Atorvastatin Treatment and Carotid Plaque Morphology in First-ever Atherosclerotic Transient Ischemic Attack/Stroke: A Case–Control Study

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Background: A relationship between echolucency of carotid plaques and the consequent risk of ipsilateral ischemic stroke has been observed. An aggressive lipid-lowering therapy may increase the echogenicity of carotid plaque in patients with elevated low-density lipoprotein cholesterol levels. The aim of this study is to prospectively evaluate the long-term effect of high-dose atorvastatin on carotid plaque morphology in patients with first-ever transient ischemic attack or stroke. *Methods:* All patients with symptomatic first ischemic atherosclerotic cerebrovascular event occurred within the previous 10 days were enrolled. Carotid Doppler ultrasound of the neck vessels with 7-11 MHz probe for the definition of the atherosclerotic carotid framework was performed. The analysis of the gray-scale median (GSM) of each plate was carried out with image processing software. *Results:* A total of 240 symptomatic plaques were included and divided into 3 groups: 80 in group A (atorvastatin 80 mg), 80 in group B (atorvastatin 40 mg), and 80 to group C (no atorvastatin). GSM score increases significantly more extensive in group A than in group B (+48.65 vs. +39.46, $P < .02$) and group C (+48.65 vs. 19.3, $P = .0002$). An inverse association between reduction of low-density lipoprotein and the increase in the GSM score ($r = -.456$, $P = .007$) has been observed. Moreover, the reduction of high-sensitive C-reactive protein correlates inversely with the increase of the GSM ($r = -.398$, $P = .021$). *Conclusions:* Dose-dependent effect of atorvastatin on symptomatic carotid plaque morphology may suggest a specific role of this drug in the atherosclerotic stroke prevention. **Key Words:** Atorvastatin—carotid plaque—carotid stenosis—carotid ultrasound—gray-scale median—stroke.

Introduction

Stroke is one of the leading causes of death worldwide and of disability in the elderly with a significant impact on individual, family, and community health.[1-4] Atherosclerotic stroke (large vessel disease) accounts for almost 20% of all ischemic strokes, and approximately 7% of all cerebrovascular events are associated with a corresponding significant carotid stenosis.[5] In addition to the degree of stenosis, increasing evidences support the role of the morphologic characteristics of carotid atherosclerotic lesions in cerebrovascular risk stratification.[6,7] Particularly, the vulnerability features of the plaque, such as surface integrity and histologic characteristics,

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significantly increased the stroke risk.[8,9] Several ultrasonographic studies observed a relationship between echolucency of carotid plaques and the consequent risk of ipsilateral ischemic stroke.[6] In this context, the quantitative measures of echogenicity, such as gray-scale median (GSM) analysis have been considered a useful marker of plaque vulnerability.[10-12] Above all, the gray-scale densitometry index or GSM seems to be a promising clinical marker of plaque stabilization because of simplicity of assessment, reliability, and ability to be measured during a standard clinical B-mode evaluation. Recently Salem et al[13] showed that a low-score GSM increases the risk of recurrent cerebrovascular events. Moreover, GSM analysis has been used to assess the effectiveness of treatment with statins in modifying the morphologic characteristics of carotid atherosclerotic plaques.[14-16] Because aggressive treatment was found to be more effective in terms of prevention of cardiovascular disease,[17-19] some authors suggested that an aggressive lipid-lowering therapy may increase the echogenicity of carotid plaque in patients with elevated LDL cholesterol levels.[16,20,21] However, potential bias of these studies are small number of samples, the variability of follow-up periods, and the lack of control groups. Further limitation is represented by the heterogeneity of the populations that included both symptomatic and asymptomatic cerebrovascular disease. More recently, Della Morte et al[21] observed an echolucency reduction and an echogenicity increase in asymptomatic carotid plaques after short-term treatment with high-dose atorvastatin, independently from low-density lipoprotein (LDL) cholesterol levels or changes. According to these results, pleiotropic mechanisms of statins accounted for remodeling of atherosclerotic plaque morphology. The purpose of this prospective study was to evaluate the long-term effect of atorvastatin on high-dose and intermediate symptomatic carotid plaque vulnerability in patients with transient ischemic attack (TIA) or stroke in the acute phase compared with the natural history of atheroma.

Materials and Methods

We enrolled all patients with symptomatic first ischemic atherosclerotic cerebrovascular event occurred within the previous 10 days (TIA, minor stroke, major stroke) that was related to the Neurosonology Unit of the Department of Medical and Surgical Sciences and Biotechnologies, Neurology Section for evaluating ultrasound. The local ethics committee approved the study, and all participants have completed and signed an informed consent. Exclusion criteria were as follows: stenosis more than 69% and/or plaque ulceration, atrial fibrillation, dilated cardiomyopathy, patent foramen ovale and atrial septal aneurysm, other possible embolic cardiomyopathies, previous or current lipid-lowering therapy, liver disease (alanine amino-transferase and gamma-glutamyl transpeptidase-y increased by approximately 2.5-fold) or renal impairment (creatinine $>$ 2.0 mg/dl), recent untreated hypothyroidism, muscular and neuromuscular diseases, vasculitis and other immune-inflammatory diseases, malignancies, other contraindications to the use of statins. Clinical parameters examined were as follows: clinical history of cardiovascular risk factors, body mass index, mean values of ambulatory blood pressure of last 10 days, the average blood glycemia of the last 48 hours, and percentage of glycated hemoglobin (HbA1C). The blood levels of total cholesterol, LDL-C, and high-density lipoprotein were scheduled but not taken into consideration for the recruitment and randomization. All patients underwent Doppler ultrasound of the neck vessels with 7-11 MHz probe (LogiQ Pro; General Electrics Medical Systems, Milwaukee, WI) for the definition of the atherosclerotic carotid framework. The diagnosis and the degree of carotid stenosis were based on the diagnostic criteria applied in our laboratory on the basis of the recommendations of the Society of Radiologists in Ultrasound (peak systolic velocity and peak systolic velocity ratio between the internal and common carotid artery) 7 and both European Carotid Surgery Trial (ratio between lumen diameter and minimal residual length at maximum narrowing in the B-mode imaging) and North America Symptomatic Carotid Endarterectomy Trial criteria (ratio between lumen diameter well beyond the stenosis and minimal residual length at maximum narrowing in the B-mode imaging).[22,23] By means of the combined evaluation, stenosis were classified as follows: less than 49%, between 50% and 69%, between 70% and 80%, subocclusion, and occlusion. The analysis of the GSM of each plate was performed with image processing software (Adobe Photoshop 9.0, Acrobat System Inc, San Jose, CA) on 3 scans of each plaque obtained in 3 cardiac cycles and the final score calculated as average of the 3 measurements. All patients with nonsurgical stenosis between 50% and 69%, GSM score less than 80 and clinical history, neurologic, and neuroimaging (computed tomography or magnetic resonance imaging) signs of ipsilateral stroke were randomly and independently from lipid profile assigned to 3 groups: group A—atorvastatin 80 mg/day, group B—atorvastatin 40 mg/day, and group C—no atorvastatin. Clinical and ultrasonographic evaluation was performed at time 0 and 12 months. The same experienced operator blinded to clinical history and study group of the patients performed the image acquisition and GSM evaluation. During the follow-up period, the concomitant antihypertensive, hypoglycemic, and antiplatelet therapies remained unchanged unless otherwise clinically indicated. A low-calorie diet and physical activity (not monitored) have been recommended for all patients. We also scheduled the blood C-reactive protein levels determined with quantitative method (high-sensitive C-reactive protein [hs-CRP]), the white