# Etiopathogenesis of Transient Ischemic Attacks and Minor Ischemic Strokes
## A Community-Based Study in Segovia, Spain

Angel P. Sempere, MD; Jacinto Duarte, MD; Carmen Cabezas, MD; Luis Erik Clavería, MD

*Background and Purpose*—We sought to analyze the etiology and underlying vascular risk factors of transient ischemic attacks (TIAs) and minor ischemic strokes (MISs).

*Methods*—We prospectively studied the vascular risk factors and etiologic categories in 235 patients with TIAs and MISs from a community-based register in a rural area of Spain. Five etiologic categories were considered: (1) cardioembolism, (2) large-artery atherosclerosis, (3) small-artery disease, (4) other etiologies, and (5) undetermined etiology. Systematic investigations included neuroimaging (CT/MRI) and vascular studies (duplex scan/MR angiography and angiography in selected cases).

*Results*—The two most frequent etiologic categories were small-artery disease (31%) and cardioembolism (26%). Large-artery atherosclerosis was detected in 11% of the patients. Significant carotid stenosis ($\geq$50%) was present in 13% of patients with carotid territory events. No cause could be found or it was uncertain in almost one third of the patients. The distribution of etiologic categories was similar in TIAs and MISs. The most prevalent vascular risk factors were as follows: arterial hypertension (50%), smoking (26%), atrial fibrillation (20%), hypercholesterolemia (17%), diabetes (15%), ischemic heart disease (12%), and peripheral vascular disease (3%). Carotid bruits were detected in 3% of the patients.

*Conclusions*—An etiologic classification of TIAs and MISs is feasible. The two most frequent pathogenetic mechanisms in our study were small-artery disease and cardioembolism. The prevalence of large-artery atherosclerosis was low. (*Stroke.* 1998;29:40-45.)

**Key Words:** atherosclerosis ■ carotid arteries ■ cerebral ischemia, transient ■ etiology ■ risk factors

It is considered that anything that causes a TIA may cause an ischemic stroke. Based on this assumption, the causes of TIAs have been inferred from the causes of cerebral infarction.[1] Although several community-based studies have addressed the epidemiology[2–5] and prognosis[6] of TIAs, they have not analyzed the pathogenetic mechanisms involved in them. On the other hand, there is little reason to distinguish TIAs from MISs since both groups are very similar in terms of age,[7,8] sex,[7,8] and vascular risk factors.[7]

The aim of this study was to analyze the underlying vascular risk factors and causes of TIAs and MISs in a community-based study.

## Subjects and Methods

This study formed part of a larger community-based study of TIAs and MISs described elsewhere.[8] The study was performed in the province of Segovia, which is a rural area located in the center of Spain with a population of 146 716 (1991 census). General practitioners and hospital emergency departments were mainly responsible for referral of the patients. General practitioners were asked to notify the neurology unit as soon as possible of all patients with a suspected TIA or nondisabling stroke. A direct telephone line to the neurology clinic was available for all general practitioners at their health centers. Patients could also be referred immediately and directly to the neurology clinic without previous appointment. All patients with suspected cerebrovascular disease attending the emergency department of our hospital were referred directly to the neurology unit, admitted to the hospital, or evaluated in the emergency department by the neurologist on call.

TIA was defined as an acute loss of ocular or focal cerebral function lasting less than 24 hours that was presumed to be due to ischemic vascular disease. A stroke was considered minor if the score on the modified Rankin Scale was 1 at the first evaluation or if the score was 0 or 1 at the 1-month follow-up (ie, no symptoms or minor symptoms that did not interfere with normal lifestyle).

All patients underwent a thorough physical and neurological examination, including neck auscultation to search for carotid bruits. Systematic investigations included cranial CT scan, 12-lead ECG, chest radiography, routine blood tests that included complete blood count, fasting glucose and cholesterol concentrations, and luetic serology. MRI of the head, with the use of a 1-T system, was performed in all patients except the carriers of pacemakers or metallic devices, claustrophobic patients, and those who were not cooperative enough for MRI. MRI consisted of conventional sagittal and transverse T1- and T2-weighted images, with 5-mm-thick slices.

