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Risk factors and treatment of stroke at the time of recurrence

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Abstract

The profile of recurrent ischemic strokes has not been much investigated. The aim of this study was to evaluate how the therapeutic strategies recommended for secondary prevention after an ischemic stroke are implemented in the real world of clinical practice. All patients admitted for a recurrent ischemic stroke or TIA were prospectively registered. The etiology was determined according to the TOAST classification. The risk factors and cardiovascular treatment at the time of the recurrence were recorded. A total of 168 patients were evaluated. Most of the patients (61%) recurred after 1 year. The recurrent stroke was not associated with a particular etiological subtype. The most frequent risk factor was hypertension (79%), followed by hypercholesterolemia (43%), smoking (25%), and diabetes (22%). Most of the patients had more than 1 risk factor (84%). Hypertension was not satisfactorily controlled in 38% of patients, hypercholesterolemia in 42%, and diabetes in 59%. A significant minority of patients (15%) were not taking any antithrombotic agent despite a history of stroke or TIA. Only 34% of the cases with a known atrial fibrillation were on anticoagulant therapy and the International Normalized Ratio was < 2.0 in 71% of them. In conclusion, stroke prevention needs to be improved by better implementation of therapeutic strategies in clinical practice. The patients should also be better informed about target values as well as the importance of physical activity and smoking cessation.

Key words: Stroke; recurrence; risk factors; treatment; secondary prevention; hypertension; hypercholesterolemia; atrial fibrillation.

Stroke is a leading cause of mortality and handicap. Despite the emergence of new acute stroke therapies, prevention remains the best way to reduce the risk of death and dependency. In the Framingham study, the risk of a recurrent stroke during the 1st year after the primary event was 12% (1). The REACH study recently showed that 3.6% of stroke patients had had a new stroke by 1 year and 5.3% a major cardiovascular event (2). Control of risk factors and antithrombotic treatment lead to a reduced incidence of cardiovascular diseases including stroke. However, adherence to preventive therapies needs to be improved and a stringent effort should be made by the medical community to implement the recommended therapeutic strategies (3).

Data regarding the profile of recurrent ischemic strokes are still limited. The aim of this study was to evaluate how the therapeutic strategies recommended for secondary prevention after an ischemic stroke are implemented in the real world of clinical practice. We, therefore, determined, at the time of a recurrent ischemic stroke, whether the current international guidelines had been fulfilled in terms of antithrombotic therapy and control of risk factors.

Patients and methods

We retrospectively evaluated all consecutive patients who were prospectively recorded in the Mont-Godinne Stroke database between June 2005 and February 2008 because of an ischemic stroke or transient ischemic attack (TIA) defined by the National Institute of Neurological Disorders and Stroke (4). From this population, we extracted all patients who had a previous history of ischemic stroke or TIA. The presence of individual risk factors (age, gender, a positive history of hypertension [current treatment with antihypertensive drugs or blood pressure values known by the patient to be higher than 140/90 mmHg], currently treated hypercholesterolemia or diabetes mellitus, active smoking, excessive alcohol consumption [≥ 2 drinks/day]), and the total number of risk factors were collected. The etiology of the recurrent stroke was defined according to the TOAST criteria as large vessel disease (LVD), small vessel disease (SVD), high-risk or medium-risk cardiac sources for embolism (CE), 'other' (any cause other than LVD, SVD, or CE), or

'undetermined' (unknown or uncertain etiology) (5). Details of current treatment used to control hypertension, diabetes, and hypercholesterolemia, and antithrombotic therapy were also recorded. The international normalized ratio (INR) was measured at the time of admission. Hypertension was considered as not controlled when the systolic and/or diastolic pressures were ≥ 140 mmHg and ≥ 90 mmHg, respectively. Hypercholesterolemia was defined as a total cholesterol or LDL-cholesterol ≥190 mg/dl and ≥ 100 mg/dl, respectively. Diabetes was considered as not controlled when the glycosylated hemoglobin was ≥ 6.5%.

For the demographic data, we present the mean or median values with SD and range. To evaluate a possible change in the antithrombotic therapy after the stroke recurrence, we compared the rate of use of each medication before and after the stroke recurrence, using a binomial test or McNemar test as appropriate.

