CME

Clinical outcome in 287 consecutive young adults (15 to 45 years) with ischemic stroke

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Abstract—*Objective:* To determine the 3-year outcome in 287 young adults (15 to 45 years old) consecutively admitted between 1992 and 1996 for an ischemic stroke. *Methods:* Follow-up was obtained with clinical examinations or telephone interviews, and data were recorded about risk factors, associated disorders, causes of stroke, and current treatments. Functional outcomes were classified with the modified Rankin Scale (mRS). Endpoints were stroke recurrence, myocardial infarction, epileptic seizures, and death. *Results:* After a mean follow-up of 3 years, no patient was lost to follow-up; 25.4% of the follow-up visits were performed by telephone interview. The authors found 1) an annual mortality rate of 4.5% during the first year and then of 1.6%; 2) an annual stroke recurrence rate of 1.4% during the first year and then of 1.0%; 3) a 0.2% annual rate of myocardial infarct; 4) epileptic seizures occurring in 6.6% of patients, during the first year in most patients; 5) independence (mRS = 0 to 2) in 94.0% of patients; 6) 4.2% of patients lost their job after stroke despite an mRS score of ≤1; 7) 7.0% of patients reported divorce; and 8) only 22.2% of smokers gave up smoking. *Conclusion:* Although young patients who experience ischemic strokes have a low risk of stroke recurrence and myocardial infarction, some patients do not regain independence.

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In Western countries, the mean age of acute stroke patients is approximately 75 years.[1-3] However, stroke can also occur in young adults, with annual incidence rates ranging from 6 to 20/100,000 inhabitants.[1-4] Most strokes occurring in this age category are ischemic in origin.[5-8] Ischemic strokes occurring between 15 and 45 years of age account for approximately 1% of all strokes in the community[9] and for 4[10] to 12%[11] in specialized tertiary centers. Most studies showed a broad range of causes, with large variations between countries and centers.[4,6,7,9,11-23] Despite an extensive diagnostic workup, the cause remains unclear in 15 to 40% of patients.[4,6,7,9,11-15,19,23] Moreover, ischemic strokes occurring in young patients may reduce life expectancy and quality of life in survivors; they may also lead to divorce or loss of job and have socioeconomic consequences.[2,20]

The short-term outcome of ischemic strokes in young adults is usually considered as favorable in terms of survival.[4,6,7,9,11-24] However, prospective studies evaluating the long-term outcome are heterogeneous: Many of them included ischemic and hemorrhagic strokes,[6-8,25] subarachnoid hemorrhages,[6-8,25] and TIA, used different age limits to define young patients, and were influenced by referral practices.[4,9,14,18,19] Moreover, many studies were conducted in small cohorts with an incomplete follow-up,[6,7,18,21,23-27] included only first-ever strokes,[9,10,25] or included only acute-stage survivors,[24] skewing the study population toward those patients who are the most likely to have a good outcome. Finally, only a few studies[9,20,21] evaluated the functional outcome in survivors.

We evaluated the 3-year mortality rate and functional outcome in 287 patients between 15 and 45 years of age consecutively admitted for an acute ischemic stroke.

Subjects and methods. *Setting.* This study was conducted over a 5-year period (January 1, 1992, to December 31, 1996) in all patients aged 15 to 45 years, admitted within 7 days of onset of an acute ischemic stroke in the Stroke Unit of the Lille University Hospital. This department usually admits two types of stroke patients: those living in Lille-Metropole (1,177,396 inhabitants) and ad-

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mitted directly as emergency patients and those referred from other hospitals of the region (3,982,988 inhabitants) after a short stay in a neurologic, medicine, or emergency department. Patients of both types were included in the study, provided they were hospitalized. The way in which the Lille University Hospital Stroke Department is currently run was detailed elsewhere.[28,29] Before March 1995, a neurologist in training at admission initially examined patients. After March 1995, a board-certified senior in-house neurologist examined them.

Inclusion and exclusion criteria. We did not include patients with TIA, primary cerebral hemorrhage, subarachnoid hemorrhage (even in case of secondary ischemia due to a spasm), spinal stroke, cerebrovascular disorders without stroke (e.g., cerebral venous thrombosis, cervical artery dissections, and cerebral vascular malformations without stroke), cerebral venous thrombosis with presumed cerebral ischemia, and patients seen only as outpatients. We defined ischemic stroke as clinical signs of focal disturbance of cerebral function lasting >24 hours with no other cause than vascular, after exclusion of primary intracerebral hemorrhage on CT or MR scan. TIA was defined as an episode of focal cerebral dysfunction lasting <24 hours and followed by return to normality with no other potential cause than vascular.

