

RECURRENT CEREBROVASCULAR EVENTS ASSOCIATED WITH PATENT FORAMEN OVALE, ATRIAL SEPTAL ANEURYSM, OR BOTH

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ABSTRACT

Background Patent foramen ovale and atrial septal aneurysm have been identified as potential risk factors for stroke, but information about their effect on the risk of recurrent stroke is limited. We studied the risks of recurrent cerebrovascular events associated with these cardiac abnormalities.

Methods A total of 581 patients (age, 18 to 55 years) who had had an ischemic stroke of unknown origin within the preceding three months were consecutively enrolled at 30 neurology departments. All patients received aspirin (300 mg per day) for secondary prevention.

Results After four years, the risk of recurrent stroke was 2.3 percent (95 percent confidence interval, 0.3 to 4.3 percent) among the patients with patent foramen ovale alone, 15.2 percent (95 percent confidence interval, 1.8 to 28.6 percent) among the patients with both patent foramen ovale and atrial septal aneurysm, and 4.2 percent (95 percent confidence interval, 1.8 to 6.6 percent) among the patients with neither of these cardiac abnormalities. There were no recurrences among the patients with an atrial septal aneurysm alone. The presence of both cardiac abnormalities was a significant predictor of an increased risk of recurrent stroke (hazard ratio for the comparison with the absence of these abnormalities, 4.17; 95 percent confidence interval, 1.47 to 11.84), whereas isolated patent foramen ovale, whether small or large, was not.

Conclusions Patients with both patent foramen ovale and atrial septal aneurysm who have had a stroke constitute a subgroup at substantial risk for recurrent stroke, and preventive strategies other than aspirin should be considered. (N Engl J Med 2001; 345:1740-6.)

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DURING the past 15 years, the potential role of patent foramen ovale and atrial septal aneurysm in the genesis of ischemic stroke in young adults¹⁻⁶ has been investigated. In addition to uncertainty about the mechanisms of stroke,⁷ therapeutic decisions are hindered by the lack of precise data on the risk of recurrent stroke. The few studies of this topic⁸⁻¹⁴ were retrospective, did not include a control group of patients with neither of these septal abnormalities, involved small numbers of patients, or used heterogeneous treatments for secondary prevention. In addition, the vari-

ability in the diagnosis of these septal abnormalities was usually not taken into account.

This follow-up study was designed to assess the absolute and relative risks of recurrent cerebrovascular events associated with these septal disorders in young patients with an otherwise unexplained ischemic stroke who were receiving aspirin and to identify subgroups of patients with a high risk of recurrent stroke.

METHODS

Patients were consecutively enrolled at 30 neurology departments in Europe between May 1, 1996, and December 31, 1998, and were followed until December 31, 2000. Eligible patients were 18 to 55 years of age and had had an ischemic stroke (defined as a neurologic deficit that lasted more than 24 hours) within the preceding three months for which no definite cause had been identified after a standardized workup. Patients were excluded if the workup had been incomplete, if there was a contraindication to aspirin therapy, or if certain circumstances made follow-up impractical or compliance with treatment uncertain.

To assess the overall proportion of patients who were included in the study, 18 centers kept a registry of all patients 18 to 55 years of age with a recent (within three months) history of ischemic stroke who were seen during the enrollment period, with the reasons for exclusion from the study. The protocol conformed to the ethical guidelines of our institutions, and all participants gave written informed consent.

Data Collection

Risk factors for stroke, past vascular events, neurologic features, and the severity of stroke¹⁵ were systematically recorded. In addition to cerebral computed tomography (in 535 patients) or magnetic resonance imaging (in 428), all patients had a standardized workup to rule out definite causes of stroke. The workup comprised routine blood tests and a coagulation study (including tests for protein S, protein C, antithrombin III, and antiphospholipid antibodies), 12-lead electrocardiography and echocardiography, and at least one of the following vascular studies (within one month after the onset of stroke): catheter angiography (in 360 patients), magnetic resonance angiography (in 220), and cervical and transcranial ultrasonography (in 495). The decisions to perform additional investigations and to search for latent venous thrombosis were left to the discretion of the patients' physicians.