Criteria for the diagnosis of carotid distribution included any of the following features: transient monocular blindness, dysphasia, and unilateral weakness or sensory disturbance. Criteria for the diagnosis of vertebrobasilar distribution were weakness or numbness involving both sides of the body, loss of vision in one or both homonymous fields, loss of balance, vertigo, diplopia, dysarthria, and dysphagia. Vertigo, dysphagia, dysarthria, and diplopia were not considered if they occurred in isolation. Unilateral weakness and/or sensory distur-

### Selected Abbreviations and Acronyms

CI = confidence interval
GPL = IgG phospholipid
MIS = minor ischemic stroke
MRA = magnetic resonance angiography
TIA = transient ischemic attack
TOF = time of flight

bance was considered carotid unless CT/MRI showed an appropriate lesion in the vertebrobasilar territory. For instance, if clinical criteria were suggestive of carotid distribution (ie, pure left hemiparesis) but MRI showed a relevant pontine infarction, the vascular event was finally classified as vertebrobasilar.

Evaluation of the carotid artery was undertaken if the carotid territory was affected. Duplex ultrasound and MRA were used as screening tests for extracranial carotid artery stenosis of >50%. In our center, the negative predictive value of duplex and MRA for the presence of ≥50% stenosis is >95%. Stenosis of the internal carotid artery <50% was considered nonsignificant, and stenosis ≥50% was considered significant. The initial choice between the two techniques depended on the cooperation of the patient or the presence of contraindications to MRI. The ultrasound criteria for the diagnosis of ≥50% stenosis was a peak systolic velocity in the internal carotid artery >120 cm/s. MRA consisted of two-dimensional TOF examination of the carotid bifurcation and three-dimensional TOF sequences. The degree of stenosis was evaluated by a neuroradiologist who was blinded to clinical data, although the neuroradiologist knew that the patient suffered from cerebrovascular disease. If duplex ultrasound or MRA showed ≥50% stenosis of the ipsilateral internal carotid artery, digital subtraction angiography was performed if the patient was considered suitable for carotid surgery and accepted the possibility of surgical treatment.

The posterior circulation was evaluated in patients with vertebrobasilar events by three-dimensional TOF MRA. MRA images of the posterior circulation included the vertebral, basilar, and proximal posterior cerebral arteries. A diagnosis of significant stenosis was made when the lumen diameter was reduced by ≥50%. The carotid bifurcation was also examined by means of two-dimensional TOF sequences in patients with vertebrobasilar events.

Other diagnostic tests were performed on an individual basis to determine etiology. Anticardiolipin IgG antibodies were measured by enzyme-linked immunosorbent assay according to international standardized methods. The results were expressed in GPL units and considered positive if >20 U on at least on two occasions 3 months apart.

We used the following definitions for vascular risk factors. Arterial hypertension was defined in three ways: (1) if the patient was being treated with antihypertensive drugs or his/her medical record gave such a diagnosis, (2) two blood pressure recordings with both a systolic blood pressure ≥140 mm Hg and a diastolic blood pressure ≥90 mm Hg, and (3) two blood pressure recordings with a systolic blood pressure ≥160 mm Hg and a diastolic blood pressure <90 mm Hg (isolated systolic hypertension). A patient was defined as a smoker if he/she was a current smoker in the last 12 months. Peripheral vascular disease was defined in two ways: (1) intermittent claudication and (2) previous peripheral vascular surgery. Atrial fibrillation was present if confirmed by ECG at presentation. Ischemic heart disease was defined by a history of angina or myocardial infarction. Diabetes mellitus was defined in two ways: (1) by history if the patient had this diagnosis and (2) if there were at least two fasting glucose concentrations >7.8 mmol/L (140 mg/dL). Hypercholesterolemia was diagnosed if the patient had this diagnosis and was on treatment or if a fasting cholesterol level was >6.2 mmol/L (240 mg/dL).

Five etiologic categories were considered: (1) cardioembolism, (2) large-artery atherosclerosis, (3) small-artery disease, (4) other etiologies, and (5) undetermined etiology.

