Recurrent Stroke and Massive Right-to-Left Shunt
Results From the Prospective Spanish Multicenter (CODICIA) Study

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Background and Purpose—Few studies have prospectively examined the risk of recurrent stroke associated with patent foramen ovale. We present the results of the Spanish right-to-left shunt (RLSh) multicenter study.

Methods—Four hundred eighty-six patients with cryptogenic stroke were included at 17 participating hospitals. Patients were examined by contrast transcranial Doppler methods at baseline. The magnitude of RLSh was quantified during the Valsalva maneuver. Transthoracic and/or transesophageal echocardiography, computed tomography scan, or magnetic resonance imaging was performed. Functional outcome and stroke recurrence were evaluated at 3 months and yearly thereafter. The independent relation between RLSh magnitude and stroke recurrence was analyzed by logistic-regression analysis in the whole group and in the younger subgroup (<55 years).

Results—Massive RLSh was detected in 200 patients (41.2%). The mean follow-up was 729±411 days. Stroke recurrence was low (5.8%, n=28) and similar in patients with massive RLSh, with nonmassive RLSh, and with no RLSh, in both the younger group (3.4% vs 2.3% vs 4.5%, respectively; P=0.75) and in the whole population (5.0% vs 6.2% vs 6.3%, respectively; P=0.58). Regression analysis found no association between massive RLSh and recurrent stroke in either group (in the whole population, odds ratio=0.94; 95% CI, 0.36 to 2.40; P=0.89; in the younger population, odds ratio=0.93; 95% CI, 0.18 to 4.91; P=0.93). These results were similar when concurrent atrial septal aneurysm and massive RLSh were analyzed and when antithrombotic treatment and concomitant stroke risk factors were included.

Conclusions—These results suggest that neither massive RLSh nor massive RLSh with concurrent atrial septal aneurysm is an independent risk factor for recurrent stroke, in either the general or younger stroke populations. (Stroke. 2008;39:3131-3136.)

Key Words: transcranial Doppler ■ patent foramen ovale ■ echocardiography ■ cryptogenic stroke

According to conventional etiologic criteria, strokes that remain undetermined after exhaustive investigation make up 30% to 40% of the total. This proportion is even higher in young stroke patients. Patent foramen ovale (PFO) and atrial septal aneurysm (ASA) have been identified as potential risk factors for stroke, particularly in patients with stroke of unknown origin. Some studies have demonstrated an association between the degree of right-to-left shunt (RLSh), the size of PFO, or the presence of ASA and the risk of stroke. However, few of them have analyzed the risk of stroke recurrence and particularly the impact of concomitant vascular risk factors for first-ever stroke on stroke recurrence. Furthermore, there is a lack of evidence about the best therapeutic option both in preventing a first stroke and in reducing recurrence.

The recurrence rate of PFO-RLSh–associated stroke has not been established, and the few studies on secondary prevention have been unable to demonstrate an effective therapeutic strategy. Despite this lack of evidence, PFO occlusion is becoming a popular treatment. The aim of this multicenter study was to prospectively investigate whether stroke recurrence was associated with the magnitude of the RLSh in patients with a first cryptogenic stroke by using contrast transcranial Doppler (c-TCD) as the reference test.
Subjects and Methods

Study Design

The Multicenter Study into RLSH in Cryptogenic Stroke (CODICIA; www.estudio-codicia.org) is a prospective, multicenter, observational study undertaken from March 2000 to October 2005 by the Cerebrovascular Diseases Group of the Spanish Neurological Society in 17 Spanish neurology departments (see Appendix). CODICIA included patients age ≥18 years, with a recent ischemic stroke or transient ischemic attack (TIA, <30 days), and a diagnosis of cryptogenic stroke according to TOAST criteria with no definite cause of stroke after a standardized etiologic protocol, including a complete medical history of vascular risk factors, a history of migraine, and potential precipitant stroke factors (such as the Valsalva maneuver, suggesting paradoxical embolism), clinical examination, routine blood and coagulation tests, brain computed tomography or magnetic resonance imaging, transcranial and celiac Doppler ultrasound, and 12-lead ECG and echocardiography. A detailed coagulation study was performed on young patients (<55 years). The performance of magnetic resonance imaging or conventional angiography, 24-hour ECG recording, lumbar puncture, and additional investigations was left to the discretion of the investigator in charge of the patient. c-TEE was used as the screening test for RLSH and as the “gold standard” in quantifying its magnitude.8,9