The following disorders were considered to be definite causes of stroke and led to exclusion¹⁶: large-artery atherosclerosis (defined by stenosis of at least 50 percent or occlusion of the corresponding vessel); lacunar stroke (defined by a small, deep infarct less than 15 mm in diameter in a patient with hypertension); cardioembolic causes, such as atrial fibrillation, recent (within four

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months before the stroke) myocardial infarction, dilated cardiomyopathy, rheumatic mitral stenosis, mitral or aortic vegetations or prostheses, left atrial or left ventricular thrombus or tumor, akinetic left ventricular segment, spontaneous echo contrast of the left atrium, and complex atheroma of the aortic arch; and other definite causes of stroke, such as nonatherosclerotic arteriopathies (e.g., dissection), coagulopathies, hematologic or systemic disorders (e.g., the antiphospholipid-antibody syndrome), or migrainous infarction.¹⁷

For each patient, the clinical, laboratory, and imaging data were reviewed by two neurologists and two neuroradiologists at the coordinating center who were unaware of the results of transesophageal echocardiography. Data on patients with a potential violation of the inclusion or exclusion criteria were reviewed by a validation committee.

Echocardiography

All patients underwent transthoracic and transesophageal echocardiography, performed by experienced sonographers according to a strictly predefined protocol.¹⁸ Patients were assessed for a patent foramen ovale and an atrial septal aneurysm at rest and during provocative maneuvers (Valsalva's maneuver and coughing), with the use of transesophageal echocardiography with contrast medium and 5-MHz multiplane transducers (in 86.4 percent of patients) or biplane transducers (in 13.6 percent). Examinations were recorded on videotape, and the videotapes were sent to the coordinating center for subsequent analysis.

To determine the degree of variability in the diagnosis of interatrial septal abnormalities, three sonographers independently reviewed, on two occasions each, videotapes from the first 100 patients.¹⁸ Given the substantial degree of disagreement among the three reviewers,¹⁸ all videotapes were reviewed independently by two sonographers who were unaware of patients' clinical data and outcomes.

A right-to-left shunt was diagnosed if at least three microbubbles appeared in the left atrium, either spontaneously or after provocative maneuvers, within three cardiac cycles after the complete opacification of the right atrium. The degree of shunting was defined as small if 3 to 9 microbubbles appeared, moderate if 10 to 30 microbubbles appeared, and large if more than 30 microbubbles appeared. An atrial septal aneurysm was diagnosed when the atrial septum extended at least 11 mm into the left or the right atrium, or both. The size of the aneurysm was classified as either 11 to 14 mm or 15 mm or more. The diagnosis of an atrial septal defect rested on the direct visualization of a septal defect on transesophageal echocardiography and on the recording of turbulent left-to-right flow across the defect on color-flow Doppler echocardiography.

The sonographers disagreed on the presence of patent foramen ovale in 13.9 percent of patients, the presence of atrial septal aneurysm in 6.6 percent, the degree of shunting in 26.6 percent, and the size of the aneurysm in 10.0 percent. In such cases, the videotapes were reviewed by the sonographers and a consensus was reached.

Treatment and Follow-up

After the index stroke but before enrollment, the use of anti-thrombotic therapy was governed by policy at each center. Secondary prevention with aspirin (300 mg daily) was started on the day of enrollment. In patients with deep venous thrombosis associated with stroke, aspirin was started after a three-to-six-month course of systemic anticoagulation. Vascular risk factors (including the use of hormonal contraception) were managed according to standard guidelines. Follow-up visits with the neurologists took place every six months. To assess a patient's compliance with aspirin therapy, the neurologist asked the patient at each visit whether he or she had temporarily stopped taking the drug since the last visit, and if so, for how long and for what reason.

The following outcome events were systematically recorded: stroke, defined by the acute occurrence of focal neurologic signs lasting for more than 24 hours in a different location from that of the previous stroke or worsening of an existing deficit that last-

ed for more than one week, or more than 24 hours if accompanied by a new lesion on neuroimaging; transient ischemic attack¹⁹; systemic embolism; myocardial infarction; and death. We assessed a patient's functional outcome after a recurrent stroke by comparing the Rankin scores recorded before and six months (plus or minus three months) after the event. In the case of a single transient ischemic attack, continuation of aspirin was recommended. In the case of multiple transient ischemic attacks, the decision whether to discontinue aspirin therapy was left to the patient's physician. All outcome events were documented and reviewed by the members of the validation committee, who were unaware of the results of echocardiography.

