCH

Impact of a public media event on the use of statins in the French population

Impact d’un événement médiatique public sur l’utilisation des statines dans la population française

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KEYWORDS
Statins; Pharmacoepidemiology; Insurance, health, reimbursement; Medication adherence; Communications media

Summary
Background. — In February 2013, a retired French professor of medicine published a book denying the benefits of statins for cardiovascular prevention. The book was the subject of extensive media coverage and multiple public discussions and debate. Aims. — To investigate the impact of this media event on use of statins among regular users. Methods. — This repeated cohort study used the French claims database sample Échantillon généraliste des bénéficiaires to identify regular statin users and quantify the number who discontinued statins after February 2013, compared to discontinuation patterns in previous years (2011 and 2012). Discontinuation was defined as a gap of at least 2 months without statin exposure.

Abbreviations: EGB, Échantillon généraliste des bénéficiaires; LTD, long-term disease groups; ICD-10, International Classification of Diseases10th revision; ATC, anatomical therapeutic chemical; PDC, proportion of days covered; IQR, interquartile range.
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Results. — In 2013, 30,725 regular statin users were identified; 29,517 in 2012 and 28,272 in 2011. Statin discontinuation at 9-month follow-up in 2013 was 11.9% (95% confidence interval [CI] 11.5–12.2), compared with 8.5% (95% CI 8.2–8.8) in 2012 and 8.5% (95% CI 8.2–8.8) in 2011. Discontinuation varied according to cardiovascular risk: 19.4% (95% CI 18.2–20.6) in low risk, 11.6% (95% CI 11.1–12.0) in moderate risk, and 7.4% (95% CI 6.8–8.1) in high risk for the 2013 cohort. These discontinuation rates were, respectively, 1.53 (95% CI 1.36–1.72), 1.40 (95% CI 1.31–1.49), and 1.25 (95% CI 1.08–1.46) times higher in 2013 than in 2012 for low risk, moderate risk, or high risk patients.

Conclusions. — The rate of statin discontinuation, overall and in each cardiovascular risk group, was greater in 2013 after the media event than in previous years. The clinical impact of the increased discontinuation could be important.

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Background

Hydroxymethylglutaryl-coA reductase inhibitors, or statins, have demonstrated efficacy in secondary prevention of coronary heart disease [1–3], yet their efficacy in primary prevention may be more controversial [4–7]. In February 2013, a retired French professor of medicine published a book entitled “La vérité sur le cholestérol” (The truth about cholesterol) arguing that cholesterol is not linked to cardiovascular diseases and refuting the validity of all studies concluding to an efficacy of statins for cardiovascular prevention [8]. Interviews with the author for the promotion of the book were widely broadcast in a variety of media [9,10]. Health authorities and scientists from the medical community protested against his theory, considered dangerous for public health [11]. An interview-based investigation showed that approximately one-quarter of statin users interviewed in March 2013 during consultations with a cardiologist intended to discontinue statin treatment [12]. As only a small number of patients were included and were interviewed only on their intention to discontinue treatment, the objective of the present study was to investigate the real impact of this extensive media outpouring on discontinuation in formerly regular users of statins. To this intent, we used the national healthcare system claims database sample to identify regular statin users and quantify the number who discontinued statins after February 2013, compared with discontinuation patterns in previous years.

Methods

Study design

This repeated cohort study used data from the French health insurance database sample (Echantillon généraliste...
des bénéficiaires [EGB]). The inclusion period for the 2013 cohort was from 1 February 2012 to 31 January 2013 and the follow-up period was from 1 February 2013 to 31 October 2013. To provide baseline information on trends in statin use in the French population, two reference cohorts corresponding to the two years previous to the media event (2011 and 2012) were constituted using the same design and the same definition of inclusion and follow-up periods (Fig. 1).