### Cardioembolism

This category included patients with TIA or MIS likely caused by an embolus arising in the heart. It was necessary to identify a potential source of cardiac embolism. Cardiac sources were classified as high risk or low risk. Large-artery disease had to be ruled out in patients with low-risk sources. The following sources of cardiac emboli were considered high-risk: atrial fibrillation, mitral stenosis, recent myocardial infarct, atrial myxoma, prosthetic valve, dilated cardiomyopathy, akinetic left ventricular segment, infective endocarditis, sick sinus syndrome, and left atrial thrombus. Mitral valve prolapse, patent foramen ovale, and atrial septal aneurysm were considered low-risk sources of cardiac emboli.

### Large-Artery Atherosclerosis

This category required evidence by duplex imaging, MRA, or angiography of a stenosis >50% in the appropriate extracranial or intracranial artery.

### Small-Artery Disease

The diagnosis of small-artery disease required all the following criteria: (1) lacunar symptoms defined as unilateral dysfunction of at least two of three body parts (face, arm, leg) in the absence of clinical evidence of cerebral cortical dysfunction (visual field defect, spatial neglect, disorder of language, writing, reading, memory, or orientation); (2) absence of cardiac sources of embolism; (3) absence of nonlacunar infarcts on CT/MRI; and (4) absence of large-artery atherosclerosis.

### Other Etiologies

This category included patients with nonatherosclerotic vasculopathies and hematologic disorders (including hypercoagulable states). We used the following definition for possible primary antiphospholipid syndrome: (1) anticardiolipin antibodies >20 GPL units on two occasions, determined at least 3 months apart, (2) negative antinuclear antibodies, and (3) absence of cardioembolism and large-artery atherosclerosis.

### Undetermined Etiology

This category included several possibilities: (1) no likely etiology after a thorough evaluation, (2) no likely etiology but evaluation was not complete, and (3) patients with two or more possible causes, eg, a patient with atrial fibrillation and ipsilateral significant carotid stenosis.

Continuous variables were compared with Student's unpaired $t$ test. Discrete variables were compared with Yates' corrected $\chi^2$ test and odds ratios with 95% CIs. Statistical significance was set at $P<.05$. All probabilities are two-tailed values.

## Results

During the study period, 235 incident cases were included: 103 TIAs and 132 MISs. The mean age of the whole group was 70.8 years; 92 were women and 143 were men. The mean age of patients with TIAs (71.8 years) and MISs (70.1 years) did not differ significantly ($P=.231$). The proportion of men in both groups also did not differ (61 of 103 with TIA [59%], 82 of 132 with MIS [62%]; $P=.65$). According to clinical features, approximately 78% of TIAs and MISs were in the carotid distribution, 19% were vertebrobasilar, and 3% were considered of uncertain vascular distribution. Neuroimaging studies changed this classification in 17 patients (7%). After CT/MRI, 170 (72.1%) of TIAs and MISs were classified as carotid, 62 (26.4%) were classified as vertebrobasilar, and 3 (1.5%) were considered of uncertain vascular distribution.

A cranial CT scan was obtained in all patients. Cranial MRI was performed in 162 patients (69%). Brain imaging (CT/MRI) showed no evidence of infarction in 70 patients (30%), and 9% of patients harbored cerebral infarcts that were considered irrelevant.

**TABLE 1.   Prevalence of Vascular Risk Factors in Patients With TIAs and MISs**

|  | All Patients | TIAs | MISs | Odds Ratio (95% CI) |
|---|---|---|---|---|
| No. patients | 235 | 103 | 132 | |
| Arterial hypertension | 118 (50%) | 45 (44%) | 73 (55%) | 0.63 (0.4-1.1) |
| Smoking | 60 (26%) | 21 (20%) | 39 (30%) | 0.61 (0.3-1.1) |
| Atrial fibrillation | 46 (20%) | 22 (21%) | 24 (18%) | 1.22 (0.6-2.3) |
| Hypercholesterolemia (>240 mg/dL) | 41 (17%) | 21 (20%) | 20 (15%) | 1.43 (0.7-2.8) |
| Diabetes mellitus | 36 (15%) | 10 (10%) | 26 (20%) | 0.44 (0.2-1) |
| Ischemic heart disease | 28 (12%) | 13 (13%) | 15 (11%) | 1.13 (0.5-2.5) |
| Peripheral vascular disease | 7 (3%) | 4 (4%) | 3 (2%) | 1.74 (0.4-7.9) |
| Carotid bruits | 7 (3%) | 5 (5%) | 2 (2%) | 3.3  (0.6-17.5) |