Statistical Analysis

Comparisons between groups were analyzed with use of the chi-square test, Fisher's exact test, t-test for unpaired data, or analysis of variance, as appropriate. Potential risk factors for recurrent cerebrovascular events that were independently associated with atrial septal abnormalities were identified by logistic-regression analysis.²⁰

Kaplan-Meier survival analysis²⁰ was used to assess the absolute risk of recurrent cerebrovascular events. The predictive value of each category of septal abnormality (no atrial septal abnormality, patent foramen ovale alone, atrial septal aneurysm alone, or both septal abnormalities) and of the degree of shunting with respect to recurrent cerebrovascular events was assessed with use of log-rank tests and Cox proportional-hazards models,²⁰ to adjust for age, sex, and the number of traditional vascular risk factors (hypertension, diabetes, hypercholesterolemia, and smoking). The same analyses were performed in the 215 patients with no traditional risk factors for stroke. All tests were two-tailed.

On the basis of a preliminary study,⁹ we estimated that a total of 600 patients was required for the study to have the statistical power to detect at a level of 95 percent confidence a sampling error of no more than 1.5 percent, given a four-year rate of recurrent stroke of 4 percent.

RESULTS

A total of 598 patients were enrolled in the study; 17 were subsequently excluded by the validation committee because they did not fulfill one or more of the inclusion criteria. Among 1340 consecutive young patients with stroke who were screened for possible inclusion in the study at 18 centers, 51.3 percent were not eligible because they had a definite cause of stroke, 21.9 percent had another reason for exclusion, and 26.8 percent were included in the study. Except for one patient who underwent surgical closure of the foramen, no patient was excluded because of the presence of a patent foramen ovale, an atrial septal aneurysm, or deep venous thrombosis.

Characteristics of the Patients

The base-line characteristics of the 304 patients without atrial septal abnormalities and the 277 patients with atrial septal abnormalities are shown in Table 1. There were no significant differences in these characteristics among the three groups with septal abnormalities — the 216 patients with patent foramen ovale alone, the 10 with atrial septal aneurysm alone, and the 51 with both abnormalities. In logistic-regression analysis, patients with septal abnormalities, as compared with those without such abnormalities, were younger, less likely to have hypertension (odds ratio, 0.52; 95 percent confidence interval, 0.31 to

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS, ACCORDING TO THE PRESENCE OR ABSENCE OF ATRIAL SEPTAL ABNORMALITIES.

CHARACTERISTIC	NO ATRIAL SEPTAL ABNORMALITY (N=304)	PATENT FORAMEN OVALE, ATRIAL SEPTAL ANEURYSM, OR BOTH (N=277)	P VALUE
Mean age (yr)	44.5	40.3	<0.001
Male sex (%)	61.8	52.7	0.03
Risk factors for stroke (%)			
Known hypertension	21.4	9.0	<0.001
Known hypercholesterolemia	23.0	11.6	<0.001
Known diabetes mellitus	5.3	2.9	0.2
Current smoking	51.6	43.7	0.06
Consumption of ≥ 40 g of alcohol/day in month preceding stroke	21.1	13.7	0.02
Current use of oral contraceptives*	39.7	51.9	0.06
Body-mass index >27 †	29.0	18.9	0.006
Migraine‡	13.5	27.4	<0.001
Prior stroke	3.3	2.2	0.5
Characteristics of qualifying stroke (%)			
Rankin score >2 at inclusion§	19.4	13.0	0.04
Circulation			0.2
Anterior	62.9	55.6	
Posterior	35.4	42.7	
Anterior and posterior	1.7	1.7	

*Oral contraceptives were defined as those containing a combination of estrogen and progesterone. The values are the percentages of women in each group who were taking oral contraceptives.

†The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡Migraine was defined according to the criteria of the International Headache Society.¹⁷

§The score was determined with use of a modified Rankin scale at the time of inclusion in the study. Scores on the scale can range from 0 (no neurologic disability) to 5 (severe disability).