Data source

The data were extracted from the EGB, a 1/97th representative sample of the population covered by the French national healthcare insurance system [13–16]. This database contains individual anonymous information on:

- sex, year of birth, area of residence;
- outpatient reimbursed healthcare expenditures, such as drugs with date of dispensing, drug strength and quantity dispensed;
- registration for a list of 30 long-term disease groups (LTD) with date and ICD-10 (International Classification of Diseases, 10th revision) code, which concern chronic conditions for which all healthcare expenses are fully reimbursed;
- hospital-discharge summaries (from the Programme de médicalisation des systèmes d’information), with ICD-10 codes for main, related and associated diagnosis, the date and duration of hospitalization, medical procedures;
- date but not cause of death, from the national death registry.

Study population

In each of the three cohorts, patients were included if they were regular users of statins during the year before inclusion (31 January) and were alive at the start of the follow-up period (1 February).

Regular users of statins (Anatomical Therapeutic Chemical ATC codes: C10AA and C10B) were defined as patients with a proportion of days covered (PDC) >80% during the year before inclusion. The PDC corresponds to the number of days in possession of statins divided by the number of days of follow-up. The number of days in possession of statins was calculated assuming use of one tablet per day. In the case of two overlapping exposure periods, the days of overlap were cumulated only if the two dispensions concerned the same statin. Owing to a potential lack of data concerning statin exposure during hospitalization, all periods of hospital stay were considered as exposed if the patient was in possession of drugs at the date of hospital admission [17].

Regular statin users were classified into three groups according to their cardiovascular risk during inclusion periods. The high cardiovascular risk patients had coronary heart disease (LTD No. 13 or hospital admission with main diagnosis ICD-10 codes I20.0, I21 or I24 [18]), or ischaemic stroke (LTD No. 1 — stroke — associated with ICD-10 code I63 or hospital admission with main diagnosis ICD-10 code I63). Moderate cardiovascular risk patients had at least one of the following: diabetes (LTD No. 8 or hospitalization with main diagnosis ICD-10 codes: E10, E11, E13 or E14), dispensation of antidiabetic drugs, antihypertensive drugs, anticoagulants (vitamin K antagonists or direct-acting anticoagulants) or antiplatelet agents. Low-risk patients included all other regular statin users not included in the first two groups.

Outcomes

The main outcome was the occurrence of statin discontinuation, measured as the occurrence of a gap of at least 2 months without statin exposure. Periods of statin exposure were estimated by number of days in possession of statins after each dispensation as defined in the eligibility criteria. The date of discontinuation corresponded to the estimated last day of treatment covered by the last dispensation before the gap.

Statistical analyses

The three cohorts were described according to age at inclusion, sex, comorbidities, cardiovascular treatments and cardiovascular risk groups. Statin discontinuation in the total population and among the three cardiovascular risk groups was described using Kaplan–Meier survival analysis. Discontinuation rates were estimated at 9 months of follow-up. Relative risks were the ratio of statin discontinuation or mortality rates between 2013 and 2012, and between 2012 and 2011, with their 95% confidence intervals (CIs).

All analyses were performed using SAS® software (SAS Institute, version 9.4, North Carolina, USA).

Ethical approval

In accordance with regulations in place at the time of the study, the National Institute of Health and Medical Research (Institut national de la santé et de la recherche médicale) was informed of the study that was to be performed using the EGB database. There was no further requirement for ethical approval or data protection agency approval for this study, which was done in fully anonymized data.

Results

In total, 30,725 patients were included in the 2013 cohort, and 29,517 in the 2012 and 28,272 in the 2011 reference cohorts (Fig. 2). There was no relevant difference over the different study years in patient characteristics at inclusion. In the 2013 cohort, the median (interquartile range) age was 68 (61–77) years, 54.0% were men and 67.7% were in the moderate-risk group (Table 1). Before inclusion, the proportions of regular statin users compared to all statin users were similar in the successive cohorts (60.1% in 2013, 59.6% in 2012 and 58.9% in 2011).

