Effect of Medical Treatment in Stroke Patients With Patent Foramen Ovale

Patent Foramen Ovale in Cryptogenic Stroke Study

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Background—Patent foramen ovale (PFO) is associated with stroke, but there are no randomized studies to evaluate the efficacy of antithrombotic therapies.

Methods and Results—The PFO in Cryptogenic Stroke Study was a 42-center study that evaluated transesophageal echocardiographic findings in patients randomly assigned to warfarin or aspirin in the Warfarin-Aspirin Recurrent Stroke Study. In this study, 630 stroke patients were enrolled, of whom 312 (49.5%) were randomized to warfarin and 318 (50.5%) to aspirin. Of these, 265 patients experienced cryptogenic stroke and 365 experienced known stroke subtypes. End points were recurrent ischemic stroke or death. PFO was present in 203 patients (33.8%). There was no significant difference in the time to primary end points between those with and those without PFO in the overall population ($P=0.84$; hazard ratio 0.96; 95% CI 0.62 to 1.48; 2-year event rates 14.8% versus 15.4%) or in the cryptogenic subset ($P=0.65$; hazard ratio 1.17; 95% CI 0.60 to 2.37; 2-year event rates 14.3% versus 12.7%). There was no significant difference among those with no, small, or large PFO ($P=0.41$ for small PFO and $P=0.16$ for large PFO; 2-year event rates for no, small, and large PFO, 15.4%, 18.5%, and 9.5%, respectively). There was no significant difference between patients with isolated PFO and those with PFO in association with atrial septal aneurysm ($P=0.84$; 2-year event rates 14.5% versus 15.9%). In patients with PFO, there was no significant difference in the time to primary end points between those treated with warfarin and those treated with aspirin ($P=0.49$; hazard ratio 1.29; 95% CI 0.63 to 2.64; 2-year event rates 16.5% versus 13.2%).

Conclusions—On medical therapy, the presence of PFO in stroke patients did not increase the chance of adverse events regardless of PFO size or the presence of atrial septal aneurysm. (Circulation. 2002;105:2625-2631.)

Key Words: stroke ■ anticoagulants ■ aspirin ■ echocardiography

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Patient foramen ovale (PFO) has been associated with stroke, especially with cryptogenic stroke, or stroke of undefined cause,1–3 which accounts for up to 40% of all ischemic strokes.4 The recurrence rate of adverse events in stroke patients with PFO, however, has not been established.5–8 Furthermore, the number of reports on the use of percutaneous devices9–11 or surgical closure12–14 in stroke patients with PFO is increasing. Consequently, it becomes ever more important to determine the rate of adverse events in medically treated stroke patients with PFO.

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A variety of studies have demonstrated the association of larger PFOs with increased shunt in patients with cryptogenic stroke.15–18 A combination of PFO and atrial septal aneurysm (ASA) has also been shown to be an increased stroke risk.19,20 Accordingly, the PFO in Cryptogenic Stroke Study (PICSS) sought to define the rate of recurrent stroke or death in stroke patients with or without PFO, defined by transesophageal echocardiography (TE), who were randomly assigned to warfarin or aspirin in a double-blind design. We also sought to determine whether the size of the PFO or the concurrent presence of PFO and ASA influenced the rate of these events.

Methods

Patient Recruitment

PICSS (National Institutes of Health [NIH] grant RO1-NS-32525, S. Homma, Principal Investigator [PI]) collaborated with the Warfarin-Aspirin Recurrent Stroke Study (WARSS: NIH grant RO1-NS-28371, J.P. Mohr, PI) for patient recruitment and follow-up. PICSS was conceived and administered independently of WARSS, however, and the hypotheses were defined before the study initiation. WARSS was a 48-center double-blind study that randomized 2206 stroke patients to either warfarin or aspirin and followed them up for stroke recurrence or death over a 24-month period.21 Patient recruit-
ment for WARSS started in June 1993, and follow-up was completed in June 2000. At each center, cryptogenic stroke patients in WARSS were solicited to undergo TE. PICSS also included all WARSS patients who underwent TE for clinical purposes. The Institutional Review Board at each participating center approved all protocols for WARSS and PICSS, and each participant gave informed consent.

Eligibility
Patients 30 to 85 years old for whom warfarin therapy was deemed safe were eligible. Eligible patients had experienced ischemic stroke within the previous 30 days and were rated ≥3 on the Glasgow Outcome Scale (severe disability, moderate disability, and no or minimal disability). Ineligible patients had baseline INR above the normal range (>1.4), had stroke related to a procedure or attributable to a cardioembolic source, or planned to undergo surgery for high-grade carotid stenosis. Patients with a contraindication to TE were excluded from consideration for participation in PICSS.

