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Comparative effects of more versus less aggressive treatment with statins on the long-term outcome of patients with acute ischemic stroke

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ABSTRACT

Background and aims: There are no studies that compared the effects of different intensities of statin treatment on the long-term outcome of patients with recent ischemic stroke. We aimed to evaluate these effects.
Methods: We prospectively studied 436 consecutive patients who were discharged after acute ischemic stroke (39.2% males, age 78.6 ± 6.7 years). Statin treatment was categorized in equipotent doses of atorvastatin. One year after discharge, the functional status was assessed with the modified Rankin scale (mRS). Adverse outcome was defined as mRS between 2 and 6. The occurrence of ischemic stroke, myocardial infarction and death was recorded.
Result: Adverse outcome rates were lower in patients treated with atorvastatin 20 mg/day or more potent doses of statins than in patients treated with atorvastatin 10 mg/day (63.5, 38.2 and 48.2%, respectively; $p = 0.004$). In binary logistic regression analysis, independent predictors of adverse outcome were the mRS at discharge (relative risk (RR) 2.33, 95% confidence interval (CI) 1.77–3.07, $p < 0.001$) whereas more aggressive treatment with statins independently predicted favorable outcome (atorvastatin 20 vs. 10 mg/day, RR 0.30, 95% CI 0.11–0.87, $p = 0.026$; atorvastatin 40 mg/day or more potent dose of statins vs. atorvastatin 10 mg/day, RR 1.66, 95% CI 0.62–4.44, p = NS). The incidence of cardiovascular events and all-cause mortality showed a trend for being lower in patients treated with atorvastatin 40–80 mg/day or rosuvastatin 10–40 mg/day than in those treated with less potent doses of statins.
Conclusion: More aggressive statin treatment improves the long-term functional outcome of patients with acute ischemic stroke more than less aggressive treatment.
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1. Introduction

Treatment with statins is an essential component of the secondary prevention of stroke and other cardiovascular events in patients with a history of ischemic stroke [1]. In the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial, treatment with atorvastatin 80 mg/day reduced the risk of recurrent stroke and of other major cardiovascular events compared with placebo in patients who had a stroke or transient ischemic attack within one to six months before study entry [2]. Observational studies and subgroup analyses of patients with a history of stroke included in other randomized, placebo-controlled studies of statins also showed similar results [3–5].

In patients with stable coronary heart disease (CHD) or acute coronary syndromes, randomized trials showed that more aggressive treatment with statins reduces cardiovascular morbidity more than less aggressive treatment [6,7]. However, in patients with a history of stroke, there are no randomized trials or observational studies comparing the effects of more and less intensive treatment with statins on cardiovascular risk reduction. On the other hand, observational studies suggest that treatment with statins prior stroke or immediately after stroke might improve the long-term functional outcome of these patients [8–12]. However, there are no studies that compared the effects of more with less aggressive

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statin treatment on this endpoint.

The aim of the present study was to compare the effects of more and less intensive statin treatment on the long-term functional outcome and on the incidence of cardiovascular events and all-cause mortality in patients discharged after acute ischemic stroke.

2. Materials and methods

We prospectively studied all patients who were discharged from our Department between September 2010 and June 2013 after hospitalization for acute ischemic stroke (n = 436; 39.2% males, age 78.6 ± 6.7 years).

At admission, demographic data (age, gender), history of cardiovascular risk factors (hypertension, type 2 diabetes mellitus (T2DM), atrial fibrillation (AF), smoking, alcohol consumption, family history of premature cardiovascular disease (CVD), chronic kidney disease) and history of concomitant CVD (CHD, previous ischemic stroke, heart failure) were recorded. Hypertension was defined as a history of physician-diagnosed hypertension or treatment with antihypertensive agents. T2DM was diagnosed as a history of physician-diagnosed T2DM or treatment with antidiabetic agents. Anthropometric parameters (weight, height, waist and hip circumference) were also measured and the body mass index and waist to hip ratio (WHR) were calculated. The severity of stroke was assessed at admission with the National Institutes of Health Stroke Scale (NIHSS).

Routine laboratory investigations were performed after overnight fasting at the first day after admission and included serum levels of glucose, total cholesterol, high-density lipoprotein cholesterol, triglycerides (TG), creatinine and uric acid. Low-density lipoprotein cholesterol (LDL-C) levels were calculated using Friedewald's formula [13]. Glomerular filtration rate (GFR) was estimated using the Modification of Diet in Renal Disease equation [14]. Chronic kidney disease was defined as estimated GFR <60 ml/min/1.73 m^2.

All patients underwent brain computed tomography at admission and a second brain computed tomography was performed if clinically indicated.

