Discontinuation of Statin Therapy and Clinical Outcome After Ischemic Stroke

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Background and Purpose—The majority of patients with previous ischemic stroke are expected to benefit significantly from long-term statin therapy. However, discontinuation of medication therapy frequently occurs in clinical practice. The aim of this study was to assess the impact of discontinued statin therapy on clinical outcome in patients discharged after an acute ischemic stroke.

Methods—The study population included 631 consecutive stroke survivors (322 men and 309 women; mean±SD age, 70.2±7.6 years) without clinical evidence of coronary heart disease. All patients were discharged on statin therapy and were followed up for 12 months after the acute ischemic stroke.

Results—Within 12 months from discharge, 246 patients (38.9%) discontinued statin therapy; the mean time from discharge to statin discontinuation was 48.6±54.9 days (median time, 30 days; interquartile range, 18 to 55 days). During follow-up, 116 patients died (1-year probability of death=0.18; 95% CI, 0.15 to 0.21). Multivariate analysis demonstrated that after adjustment for all confounders and interactions, statin therapy discontinuation (hazard ratio=2.78; 95% CI, 1.96 to 3.72; P=0.003) was an independent predictor of all-cause 1-year mortality.

Conclusions—A large number of patients discontinue their use of statins early after acute stroke. Moreover, patients discontinuing statins have a significantly increased mortality during the first year after the acute cerebrovascular event. These findings suggest that patient care should be improved during the transition from a hospital setting to outpatient primary care. (Stroke. 2007;38:000-000.)

Key Words: adherence ■ statins ■ stroke

Statin therapy is known to be effective in preventing major adverse cardiovascular events in patients with established coronary heart disease (CHD) and in asymptomatic subjects with a high cardiovascular risk.1–6 Also, even in the absence of concurrent CHD, the vast majority of patients with previous ischemic stroke are expected to benefit significantly from long-term statin therapy.7,8 However, despite the sound evidence from randomized controlled trials, discontinuation of statin therapy frequently occurs in clinical practice and has been associated with an adverse outcome in several conditions, including acute coronary syndromes9,10 and acute stroke.11 Moreover, whereas the unfavorable effects of statin discontinuation after discharge for acute myocardial infarction have been recently shown,12 the clinical relevance of statin therapy interruption after ischemic stroke in community-based populations is presently unknown. Accordingly, the present study was designed to assess the impact of discontinued statin therapy on clinical outcome in patients discharged after an acute ischemic stroke.

Methods

Patients

Consecutive stroke survivors discharged from our institution during a 4.5-year period (January 2000 to June 2005) were prospectively screened for inclusion. Our institution is a 750-bed public hospital providing primary and tertiary care to an urban area with ~250,000 inhabitants. In the prespecified selection period, 3974 consecutive patients with acute stroke were discharged from our institution. Patients were included in the study only if they fulfilled all of the following criteria: (1) discharge after acute ischemic stroke; (2) absence of any major concurrent illness, including renal failure and malignancies; (3) absence of any clinical and laboratory evidence of CHD or of any other major cardiac affect or cardiac embolism; and (4) discharge on statin therapy.

After prospective selection, 631 consecutive patients (322 men and 309 women; mean±SD age, 70.2±7.6 years) fulfilled the aforementioned criteria, provided informed consent, and were included in the study. Stroke severity on the index admission was assessed by the National Institutes of Health Stroke Scale (NIHSS).13 No patient received thrombolytic therapy during the index admission.

Neuroimaging studies (computed tomography or magnetic resonance imaging) were performed on admission in all cases and repeated by the end of the first week to confirm brain infarct size and localization. The volume of each stroke was calculated from the computed tomography or magnetic resonance imaging films according to the modified ellipsoid method.14 The presumed cause of stroke was defined by the attending physician on the basis of clinical judgment and laboratory features and was subsequently classified according to the Trial of ORG 10172 in Acute Stroke Treatment criteria.15

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The presence of concurrent CHD was ruled out during the index admission in all cases by a comprehensive clinical evaluation, which included history, physical examination, 12-lead ECG, and echocardiography. Consequently, patients with any evidence of CHD, including a history of myocardial infarction, angina pectoris, or myocardial ischemia by stress testing, prior coronary artery bypass grafting or percutaneous coronary angioplasty, and abnormal coronary angiography, were preliminarily excluded. Also, particular care was taken to exclude any other major concurrent cardiac disease, including congestive heart failure, moderate to severe valvular dysfunction, and any cardiomyopathy. Finally, patients with atrial fibrillation or any other presumed cardiac source of embolism were also excluded. Transthoracic echocardiography was performed in all cases, whereas transesophageal echocardiography was performed for clinical reasons in 261 cases (41.3%).