The prevalence of vascular risk factors is shown in Table 1. There were no significant differences between patients with TIAs and MISs. Mean fasting cholesterol concentration was 5.4 mmol/L (208 mg/dL) (95% CI, 5.25 to 5.51 mmol/L). Mean cholesterol levels were nonsignificantly higher in the TIA patients than in those with MIS (5.51 mmol/L and 5.28 mmol/L, respectively; $P>.10$). Women were older than men (73.3 and 69.3 years, respectively; 95% CI, 1.2 to 6.9 years) and had a higher prevalence of arterial hypertension and diabetes (Table 2). Men smoked more often and had a higher prevalence of ischemic heart disease.

Overall, vascular studies were obtained in 189 of the 235 patients (80%). Carotid duplex ultrasound was performed in 78 patients (33%) and MRA in 133 patients (57%); some patients underwent both procedures. Noninvasive vascular studies (duplex ultrasound, MRA, or both) were performed in 155 of 170 patients with carotid TIAs/MISs (91%). Significant carotid stenosis was suspected by noninvasive vascular studies in 25 patients (16%). Intra-arterial angiography was performed in 2 patients without previous noninvasive vascular studies. Of the 13 patients who had no vascular studies performed, 10 had a high-risk cardiac disorder. Intra-arterial angiography was performed in 15 of the 25 patients with suspected carotid stenosis, confirming the presence of significant carotid stenosis in 11 patients. MRA showed 50% to 69% stenosis of the ipsilateral internal carotid artery in 4 patients, but this finding was not confirmed by intra-arterial angiography (<50% stenosis). Intra-arterial angiography was not performed in the other 10 patients because of the following reasons: unsuitable for surgery (6 patients), refusal of the patient (3 patients), and allergy to iodine contrast (1 patient). One patient with bilateral internal carotid artery occlusion was diagnosed with pseudoxanthoma elasticum by skin biopsy. Symptomatic carotid stenosis was finally diagnosed in 20 of the 157 patients with carotid TIAs/MISs who had vascular studies performed (13%; 95% CI, 8% to 18%). Seven patients had occlusion of the ipsilateral internal carotid artery (5 diagnosed by MRA and confirmed by angiography and 2 diagnosed by duplex and MRA), 7 patients had 70% to 99% stenosis of the ipsilateral internal carotid artery (5 diagnosed by duplex and/or MRA and confirmed by angiography and 2 diagnosed by duplex and MRA), and 6 patients had 50% to 69% stenosis of the ipsilateral internal carotid artery (5 diagnosed by duplex and/or MRA and 1 diagnosed by MRA and angiography). MRA was performed in 32 of 62 patients with vertebrobasilar TIAs/MISs. No significant stenosis of the carotid or vertebrobasilar arteries was observed in 30 patients. MRA in the other 2 patients disclosed stenosis of the basilar artery and occlusion of a vertebral artery, respectively.

Transthoracic echocardiography was performed in 84 patients (36%). Only 2 patients had a potential cardiac source of emboli without any clinical evidence of cardiac disease: a 50-year-old man with a mitral valve prolapse and a 62-year-old woman with a left atrial thrombus. Transesophageal echocardiography was performed in 13 patients (6%), detecting two cases of severe aortic arch disease and one case of patent foramen ovale. None of these patients had clinical evidence of cardiac disease. Holter ECG was performed in 3 patients (1%) with negative results. Excluding patients with known heart disease (ie, atrial fibrillation, sick sinus syndrome, prosthetic cardiac valve), an echocardiogram was not obtained in 117 patients (50%), although none of them had any clinical evidence of heart disease.