There was a greater proportion of men in the high-risk group than in the other cardiovascular risk groups for each cohort: in the 2013 cohort, 73.6% of high-risk patients were male, 50.3% in the moderate-risk group and 45.5% in the low-risk group (Tables 1–3, Supplementary file). Patients were younger in the low-risk group than in the other risk groups [in the 2013 cohort, median (IQR) age at inclusion in the low-risk group was 63 (55–69) years, compared to 69 (62–78) years in the moderate-risk group, and 71 (62–80) years in the high-risk group].

The probability of statin discontinuation during the 9 months of follow-up was 11.9% (95% CI 11.5–12.2) in the 2013 cohort, 8.5% (95% CI 8.2–8.8) in the 2012 and 8.5% (95% CI 8.2–8.8) in the 2011 cohorts (Table 2). Overall, the relative risk of discontinuation was 1.40 (95% CI 1.33–1.48) in 2013 versus 2012, compared to 1.00 (95% CI 0.94–1.06) in 2012 versus 2011 (Table 3).

There was a gradient in the 2013 discontinuation rate from the high-risk to low-risk groups, from, respectively, 7.4% (95% CI 6.8–8.1) in the high-risk group, 11.6% (95% CI 11.1–12.0) in the moderate-risk group, to 19.4% (95% CI 18.2–20.6) in the low-risk group (Table 2). Discontinuation rates in 2013 were, respectively, 1.25 (95% CI 1.08–1.46), 1.40 (95% CI 1.31–1.49) and 1.53 (95% CI 1.36–1.72) times higher than in 2012 equivalent high-risk, moderate-risk or low-risk patients (Table 3).

All-cause mortality during follow-up was 1.7% in 2013 versus 1.4% in 2012 and 1.4% in 2011 (Table 2). The relative risk of death in 2013 versus 2012 was 1.17 (95% CI 1.02–1.33). The relative risk of death in 2013 versus 2012 decreased according to risk group, from 1.26 (95% CI 0.98–1.61) in high-risk patients to 1.00 (95% CI 0.42–2.41) in low-risk patients (Table 3).

Discussion

In 2013, patients who were regular statin users before the media event had a higher rate of statin discontinuation and a higher overall mortality than similar patients in previous years. There was a gradient in discontinuation rate according to the cardiovascular risk group, with fewer high-risk patients discontinuing statins than low-risk patients, and the opposite gradient for all-cause deaths.

The EGB database used was representative of 78% of the French population at the time of the study [13], which ensures the representativeness of the study results to the national level. The constitution of cardiovascular risk groups was not based on exhaustive data, as cardiovascular risk factors, such as smoking, family history, blood pressure and dyslipidaemia are not included in this claims database, but there was sufficient information to ensure the coherence of the groups. For example, the LTD registration used to create the high-risk group (coronary disease, ischaemic stroke) has been validated by the health insurance system [19], which confirms that these patients were eligible for secondary prevention. Those included in the moderate-risk group had dispensations for the treatment of cardiovascular risk factors, whereas those in the low-risk group did not. Because there is universal healthcare in France, and all included patients exhibited regular statin use, access to healthcare would not be a limiting/deciding factor for classification as low risk. Furthermore, the low-risk group contains more women and younger patients than the two higher cardiovascular risk groups, which is consistent with a lower cardiovascular risk. The all-cause death rates tend to support the differences in risk groups, with a death rate of 2.6% in the high-risk group compared with 1.7% in the moderate-risk group and 0.2% in the low-risk group. All risk groups had higher statin discontinuation rates in 2013 than in previous years. Shorter and longer discontinuation gaps (30, 90 and 120 days) were tested in sensitivity analyses but did not affect the relative risks of discontinuation between 2013 and 2012 overall and in the different risk groups (data not shown).

The low-risk group corresponds to patients using statins for primary prevention, with little or no coronary risk and low death rates, and concerned relatively few patients. This would translate to a small expected benefit, consistent with unchanged overall death rates despite the greatest statin discontinuation rate. The moderate-risk group represents “primary” prevention in patients with cardiovascular risk factors, whose characteristics are close to those in the primary prevention group of the EVANS study [12], and in major statin cardiovascular prevention studies. The moderate-risk group represents over two-thirds of regular statin users. The effect in terms of public health could be more important, even though the discontinuation rate was less than expected from the EVANS study (24% intent to discontinue). This difference is likely to be explained by methodological aspects: the EVANS study evaluated intent to discontinue whereas here actual discontinuation was measured. The 40% greater discontinuation rate in 2013 compared with 2012 was accompanied by a 17% increase in overall death rate.