Initial diagnostic workup. The diagnostic workup consisted of the following: 1) at admission in all patients: clinical examination including a neurologic examination, a search for previous stroke or TIA, cervical pain, headache, spontaneous abortion, livedo reticularis, palpitations, Valsalva maneuver, and factors predisposing to deep venous thrombosis, noncontrast CT scan performed by a board-certified neuroradiologist, chest radiography, 12-lead EKG, and routine standard blood tests (hemoglobin, hematocrit, platelets, leukocytes, erythrocyte sedimentation rate, blood glucose, electrolytes, triglycerides, total and high-density lipoprotein cholesterol, prothrombin time, activated partial thromboplastin time, fibrinogen); 2) within 24 hours after admission in all patients: urine tests, Doppler ultrasonography, and B-mode echotomography of the cervical arteries, transthoracic echocardiography (TTE); 3) in all patients: a delayed brain imaging procedure, either MRI or CT; and 4) on an optional basis, in selected patients: 24-hour EKG recording, TEE, MR scan, MR angiography (MRA) or conventional angiography, blood tests for coagulation factors (proteins C and S, factor Leiden, and antithrombin III activities), lupus anticoagulant, anti-phospholipid and anti-cardiolipin antibodies (IgM and IgG), cryoglobulinemia, antinuclear antibodies, other autoantibodies (anti-SSA, anti-SSb, anti-SM, anti-ds-DNA, anti-RNP, anti-nuclear cytoplasmic antibody), rheumatoid factor, dosage of immunoglobulins, CH50, C3, and C4, syphilis, hepatitis B and C, and HIV serologies. During the study period, the diagnostic workup has progressively changed toward less conventional angiographies, more MRA and more MRI, as the equipment has been upgraded or replaced and new techniques have become available and validated.

Risk factors and causes. In all patients, we prospectively collected the following data: age, sex, presence of arterial hypertension and diabetes mellitus according to previously reported rules,[30] dyslipidemia defined as fasting serum level of triglycerides of >1.5 g/L or fasting cholesterol serum level of >2.5 g/L or current treatment with hypolipidemic agents, previous TIA or stroke as defined above, current atrial fibrillation, and cervical artery stenosis of >50% on angiography or MRA. Patients were considered as smokers when they currently smoked every day or when they had stopped <1 year before stroke; they were considered as being under oral contraceptive therapy if they currently received oral contraceptive therapy or if they were receiving oral contraceptive therapy for at least 30 consecutive days during the last 3 months. Migraine was defined according to the International Headache Society criteria.[31] Alcoholism was defined as a usual consumption of more than three glasses of wine or an equivalent amount of alcohol every day, as reported by the patient or a relative. Use of illicit drugs was recorded only when recognized by the patient or proven by a biologic test. A toxicology screen was not performed in all patients, but only when no obvious cause was found with the very first examinations, provided the patients gave consent for this search. We did not routinely perform pregnancy tests in women, except when conventional angiography was planned or when there was clinical evidence for pregnancy.

Peripheral artery disease was defined according to the Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events Study (CAPRIE) criteria.[32] We defined the presumed cause of ischemic stroke according to the TOAST criteria[33] for large-vessel atherosclerosis, high-risk cardiopathies, small-vessel occlusion, other definite causes, and "undetermined causes," defined as the association of two potential causes or more or a complete and negative diagnostic workup or an incomplete workup. Patients with isolated low-risk cardiopathies were classified in the "undetermined" group. Patent foramen ovale and interatrioseptal aneurysms, defined according to criteria previously used in our center,[34] were not regarded as causes of stroke but as coincidental findings, unless an intracardiac thrombus or a paradoxical embolism was proven. We defined cervical artery dissections according to the criteria used in the DONALD study.[35] Patients with CADASIL were classified in the group of "other definite causes," not in that of small-vessel occlusion.