Follow-Up and Primary End Point
A follow-up period of 12 months after the index acute event was planned for all patients. The primary end point of the study was death from any cause within 12 months of discharge. This end point was preferred to cardiovascular mortality, as the latter has several possible inherent limitations, including incorrect documentation and inaccurate assessment in an environment with low autopsy rates. In case of death, every effort was made to obtain hospital records or death certificates.

As in previous studies, adherence to prescribed medical therapies was assessed by telephone interviews at 1, 6, and 12 months after discharge. During these interviews, patients were asked to provide all information about their pharmacological treatments, including drug name, dose, and schedule. Interviews were conducted by a trained nurse; various attempts were made to contact individual patients. In case of failure to contact the patient, all relevant data, including survival status, were collected through their primary care physicians, who are responsible for refilling prescriptions in the Italian National Health Service. In case of discontinuation of any cardiovascular drug, particular care was taken to record the date and possible reasons for such event. As in other studies, switching from one particular cardiovascular agent to another in the same class was considered adherence to the prescribed therapy. Overall, this approach, which involved telephone follow-up and controls through primary care physicians, allowed collection of all information about pharmacological therapies and clinical outcome in all cases during the 12-month follow-up period; in fact, no patient was lost to follow-up.

Statistical Analysis
Means (±SDs) were calculated for continuous variables, whereas frequencies were measured for categorical variables. Distributions of continuous variables were determined by the Kolmogorov-Smirnov test. In case of normal distribution, group differences for continuous data were examined by an unpaired Student t test, whereas the Mann-Whitney 2-sample test was applied in the case of nonnormal distribution. Group differences for categorical variables were examined by χ² or Fisher exact test, as appropriate. In particular, the Fisher exact test was applied in the case of an expected frequency of <5. The cumulative risks of experiencing the primary end point (12-month all-cause mortality) or discontinuing statin therapy were estimated by means of the Kaplan-Meier method.

Univariate and multivariate Cox proportional-hazards regression analyses were performed to identify risk factors for time-related occurrence of the primary end point (12-month all-cause mortality). Demographic variables (age and sex), clinical history features (hypertension, diabetes mellitus, prior stroke, obesity, chronic lung disease, and smoking habits), and variables related to the index stroke event (NIHSS score, infarct volume, and stroke subtype) were all considered potential predictors of the study end point. All variables showing a probability value <0.10 in the initial univariate analysis were considered potential predictors of the study end point. All variables were then analyzed in a stepwise fashion to develop Cox models of the study end point (12-month all-cause mortality). The assumption of proportionality for Cox models was tested and met for all covariates. Because patients could interrupt statin treatment or any other pharmacological treatment at any moment during the follow-up period, Cox models for the association of discontinuation of medical therapies with the primary end point included discontinuation of prescribed medications as a time-dependent covariate. This approach has already been used in similar previous studies because patients can be transferred from 1 risk class to another at the moment of documented discontinuation of pharmacological treatment. The results of the Cox proportional-hazards models are presented as hazard ratios (HRs) and 95% CIs. Moreover, as in cohort studies, patients were reevaluated over time for risk exposure and outcome status. According to a statistical approach already used in previous studies, the HRs for all-cause mortality over time in the study population according to the time of statin treatment discontinuation were also calculated. Univariate and multivariate Cox proportional-hazards regression analyses were also used to identify clinical and demographic variables associated with statin therapy discontinuation during the 12-month follow-up period. Data analysis was performed with the SPSS statistical software package (SPSS 11.5). A value of P<0.05 was considered statistically significant.