Although the increased rate of statin discontinuation in 2013 for the high-risk group was less than for other cardiovascular risk groups, it appeared to have the greatest impact. The discontinuation rate was only 25% higher than in previous years, but the overall mortality in that group was also 25% higher than in previous years. The high-risk group contains patients with known coronary heart disease or a
previous ischaemic stroke, in whom secondary prevention with statins has been shown to reduce mortality and recurrence of events. Statin discontinuation or non-adherence in patients treated for secondary prevention is known to increase the occurrence of cardiovascular events and/or death [19,20].

This study is ecological: although discontinuations and deaths are certain, as is their occurrence in the various cardiovascular risk groups, we cannot affirm causality. Statin discontinuation may have had no relationship with the media intervention, and changes in death rates may be unrelated to statin discontinuations. Of course the contrast with previous years is consistent, as are the changes in death rates according to the cardiovascular risk groups, and the temptation to link all is strong. In addition, a recent Danish study found that early statin discontinuation related to negative statin-related news stories identified in the media (odds ratio 1.09; 95% CI 1.06–1.12), increased the occurrence of myocardial infarction (hazard ratio 1.26; 95% CI 1.21–1.30) and death from cardiovascular disease (hazard ratio 1.18; 95% CI 1.14–1.23) [21]. The EGB database has sufficient power to study actual discontinuation rates, and affirm differences between years, which may be related to the media event, but not enough to study precisely the impact of discontinuation on events, such as myocardial infarction or death. The latter had an occurrence rate of only 2.1% in 2012 and 2.6% in 2013 in the high-risk group. The number of events in EGB is not important enough for precise analysis. To that intent, we will need to access the full national SNIIRAM (Système national d’information inter-régimes de l’Assurance maladie) database (66 million persons), which will give us the power to study more precisely the association between statin discontinuation and the occurrence of cardiovascular events or death.

Figure 2. Flow chart of the study population selection process.
**Table 1** Characteristics of the study populations.

<table>
<thead>
<tr>
<th></th>
<th>2013 cohort (n = 30,725)</th>
<th>Reference cohorts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2012 (n = 29,517)</td>
<td>2011 (n = 28,272)</td>
</tr>
<tr>
<td><strong>Men, n (%)</strong></td>
<td>16,584 (54.0)</td>
<td>15,881 (53.8)</td>
</tr>
<tr>
<td><strong>Age at inclusion, years, median (IQR)</strong></td>
<td>68 (61—77)</td>
<td>68 (61—77)</td>
</tr>
<tr>
<td><strong>Cardiovascular disease at inclusion, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary disease</td>
<td>5448 (17.7)</td>
<td>5209 (17.6)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>331 (1.1)</td>
<td>305 (1.0)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>7273 (23.7)</td>
<td>6616 (22.4)</td>
</tr>
<tr>
<td><strong>Cardiovascular comedication in the year before inclusion, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>2740 (8.9)</td>
<td>2555 (8.7)</td>
</tr>
<tr>
<td>Antiplatelet agents</td>
<td>13,809 (44.9)</td>
<td>13,000 (44.0)</td>
</tr>
<tr>
<td>Antihypertensive drugs</td>
<td>24,376 (79.3)</td>
<td>23,247 (78.8)</td>
</tr>
<tr>
<td>Antidiabetic drugs</td>
<td>8775 (28.6)</td>
<td>8147 (27.6)</td>
</tr>
<tr>
<td><strong>Cardiovascular risk factor group, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High risk</td>
<td>5728 (18.6)</td>
<td>5478 (18.6)</td>
</tr>
<tr>
<td>Moderate risk</td>
<td>20,803 (67.7)</td>
<td>19,832 (67.2)</td>
</tr>
<tr>
<td>Low risk</td>
<td>4194 (13.7)</td>
<td>4207 (14.3)</td>
</tr>
</tbody>
</table>

IQR: interquartile range.