Study population. During the study period, of 6,021 patients admitted for a presumed acute cerebrovascular event, 287 (4.8%) met inclusion criteria. Therefore, the study population consisted of 159 men (55.4%) and 128 women (44.6%), with a mean age of 36.0 years (range 15 to 45 years). The annual number of patients admitted was 36 (12.5%) in 1992, 47 (16.4%) in 1993, 38 (13.2%) in 1994, 75 (26.1%) in 1995, and 91 (31.7%) in 1996. The delay between stroke onset and admission was lower than 24 hours in 237 patients (82.6%) and lower than 3 days in 273 patients (95.1%). Of 287 patients, 282 (98.3%) had an ischemic stroke and 5 (1.7%) had hemorrhagic changes within the infarct on the CT scan performed at admission. All investigations described as systematic above were performed in all patients (except a chest radiography in one). Investigations described as optional above were performed as follows: conventional angiography in 189 (65.9%), MRA in 91 (31.7%), TEE in 108 (37.6%), 24-hour EKG recording in 71 (24.7%), and specialized biologic tests in 203 (70.7%). The breakdown of causes is reported in table 1. The breakdown of risk factors for stroke in each etiologic category is reported in table 2. Of 124 patients who had no cause of

Table 1 *Causes of ischemic strokes*

Cause	No. of patients (%)
Cervical artery atheroma	24 (8.4)
High-risk cardiopathies*	15 (5.2)
Atrial fibrillation	13 (4.5)
Bacterial endocarditis	3 (1.0)
Mechanical prosthetic valve	2 (0.7)
Mitral stenosis	2 (0.7)
Thrombus in left atrium	2 (0.7)
Small-vessel occlusion	5 (1.7)
Other definite causes	64 (22.3)
Cervical artery dissections†	54 (18.8)
Angiitis and acute angiopathies‡	5 (1.7)
CADASIL	3 (1.0)
Pseudovalvular fold in ICA artery	1 (0.3)
Intracranial ICA dissection	1 (0.3)
Undetermined	179 (62.4)
No cause despite complete diagnostic workup	124 (43.2)
>1 potential cause	31 (10.8)
Incomplete diagnostic workup	24 (8.4)

* Several causes are associated in several patients.
† Fifty-six dissections in 54 patients: 24 carotid, 32 vertebral.
‡ Heroin (one), vasoconstrictor (one), anorexigen (one), lupus plus antiphospholipid antibodies (one), postpartum (one).

CADASIL = cerebral autosomal dominat arteriopathy with subcortical infarcts and leukoencephalopathy; ICA = internal carotid artery.

stroke despite an extensive diagnostic workup, 110 (88.7%) had at least one risk factor for stroke.

Treatments. At admission, 141 (49.1%) patients received unfractionated heparin, 143 (49.8%) patients received oral aspirin (300 mg daily), and 3 (1.0%) did not receive any antithrombotic treatment (1 because of intracranial dissection and 2 because of severe hemorrhagic changes within the infarct). The decision to prescribe either heparin or antiplatelet drugs was based on the decision of the neurologist in charge of the patient. At discharge, antiplatelet drugs were given in 201 of the 277 survivors (72.6%) and oral anticoagulant in 73 (26.4%), and 3 patients (1.1%) did not receive antithrombotic treatment (hemorrhagic infarcts in 2 and intracranial dissection in 1). During the study period, the therapeutic approach toward treating ischemic strokes changed toward less heparin and more aspirin at the acute stage, although scientific evidence for the lack of efficacy of heparin and a small effect of aspirin was published after the end of the inclusion period.[36,37] Patients with arterial dissections received heparin and then a 3- to 6-month course of oral anticoagulation. Strict medical control and optimal treatment of vascular risk factors were encouraged at discharge and at follow-up visits in all patients.

Follow-up. We suggested all survivors be clinically followed up annually over a 3-year period, as we usually do in this age category, by a staff member of our department any time it was possible or in a few patients by another neurologist. In all visits, we recorded the three following categories of information: 1) occurrence of a new acute event such as stroke, epileptic seizure, and myocardial infarction; 2) current drug therapies and management of risk factors for stroke; and 3) modified Rankin Scale (mRS) score.[38] All follow-up information was documented by patient and family interviews, clinical examination of the patient, and any report from the general practitioner or a specialist. No specific investigation was performed after the clinical follow-up visit, except when it was required by the cause of ischemia (e.g., follow-up of cervical artery dissections by ultrasonography and MRA) or when an endpoint as defined below was suspected. In 1999, we contacted by letter all survivors who had not been examined by a neurologist at least 2 years after stroke onset and their general practitioners. Then, one of us contacted them by telephone 3 weeks later. When patients were not able to answer our questions, we contacted the general practitioner, a close relative, or both. When the last contact was a telephone interview, the mRS was recorded by telephone. The Oxford Handicap Scale is relevant,[39] is simple enough to be used reliably over the telephone, and is therefore useful in large studies, without any clear difference between self- or caregiver-completed questionnaires.[40] Actually, the modified version of the Rankin scale we used is similar to the Oxford Handicap Scale, with the addition of a score of 6 (meaning death). When no new clinical event had occurred