Results
Statin Therapy
At discharge, 409 patients (77.6%) were prescribed atorvastatin (mean dosage, 17.5±4.3 mg/d; range, 10 to 20 mg/d), and 222 patients (22.4%) were prescribed simvastatin (mean dosage, 24.7±8.5 mg/d; range, 20 to 40 mg/d). During the 12-month follow-up period, 246 patients (38.9%) discontinued statin therapy, and 87 patients (13.7%) switched from the initially prescribed statin to another. The mean time from discharge to statin discontinuation was 48.6±54.9 days (median time to discontinuation, 30 days; interquartile range, 18 to 55 days). Kaplan-Meier actuarial estimates of statin discontinuation after 1, 3, 6, and 12 months were 21.5%, 32.6%, 37.4%, and 38.9%, respectively. The discontinuation rate was similar for atorvastatin and simvastatin (163 patients, 39.8%, discontinued atorvastatin and 83, 37.3%, discontinued simvastatin; P=0.544). The reason for statin discontinuation was mild side effects in 71 of 246 cases (28.8%), including dyspepsia (31 cases), fatigue (16 cases), headache (12 cases), myalgias (8 cases), and an asymptomatic rise in plasma levels of liver enzymes (2 cases) or total creatine kinase (2 cases), as reported by patients. However, no case of major adverse reaction, such as rhabdomyolysis, was reported. In the remaining 175 cases (71.2%), neither the patient nor the primary care physician could provide any specific medical reason for statin discontinuation.

Patients discontinuing statins were found to be significantly older (71.4±7.1 versus 69.5±7.7 years, P=0.002) and more frequently female (138 of 246 versus 171 of 386, P=0.004). By contrast, patients were less likely to discontinue statin treatment in case of diabetes (66 of 246 versus 162 of 386, P=0.001) or previous stroke (22 of 246 versus 56 of 385, P=0.038). No other significant difference in baseline characteristics was noted between patients discontinuing statins and the rest of the study population.

Multivariate analysis demonstrated that increasing age (HR=1.006 per year; 95% CI, 1.004 to 1.009; P=0.01) and female sex (HR=1.107; 95% CI, 1.03 to 1.11; P=0.02) were associated with a higher risk of statin therapy discontinuation.

On the other hand, diabetic patients were more likely to
continue statins during follow-up (HR = 0.86; 95% CI, 0.79 to 0.91; \( P = 0.03 \)).

All-Cause Mortality

During the 12-month follow-up period, the primary end point (death from any cause) occurred in 116 of the 631 patients. Consequently, the overall 1-year probability of death was 0.18 (95% CI, 0.15 to 0.21). This finding is consistent with available data concerning mortality after ischemic stroke in Italy.\(^\text{24}\) Kaplan-Meier actuarial estimates of all-cause mortality after 1, 3, 6, and 12 months were 5.0%, 13.5%, 16.2%, and 18.4%, respectively (the Figure). According to available clinical records and death certificates, death was considered cardiovascular in 93 cases (80.1%), and noncardiovascular in 8 (6.9%). Owing to a lack of consistent data, the cause of death was unknown in the remaining patients (15 cases, 13.0%).

Patients were more likely to die during follow-up if they were older (73.6±5.0 versus 69.4±7.8 years, \( P = 0.0001 \)), diabetic (52 of 116 versus 176 of 551, \( P = 0.030 \)), obese (66 of 116 versus 230 of 515, \( P = 0.017 \)), with a previous stroke (21 of 116 versus 57 of 515, \( P = 0.037 \)), and with a more severe presenting clinical deficit, as assessed by the NIHSS on admission during the index event (10.8±1.8 versus 8.9±2.6, \( P = 0.0001 \)). Survivors and nonsurvivors were similar for all other baseline features, including stroke volume, stroke subtypes, the proportion of female patients, hypertension, smoking habit and chronic lung disease, and lipid profile at discharge (total, HDL, and LDL cholesterol and triglyceride values).

Other Cardiovascular Pharmacological Treatments

Cardiovascular pharmacological therapies prescribed at discharge after the index stroke event were similar in survivors and nonsurvivors (the Table). Discontinuation rates during 12 months for all cardiovascular drugs prescribed at discharge are shown in the Table. In particular, pharmacological treatments, including antiplatelet agents, statins, diuretics, and \( \beta \)-blockers, had a higher risk of being discontinued. However, only the rates of discontinuation for statins and antiplatelet agents were significantly higher in nonsurvivors than in survivors.