The two most common etiologies were small-artery disease and cardioembolism (Table 3). Small-artery disease was the etiology responsible for TIAs and MISs in 41% of women and 24% of men, and cardioembolism was diagnosed in 27% of women and 25% of men. The distribution of etiologic categories was similar in TIAs and MISs. Large-artery atheroscle-

**TABLE 2.   Sex-Specific Prevalence of Vascular Risk Factors in Patients With TIAs and MISs**

|  | Women | Men | Odds Ratio (95% CI) |
|---|---|---|---|
| No. patients | 92 | 143 | |
| Arterial hypertension | 59 (64%) | 59 (41%) | 2.55 (1.5-4.4) |
| Smoking | 2 (2%) | 58 (41%) | 0.03 (0.0-0.1) |
| Atrial fibrillation | 20 (22%) | 26 (18%) | 1.25 (0.7-2.4) |
| Diabetes mellitus | 23 (25%) | 13 (9%) | 3.33 (1.6-6.9) |
| Hypercholesterolemia (>240 mg/dL) | 21 (23%) | 20 (14%) | 1.82 (0.9-3.6) |
| Ischemic heart disease | 3 (3%) | 25 (18%) | 0.16 (0.1-0.5) |
| Peripheral vascular disease | 2 (2%) | 5 (4%) | 0.61 (0.1-2.8) |
| Carotid bruits | 1 (1%) | 6 (4%) | 0.25 (0.0-1.6) |

**TABLE 3.  TIAs and MISs: Etiologic Categories**

|  | All Patients (n=235) | TIAs (n=103) | MISs (n=132) |
|---|---|---|---|
| Cardioembolism | 61 (26%) | 32 (31%) | 29 (22%) |
| Large-artery atherosclerosis | 25 (11%) | 8 (8%) | 17 (13%) |
| Small-artery disease | 72 (31%) | 30 (29%) | 42 (32%) |
| Others | 15 (6%) | 6 (6%) | 9 (7%) |
| Uncertain | 62 (26%) | 27 (26%) | 35 (27%) |

rosis was detected in 11% of the patients (12% of men and 9% of women). Within the cardioembolic category, the most common cardiac disorder was nonvalvular atrial fibrillation (67%) followed by mitral stenosis (8%), prosthetic cardiac valve (5%), cardiomyopathy (5%), sick sinus syndrome (5%), akinetic left ventricular segment (3%), left atrial thrombus (3%), patent foramen ovale (1.6%), and mitral valve prolapse (1.6%). Unusual etiologies were discovered in 7 patients, which represents 3% of the whole group: fibromuscular dysplasia (1), essential thrombocythemia (1), migraine (1), pseudoxanthoma elasticum (1), herpes zoster vasculitis (1), hereditary protein C deficiency (1), and disseminated intravascular coagulation (1). Eight patients were diagnosed of possible primary antiphospholipid syndrome.

In the group of undetermined etiology, vascular studies were not obtained in 17 patients and echocardiography was not performed in 35 patients, although none of them had any clinical evidence of heart disease. We did not find any patient with multiple causes.

## Discussion

Our study is the first community-based series that analyzes the etiology of TIAs and MISs. Community-based studies have more difficulty in obtaining diagnostic tests such as neuroimaging, vascular studies, and echocardiography than hospital-based studies. Many patients are not admitted to the hospital, and some of them, especially among the elderly, refuse to undergo further studies. We do not know how many patients with a TIA were seen by general practitioners and not referred to the neurology unit. To estimate the number of cases not ascertained, we assessed the possibility of a preceding TIA in all patients with a stroke who were admitted to the hospital. During the study period we found two patients who had not been referred to the neurology unit by their general practitioners and had later suffered a stroke. A more important problem is that many patients do not seek medical attention. We succeeded in obtaining a high rate of brain imaging and vascular tests, although vascular evaluation was not performed in half of the patients with vertebrobasilar events. Investigation of cardioembolic disorders was also limited; transthoracic and transesophageal echocardiography were performed in 36% and 6% of the patients, respectively.