Table 2 *Risk factors for stroke*

Risk factor	Atheroma, n = 24	Cardioembolism, n = 15	Lacune, n = 5	Other, n = 64	Undetermined, n = 179	*p*
Smoking	16	6	2	15	69	0.27
Arterial hypertension	7	4	2	10	53	0.14
Hypercholesterolemia	14	3	1	10	40	0.49
Hypertriglyceridemia	10	1	1	7	34	0.65
Oral contraceptive therapy	8	0	0	7	30	0.51
Migraine*	3	3	0	14	19	0.28
Diabetes mellitus	1	1	1	2	18	0.04
Age, y	39.9	38.7	36.4	34.4	35.8	0.33

Numbers of patients are given for each risk factor in each diagnostic category. For oral contraceptive therapy, the percentage was calculated in women only. The *p* value was determined by χ^2 test for all factors except age (Mann–Whitney *U* test comparing patients with an undetermined cause and those with a known cause considered in a single group).

* Calculated in 284 patients (after exclusion of 3 patients in whom the diagnosis was not possible because of early death).

Table 3 *Follow-up*

Outcome	Atheroma, n = 24	Cardioembolism, n = 15	Lacune, n = 5	Other, n = 64	Undetermined, n = 179	p*
Recurrent stroke	1	2	0	0	7	0.61
Myocardial infarction	1	1	0	0	0	NA
Epileptic seizure	2	2	1	4	11	0.49
Death	2	2	0	3	15	0.56

Breakdown of the outcome events in stroke subtypes at the end of the follow-up period. Numbers of patients with the risk factor are given.

* χ^2 test between patients with an undetermined cause and patients with a known cause considered in a single group.

since the last visit, follow-up data were gathered from the last clinical and radiologic examination available.

Endpoints. End points were 1) recurrent stroke (ischemic or hemorrhagic) as defined above; 2) epileptic seizures occurring after discharge; 3) myocardial infarction diagnosed by the presence of at least two of the following: typical ischemic chest pain lasting for >30 minutes, specific serum enzyme elevations, and new pathologic Q waves on EKG; and 4) death. TIA were not considered as endpoints, and epileptic seizures occurring at the acute stage, that is, before discharge, were not taken into account. The functional outcome was assessed by the mRS.[38] Patients with an mRS score from 0 to 2 were classified as independent, and patients with mRS scores from 3 to 6 to were considered as dependent (mRS = 3 to 5) or dead (mRS = 6). All events were documented by hospital records, specialist or general practitioner reports, and patients or family information.

Ethics. This study was observational, and all patients were investigated and treated according to the rules currently applied in our institution. Data used for the study were only data usually recorded in the medical file of patients.

Statistics. We performed statistics with SPSS 9.0 for Windows (Chicago, IL). We used the χ^2 test with Yates correction or Fisher's exact test when appropriate, along with Mann–Whitney U tests.

Results. Of 287 patients, 247 (86.1%) attended at least one neurologic visit, 179 (62.4%) attended two visits, 156 (54.4%) attended three visits, and 142 (49.5%) attended four visits or more. The final contact with the patients was a neurologic visit in 214 (74.6%) patients and a telephone call with the patient, a relative, or the general practitioner in the 73 (25.4%) remaining. Of 214 patients whose last contact was a neurologic visit, 139 (48.4% of the whole group) were seen >3 years after onset. The final neurologic visit was made by a neurologist from the Stroke Department in 201 patients (70.0% of the whole group), from another hospital in 11 patients (3.8%), and by a private neurologist in 2 patients (0.7%). The median duration of follow-up was 3 years. No patient was lost to follow-up. At the end of the follow-up period, 204 patients (71.1%) were treated with antiplatelet therapy (aspirin in 157, clopidogrel in 21, aspirin dipyridamole in 15, ticlopidine in 11) and 37 were treated with oral anticoagulant therapy (12.9%). Of the 46 remaining, 21 did not receive any antithrombotic drug anymore (7 dissections, 3 patients because of intolerance, 4 patients who decided to stop, and for an unknown reason in 7), the current therapy remained unknown in 3, and 22 patients were dead. An antihypertensive treatment was prescribed in 54 (91.5%) of the 59 survivors with arterial hypertension. Oral contraceptives were discontinued by 44 of the 45 survivors who were current users. Only 22 of 99 current smokers who survived stopped smoking.