Stroke Subtyping
All baseline strokes were subtype by a local neurology PI on the basis of predefined criteria modeled after the NINDS Stroke Data Bank and the Trial of OrganoNoon in Acute Stroke Therapy (TOAST). Subtypes were lacunar, large-vessel, cryptogenic, other determined cause, and conflicting mechanisms. Cryptogenic strokes typically have no definite source of the stroke despite an adequate diagnostic evaluation.

Medications and Blinding
Medications used were aspirin (Sterling-Winthrop, now Bayer), 325-mg tablets taken once daily, and warfarin (DuPont) in 2-mg scored tablets taken daily, adjusted to achieve and maintain INR 1.4 to 2.8. Patients were randomized to active aspirin or warfarin and an identical placebo.

Follow-Up
All patients were followed up for 2 years, operationalized as 24±1 months (maximum 761 days). Follow-up was made on a monthly basis by phone or in person to assess compliance and to regulate INRs. Quarterly and annual in-person follow-ups for detailed examination were also made.

TE Protocol
All patients underwent TE guided by a predefined PICSS protocol using either a biplane or multplane probe. The TE protocol emphasized delineation of TE-associated embolic sources, including extensive characterization of PFO. Saline contrast injection was performed at rest as well as with Valsalva maneuver or cough. Ongoing quality control was maintained with feedback to the site regarding TE study quality.

Analysis of Tapes
All TE tapes were analyzed by a single observer (S.H.) blinded to treatment assignment, stroke subtype, or outcome. PFO was determined to be present if, on saline contrast injection, ≥1 microbubble appeared in the left atrium within 3 cardiac cycles after opacification of the right atrium. PFO size was determined by use of a caliper on a video frame demonstrating the maximum separation of the septum primum from the septum secundum. The number of microbubbles was counted from a video frame demonstrating the maximum number on a video frame within 3 cardiac cycles from the opacification of the right atrium. PFOs with separation of the septum primum from the septum secundum or with ≥10 microbubbles appearing in the left atrium were classified as large, and all other PFOs as small. ASA was defined as a movement of the atrial septum into the left or right atrium ≥10 mm from its midline position.

Assessment of End Points
The primary end point was recurrent ischemic stroke or death from any cause. Clinical evidence of a recurrent ischemic stroke was a new lesion on CT or MRI, or when new lesions were absent, a clinical syndrome consistent with stroke of >24 hours’ duration. Major hemorrhage was defined as intracranial, intraspinal, intracerebral, subarachnoid, subdural, or epidural hemorrhage or any other bleeding requiring transfusion. Bleeding episodes not classified as major were defined as minor. All clinical and radiological events were adjudicated independently by a panel, and all hemorrhages were adjudicated by a treatment-blinded adjudicator who classified them as major or minor.

Statistical Analysis
The primary null hypothesis was that the presence or absence of a PFO did not affect the time to recurrent ischemic stroke or death from any cause in patients treated with either warfarin or aspirin. Secondary null hypotheses were that PFO size or the degree of shunt did not influence the time to recurrent ischemic stroke or death, that treatment with either warfarin or aspirin did not differentially affect the time to primary end point, that the presence of a PFO did not affect the time to primary end point or transient ischemic attack (TIA), and that the presence of ASA did not modify the risk of recurrent ischemic stroke or death associated with PFO.

The original target sample size for the primary null hypothesis was 474 patients, which was estimated to have 80% power for detecting a doubling of the risk of the primary end point (α=0.05). The final sample size provided for 80% power with a relative hazard ratio of 1.86. Kaplan-Meier curves were constructed, and a log-rank test was used to compare curves for those with and without PFO. A Cox proportional-hazards model was used to determine the relative hazards ratio and associated CI. Similar analyses were performed for secondary hypotheses. For the primary null hypothesis, a multivariate proportional-hazards model was used to adjust for variables that significantly (P<0.05) affected outcome and were out of balance between patients with and without PFO. Variables were defined as out of balance when the difference in means or proportions was significant at the 0.20 level. Reported event rates are actuarialized estimates from the Kaplan-Meier curves that adjust for censoring. A value of P<0.05 was considered significant for all analyses.