We considered five etiologic categories: cardioembolism, large-artery atherosclerosis, small-artery disease, other etiologies, and undetermined etiology. Our etiologic classification is similar to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) subtype classification system of acute ischemic stroke, which includes five subtypes: large-artery atherosclerosis, cardioembolism, small-artery occlusion (lacune), stroke of other determined etiology, and stroke of undetermined etiology.[9] A more simple classification, based on clinical findings, was developed by the Oxfordshire Community Stroke Project[10] for cerebral infarctions, but it is not useful for TIAs and MISs. A clinical classification of TIAs with two subtypes (lacunar versus nonlacunar or cortical) has been proposed.[11–13] This classification of TIAs has pathogenetic and prognostic implications. Nonlacunar TIAs are associated with cardiac and arterial sources of thromboembolism and carry a better prognosis.[13] However, this classification of TIAs does not distinguish cardioembolism from large-artery atherosclerosis. A further problem is the different definitions of lacunar syndromes that have been used in those studies, although all of them required the absence of symptoms suggestive of cortical dysfunction for the diagnosis.

Diagnostic difficulties arise when the neurologist tries to classify TIAs as carotid or vertebrobasilar. The most common symptoms in patients with carotid TIAs are contralateral weakness and/or sensory disturbance. Although these "hemiphenomena" are usually regarded as carotid distribution, vascular territory may be either carotid or vertebrobasilar. In the absence of localizing symptoms such as dysphasia (carotid) or diplopia (vertebrobasilar), it is difficult to be sure of the site of the ischemia unless there is CT or MRI evidence of recent infarction. However, in many patients (30% in our series) there is no evidence of infarction, and when there is, it may be irrelevant to the presenting complaint.

The diagnosis of small-artery disease is particularly difficult in the setting of TIAs. The absence of clinical evidence of cortical dysfunction on history does not eliminate the possibility that this feature was present since it is seldom possible to examine the patient during the attack. The definition of the lacunar syndrome has not been the same in all studies. The study of Kapelle et al[12] required unilateral dysfunction of at least one of three body parts (face, arm, leg). Landi et al[13] required involvement of at least two of the three body parts, partially or completely. Hankey and Warlow[11] adopted stricter criteria since they required complete involvement of at least two of the three body parts. We used restrictive criteria for the diagnosis of small-artery disease since we required the presence of the lacunar syndrome, absence of a cardiac source of embolism and large-artery disease, and absence of a nonlacunar infarct on CT/MRI. Again, brain imaging is slightly helpful since no lesions are detected on CT/MRI in a substantial proportion of patients.

Our etiologic classification of TIAs and MISs seems feasible and has the advantage of being applicable to TIAs and ischemic strokes. It has the potential problem of requiring a rather large number of diagnostic studies. However, appropriate diagnostic evaluation is essential to identify specific pathogenetic subtypes of TIAs and MISs. Neuroimaging studies are useful to rule out nonischemic causes[14] and to assist clinicians in localizing the vascular territory involved.[15,16] Duplex scan and MRA provide noninvasive imaging of the extracranial and intracranial vasculature, which is essential to distinguish large-artery atherosclerosis from small-artery disease, although MRA tends to overestimate the degree of stenosis.[17] The yield of transthoracic echocardiography is low in patients without clinical, ECG, or

chest x-ray evidence of heart disease.[18] However, it is a noninvasive method that can change the management of some patients. Transthoracic echocardiography identified a potential source of embolism in two patients in our series who had no evidence of heart disease, resulting in change of therapy in one. Transesophageal echocardiography increases the detection of potential sources of embolism but has the disadvantage of its invasive nature.[19] Anticardiolipin antibodies have been reported to be an independent risk factor for ischemic stroke in a case-control study,[20] but it has been suggested that these antibodies may be a nonspecific accompaniment of vascular disease.[21] Furthermore, anticardiolipin antibodies are not associated with an increased risk of thrombo-occlusive events or death.[22] Routine testing for anticardiolipin antibodies does not seem justified.