Over a 3-year period of follow-up, 22 (7.7%) patients died: 13 during the first year (all from cerebral lesions) and 9 after the first year after stroke (cardiac in 4, cancer in 2, trauma in 1, and unknown in 2). The median delay between stroke and death was 1 year, ranging from 0 (death at the acute stage) to 3 years. The average annual mortality rate of the cohort was 4.5% (95% CI 2.1 to 6.9%) during the first year and 1.6% (95% CI 0.6 to 2.6%) during the subsequent 2 years. Ten patients (3.5%) had recurrent cerebral ischemia (one atheroma, one cardioembolism, two other definite, and six undetermined), none of them leading to death. Of 10 recurrent strokes, 4 (1.4%) occurred during the first year and 3 (1.0%) during each of the following 2 years. Two patients had a myocardial infarction (one atheroma, one cardioembolism) after 2 and 3 years. Nineteen patients developed epileptic seizures, which occurred in 15 during the first year and in 4 >1 year after onset.

The breakdown of recurrent stroke, myocardial infarction, epileptic seizures, and deaths in stroke subtypes at the end of the follow-up period is presented in table 3.We found no significant differences in mortality, recurrence rate, dependency, and epilepsy 1) between patients examined at a neurologic visit and those followed by telephone interview, 2) between patients directly admitted in the stroke unit and those referred from another hospital, or 3) according to the antithrombotic regimen at discharge and at the last visit or contact. The influence of those factors on the rate of myocardial infarction was not evaluated because only a few patients developed myocardial infarction. At the end of the follow-up period, 151 patients had an mRS score of 0, 72 a score of 1, 26 a score of 2, 10 a score of 3, 2 a score of 4, 4 a score of 5, and 22 a score of 6. Of 265 survivors, 249 (94.0% of survivors, 86.8% of all patients) were independent (mRS = 0 to 2). In two patients with an mRS score of 1 and in three with a mean mRS of 2, the disability was due to focal upper limb dystonia.

A bivariate comparison of demographic factors, risk factors for stroke, causes of stroke, stroke characteristics, and outcome events between patients with bad (mRS = 3 to 6) and good (mRS = 0 to 6) outcomes is reported in table 4.

At the end of the follow-up period, of 265 survivors, 8 (3.0%) did not want to work for personal reasons, 142

Table 4 *Bivariate comparison of demographic factors, risk factors for stroke, causes of stroke, stroke characteristics, and outcome events between patients with bad (mRS-3–6) and good (mRS-0–6) outcomes*

Factors	Independent, mRS = 0–2; n = 249	Dependent or dead, mRS = 3–6, n = 38	*p*
Demographic factors			
Age	35.4	40.3	0.0001†
Women	116 (46.6)	12 (31.6)	0.08‡
Risk factors for stroke			
Previous emboli*	13 (5.2)	4 (10.5)	0.26‡
CHD	2 (0.8)	1 (2.6)	0.35‡
Cardiac failure	6 (2.4)	0 (0.0)	0.99‡
PAD	2 (0.8)	1 (2.6)	0.35‡
Pregnancy	3 (1.2)	0 (0.0)	0.99‡
Hypertension	61 (24.5)	14 (36.9)	0.11‡
Patent foramen ovale	42 (16.9)	3 (7.9)	0.33‡
Atrioseptal aneurysm	40 (16.1)	1 (2.6)	0.08‡
Cigarette smoking	94 (37.8)	14 (36.8)	0.91‡
Alcoholism	41 (16.5)	16 (42.1)	0.0002‡
Diabetes mellitus	15 (6.0)	7 (18.4)	0.02‡
Hypercholesterolemia	64 (25.7)	4 (10.5)	0.04‡
Hypertriglyceridemia	49 (19.7)	3 (7.9)	0.08‡
Statin or fibrate use	31 (12.5)	1 (2.6)	0.04‡
Birth control pills§	45 (38.8)	0 (0.0)	0.018‡
Stroke characteristics			
Hemorrhagic changes	2 (0.8)	2 (5.3)	0.09‡
Cause of stroke			
Cervical atheroma	19 (7.6)	5 (13.2)	0.69‡
High-risk cardiopathy	14 (4.4)	5 (10.5)	0.16‡
Cervical artery dissection	49 (19.7)	5 (13.1)	0.34‡
Lacunes	4 (1.6)	1 (2.6)	0.51‡
Unknown	157 (63.1)	22 (57.9)	0.54‡
Outcome events			
Stroke recurrence	8 (33.2)	2 (5.3)	0.63‡
Myocardial infarction	1 (0.4)	1 (2.6)	0.25‡
Epileptic seizures	15 (6.0)	5 (13.2)	0.14‡

All values are numbers (percentage) of patients, except for age, which are mean values.