All-Cause Mortality Predictors

Multivariate analysis, performed with the Cox proportional-hazards regression method with discontinuation of pharmacological therapies as a time-dependent covariate, demonstrated that age (HR = 1.08 per year; 95% CI, 1.05 to 1.12; \( P = 0.001 \)), stroke severity on admission (HR = 1.11 per unit of NIHSS score; 95% CI, 1.08 to 1.19; \( P = 0.002 \)), statin
specific reasons for nonadherence to statin therapy remain unknown. As to the individual profile of nonadherent subjects, in this study, patients who discontinued statins were found to be older and female, whereas diabetic patients were more likely to adhere to long-term statin therapy. These findings are consistent with those reported in previous studies. Indeed, older patients are known to be less adherent to statin therapy, whereas major comorbidities, such as diabetes or chronic CHD, have been associated with lower statin discontinuation rates.\textsuperscript{17,18}

A point of major interest emerging from our study is that statin therapy discontinuation during the 12-month follow-up period was associated with higher all-cause mortality, even after adjustment for demographics (age, sex), clinical history (presence of hypertension, diabetes mellitus, prior stroke, obesity, chronic lung disease, and smoking habits), variables related to the index stroke event (NIHSS score, infarct volume, and stroke subtype), and other concurrent treatments. Actually, the association between statin discontinuation and adverse clinical outcome has already been reported for patients with CHD.\textsuperscript{12,21} However, to the best of our knowledge, this is the first evidence linking discontinuation of statins to increased mortality in stroke survivors without any clinical evidence of CHD.

As to other secondary prevention treatments, in accordance with previous reports, this study further confirms that nonadherence to antiplatelet medications after ischemic stroke may be rather high (17.4%) and is associated with an unfavorable clinical outcome.\textsuperscript{28} Also, discontinuation of diuretic therapy over 1 year appeared particularly frequent in our study cohort (25.5%). However, even when diuretics are known to improve clinical outcome after stroke,\textsuperscript{29} withdrawal from such treatment was not associated with increased mortality in our series. This finding may be explained by the relatively low rate of prescription of these agents at discharge after the index event in our study population (41.5%).

Indeed, the relation between adherence to pharmacological treatments and clinical outcome is complex. In fact, medication therapy discontinuation may also be correlated with individual self-care behaviors that may be directly or indirectly related to clinical outcomes.\textsuperscript{12} In particular, nonadherence to medication therapies has been associated with worse outcomes regardless of treatment assignment in randomized, controlled clinical trials.\textsuperscript{20} Furthermore, nonadherence is known to be related to particular psychosocial factors, includ-

### Table: Discontinuation Rates of Cardiovascular Pharmacological Treatments in the Study Population

<table>
<thead>
<tr>
<th>Prescription Rate at Discharge</th>
<th>12-Month Discontinuation Rate</th>
<th>Overall</th>
<th>Survivors</th>
<th>Nonsurvivors</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiplatelet agents, patients (%)</td>
<td>618 (97.9)</td>
<td>108 (17.4)</td>
<td>47 (9.3)</td>
<td>61 (53.5)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Statins, patients (%)</td>
<td>631 (100.0)</td>
<td>246 (38.9)</td>
<td>154 (29.9)</td>
<td>92 (79.3)</td>
<td>0.0001</td>
</tr>
<tr>
<td>ACE inhibitors, patients (%)</td>
<td>221 (35.0)</td>
<td>24 (10.8)</td>
<td>19 (10.6)</td>
<td>5 (11.9)</td>
<td>0.808</td>
</tr>
<tr>
<td>Calcium channel blockers, patients (%)</td>
<td>271 (43.1)</td>
<td>32 (11.8)</td>
<td>24 (10.9)</td>
<td>8 (15.6)</td>
<td>0.340</td>
</tr>
<tr>
<td>Angiotensin receptor blockers, patients (%)</td>
<td>123 (19.4)</td>
<td>10 (8.1)</td>
<td>8 (7.8)</td>
<td>2 (9.5)</td>
<td>0.679</td>
</tr>
<tr>
<td>β-blockers, patients (%)</td>
<td>48 (7.6)</td>
<td>9 (18.7)</td>
<td>7 (19.4)</td>
<td>2 (16.6)</td>
<td>1.0</td>
</tr>
<tr>
<td>Diuretics, patients (%)</td>
<td>262 (41.5)</td>
<td>67 (25.5)</td>
<td>51 (24.1)</td>
<td>16 (31.3)</td>
<td>0.290</td>
</tr>
</tbody>
</table>

*Comparison between survivors and nonsurvivors.