RLSH and PFO Investigation Protocol

The presence of RLSH was investigated with a 2-MHz probe for monitoring the middle cerebral artery through the temporal window, as previously described.8 In brief, a mixture of saline solution (9 mL) and air (1 mL) agitated between two 10-mL syringes connected by a 2-way stopcock was used as the study contrast agent. The solution was immediately injected in the antecubital vein through a 20-gauge/32-mm catheter to obtain a bolus of air microbubbles. This procedure was performed 3 times during normal breathing and 3 times during the Valsalva maneuver. Standardization of the Valsalva maneuver was achieved by asking patients to blow into a manometer until 50 to 60 mm Hg of pressure was reached and held for at least 5 to 7 seconds. The air microbubbles were injected as a bolus in 1 to 2 seconds. The patients had been previously instructed as to how the Valsalva maneuver should be performed. Efficacy was demonstrated by a reduction of the mean velocity in the middle cerebral artery of at least 25%. We quantified the magnitude of RLSH (defined by the appearance of microbubbles in the first 7 seconds after bolus infusion) by counting the number of microbubbles in the middle cerebral artery. Patients were divided into 5 groups on the basis of the maximum number of microbubble signals in the middle cerebral artery in any single frame after venous injection of the agitated saline solution: “normal” TCD study= no microbubbles, “small” =<10 microbubbles, “moderate” = 10 to 25 microbubbles, “shower” pattern = > 25 microbubbles, and “curtain” pattern = uncountable microbubbles. To analyze the main objective of CODICIA, we reallocated the patients into 3 groups: “no RLSH”, “nonmassive RLSH” (=5 microbubbles), and “massive RLSH” (m-RLSH; corresponding to the shower and curtain patterns).8 Further details, including video images of the performance of the procedure, can be seen on the study’s website (www.estudio-codicia.org).

All patients underwent an echocardiography study as part of the routine etiologic work-up for cryptogenic stroke. The indication for transthoracic or transesophageal echocardiography (TEE) was made according to the best judgment of the neurologist, unless specifically indicated by the CODICIA protocol, and was always performed by the cardiologist at the participating center. TEE examination was required when m-RLSH was detected by c-TCD. The TEE study was performed after topical anesthesia of the oropharynx and mild sedation with intravenous midazolam (0.5 to 1.5 mg). The echoscope was inserted into the esophagus. Contrast material was injected through the antecubital vein as previously described. PFO was diagnosed when microbubbles were detected in the left atrium within 3 cardiac cycles of their appearance in the right atrium. ASA was diagnosed when the atrial septum exhibited an excursion of >15 mm.

Outcome Variables and Follow-Up

Baseline stroke severity was assessed with the Canadian Stroke Scale at admission. Functional outcome was evaluated at discharge, at 3 months, and annually thereafter by use of the modified Rankin scale, as were stroke or TIA recurrence, vascular events, and death (see downloadable clinical report form). Treatment decisions (antiplatelet treatment or anticoagulation) were at the discretion of the neurologist for each patient.

Statistical Analysis

Proportions between groups were compared with the χ² test. Continuous variables were expressed as mean±SD or median and quartiles and were compared by the Student t test or the Mann-Whitney test, as appropriate. The risk of stroke recurrence for RLSH magnitude was determined by means of logistic-regression analysis according to the enter method. Those variables with a P<0.05 in the bivariate analysis were included as covariates in the multivariate analysis (age, inclusion event, and classic vascular risk factors, together with RLSH magnitude). Although treatment was not selected as a predictor of stroke recurrence in the bivariate analysis, we decided to repeat the logistic model after adjusting for this variable and to analyze the potential interaction between treatment and RLSH.

Results

Four-hundred eighty-six consecutive patients with cryptogenic stroke were included. Three-hundred eighty-eight patients (79.8%) had an ischemic stroke and 98 (20.2%), a TIA. All patients were evaluated by a neurologist before inclusion in the study to confirm the cryptogenic nature of the event. The mean time from stroke onset to inclusion was 9.3±10.3 days. Twenty-four additional patients were lost to follow-up and thus, were excluded from the analysis.

RLSH was found in 61.1% of patients, and 41.2% of patients had an m-RLSH. The prevalence of both RLSH and m-RLSH was higher in younger patients than in the whole group (70.7% vs 52.5%, and 51.5% vs 31.9%, respectively; both P<0.001). c-TEE was performed in 295 patients in the whole group and in 170 of 229 in the younger group. Similar to other prospective c-TEE11,12 and c-TCD studies, the proportion of patients with RLSH detected by c-TCD (61.1%, massive in 41.2%) was higher than in those with PFO shown by c-TEE (45.7%, moderate or large in 34.1%). ASA together with PFO was detected by c-TEE in 28.5% of patients in the whole population and in 27.6% in the younger group.