Results

During the study period, 168 of the 532 patients (31.6%) were admitted for a recurrent cerebral ischemic event (stroke, 105; TIA, 62; amaurosis fugax, 1). Mean age was 72.0 ± 13.3 years (range, 20-96 years), with a male:female ratio of 1.13 (89 men). One patient died before the hospital discharge. In most of the patients (60.7%), the recurrent ischemic event occurred more than 12 months after the first event; 11.9% occurred within 1 month of the first event, 2.4% between 1 and 3 months, and 16.6% between 3 and 12 months. The etiology was LVD in 37 patients (22.0%), SVD in 32 (19.0%), CE in 53 (31.5%), and classified as 'other' in 5 (3.0%) and 'undetermined' in 41 (24.4%). The most frequent risk factor was hypertension (133; 79.2%), followed by hypercholesterolemia (72; 42.8%), smoking (42; 25.0%), diabetes (37; 22.0%), and alcohol consumption (9; 5.4%). Twenty-six patients (15.5%) had a single risk factor, 48 (28.6%) had two risk factors, and 94 (55.9%) more than two risk factors. Forty-one patients (24.4%) had a positive history of atrial fibrillation and 41 of ischemic heart disease (24.4%). Valve disease (10; 5.9%), prosthetic valve (9; 5.4%), and interatrial septal defect (2; 1.2%) were less frequent.

Hypertension was not satisfactorily controlled in 50 patients (37.6%). Thirty-two of these patients (64%) had been instructed to take at least one antihypertensive agent and were still supposed to be doing so at the time of the recurrent stroke. A change in the therapeutic strategy was consequently ordered in these patients to reach the recommended blood pressure values (systolic and diastolic blood pressure < 140 and < 90 mmHg, respectively) . Antihypertensive treatment was initiated in the other 18 patients who were not already receiving medication. Seventy patients (41.7%) had a total cholesterol level ≥ 190 mg/dl and 90 (53.6%) an LDL-cholesterol level ≥ 100 mg/dl at the time of stroke recurrence. Of the 72 patients who had previously been instructed to take a lipid-lowering therapy and were still supposed to be doing so at the time of the recurrent stroke, 22 (30.5%) required an adjustment in dosage or a change in drug to reach the target values. A history of diabetes was present in 37 patients, of whom 22 (59.5%) had a glycosylated hemoglobin ≥ 6.5%.

One hundred and forty-two patients (84.5%) were receiving antithrombotic therapy when they had the recurrent event (antiplatelet agent, 121; oral anticoagulant, 17; antiplatelet agent plus oral anticoagulant, 4) (Table 1). In contrast, 26 patients (15.5%) were not taking any antithrombotic agent at the time of admission. Fourteen patients (34.1%) with known atrial fibrillation were on anticoagulant therapy but in 10 of them the INR was < 2.0 at the time of stroke recurrence. Aspirin was the most frequently used antiplatelet agent (38.0%) followed by clopidogrel alone (14.8%) or in addition to aspirin (16.9%), and dipyridamole combined with aspirin (12.0%). Two patients were discharged without any antithrombotic treatment due to contraindications. At discharge, the rate of aspirin use had decreased to 10.3% ($p < 0.001$) with a shift to either clopidogrel alone (27.3%; $p < 0.001$) or the combination of dipyridamole and aspirin (23.6%; $p = 0.005$). Use of anticoagulation therapy increased from 12.0% to 18.8% ($p = 0.003$).

Discussion

In this study, 32% of patients were admitted for a recurrent stroke or TIA. This recurrence rate remains high despite the availability of new preventive strategies. One in ten patients had a new cerebrovascular event within a month but in the vast majority of patients (61%) the recurrence occurred after 1 year as already reported in the RESQUE study (75%) (6). This suggests that aggressive preventive therapy should be started early, at the time of discharge, but also needs to be maintained in the long-term.

In this population of patients, recurrent stroke was not associated with a particular etiological subtype, since the rates of cardiac-source cerebral embolism, atherothrombotic stroke, or small vessel disease were in the same range. However, the proportion of atherothrombotic strokes was higher than that observed in a first-ever stroke registry (22% vs. 13%) (7).