0.88), less likely to have hypercholesterolemia (odds ratio, 0.60; 95 percent confidence interval, 0.37 to 0.98), less likely to be current smokers (odds ratio, 0.70; 95 percent confidence interval, 0.49 to 0.99), and more likely to have migraine (odds ratio, 1.96; 95 percent confidence interval, 1.24 to 3.12). The prevalence of atrial septal aneurysm was higher among patients with a patent foramen ovale than among those without it (19.1 percent vs. 3.2 percent, $P < 0.001$) and increased with the degree of shunting (4.4 percent, 12.5 percent, and 25 percent in patients with small, moderate, and large shunts, respectively; $P < 0.001$). No significant relation was found between the size of the aneurysm and the degree of shunting. Eleven patients had an atrial septal defect.

Recurrent Events

Of the 581 patients, 2 were lost to follow-up. Neither had septal abnormalities. Table 2 shows the out-

TABLE 2. OUTCOME ACCORDING TO THE PRESENCE OR ABSENCE OF ATRIAL SEPTAL ABNORMALITIES.

OUTCOME	NO ATRIAL SEPTAL ABNORMALITY (N=304)	PATENT FORAMEN OVALE ALONE (N=216)	ATRIAL SEPTAL ANEURYSM ALONE (N=10)	PATENT FORAMEN OVALE AND ATRIAL SEPTAL ANEURYSM (N=51)
	no. of patients			
Recurrent stroke*	12†	6‡	0	6‡
Transient ischemic attack§	4	7	0	2
Aspirin replaced by other agent	1	3	0	0
Myocardial infarction	3	0	0	0
Systemic embolism	1	0	0	0
Death¶	5	1	0	0

*There were 23 cases of ischemic stroke and 1 case of cerebral hemorrhage in a patient with no septal abnormality.

†Of the 11 recurrent ischemic strokes, 2 were lacunar and 9 were of undetermined cause.

‡The cause of all six recurrent ischemic strokes was undetermined.

§No stroke was preceded by a transient ischemic attack. Two patients had recurrent transient ischemic attacks (one with no atrial septal abnormality and one with a patent foramen ovale). In four patients, aspirin was discontinued after a transient ischemic attack and replaced by another antiplatelet agent (in three) or oral anticoagulants (in one).

¶Five deaths were from nonvascular causes (three from neoplasm, one from a diabetic coma, and one from an unexplained coma with no vascular cause identified at autopsy), and one death occurred during coronary-artery bypass surgery, 11 months after a myocardial infarction. One patient died from neoplasm 26 months after an ischemic stroke.

come events during a mean (\pm SD) follow-up of 37.8 ± 9.7 months. Of the 24 patients with a recurrent stroke, only 7 had a decrease in functional status, according to the Rankin score; 6 of the 7 had no septal abnormalities ($P = 0.07$). None of the patients with an atrial septal defect had a recurrent cerebrovascular event.

Aspirin therapy was initiated a mean of 25.1 ± 20.7 days after the index stroke in the population as a whole, and the time of initiation did not differ significantly among the four groups of patients ($P = 0.1$). Aspirin was discontinued in 20 patients because of an outcome event, in 21 at the request of the patient or his or her physician, in 16 because of a drug-induced adverse event, and in 16 for other reasons. Aspirin was replaced by another antiplatelet agent in 31 patients and by oral anticoagulants in 18 patients, whereas 24 patients received no further treatment. Overall, 92 percent of the patients received antiplatelet drugs for more than 90 percent of their follow-up period, with no significant difference in treatment rates among patients with no atrial septal abnormalities, those with both abnormalities, those with patent foramen ovale alone, and those with atrial septal an-

eurysm alone. All recurrent cerebrovascular events were in patients who were taking antiplatelet drugs.

The risk of recurrent cerebrovascular events according to the presence or absence of atrial septal abnormalities is shown in Table 3 and Figure 1. The likelihood of survival free from stroke (P=0.03) or from stroke or transient ischemic attack (P=0.04) differed significantly between groups. In Cox analyses (Table 4), the presence of both atrial septal abnormalities was a significant predictor of an increased risk of recurrent cerebrovascular events, whereas the presence of a patent foramen ovale alone or an atrial septal aneurysm alone was not. The risk of recurrent stroke increased with age. The risk was higher in males than in females, but not significantly so, and it increased with the number of vascular risk factors, but not significantly so.