Results
In this study, 630 patients were randomized at a steady rate during the recruitment phase. After the planned 2 years of follow-up, end-point status was known for 620 patients (98.4%). The remaining 10 (1.6%) withdrew consent or were lost to follow-up at a mean of 13.2±10.5 months after randomization. Of the 2206 patients enrolled and randomized in WARSS, 630 (28.6%) were enrolled in PICSS. When the strokes among the 630 PICSS patients were subtyped, 265 (42.1%) were cryptogenic, 244 (38.7%) lacunar, 68 (10.8%) large-vessel, 27 (4.3%) other determined cause, and 26 (4.1%) conflicting mechanism.

Laboratory Testing
Of the 630 patients, 312 (49.5%) were randomized to warfarin and 318 (50.5%) to aspirin. The mean INR in the warfarin-treated patients was 2.04±0.99 (median 1.86).

Baseline TE Findings
Of 630 patients, TE studies were available for analysis in 627. Of these, 601 (95.9%) had TE images adequate for analysis of PFO and 600 (95.7%) for analysis of ASA. PFO was present in 203 (33.8%) of the patients, of which 58.6% (119/203) were classified as small and 41.4% (84/203) as large. ASA was present in 11.5% (69/600) of the patients. Baseline
characteristics of the patients with and without PFO are shown in Table 1.

**Association of PFO and PFO Size With Cryptogenic Stroke**

Among the patients with TE images adequate for PFO analysis, PFO was found in 39.2% (98/250) of patients with cryptogenic stroke, compared with 29.9% (105/351) in patients with known cause of stroke (\(P=0.02\)). Large PFOs were found in 20.0% (50/250) of cryptogenic stroke patients compared with 9.7% (34/351) in those with known cause (\(P=0.001\)).

**End Points**

The analyses were adjusted for the 10 patients lost to follow-up by use of a prespecified imputation procedure. With this model, the overall primary event rate was 15.9%. Among the 601 patients with TE images adequate for PFO analysis, there were a total of 92 end points (15.3%). Seventy-one strokes and 21 deaths occurred. In addition, 34 TIsAs occurred, including 7 that occurred before the primary event. The rate of major hemorrhage was similar between the patients receiving warfarin and those receiving aspirin (1.78 events/100 patient-years on warfarin versus 1.91 events/100 patient-years on aspirin; rate ratio 0.93, \(P=1.0\)).

The rate of minor hemorrhage, however, was significantly higher in patients on warfarin compared with those on aspirin (22.9 events/100 patient-years on warfarin versus 8.66 events/100 patient-years on aspirin; rate ratio 2.64; \(P<0.001\)).

**Primary Events in Relation to PFO Status**

**Presence of PFO**

For the entire group, there was no significant difference in the time to recurrent stroke or death between the patients with and without PFO enrolled in our study (\(P=0.84\); hazard ratio 0.96; 95% CI 0.62 to 1.48; 2-year event rates 14.8% versus 15.4%) (Figure). In a multivariate analysis adjusting for factors that significantly influenced outcome and were unevenly distributed (age, marital status, sedentary lifestyle, diabetes, hypertension, Glasgow score, alcohol consumption), the presence of PFO did not significantly affect the time to stroke recurrence or death (\(P=0.36\); hazard ratio 1.24; 95% CI 0.79 to 1.95). In the cryptogenic group, there was also no significant difference in the time to primary events between patients with and those without PFO (\(P=0.65\); hazard ratio 1.17; 95% CI 0.60 to 2.37; 2-year event rates 14.3% versus 12.7%).

**PFO Size and ASA**

The effect of PFO size and the degree of shunt on outcome is demonstrated in Table 2. There was no significant difference in the time to stroke recurrence or death among those with no, small, or large PFO. When the event rates in patients with
isolated PFO (n = 159) and those with PFO and ASA (n = 44) were compared, there was no significant difference (P = 0.84; 2-year event rates 14.5% versus 15.9%).

**Treatment With Warfarin or Aspirin**
As shown in Table 3, when the groups with and without PFO were analyzed in relation to the efficacy of warfarin or aspirin, no significant differences were found for the time to primary events. Although the 2-year risk of stroke or death was lower among warfarin-treated cryptogenic stroke patients with PFO, this was also true for cryptogenic stroke patients without PFO, and the differences were not statistically significant.