At discharge, the prescribed pharmacological treatment was recorded. Statin treatment was categorized in equipotent doses of atorvastatin based on the following equivalence of LDL-C-lowering efficacy of statins: simvastatin 40 mg/day = atorvastatin 20 mg/day = rosuvastatin 5 mg/day [15]. The functional outcome at discharge was assessed with the modified Rankin scale (mRS).

Approximately 1 year after discharge, the patients and/or their proxy were contacted by phone and the functional status was assessed with the mRS. Adverse outcome was defined as mRS between 2 and 6 (i.e. dependency or death). The occurrence of ischemic stroke, myocardial infarction (MI) and death was recorded. In patients who died during follow-up, the cause of death was also recorded.

The study was performed in agreement with Helsinki declaration and was approved by the local ethic committee.

2.1. Statistical analysis

All data were analyzed with the statistical package SPSS (version 17.0; SPSS, Chicago, IL, USA). Data are presented as percentages for categorical variables and as mean and standard deviation for continuous variables. Differences in categorical variables between groups were assessed with the χ^2 test. Differences in continuous variables between groups were assessed with one-way analysis of variance and post-hoc comparisons between groups were performed with the Holm–Sidak test. Binary logistic regression analysis was used to identify independent predictors of adverse outcome, cardiovascular events (ischemic stroke, MI and cardiovascular death) and all-cause mortality during follow-up. In all cases, a two-tailed $p < 0.05$ was considered significant.

3. Results

Clinical and laboratory characteristics of the total study population are shown in Table 1. At discharge, a statin was administered to 308 patients (70.6% of the total study population). Most patients were prescribed atorvastatin (n = 244) whereas rosuvastatin and simvastatin were administered to 37 and 25 patients, respectively. Among patients who were treated with a statin, atorvastatin 10, 20, 40 and 80 mg/day or equipotent doses of other statins, were administered to 171, 68, 56 and 11 patients, respectively; 2 patients were prescribed rosuvastatin 40 mg/day. Due to the small number of patients treated with atorvastatin 80 mg/day or rosuvastatin 20–40 mg/day (n = 13), the latter patients were analyzed together with patients treated with atorvastatin 40 mg/day or equipotent doses of other statins. Characteristics of patients treated with atorvastatin 10 mg/day, 20 mg/day and more potent doses of statins are shown in Table 2. Patients who were prescribed more aggressive statin treatment were younger, had higher prevalence of CHD, lower LDL-C levels, less severe stroke at admission and better functional status at discharge.

At 1 year after discharge, patients who were treated with atorvastatin 20 mg/day and more potent doses of statins had lower mRS than patients treated with atorvastatin 10 mg/day [1.8 ± 2.2, 2.2 ± 2.2 and 2.7 ± 2.2, respectively; p = 0.029 (atorvastatin 10 vs. 20 mg/day, p = 0.029; atorvastatin 10 vs. atorvastatin 40 mg/day or more potent doses of statins, p = NS)]. Adverse outcome rates were also lower in patients who were treated with atorvastatin 20 mg/day and more potent doses of statins than in patients treated with atorvastatin 10 mg/day (63.5, 38.2 and 48.2%, respectively;

Table 1
Clinical and laboratory characteristics of the total study population (n = 436).

Age (years)	78.6 ± 6.7
Males (%)	39.2
Hypertension (%)	82.1
Type 2 diabetes mellitus (%)	32.1
Duration of type 2 diabetes mellitus (years)	11.4 ± 8.2
Atrial fibrillation (%)	32.6
Smoking (current/past, %)	12.2/21.3
Package-years	59 ± 50
Alcohol (units/week)	1.9 ± 10.8
Family history of cardiovascular disease (%)	14.7
Coronary heart disease (%)	27.1
Heart failure (%)	19.7
Chronic kidney disease (%)	32.8
Overweight/obesity (%)	41.3/25.0
Body mass index (kg/m^2)	27.5 ± 5.0
Waist (cm)	104 ± 12
Waist/hip	0.98 ± 0.07
Glucose (mg/dl)	112 ± 46
Low-density lipoprotein cholesterol (mg/dl)	113 ± 39
High-density lipoprotein cholesterol (mg/dl)	46 ± 14
Triglycerides (mg/dl)	122 ± 59
Uric acid (mg/dl)	5.7 ± 1.9
Estimated glomerular filtration rate (ml/min/1.73 m^2)	70 ± 23
National Institutes of Health Stroke Scale score at admission	6.9 ± 7.2
Modified Rankin scale score at discharge	2.3 ± 1.9
Days of hospitalization	6.7 ± 4.1
Antiplatelet treatment at discharge (%)	62.4
Anticoagulant treatment at discharge (%)	17.4
Antihypertensive treatment at discharge (%)	65.8
Antidiabetic treatment at discharge (%)	23.4

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