The degree of shunting was not a significant predictor of the risk of recurrent cerebrovascular events (hazard ratio for small shunts, as compared with the absence of shunts, 1.01; 95 percent confidence interval, 0.23 to 4.52; hazard ratio for large shunts, 1.10; 95 percent confidence interval, 0.39 to 3.11; and hazard ratio for medium shunts, 1.60; 95 percent confidence interval, 0.57 to 4.51). The small number of patients with an atrial septal aneurysm precluded meaningful analysis of the role of the size of the aneurysm in the recurrence of stroke. The predictive value of the presence of both cardiac abnormalities remained significant in the subgroup of 215 patients with no traditional vascular risk factors (hazard ratio, 5.37; 95 percent confidence interval, 1.31 to 21.92).

DISCUSSION

In this prospective, multicenter study, we used a standardized treatment to assess the relative and ab-

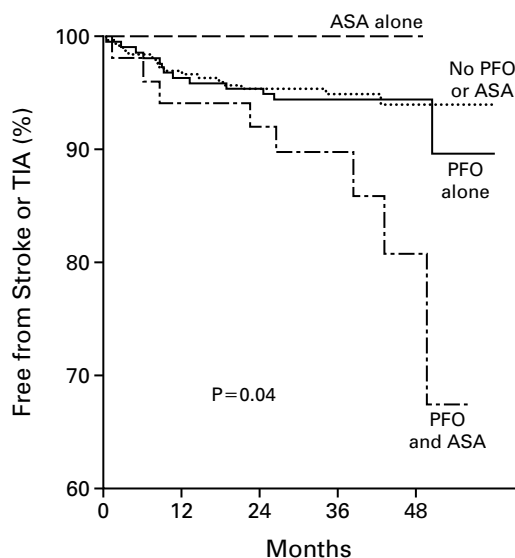
solute risks of recurrent cerebrovascular events associated with the presence of a patent foramen ovale, an atrial septal aneurysm, or both abnormalities. We selected patients who were no older than 55 years of age because the higher prevalence of large-vessel atherosclerosis or small-artery disease in the elderly makes the diagnosis of cryptogenic stroke less frequent than in the young. In addition, the association of patent foramen ovale with cryptogenic stroke has been consistently reported in this age group, whereas the association in those older than 55 years remains uncertain.⁶ Reported rates of detection of atrial septal abnormalities in patients who have had a cryptogenic stroke range from 31 to 77 percent for patent foramen ovale and from 4 to 25 percent for atrial septal aneurysm.⁶ In the present study, an independent review of echocardiograms yielded results within these ranges.

An important finding of this study is that patients with both a patent foramen ovale and an atrial septal aneurysm who had had a cryptogenic stroke had a higher risk of recurrent stroke while taking aspirin than did patients with no septal abnormality or either septal abnormality alone. Indeed, the presence of both abnormalities was the only septal disorder significantly associated with an increased risk of recurrent stroke, and this finding remained significant when the analysis was restricted to patients who had no traditional vascular risk factors. This result is consistent with the results of our previous retrospective study,⁹ in which the combination of both septal abnormalities was also the only septal disorder predictive of an increased risk of recurrent stroke. Patients with both cardiac lesions in that study had an annual rate of recurrent stroke of 4.4 percent, which is very close to the rate we found in the present study. Case-control studies

TABLE 3. KAPLAN-MEIER ESTIMATES OF THE RISK OF RECURRENT CEREBROVASCULAR EVENTS WITHIN FOUR YEARS AFTER THE INDEX STROKE.*

GROUP	AT 1 YEAR		AT 2 YEARS		AT 3 YEARS		AT 4 YEARS	
	RISK OF STROKE	RISK OF STROKE OR TIA	RISK OF STROKE	RISK OF STROKE OR TIA	RISK OF STROKE	RISK OF STROKE OR TIA	RISK OF STROKE	RISK OF STROKE OR TIA
percent (95 percent confidence interval)								
No atrial septal abnormality	2.0 (0.4-3.6)	3.0 (1.1-4.9)	3.7 (1.6-5.8)	4.7 (2.3-7.1)	4.2 (1.8-6.6)	5.2 (2.6-7.8)	4.2 (1.8-6.6)	6.2 (3.0-9.3)
No. at risk	304	304	294	291	270	267	159	158
Patent foramen ovale alone	1.8 (0.05-3.6)	3.7 (1.1-6.2)	1.8 (0.05-3.6)	4.6 (1.8-7.4)	2.3 (0.3-4.3)	5.6 (2.5-8.7)	2.3 (0.3-4.3)	5.6 (2.5-8.7)
No. at risk	216	216	211	207	204	198	125	122
Atrial septal aneurysm alone	0	0	0	0	0	0	0	0
No. at risk	10	10	10	10	9	9	4	4
Patent foramen ovale and atrial septal aneurysm	2.0 (0.0-5.8)	5.9 (0.0-12.4)	4.0 (0.0-9.4)	8.0 (0.5-15.5)	6.3 (0.0-13.2)	10.3 (1.7-18.9)	15.2 (1.8-28.6)	19.2 (5.0-33.4)
No. at risk	51	51	48	46	46	44	27	25

*TIA denotes transient ischemic attack.