* Includes previous stroke, TIA, or systemic emboli.
† Mann–Whitney *U* test.
‡ χ^2 test with Yates correction or Fisher's exact test when appropriate.
§ In women only.

mRS = modified Rankin Scale; CHD = coronary heart disease (includes myocardial infarction and angina pectoris); PAD = peripheral artery disease.

(49.5%) returned to the same work (10 with adjustment in their occupation), 30 (10.5%) found a new job, and 43 (15.0%) were considered by the social insurance as unable to work for medical reasons: The mRS scores were 3 to 5 in 15 patients, 2 in 15 patients, 1 in 12 patients, and 0 in 1 patient with depression. Of the 42 remaining who wanted to work but were unemployed, 30 were already unemployed before stroke and 12 lost their work after stroke despite an apparently good recovery (mRS = 0 in eight patients and 1 in four); these 12 patients had attended school for 8 to 11 years. Twenty patients (7.0%), including 14 men and 6 women, spontaneously reported changes in their family structure with divorce.

Discussion. Our study showed that 3 years after an acute ischemic stroke occurring between 15 and 45 years of age, 1) the annual mortality rate was 4.5% during the first year and then 1.6%; 2) the annual rate of stroke recurrence was 1.4% during the first year and then 1.0%; 3) there was a 0.2% annual rate of myocardial infarct; 4) 87.5% of patients were independent (Rankin score = 0 to 2); 5) factors associated with a good outcome (mRS = 0 to 2) at the bivariate analysis were decreasing age, absence of alcoholism or diabetes mellitus, and presence of hypercholesterolemia, or treatment with statin or fibrate, or oral contraceptive therapy; 6) the cause of stroke, stroke recurrence, and occurrence of myocardial infarction or epileptic seizure did not influence the outcome; 7) 4.2% of patients lost their work after stroke despite an apparently good recovery; 8) 7.0% of patients reported divorce; and 9) if most patients were still treated according to guidelines in most domains, only 22% of smokers gave up cigarette smoking.

Our study included one of the largest cohort of young adults with ischemic stroke followed up in a single center. No patient was lost to follow-up, suggesting that our results are valid in terms of case fatality. The 74.6% rate of neurologic visits at the end of the follow-up, with telephone contacts in the remainders, is close to the rates seen in other studies.[9] This study was observational, meaning that no test was done specifically without being part of the current practice in our center, except in patients included in another study. The major advantage of such an observational study is to evaluate patients in conditions as close as possible to true life and to include all consecutive patients admitted during the study period. However, with patients having had a diagnostic test only when this test was thought to be useful, a small degree of heterogeneity in the diagnostic workup is possible. Therefore, the frequency of factors that can be identified only with optional procedures, such as interatrioseptal abnormalities in TEE, may be underestimated. Accordingly, because no reference to ethnicity is allowed in patients' files according to the French law, this variable cannot be taken into account in any observational study. However, this is not a major issue, because the proportion of non-Caucasian patients in our area is very low, and we can consider that almost all (and maybe all) patients were Caucasian. We also cannot exclude an underestimation of toxic angiopathies in our study population because a toxicology screen was not performed in all patients, but only when no obvious

cause was found with the very first examinations, provided the patient gave consent, as required by the French law.

Studies conducted in university hospitals may suffer recruitment bias[9]: Tertiary-level hospitals may enroll more complicated cases,[20] but they may also recruit patients with etiologies requiring specific investigations that are not available in other centers. Our center is the only one providing the expertise of a senior in-house neurologist and neuroradiologist, with neuroimaging facilities 24 h/day, for a population of almost 4 million inhabitants. Therefore, a recruitment bias probably explains the high rate of cervical artery dissections. Changes in the number of patients recruited in 1995 and after are probably the consequence of the presence 24 h/day of a senior neurologist and the availability of neuroimaging facilities after this date. This organization might have led to admission of patients who would probably have been admitted in other hospitals before 1995 and probably skewed the recruitment toward younger patients and causes requiring specialized neurologic and neuroradiologic expertise, such as dissections.