The two most common etiologies of TIAs and MISs in our study were small-artery disease and cardioembolism, which accounted for over half of the patients. We found a low prevalence of large-artery atherosclerosis in Spanish patients with TIAs and MISs. Overall, large-artery atherosclerosis was diagnosed in 11% of the patients. Only 13% of the patients with carotid territory events had ≥50% stenosis of the symptomatic internal carotid artery. Previous Spanish hospital-based studies have also shown a similar low prevalence of carotid atheromatosis.[23–25] An Italian community-based study detected ≥50% stenosis of the carotid artery in 14% of the patients with a TIA in the carotid distribution who underwent duplex scanning of cervical vessels.[5] The prevalence of severe carotid atheromatosis seems to be higher in northern Europe and the United States than in Mediterranean countries like Spain and Italy. In a British hospital-based study, 39% of carotid TIAs had ≥50% stenosis of the symptomatic internal carotid artery.[26] In hospital series from the United States, severe extracranial carotid stenosis has been found in 40% to 60% of patients with carotid TIAs.[27,28] Vascular studies have not been routinely performed in community-based studies. However, we can use the prevalence of carotid bruits as a rough measure of the prevalence of carotid stenosis. In the TIA series from Oxfordshire, carotid bruits were detected in 21% of the patients,[7] compared with only 3% of patients with carotid bruits in our study. The prevalence of carotid bruits in hospital-based studies of TIAs and MISs in Spain ranged between 1% and 4%.[23–25] We also found a low prevalence (6%) of large-artery stenosis in vertebrobasilar events. We are unaware of any prospective series of MRA in vertebrobasilar TIAs. A prospective study of 70 patients from Switzerland with infarcts in the posterior circulation disclosed a high frequency of severe intracranial large-artery disease.[29]

If extracranial carotid atherosclerosis is less frequent in Mediterranean countries than in the United States and northern Europe, what are the reasons for that difference? The most significant risk factors for extracranial carotid atherosclerosis in the Framingham Study were age, cigarette smoking, systolic blood pressure, and cholesterol.[30] It is difficult to compare the prevalence of vascular risk factors among studies because of the different definitions that have been used. The prevalence values of arterial hypertension and current smokers in Oxfordshire and in our study were similar (49% versus 50% and 27% versus 26%, respectively). However, we found a striking difference in cholesterol levels between both studies. Mean cholesterol levels were 5.4 mmol/L (208 mg/dL) in our study compared with 6.9 mmol/L in Oxfordshire.[7] Hypercholesterolemia (fasting plasma cholesterol ≥7 mmol/L or treated hypercholesterolemia) was diagnosed in 52% of TIA patients in Oxfordshire,[31] while only 17% of the patients were diagnosed with hypercholesterolemia in our study (fasting plasma cholesterol ≥6.2 mmol/L or treated hypercholesterolemia). Mediterranean diet has been related to lower total cholesterol values.[32] Hispanic Americans have lower levels of serum cholesterol than non-Hispanic whites.[33] Higher HDL-cholesterol and lower triglyceride serum levels, as well as dietary factors, may also play an important role in the protection against severe extracranial carotid atheromatosis.[25]

The prevalence of vascular risk factors and the distribution of etiologic categories were similar in TIAs and MISs. Another community-based study found no significant differences between both groups in the prevalence of vascular risk factors except for cholesterol levels that were higher in the TIA group.[7] Mean cholesterol levels were also higher in the TIA patients in our study, although the difference was not statistically significant. This difference may be explained by the transient fall in cholesterol levels observed after a stroke.[34] We found a higher prevalence of arterial hypertension and diabetes in women. Women also suffered from arterial hypertension more frequently than men in one Italian study[4]; this could be explained by the older age of women in both studies. The lower prevalence of ischemic heart disease in women could be explained, at least in part, by the different smoking habits.

Treatment of patients with TIA must be tailored to the underlying stroke mechanism.[35] As Caplan said, we need to know what is wrong with Mr Jones before we begin to think about treatment.[36] Clinical research on TIAs should focus on the role of etiologic categories in their prognosis and treatment.

## Acknowledgments

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