Discussion

In this study that assessed the rate and clinical impact of statin therapy discontinuation after acute ischemic stroke, we found that 38.9% of patients discontinued the use of these lipid-lowering agents within 12 months of the acute event. This finding is in accordance with data recently published by the Italian National Drug Agency, which reported that in the primary care setting of Italy, the risk of discontinuing statins without any specific reason within 1 year from the beginning of treatment may reach 50%.\textsuperscript{24} Similar figure have also been reported from other Western countries, including Canada\textsuperscript{18} and the United States.\textsuperscript{26} Overall, in our study, the magnitude of nonadherence to prescribed statin therapy is particularly high and cannot be related to either drug cost or adverse reactions. In fact, as in Canada and the United Kingdom, in Italy all medication costs are covered by the National Health Service, except for a small copayment per prescription. Also, the incidence of major side effects or relevant adverse reactions in statin-treated patients is usually low. In randomized, controlled trials, the incidence of major side effects requiring interruption of active statin treatment hardly reached 5%\textsuperscript{1,4} Actually, in this study, 11.2% of patients (71 of 631) experienced mild side effects during statin therapy, but no major adverse events were reported. On the other hand, in 71.2% of cases of statin discontinuation, neither the patient nor the primary care physician could provide any specific medical reason to account for therapy interruption. Indeed, the etiology of nonadherence is complex and difficult to analyze.\textsuperscript{27} Contributing factors may be related to patient behavior and beliefs, provider behavior and beliefs, and features of the current health care system itself. As a matter of fact, as already reported in previous studies, in most cases the specific reasons for nonadherence to statin therapy remain unknown.\textsuperscript{27}
ing depression, which may in turn favor an adverse outcome. In particular, poststroke depression occurs in 20% to 40% of patients and represents a serious problem deserving prompt attention, as it may impede participation in rehabilitation programs, and it has also been linked to a higher 12-month mortality. Conversely, adherent patients may be more likely to follow lifestyle recommendations and other healthy behaviors, leading to improved outcomes. Therefore, the association between discontinuation of medication therapy and adverse outcomes is likely multifactorial, and future studies should evaluate whether interventions to improve self-care behaviors and lifestyles might also influence medication persistence.

Limitations of the Study
The main limitations of the present study derive from the potential selection bias that is inherent in any observational analysis. In fact, this was a single-center observational study, in which patients were prospectively included by the investigators. Consequently, selection bias due to some form of “self-selection” cannot be excluded. Moreover, the size of the study population was based on the availability of consecutive patients with specific clinical and laboratory characteristics in a reasonably long time frame, rather than on statistical considerations. We attempted to account for the potential selection bias as much as possible by using multivariable time-dependent covariate-adjustment models. Actually, in our multivariable models, we adjusted for >20 variables, including demographic characteristics, clinical history features, variables related to the index stroke event, and concurrent drug therapies. However, several other potentially relevant variables that could affect outcomes were not collected or evaluated (ie, the incidence of poststroke depression), while there is no assurance that any statistical adjustment can be guaranteed to be fully precise. As a matter of fact, as in all observational investigations, we cannot exclude the possibility that our results might have been partially conditioned by some form of unmeasured confounding. As to methodology, in most cases, medication use was assessed by patient self-report. However, medication use based on self-report is considered specific and has been positively correlated with pill counts. Conclusions
This study was aimed at defining the rate and clinical relevance of statin therapy discontinuation in a cohort of ischemic stroke survivors without clinical CHD. We showed that a sizable proportion of patients discontinue the use of prescribed statin therapy early after the acute event. Moreover, patients discontinuing statins have a significantly increased all-cause mortality during the first year after acute stroke. These findings suggest that patient care should be improved during the transition from a hospital setting to outpatient primary care. Indeed, effective clinical strategies are needed to bring about a significant increase in adherence to evidence-based medical treatments. Finally, additional research should be carried out to determine whether the benefits of statin therapy observed in randomized, controlled trials actually apply to the “real world” of clinical practice.

Disclosures
None.

References


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