We included only patients with arterial ischemic strokes. Many other studies also included patients with hemorrhagic strokes,[6-8,25] subarachnoid hemorrhages,[6-8,25] and TIA,[4,9,14,18,19] who have different mortality and recurrence rates. Accordingly, young ischemic stroke patients accounted for only 4.8% of patients admitted in our Stroke Department during the study period. This proportion is in the lower range of the proportion of young patients in most stroke units, ranging from 4 to 12%,[11] and is lower than the percentage of young patients admitted in our Stroke Department.[29] The most likely explanation is that we excluded patients with TIA, venous strokes, or cerebrovascular disorders without stroke (e.g., dissections and cerebral venous thrombosis without stroke). Moreover, our Stroke Department admits 15% of patients whose final diagnosis is not a cerebrovascular disorder,[28,29] and many of these patients are young. Causes of ischemic stroke encountered in our study are similar to those of young ischemic stroke patients reported in other Western studies,[4,7-9,14,18-20] with a slightly higher proportion of dissections. Conversely, several classic causes of ischemic strokes in the young, such as Sneddon syndrome, cardiac fibroelastoma, and cardiac myxoma, were not found in our patients.

Risk factors for stroke were frequent in our patients, especially in those who had no clear causes for ischemic stroke: Of 124 patients with no clear cause of stroke, only 14 were free of any risk factor. Risk factors did not differ from those encountered in similar studies in Western populations.[4,8,9,20] Because of the young age of the patients, the rates of associated coronary disease, peripheral artery disease, cardiac failure, and previous stroke or TIA were low.

Because of the low rate of new events in this age category, our study, like all other studies, was underpowered, as confirmed by the wide CI. Moreover, although 82.6% of patients were admitted during the first 24 hours and 95.1% within 3 days of stroke onset, we cannot exclude a small under-representation of patients with very early death. Antithrombotic treatments at the end of the follow-up period were not optimal in 14 patients. However, we did not interview general practitioners on this question, and for those who were not seen at a neurologic visit but only had a telephone call, it is possible that the reason to stop antithrombotic treatments was appropriate. However, 8.5% of hypertensive patients were not under antihypertensive therapy, and we did not explore, in those who were treated, whether the treatment actually lowered blood pressure toward proper levels. If advice to stop oral contraceptive therapy was followed in 44 of 45 patients, only 22 of 99 smokers gave up smoking. This is a major problem in terms of prevention, because the effectiveness of cigarette withdrawal reduces the risk of new vascular event in stroke patients.[41]

We found annual mortality rates of 4.5% (95% CI 2.1 to 6.9%) after the first year and 1.6% (95% CI 0.6 to 2.6%) during the subsequent 2 years, which are close to the 6.3 and 2.8% found during the same periods in the L'Aquila cohort.[9] Other studies found lower[18,19] or higher[6-8] mortality rates because they did not evaluate separately ischemic stroke, TIA, and intracerebral hemorrhages. Moreover, because of different inclusion criteria, possible recruitment bias, small number of events, and width of the CI, comparisons between studies remain difficult. Although the absolute survival rate of our cohort was high, the occurrence of an ischemic stroke in young adults cannot be regarded as a benign event, when a 8.7% mortality rate is found after a mean follow-up of 3 years. Ischemic stroke in young adults is serious event, associated with an increased risk of death in the subsequent few years.[9] The mortality rate was higher during the first year than during the following 2 years, but the follow-up was too short in our study to determine whether, as described in the L'Aquila cohort,[9] the average annual mortality rate remains stable over time after the first year.

The annual risk of stroke recurrence was 1.4% during the first year and then 1.05% during the following 2 years, which is similar to that found in most studies.[4,9,10,14,18-20,22,24,25] Only two cases of myocardial infarction occurred, and both were delayed after the first year: This low rate is similar to that found in other series.[6,9,14,20] Epileptic seizures occurred in 6.6% of patients, that is, more frequently than stroke recurrence. This risk was not clearly evaluated in other series.

