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CME Practice Parameter: Recurrent stroke with patent foramen ovale and atrial septal aneurysm

Report of the Quality Standards Subcommittee of the American Academy of Neurology*

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Abstract—Objectives: 1) To evaluate the risk of subsequent stroke or death in patients with a cryptogenic stroke and a patent foramen ovale (PFO), atrial septal aneurysm (ASA), or both. 2) To establish the optimal method of stroke prevention in this population of patients. **Methods:** MEDLINE, the Cochrane database of systematic reviews, key meeting abstracts from 1997 to 2002, and relevant reference lists were searched to select studies that prospectively collected outcome data in cryptogenic stroke patients with and without interatrial septal abnormalities. Studies were also selected that prospectively compared at least two treatment options. The quality of each study was graded (class I to IV) using a standard classification-of-evidence scheme for each question. Risk analyses were performed and data were pooled when appropriate. **Results:** The literature search generated 129 articles of which only four fulfilled the inclusion and exclusion criteria. Two studies were graded class I, one study was graded class II, and one study was graded class IV for prognosis. Pooled results of the two class I and one class II studies demonstrated no increased risk of subsequent stroke or death in patients with PFO compared to those without (RR = 0.95, 95% CI 0.62 to 1.44). One class I study found increased risk of recurrent stroke in patients with PFO and ASA (annual rate = 3.8% versus 1.05%, RR = 2.98, 95% CI 1.17 to 7.58) but not increased risk of a composite of stroke and death (annual rate = 3.8% versus 1.8%, RR = 2.10, 95% CI 0.86 to 5.06). Regarding therapy, one study was graded class II, one study class III, and two studies class IV. Among patients with cryptogenic stroke and PFO or ASA, there was no significant difference in stroke or death rate in warfarin-treated patients relative to aspirin-treated patients and the confidence intervals were unable to rule out a benefit of one drug over the other (annual rate = 4.7% versus 8.9%, RR = 0.53, 95% CI 0.18 to 1.58). Minor bleeding rates were higher in the cohort of patients who received warfarin (22.9/100 patient-years versus 8.66/100 patient-years, rate ratio = 2.64, $p < 0.001$). No studies compared medical therapy with surgical or endovascular closure. **Conclusion:** PFO is not associated with increased risk of subsequent stroke or death among medically treated patients with cryptogenic stroke. However, both PFO and ASA possibly increase the risk of subsequent stroke (but not death) in medically treated patients younger than 55 years. In patients with a cryptogenic stroke and an atrial septal abnormality the evidence is insufficient to determine if warfarin or aspirin is superior in preventing recurrent stroke or death, but minor bleeding is more frequent with warfarin. There is insufficient evidence to evaluate the efficacy of surgical or endovascular closure.

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Mission statement. The Quality Standards Subcommittee (QSS) develops evidence based, clinically relevant guidelines to aid in the practice of neurology. This practice parameter assesses the risk of re-

current stroke and the therapeutic options available to patients with a cryptogenic stroke and a patent foramen ovale (PFO), atrial septal aneurysm, or both.

*See Appendix 3 on page 1049 for a listing of QSS members.

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Background and justification. A PFO develops when fibrous adhesions fail to seal the atrial septum after birth, allowing the persistence of a potential shunt between the right and left atria of the heart.¹ This is a common finding in the general population: autopsy series have reported an overall prevalence ranging from 17% to 27%.^{2,3} Echocardiographic studies have reported widely variable estimates of PFO prevalence depending on the methods used, although a large population-based study using transesophageal echocardiography (TEE) found PFO in 25.6%.⁴ An atrial septal aneurysm (ASA) is present when redundant tissue in the region of the fossa ovalis results in excessive septal wall motion during respiration (usually defined as >10 to 15 mm excursion).¹ The reported prevalence of ASA has also varied tremendously although the population-based TEE study reported a prevalence of 2.2%.⁴ Up to 83% of patients with ASA also have a right-to-left shunt,⁵ and in patients with PFO, the presence of an ASA has been associated with a larger separation between the septum primum and secundum, a prominent eustachian valve, presence of a Chiari network, and a larger right-to-left shunt.⁶⁻⁹

Among patients younger than 55 years, as many as 40% of strokes are described as cryptogenic, with no identified cardioembolic or large vessel source, and in a distribution that is not consistent with small vessel disease.¹⁰ Numerous studies have established that there is an increased prevalence of PFO and ASA in patients who have had a cryptogenic stroke.¹¹⁻¹⁶ A comprehensive meta-analysis of case-control studies comparing patients under 55 years of age who had an ischemic stroke to control groups of non-stroke patients reported an increased likelihood of finding a PFO (OR = 3.1; 95% CI, 2.3 to 4.2) or an ASA (OR = 6.1; 95% CI, 2.5 to 15.2) in stroke patients.¹⁷ Moreover, multiple studies have shown an association between degree of shunt or size of PFO and the risk of stroke and stroke recurrence.¹⁸⁻²²

These findings have suggested a causal relationship between atrial septal abnormalities and stroke, although this association and the mechanism by which it may cause a stroke have been debated. While paradoxical embolism is the most commonly ascribed mechanism, there is some evidence to support alternative etiologies such as cardiac in situ thrombus formation and atrial arrhythmias.^{5,14,16,23-25} These alternative etiologies may have implications for management of these patients, as atrial arrhythmias are unlikely to resolve following closure procedures.