Table 1

Antithrombotic therapy before and after the stroke recurrence

	Before n = 142	After n = 165	*p*
Aspirin	54 (38.8)	17 (10.3)	< 0.001
Clopidogrel	21 (14.8)	45 (27.3)	< 0.001
Clopidogrel + Aspirin	24 (16.9)	24 (14.5)	NS
Ticlopidine	2 (1.4)	1 (0.6)	NS
Aspirin + dipyridamole	17 (12.0)	39 (23.6)	0.005
Dipyridamole	3 (2.1)	0 (0)	NS
OAC*	17 (12)	31 (18.8)	0.003
OAC + antiplatelet	4 (2.8)	5 (3.0)	NS
Trial**	–	3 (1.8)	

*OAC: oral anticoagulant; ** Trial: patients included in the PERFORM trial. Percentages are shown in parentheses.

Control of risk factors with good patient adherence to treatment remains the key to preventing stroke. Hypertension is known to be the main stroke risk factor. The PROGRESS (8) and MOSES (9) studies demonstrated that blood pressure control was effective in preventing secondary stroke after a first cerebrovascular attack. In our population of patients with recurrent stroke, 79% were hypertensive and 37% of these were not satisfactorily controlled according to the recommended target values of blood pressure. Likewise, in the REACH registry, 83% of patients with cerebrovascular disease (CVD) were being treated for hypertension and in 54% the blood pressure was still > 140/> 90 mmHg (3). The same is true for hypercholesterolemia. The SPARCL (10) and HPS (11) studies showed that atorvastatin and simvastatin significantly reduced the risk of major cardiovascular events after a stroke. These results, therefore, support the view that control of hypercholesterolemia is needed in secondary prevention. In our study, despite a history of stroke, 54% of the patients still had a LDL-cholesterol level greater than 100 mg/dl, and 30% of those already being treated with a lipid-lowering therapy required a change in dosage or agent. The REACH registry also reported that a large number of CVD patients had uncontrolled hypercholesterolemia (46%) (3). Besides, twenty-five percent of our patients were unable to stop smoking despite the threat of a new stroke. This rate is higher than that observed in the REACH registry (15%) for CVD patients included in Western Europe (3).

Antithrombotics are recommended in secondary stroke prevention (12, 13). In spite of these guidelines, 15% of the patients were not taking any antithrombotic treatment at the time of the stroke recurrence. This rate is similar to that reported in the REACH registry (18%) (3). Our study does not provide any explanation for this finding, because the reasons why antithrombotic agents were not being taken were not prospectively recorded. As already reported by others (14, 15), a vast majority of patients (66%) with known atrial fibrillation were not on anticoagulant therapy despite a previous history of stroke and in many of those already treated the therapeutic target (INR 2.0-3.0) was not achieved. Besides, most of the recurrent strokes occurred in patients treated with aspirin. This finding is not really surprising since a meta-analysis showed that aspirin reduced the risk of any cardiovascular event by only 13% (16). However, one third of the patients were on clopidogrel alone or combined with aspirin, and 12% on aspirin plus dipyridamole at the time of the stroke recurrence. This clinical 'non responsiveness' to antiplatelet agents could be explained in some patients of our study by the presence of atrial fibrillation, which was either unknown or not treated with anticoagulant at the time of the recurrent stroke. This underscores the view that the etiology and related preventive therapy must be re-examined in patients with recurrent ischemic events. As expected, at the time of discharge there was a shift towards a higher use of clopidogrel, aspirin plus dipyridamole, or anticoagulant therapy in agreement with the international recommendations (17).

The main limitation of our study is the small number of patients recorded in a single center, so that our results cannot be generalized. However, the observed high rate of stroke recurrence is challenging, as it could be attributed in many patients to poor control of risk factors and a lack of or inappropriate antithrombotic therapy. A well-designed discharge form might improve documentation of stroke and long-term patient care (18). This should include a prediction of the patient's overall risk of cardiovascular events, an explanation of the need for close

monitoring and appropriate therapy, a list of the individual risk factors and other vascular territories possibly implied in a more widespread atherothrombotic disease, and advice how to achieve the international stroke guidelines. A patient diary reporting the follow-up data on the risk factors and the target values to be reached might improve adherence to the preventive treatments.