Stroke subtypes probably influence the occurrence of outcome events, but our study, like previous ones, was not powered to evaluate outcome events separately in each category. Patients with stroke of atherothrombotic and cardioembolic origins were at higher vascular risk, as shown by a tendency toward higher rates of recurrent strokes, myocardial infarc-

tion, and death. Conversely, patients with cerebral ischemia included in the "other definite causes" diagnostic group were at low risk of recurrence, myocardial infarction, and death. This finding may be the consequence of the important weight in this group of patients with cervical artery dissections, who have low risks of death and stroke recurrence after the acute stage.[36,42]

The functional outcome was reported as favorable in most studies conducted in young patients who survived an ischemic stroke.[4,6,9,11,14-19,21-24] Of 265 survivors, 249 (94.0% of survivors) were independent (mRS = 0 to 2), including 151 patients (57.0% of survivors) free of any residual symptom or sign. Other studies found less favorable functional outcomes.[9,20] Possible explanations for such discrepancies may be that in our study, 1) the follow-up was shorter; 2) patients were recruited years after those studies with less favorable functional outcomes, when imaging techniques were able to diagnose minor strokes and prevention made substantial improvements; and 3) the breakdown of causes was slightly different. The low rate of dependency in this age category leads to the opinion that invasive and potentially dangerous acute stroke therapies should be used only in the small group of patients who are unlikely to survive without dependency. Although the risk of cerebral bleeding increases with age and thrombolysis is useful in selected patients, patients who are the most likely to benefit from thrombolysis are probably not in this age category.

We found no significant differences in mortality, recurrence rate, dependency, and epilepsy 1) between patients examined at a neurologic visit and those followed by telephone interview, 2) between patients directly admitted in the stroke unit and those referred from another hospital, and 3) according to the antithrombotic regimen at discharge and at the last visit or contact. This lack of difference may be due to the lack of power of the statistical analysis, the number of subjects in each group being too small to allow the detection of a small difference. One could, for instance, have expected a worse outcome in patients referred from another hospital, that is, more likely to be the most severe at onset, but this was not the case. We were, however, less surprised to find no difference of outcome according to the antithrombotic regimen for the following two reasons: 1) the small number of patients, which did not allow sufficiently powered statistics; and 2) the heterogeneity of patients in each antithrombotic regimen in terms of stroke etiology and therefore stroke outcome. The influence of those factors on the rate of myocardial infarction was not evaluated because of the small number of patients who developed myocardial infarction.

Factors associated with a good outcome (mRS = 0 to 2) at the bivariate analysis were decreasing age, absence of alcoholism or diabetes mellitus, and presence of hypercholesterolemia or treatment with statin or fibrate or oral contraceptive therapy. However, the cause of stroke, stroke recurrence, and occurrence of myocardial infarction or epileptic seizure did not influence the outcome. We should, however, be careful in the interpretation of these results: First, the study was not designed to identify predictors of outcome; second, a potential important predictor of outcome such as the intensity of the clinical deficit at onset was not recorded because of the heterogeneity in the delay of admission (0 to 7 days); finally, we did not perform a multivariate analysis because of the impossibility to take into account an important factor such as the severity of the deficit and also because of the small number of subjects in each category. The lack of association between the cause of stroke, stroke recurrence, and occurrence of myocardial infarction or epileptic seizures with the outcome is probably due to the lack of power of the statistics. The association between hypercholesterolemia with a good outcome was also reported in older subjects,[43] leading to the hypothesis that cholesterol might have a neuroprotective effect.[43] Another hypothesis may be that patients with hypercholesterolemia are more likely to receive statins or fibrates, which both have a neuroprotective effect in experimental stroke.[44] The association of statin or fibrate therapy with a good outcome in our study supports this hypothesis, but without a multivariate analysis, this result should be considered with caution: We cannot exclude that patients with hypercholesterolemia and statin or fibrate therapy have different stroke subtypes with a better spontaneous outcome.[45] Accordingly, the association of oral contraceptive therapy with a good outcome may just reflect that oral contraceptive therapies are less often given in women with medical conditions predisposing to stroke, comprising those women most likely to have a bad outcome.

We found that 15.0% of patients who were regarded by health insurance as able to work were still unemployed. Of course, two thirds of them were already unemployed before stroke, and the study was conducted during the worst period of unemployment in France. Factors such as subtle cognitive or behavioral changes, depression, and fatigue may have influenced social recovery,[21] but we did not make a systematic neuropsychological and behavioral assessment because of the observational design of the study. Besides, our study was not designed to answer the question of whether social and familial impairments were more frequent after an ischemic stroke but to evaluate the frequency of various endpoints, including social and familial impairments. Without controls, we cannot know whether the frequency of social and familial impairments is higher than that observed in the general French population in this age category.

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