The clinical characteristics are shown in Table 1. Migraine was more prevalent in m-RLSH patients in both the whole group (14.7 vs 6.9; P=0.02) and the younger population (21.2 vs 9.1; P=0.02) as was the presence of ASA (whole population=48.2 vs 3.1, P<0.001; younger population=46.0 vs 2.6, P<0.001). Diabetes and hypertension were significantly more frequent in patients without m-RLSH. Bilateral topography of acute brain infarction was more frequent and infarct volume was smaller (whole population=11.85 [2.00 to 25.1] vs 7.7 [1.30 to 17.75], P=0.08; younger population=14.3 [1.5 to 35.4] vs 6.5 [1.3 to 16.6], P=0.02) in patients with m-RLSH.

Patients with m-RLSH had a less severe stroke at admission and a better modified Rankin Scale score at discharge and follow-up in both the whole population and after excluding patients with TIA (Table 1). The coexistence of ASA was unrelated to either stroke severity or functional outcome.
Risk of Stroke Recurrence

The mean time of follow-up was 729.2 ± 410.8 days. Stroke recurrence occurred in 28 patients (5.8%) in the whole population and was similar both in patients with m-RLSh and in patients with nonmassive or no RLSh, both in the younger group (3.4% vs 2.3% vs 4.5%, respectively; P = 0.23) and in the whole population (5.0% vs 6.2% vs 6.3%, respectively; P = 0.75) and in the whole population (odds ratio = 3.31; 95% CI, 1.48 to 7.41; P = 0.003).

Outcome by Treatment

Three hundred eighty-four patients (79%) received antiplatelet treatment after admission and 102 (21%) received anticoagulation therapy with acenocoumarol (target international normalized ratio of 2 to 3). No statistically significant differences were found in stroke recurrence in patients with m-RLSh with respect to the treatment received (antiplatelet vs anticoagulation) in either group (younger population, 3.5% vs 3.2%; P = 0.94; population as a whole, 6.6% vs 1.6%; P = 0.18).

Logistic-regression analysis, adjusted by treatment (as well as variables associated with increased stroke risk recurrence in the bivariate analysis), revealed no association between m-RLSh and recurrent stroke (odds ratio = 1.44; 95% CI, 0.46 to 4.48; P = 0.53). As expected, neither treatment was associated with recurrent stroke, nor was the interaction between treatment and RLSh found to be significant.

Discussion

Although the association between RLSh due to PFO and cryptogenic stroke has been well established,2–10 there are few data and widely varying results with regard to the
relevance of PFO as a predictor of stroke recurrence in prospectively designed studies. Only 1 of those studies analyzed treatment for preventing stroke recurrence. The CODICIA study is a multicenter, prospective, observational study of patients with a first cryptogenic stroke that analyzed the risk of stroke recurrence and evaluated the efficacy of medical treatment as a secondary objective. CODICIA has been conducted exclusively by neurologists, in both evaluation of the target event and evaluation of stroke recurrence and is the only study to use both c-TCD and c-TEE in detecting PFO-related RLSh.

Our study confirms the results of the PFO-ASA and PICCS studies regarding the risk of stroke recurrence in patients with PFO. In the CODICIA study, this recurrence was low and was similar in patients with and without RLSh and in those with RLSh with concurrent ASA. In line with previous results, where only m-RLSh was associated with cryptogenic stroke, we considered RLSh as massive, nonmassive, and absent for analysis of the main objective. However, no differences were found when the risk of stroke recurrence was analyzed by each magnitude of RLSh. As in other studies, c-TCD showed a higher sensitivity than did c-TEE in RLSh detection and quantification.

The 3 previous studies, together with the present study, can be seen as only providing complementary information, given the lack of uniformity in their design (Table 3). The French

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**Table 2. Factors Associated With Stroke Recurrence in the Whole and Younger Groups**