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REFERENCES

1. Petty GW, Brown RD, Whisnant JP, Sicks JD, O'Fallon WM. *et al*. Survival and recurrence after first cerebral infarction. A population-based study in rochester, minnesota, 1975 through 1989. Neurology. 1998;50:208-216.
2. Steg PG, Bhatt DL, Wilson PW, D'Agostino R Sr, Ohman EM. *et al*. One-year cardiovascular event rates in outpatients with atherothrombosis. JAMA: The Journal of the American Medical Association. 2007;297:1197-1206.
3. Rother J, Alberts MJ, Touze E, Mas JL, Hill MD. *et al*. Risk factor profile and management of cerebrovascular patients in the reach registry. Cerebrovasc Dis. 2008;25:366-374.
4. National Institute of Neurological Disorders and Stroke. Special report from the national institute of neurological disorders and stroke: Classification of cerebrovascular diseases iii. Stroke. 1990;21:637-676.
5. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB. *et al*. Classification of subtype of acute ischemic stroke: Definitions for use in a multicenter clinical trial. Stroke. 1993;24:35-41.
6. Leoo T, Lindgren A, Petersson J, von Arbin M. Risk factors and treatment at recurrent stroke onset: Results from the recurrent stroke quality and epidemiology (RESQUE) study. Cerebrovasc Dis. 2008;25:254-260.
7. Kolominsky-Rabas PL, Weber M, Gefeller O, Neundoerfer B, Heuschmann PU. Epidemiology of ischemic stroke subtypes according to TOAST criteria: Incidence, recurrence, and long-term survival in ischemic stroke subtypes: A population-based study. Stroke. 2001;32:2735-2740.
8. Progress Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. Lancet. 2001;358:1033-1041.
9. Schrader J, Luders S, Kulschewski A, Hammersen F, Plate K. *et al*. Morbidity and mortality after stroke, eprosartan compared with nitrendipine for secondary prevention: Principal results of a prospective randomized controlled study (MOSES). Stroke. 2005;36:1218-1224.
10. Amarenco P, Goldstein LB, Szarek M, Sillesen H, Rudolph AE. *et al*. Effects of intense low-density lipoprotein cholesterol reduction in patients with stroke or transient ischemic attack: The stroke prevention by aggressive reduction in cholesterol levels (SPARCL) trial. Stroke. 2007;38:3198-3204.
11. Collins R, Armitage J, Parish S, Sleight P, Peto R. Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20536 people with cerebrovascular disease or other high-risk conditions. Lancet. 2004;363:757-767.
12. Antiplatelet Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ. 2002;324:71-86.
13. Hacke W, Kaste M, Olsen TS, Orgogozo JM, Bogousslavsky J. Recommendations of the European stroke initiative for the management and treatment of stroke. Nervenarzt. 2001;72:807-819.
14. Deplanque D, Leys D, Parnetti L, Schmidt R, Ferro J. *et al*. Secondary prevention of stroke in patients with atrial fibrillation: Factors influencing the prescription of oral anticoagulation at discharge. CerebrovascDis. 2006;21:372-379.
15. Weimar C, Benemann J, Katsarava Z, Weber R, Diener HC. Adherence and quality of oral anticoagulation in cerebrovascular disease patients with atrial fibrillation. Eur Neurol. 2008;60:142-148.
16. Algra A, Van Gijn J. Cumulative meta-analysis of aspirin efficacy after cerebral ischemia of arterial origin. J Neurol Neurosurg Psychiatry. 1999;66:255.
17. Adams RJ, Albers G, Alberts MJ, Benavente O, Furie K. *et al*. Update to the AHA/ASA recommendations for the prevention of stroke in patients with stroke and transient ischemic attack. Stroke. 2008;39:1647-1652.
18. Carolei A, Chamorro A, Laloux P, Leys D, Rother J. *et al*. Identification and management of polyvascular disease in patients with noncardioembolic ischaemic stroke. Int J Stroke. 2008;3:237-248.

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