**Table 2** Probability of statin discontinuation and all-cause mortality after 9 months of follow-up.

<table>
<thead>
<tr>
<th></th>
<th>2013 cohort</th>
<th>Reference cohorts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2012</td>
<td>2011</td>
</tr>
<tr>
<td><strong>All patients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients at risk, n</td>
<td>30,725</td>
<td>29,517</td>
</tr>
<tr>
<td>Number of statin discontinuation, n</td>
<td>3631</td>
<td>2503</td>
</tr>
<tr>
<td>Probability of discontinuation, % (95% CI)</td>
<td>11.9 (11.5—12.2)</td>
<td>8.5 (8.2—8.8)</td>
</tr>
<tr>
<td>All-cause mortality, n (%)</td>
<td>513 (1.7)</td>
<td>423 (1.4)</td>
</tr>
<tr>
<td><strong>High-risk patients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients at risk, n</td>
<td>5728</td>
<td>5478</td>
</tr>
<tr>
<td>Number of statin discontinuation, n</td>
<td>422</td>
<td>324</td>
</tr>
<tr>
<td>Probability of discontinuation, % (95% CI)</td>
<td>7.4 (6.8—8.1)</td>
<td>5.9 (5.3—6.6)</td>
</tr>
<tr>
<td>All-cause mortality, n (%)</td>
<td>150 (2.6)</td>
<td>114 (2.1)</td>
</tr>
<tr>
<td><strong>Moderate-risk patients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients at risk, n</td>
<td>20,803</td>
<td>19,832</td>
</tr>
<tr>
<td>Number of statin discontinuation, n</td>
<td>2397</td>
<td>1645</td>
</tr>
<tr>
<td>Probability of discontinuation, % (95% CI)</td>
<td>11.6 (11.1—12.0)</td>
<td>8.3 (7.9—8.7)</td>
</tr>
<tr>
<td>All-cause mortality, n (%)</td>
<td>353 (1.7)</td>
<td>299 (1.5)</td>
</tr>
<tr>
<td><strong>Low-risk patients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients at risk, n</td>
<td>4194</td>
<td>4207</td>
</tr>
<tr>
<td>Number of statin discontinuation, n</td>
<td>812</td>
<td>534</td>
</tr>
<tr>
<td>Probability of discontinuation, % (95% CI)</td>
<td>19.4 (18.2—20.6)</td>
<td>12.7 (11.7—13.7)</td>
</tr>
<tr>
<td>All-cause mortality, n (%)</td>
<td>10 (0.2)</td>
<td>10 (0.2)</td>
</tr>
</tbody>
</table>

CI: confidence interval.
From these results, it would seem that the population effect of statin discontinuation might have been inversely related to risk groups: though it was the one with the highest risk of discontinuation, there was little or no effect in the lowest risk group, which is consistent with results showing little benefit of statins in primary prevention. For moderate-risk and especially high-risk groups, statin discontinuation seemed associated with increases in death rates, which could support a benefit of statins and the link between cholesterol and atherosclerosis [22–24]. This increasing death rate may not be related entirely to this media event, but even if a fraction were, it would be of concern. In addition, we did not study rates of myocardial infarction or reinfarction because of a lack of power in the sample. Further studies with more power, in the same population, will measure the actual impact of this media intervention in terms of excess cardiovascular events or mortality, and especially the exposure status at the time of the event.

Sources of funding

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Disclosure of interest

The authors declare that they have no competing interest.

All authors disagreed with the message of the media intervention of Prof. Even and the absence of scientific support for the hypotheses put forward. However, we provide an objective evidence-based scientifically grounded evaluation of its potential consequences on patient management, and hope to have succeeded in this aim.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.acvd.2016.05.002.

References