No. AT RISK					
	0	12	24	36	48
No PFO or ASA	304	291	267	158	48
PFO alone	216	207	198	122	43
ASA alone	10	10	9	4	1
PFO and ASA	51	46	44	25	10

Figure 1. Probability That Patients Will Remain Free from Recurrent Stroke or Transient Ischemic Attack (TIA), According to the Presence or Absence of Atrial Septal Abnormalities. The log-rank test was used to calculate the P value. PFO denotes patent foramen ovale, and ASA atrial septal aneurysm.

have also shown that the presence of both abnormalities is consistently more strongly associated with an increased risk of ischemic stroke than is the presence of either factor alone.^{5,6,8} Given the prognostic and potential therapeutic implications, young patients who have had an ischemic stroke should be examined for both septal disorders.

Another important finding of this study is that young patients with patent foramen ovale alone, whether small or large, who had had a cryptogenic stroke did not have a higher risk of recurrent stroke while taking aspirin than patients with no septal abnormalities. The low absolute risk of recurrent cerebrovascular events in these patients is consistent with rates reported in previous smaller, retrospective studies.⁸⁻¹⁴ This finding apparently contrasts with the results of case-control studies showing that patent foramen ovale is significantly associated with an increased risk of cryptogenic stroke, particularly in patients with a large degree of shunting.^{6,10,14,21-24} These studies, however, did not focus on the risk of recurrent stroke.

Potential mechanisms of stroke in patients with atrial septal abnormalities include paradoxical embolism from a venous source,^{7,25} direct embolization from thrombi formed within the aneurysm,²⁶⁻²⁸ and the formation of thrombus as a result of atrial arrhythmias.²⁹ In patients with both septal abnormalities, the motion of the fossa ovalis membrane could be responsible. The motion of the fossa ovalis membrane may promote paradoxical shunting through mechanical action by enhancing the preferential orientation

TABLE 4. COX PROPORTIONAL-HAZARD MODELS OF THE PREDICTORS OF RECURRENT CEREBROVASCULAR EVENTS.*

VARIABLE	RECURRENT STROKE		RECURRENT STROKE OR TIA	
	HAZARD RATIO (95% CI)	P VALUE	HAZARD RATIO (95% CI)	P VALUE
Atrial septal abnormality		0.03†		0.03†
Neither‡	1.0	—	1.0	—
Patent foramen ovale alone	0.86 (0.31–2.36)	0.77	1.34 (0.62–2.90)	0.45
Atrial septal aneurysm alone	—	0.98	—	0.97
Patent foramen ovale and atrial septal aneurysm	4.17 (1.47–11.84)	0.007	3.91 (1.59–9.59)	0.003
Age (per year of age)	1.06 (1.00–1.13)	0.04	1.02 (0.98–1.07)	0.25
Male sex	2.41 (0.91–6.37)	0.08	1.68 (0.81–3.48)	0.16
Number of vascular risk factors		0.81†		0.61†
0‡	1.0	—	1.0	—
1	0.82 (0.32–2.10)	0.68	0.98 (0.46–2.08)	0.95
2	0.97 (0.28–3.37)	0.97	1.28 (0.46–3.55)	0.64
3	1.77 (0.37–8.44)	0.47	2.20 (0.61–7.89)	0.23

*TIA denotes transient ischemic attack, and CI confidence interval.

†The P value is for the overall comparison.

‡This group served as the reference group.

of the flow from the inferior vena cava toward the foramen ovale.¹⁴ The combination of both septal disorders may also indicate the presence of more severe disease of the atrial septum, which increases the likelihood of the local formation of thrombus, arrhythmias, or both. The patency of the foramen may allow a thrombus formed on the right atrial side of the aneurysm to reach the systemic circulation.