**Inclusion of TIA as End Point**
When TIA was included as an end point along with recurrent stroke or death, overall, there was no significant difference between patients with and without PFO (P = 0.99; hazard ratio 1.00; 95% CI 0.68 to 1.46; 2-year event rates 19.7% versus 19.4%). No significant difference was observed in the multivariate analysis either (P = 0.40; hazard ratio 1.19; 95% CI 0.80 to 1.76). In the cryptogenic subset, no significant difference was observed between patients with and without PFO (P = 0.49; hazard ratio 1.23; 95% CI 0.69 to 2.20; 2-year event rates 20.4% versus 16.6%). Among all patients with PFO, no significant difference was observed between warfarin- and aspirin-treated patients (P = 0.15; hazard ratio 1.59; 95% CI 0.85 to 2.97; 2-year event rates 23.7% versus 16.0%). Similarly, no significant difference was observed between cryptogenic stroke patients with PFO treated with warfarin or aspirin (P = 0.48; hazard ratio 0.72; 95% CI 0.29 to 1.81; 2-year event rates 16.7% versus 23.2%).

**Discussion**
An association of PFO with cryptogenic stroke was recently demonstrated by several groups.1–4 The number of patients in each report, however, was small. In this study, with a significantly larger number of patients, we confirm that PFO is associated with cryptogenic stroke. The prevalence of PFO among the general population is high. Autopsy studies indicate that there is a prevalence of up to 29%.28 The size and the degree of shunt appear to be important in determining the significance of PFO.15–18 In this study, with a large number of prospectively studied patients, we also confirm that larger PFOs are associated with cryptogenic stroke.

We demonstrate that when the stroke patients are treated medically, the rate of recurrent stroke or death is similar between patients with and without PFO. This was seen for the entire cohort and in the cryptogenic subset, with and without inclusion of TIA as an end point. This implies that on medical therapy, the effect of the presence of PFO does not manifest itself, at least for the 2-year duration after ischemic stroke. Furthermore, when the size or the degree of shunt through the PFO was evaluated, the rate of adverse events did not differ depending on PFO size. Thus, in our study, although PFOs and in particular large PFOs were associated with cryptogenic stroke, this did not increase the risk for adverse events while on medical therapy.

Mas and others have reported that a combination of PFO and ASA imparts an increased risk of stroke.19,20 In our study, however, we found that the patients with PFO alone and those with PFO and ASA experienced similar event rates, which in turn were similar to those of the patients without PFO. The difference in findings may be a result of several factors, including the older patient population in our study, inclusion of noncryptogenic as well as cryptogenic stroke subtypes in our study, and inclusion of death as an end point.

When the efficacy of warfarin was compared with that of aspirin in patients with PFO, there was no significant differ-

**TABLE 2. Two-Year Rates of Recurrent Stroke or Death in Patients With Different PFO Size and Shunt**

<table>
<thead>
<tr>
<th></th>
<th>No PFO (n=398)</th>
<th>Small PFO (n=119)</th>
<th>Large PFO (n=84)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event rate, %</td>
<td>15.4</td>
<td>18.5</td>
<td>9.5</td>
</tr>
</tbody>
</table>

Hazard ratio, small PFO, 1.23; 95% CI 0.76–2.00; P = 0.41. Hazard ratio, large PFO, 0.59; 95% CI 0.28–1.24, P = 0.16.

*Event rates are calculated from Kaplan-Meier curves at 2 years. Hazard ratios are calculated with no PFO as the reference group.
ence in the time to primary end points. Among the cryptogenic subgroup, in patients with and without PFO, there was a trend toward primary event reduction in warfarin-treated patients, as was seen in WARSS.²⁷ With and without inclusion of TIA as an end point, however, no significant difference was observed between warfarin- and aspirin-treated cryptogenic stroke patients with PFO. Thus, in stroke patients with PFO, therapy with warfarin or aspirin results in similar rates of adverse events. Whether the patients with PFO will experience further reduction in adverse events with closure of PFO remains to be seen. The mean INR achieved was 2.04 in our patients assigned to warfarin. WARSS has demonstrated that event rates decrease when INR is ≥1.5, and this effect remained similar for higher INRs.²⁷ Thus, we feel that appropriate anticoagulation was achieved in our patients.