<table>
<thead>
<tr>
<th>Stroke Recurrence</th>
<th>Whole Group</th>
<th>Younger Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean±SD, y</td>
<td>60.7±13.4</td>
<td>55.9±15.3</td>
</tr>
<tr>
<td>Sex, % men</td>
<td>46.4</td>
<td>60.7</td>
</tr>
<tr>
<td>Inclusion event, % stroke</td>
<td>57.1</td>
<td>81.2</td>
</tr>
<tr>
<td>Alcohol intake &gt;40 g/d, %</td>
<td>10.7</td>
<td>8.1</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>28.6</td>
<td>32.2</td>
</tr>
<tr>
<td>Arterial hypertension, %</td>
<td>50.0</td>
<td>33.8</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>25.0</td>
<td>10.9</td>
</tr>
<tr>
<td>Ischemic cardiac heart disease, %</td>
<td>3.6</td>
<td>5.0</td>
</tr>
<tr>
<td>Migraine history, %</td>
<td>10.7</td>
<td>9.8</td>
</tr>
<tr>
<td>Stroke recurrence by RLSh magnitude</td>
<td>0.83</td>
<td>0.82</td>
</tr>
<tr>
<td>Non-RLSh</td>
<td>42.9</td>
<td>38.6</td>
</tr>
<tr>
<td>Non—m-RLSh</td>
<td>21.4</td>
<td>19.9</td>
</tr>
<tr>
<td>Massive RLSh</td>
<td>35.7</td>
<td>41.5</td>
</tr>
<tr>
<td>m-RLSh plus ASA*</td>
<td>37.5</td>
<td>28.0</td>
</tr>
<tr>
<td>Treatment during follow-up, % anticoagulation</td>
<td>14.3</td>
<td>20.9</td>
</tr>
<tr>
<td>Infarct volume, cm³†</td>
<td>11.2±12.9</td>
<td>18.8±27.3</td>
</tr>
<tr>
<td>Stroke severity at admission (Canadian stroke scale)†</td>
<td>9 [6.0–9.5]</td>
<td>8.5 [6.5–10]</td>
</tr>
</tbody>
</table>

*Including patients for whom TEE was performed (n=295 and n=170 in the whole and younger groups, respectively).
†Excluding patients with TIA.
study, which included only young patients (<55 years) with cryptogenic stroke, found an increased risk of recurrence in patients who had PFO together with ASA. These results were not confirmed by the PICSS nor by the present study. Like the French study, the PICSS was conducted with c-TEE only, although in this case, the age range was unrestricted. None of these studies showed that PFO, whatever the degree of shunting, was a significant predictor of stroke recurrence.

In recent years, anticoagulation and PFO closure have increasingly been used in patients with m-RLSh, particularly when associated with ASA. In CODICIA, 30% of patients with m-RLSh received anticoagulant therapy. As in the PICSS study, no differences were detected in rates of stroke recurrence between patients treated with antiplatelet agents and those who received anticoagulation therapy. However, no definitive conclusions can be drawn with regard to the best treatment option, because treatment in the CODICIA study was not randomized and was always left to the best judgment of the clinician.

An interesting finding of the CODICIA study was the lower stroke severity in patients with cryptogenic stroke associated with m-RLSh in comparison with non–m-RLSh, a difference that was still seen in the modified Rankin Scale scores during the entire follow-up period. No differences in stroke subtype were found, and the cause may lie in the smaller infarct volume in patients with m-RLSh. This finding would suggest that m-RLSh is less dangerous than the classic stroke risk factors (Table 1). Similar results were previously reported by the French PFO-ASA study, in which the modified Rankin Scale only was used at admission.17

Our study has certain limitations. The statistical power of the analysis of stroke recurrence, and particularly of the therapeutic efficacy in preventing stroke recurrence, was low due to the small number of events. However, the early inclusion of patients into the study during the acute phase by the neurologist in charge of the patient, together with the use of c-TCD as a tool for determining inclusion, makes it unlikely that a bias in stroke selection would have occurred against patients with early stroke recurrence.

A further possible limitation is that c-TEE was not routinely performed in the CODICIA study, and hence, the results as they relate to ASA should be interpreted with caution. The study was designed to examine RLSh by TCD to mimic as closely as possible the situation in daily clinical practice. c-TCD was therefore considered the reference test to evaluate RLSh in patients diagnosed as having cryptogenic stroke. c-TEE was used as a diagnostic tool of potential cardioembolic sources of stroke according to accepted guidelines and also to provide complementary information when m-RLSh was observed. However, in evaluating the importance of this possible drawback, it should be noted that previous studies, as well as the CODICIA study itself, have shown that c-TCD is as sensitive or more sensitive than c-TEE in the detection and particularly the quantification of RLSh through a PFO.

A cautious interpretation should be made of the efficacy of medical treatment, because this was not randomized. However, given the low risk of stroke recurrence, particularly in younger patients, the low severity of recurrences, and the well-known iatrogenic effect of anticoagulation in long-term therapy, the use of anticoagulants in patients with m-RLSh as a preventive treatment against recurrences should probably not be encouraged.

In conclusion, the results of the CODICIA study show that there is a low risk of stroke recurrence in patients with cryptogenic stroke when m-RLSh is present, when m-RLSh is not present, and when RLSh of any type is present with ASA. Because the risk of stroke recurrence was low and no significant differences were found between the use of antiplatelet and anticoagulant agents, our results offer no justification for the use of potentially dangerous or aggressive treatments. Hence, although this was not 1 of the objectives of our study, we are led to conclude that invasive treatments such as percutaneous PFO occlusion should be performed only within the framework of a current clinical trial.

Appendix: Participating Centers and Investigators of the CODICIA Study
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Disclosures

None.

References

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