Secondary prevention for patients with a patent foramen ovale or an atrial septal aneurysm who have had a stroke is a subject of considerable debate. Accordingly, these patients have been treated empirically with antiplatelet drugs or anticoagulants, transcatheter closure of the foramen, or open-heart surgery.^{30,31} Our findings suggest that secondary prevention with aspirin is sufficient in young patients who have an isolated patent foramen ovale and who have had a single otherwise unexplained ischemic stroke. Together with previous evidence, our findings strongly suggest that patients with both a patent foramen ovale and an atrial septal aneurysm who have had a cryptogenic stroke constitute a subgroup with a higher risk of recurrent stroke. Whether these patients would benefit from more aggressive therapeutic strategies, such as a combination of antiplatelet drugs, long-term anticoagulation, or closure of the foramen ovale, needs to be assessed in randomized clinical trials.

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APPENDIX

The members of the study group and the numbers of patients enrolled at each center (given in parentheses) were as follows: **Coordinating center, Sainte-Anne Hospital, Paris** — J.L. Mas, C. Arquiza, C. Lamy, M. Zuber, C. Giancesini, D. Trystram, J.F. Méder; **Scientific committee** — J.L. Mas (chair), Y. Bernard, B. Bertrand, J. Bogousslavsky, F. Chollet, L. Cabanes, A. Cohen, J.M. Ferro, H. Kwicinski, J.P. Lesbre, D. Leys, T. Moulin, J.F. Pinel, R. Roudaut, D. Saudeau, F. Woimant; **Transesophageal echocardiography committee** — L. Cabanes, G. Derumeaux, X. Jeanrenaud, A. Cohen; **Validation committee** — P. Césaro, M. Giroud, F. Nicoli, S. Weber; **Participating institutions and investigators** — Centre Hospitalier Universitaire (CHU) Besançon, Besançon, France (62): T. Moulin, L. Tatu, A. Vuilleminot, D. Magnin, M.F. Seronde, F. Apffel, N. Meneveau, Y. Bernard; CHU Lariboisière and Saint-Antoine, Paris (61): F. Woimant, P. Amarengo, N. Kubis, K. Vahedi, I. Crassard, G. Ast, H. Chabriat, M. Sarazin, M. Haguenu, J.M. de Kermadec, A. N'Guyen Van Cao, S. Mazouz, B. Benhalima, C. Albo, A. Cohen, M. Khireddine, N. Lamisse; Sainte-Anne Hospital and CHU Cochin Port-Royal, Paris (52): L. Cabanes, I. Cornuejols, E. Lombard; CHU Nancy, Nancy, France (41): X. Ducrocq, J.C. Lacour, J.F. Bruntz, I. Magnin-Poull; CHU Tours, Tours, France (38): D. Saudeau, A. Sirinelli; CHU Rennes, Rennes, France (33): J.F. Pinel, C. de Place, M. Laurent, C. Bossee-Pilon; Medical University of Warsaw, Warsaw, Poland (27): H. Kwicinski, B. Szyluk, A. Opuchlik, J. Mieszkowski, A. Torbicki, P. Pruszczyk, A. Kuch-Wocial; CHU Poitiers, Poitiers, France (21): J.P. Neau, C. Couderq, D. Coisne, G. Bacque, L. Christiaens, C. Couderq, P. Raud-Raynier; CHU Vaudois, Lausanne, Switzerland (21): P. Arnold, M. Altieri, J. Bogousslavsky, M. Nasrattullah, N. Aebischer, X. Jeanrenaud; CHU Rouen, Rouen, France (20): E. Guégan-Massardier, B. Mihout, D. Thomas, G. Derumeaux, J.L. Gauthier; CHU Pitié-Salpêtrière, Paris (19): R. Manai, Y. Samson, G. Rancurel, E. Coignard, R. Isnard; CHU La Timone, Marseilles, France (18): L. Milandre, G. Habib; CHU Lille, Lille, France (16): D. Leys, C. Lucas, C. Savoye, L. Goullard, E. Chammer, Centre Hospitalier Général, Meaux, France (16): F. Chedru, A. Ameri, J.F. Lefort; CHU Saint-Etienne, Saint-Etienne, France (14): P. Garnier, D. Michel, C. Comtet, I. Cusey; Santa Maria Hos-

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