The best treatment modality to prevent recurrent stroke in patients with PFO has not been defined. There are 4 major choices: surgical closure, percutaneous device closure, medical therapy with anticoagulant, and medical therapy with antiplatelet agents. In terms of surgical closure, we reported our experience in 28 cryptogenic stroke patients. With a mean follow-up time of 19 months, we saw 4 neurological events, all in patients ≥45 years old.¹² Devuyst et al¹³ followed up 30 patients with stroke and surgical PFO closure without any recurrent ischemic events. Dearani et al¹⁴ reported 8 TIAs in 91 patients with a mean follow-up of 2 years. For percutaneous closure, Bridges et al⁹ reported PFO closure in 36 patients with presumed paradoxical embolism and saw 4 TIAs in 8.4 months. Windecker et al¹⁰ reported 8 recurrent embolic events in 80 patients with a 1.6-year follow-up. Hung et al¹¹ reported on 63 patients followed up for 2.6 years with 4 recurrent neurological events. Reasons for recurrent ischemic events after either surgical or percutaneous PFO closure remain unclear. The cause for initial or subsequent stroke may not be paradoxical embolization, and thrombus formation at the site of surgical or device closure has been reported, which could serve as a potential source of embolism.²⁹,³⁰ Furthermore, incomplete closure of a PFO may lead to subsequent paradoxical embolization.

In terms of medical therapy, Bogousslavsky et al⁷ reported 5 deaths and 16 neurological events in 140 patients ≤60 years old treated with aspirin, warfarin, or surgery at 36 months of follow-up. Recently, Cujec et al⁸ reported on 52 cryptogenic stroke patients ≤60 years old with PFO followed up for 46 months compared with 38 without PFO; 14 with PFO experienced recurrent neurological events, compared with 6 without PFO. Most recently, Mas et al²⁰ reported a 4.5% recurrent stroke rate in 267 cryptogenic stroke patients ≤55 years old with PFO with 4 years of follow-up.

In interpreting the results of previously published studies, in addition to the small number of patients in most studies, most problematically, none of the studies randomized the therapy. As such, our data are unique in that the patients were randomly assigned to warfarin or aspirin in a double-blind manner. Furthermore, in our study, all TE studies were analyzed at a central location, and the patients were then rigorously followed up. Paradoxical embolization is one of the mechanisms for stroke in patients with PFO. This is consistent with the finding of an association of large PFO with cryptogenic stroke and a higher prevalence of deep venous thrombus in stroke patients with PFO as well as with the reports of trapped thrombus in PFO.³¹,³² Nevertheless, it is likely that ischemic stroke in patients with PFO has multiple causative mechanisms, including potential atrial vulnerability to arrhythmia.³³ Our results indicate that when receiving medical therapy, ischemic stroke patients with and without PFO have similar adverse event rates. Although the closure of PFO may further reduce the event rates, this remains to be demonstrated. Currently, we do not believe that it is necessary to close a PFO unless the patient has a contraindication to medical therapy or has a recurrent event on medical therapy.

**Limitations**

The association of PFO with cryptogenic stroke has not been shown consistently in all age groups. Thus, our findings may not apply to all age groups or to those who meet unambiguous criteria for paradoxical embolism. Because the mean INR in our warfarin-treated patients was 2.04, a higher INR might have given different results. Finally, the role of other antiplatelet agents remains untested.

**Appendix**

**Study Participants**

National Institute of Neurological Disorders and Stroke (NINDS): J.R. Marler, Program Director.


| TABLE 3. Two-Year Rates of Recurrent Stroke or Death* in Patients With and Without PFO Assigned to Warfarin or Aspirin |
|---|---|---|---|---|
| Entire PICSS cohort | Warfarin | Aspirin | Hazard Ratio (95% CI) | P |
| With PFO (n=203) | 16.5% (n=32) | 13.2% (n=26) | 1.29 (0.63–2.64) | 0.49 |
| No PFO (n=398) | 13.4% (n=195) | 17.4% (n=203) | 0.80 (0.49–1.33) | 0.40 |
| Cryptogenic cohort | With PFO (n=98) | 9.5% (n=42) | 17.9% (n=56) | 0.52 (0.16–1.67) | 0.28 |
| Without PFO (n=152) | 8.3% (n=72) | 16.3% (n=80) | 0.50 (0.19–1.31) | 0.16 |

*From Kaplan-Meier curves.


Hemorrhage Adjudicator: A.G.G. Turpie.

Institution, Names of Local Neurology PI, Cardiology Investigator, Coordinators, and Number of Patients Contributed to PICSS


Long Island–Jewish Medical Center: R. Libman, S. Roth, R. Gonzaga-Camfield (53).

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Maynmond Medical Center: A. Miller, A. Greengart, K. Chin, T. LaRocca (1).


University of Vermont: J. Dissin, R. Battle, R. Hamill, P. Krusinski, M. Fitzpatrick (1).

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References


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