There are very few data regarding the risk of a first stroke in people who have an atrial septal abnormality. A review of the literature revealed only one abstract that describes a prospective population-based cohort who had a transthoracic echocardiogram [TTE] to evaluate for atrial septal abnormalities. Incidence of ischemic stroke was 1.10/100 person-years in subjects with PFO and 0.97/100 person-years in those without PFO.²⁶ In patients less than 60 years of age, the incidence of stroke in patients with PFO was only 0.52%

Table Inclusion and exclusion criteria used for the literature search

Inclusion	Exclusion
Type of paper	Not relevant to the clinical question
Abstracts, original papers, reviews	Types of studies
Relevant to the clinical questions	Retrospective cohort
Human subjects	Case control
Possible interventions	Case series
No treatment	Case reports
Antiplatelet therapy	Animal subjects
Closure with surgery	
Closure with percutaneous device	
Outcome measures	
Recurrence rate of stroke, or death	
Rate of adverse events	
Types of studies	
Randomized controlled trials	
Prospective cohort studies	
Any language	

over the total follow-up period. These data suggest that primary preventative interventions may be unlikely to have a worthwhile risk-to-benefit ratio for patients with PFO. Regardless, the clinical problem often faced by neurologists is how to manage patients who are found to have an atrial septal abnormality after they have had a cryptogenic stroke.

The natural history without treatment for patients who have an atrial septal abnormality and have already had a stroke has not been well established. Instead, multiple studies have attempted to determine the risk of recurrence in the setting of at least one type of intervention. Therapeutic options range from antiplatelet therapy and anticoagulation to surgical or endovascular closure of the atrial shunt and reports have varied considerably (between 0 and 19%) for annual risk of recurrent stroke or TIA.^{6,21,27-32} Thus, optimal management of these patients remains a difficult challenge.

We performed a systematic review and critical appraisal of the literature to answer two clinically relevant questions:

- What is the risk of recurrent stroke in patients with cryptogenic stroke and a PFO, an ASA, or both a PFO and an ASA?
- What is the best intervention to reduce the risk of subsequent stroke while minimizing adverse effects?

Based upon our results, we propose recommendations for management and future avenues of research.

Process. *Identification and selection of studies.* Literature searches were performed using the following keywords and search paradigm: (“stroke” or “CVA” or “cerebrovascular disease”) and (“PFO” or “patent foramen ovale” or “atrial septal defect” or “atrial septal

aneurysm”) and (“aspirin” or “anti-platelet” or “warfarin” or “anticoagulation” or “closure”). This search was applied to the following databases on June 24, 2002: the National Library of Medicine’s Pub Med search engine, which includes citations from 1966 through June 2002; the Cochrane database of systematic reviews; abstracts from the American Heart Association Stroke meetings, 1997–2002; and abstracts from American Academy of Neurology meetings, 1997–2002.

We screened the resulting articles and their references using the inclusion and exclusion criteria described in the table. Specifically, we selected randomized-controlled trials (RCT) or prospective cohort studies that made one of two comparisons:

- Event rates in patients with cryptogenic stroke and atrial septal abnormalities versus patients with a cryptogenic stroke and no atrial septal abnormality
- Event rates in patients with cryptogenic stroke and atrial septal abnormalities who received different treatments

We chose to limit our analysis to RCT and prospective cohort studies for a number of reasons. First, retrospective studies for this type of clinical question have tremendous potential for bias that significantly degrades their validity. For example, in studies that are retrospective or nonrandomized, the largest PFO would likely be considered more strongly for closure or warfarin therapy while the smallest PFO might be treated with aspirin (i.e., confounding by indication). Second, every one of the therapeutic interventions that are used in this patient population has the potential for significant adverse effects. Thus, we used the strictest, most conservative criteria for inclusion in our analysis in order to make the most valid recommendation possible.

Data extraction and grading the evidence. The articles that met the inclusion and exclusion criteria were evaluated by each of the authors. For each of the clinical questions, the selected articles were graded for potential bias according to the classification-of-evidence scheme described in Appendix 1 (a given article may have received different grades for each question depending on the methods employed). As noted in previous practice parameters, class I evidence is expected to have the lowest risk of bias, while class IV evidence is judged to have a high risk of bias. The authors rated each study independently and resolved any discrepancies later. Outcome data were organized into a data extraction table (please refer to Appendix 2).

Measures of recurrent stroke risk and therapeutic effect. The primary outcome was recurrent stroke or death. In order to determine the risk associated with the presence of an atrial septal abnormality we compared the proportion of patients who had a stroke or death in the group of patients with atrial septal abnormalities to the group of patients without such abnormalities. We then calculated the relative risks using the formula:

$$RR = [A/(A + C)]/[B/(B + D)]$$

	Stroke or death	No stroke or death
Atrial septal abnormality	A	C
No atrial septal abnormality	B	D

Similarly, we compared the relative risks of stroke or death for each of the available therapies using aspirin as the reference. When appropriate, we selectively pooled the data from comparable studies using general variance-based meta-analytic techniques. We determined 95% confidence intervals for all calculations. Final recommendations are graded according to the scheme described in Appendix 1.

Analysis of evidence. *Study characteristics.* The literature search produced a list of 129 articles, of which only four fulfilled all of the inclusion and exclusion criteria.

The Lausanne Stroke Registry prospectively evaluated 340 patients less than 60 years of age with an acute stroke or TIA and found that 140 (41%) had a PFO or ASA.²⁷ The average age of the patients in this study was 44 ± 14 years. Investigators who followed the patients were not blinded to treatment and there was no adjudication of endpoints by a blinded committee or evaluator. Patients received one of three treatment regimens. Surgical closure was offered to patients with no concomitant stroke etiology and at least two of the following characteristics: an ASA, major right-to-left shunt (defined as >50 microbubbles on a TTE with a saline contrast study [often referred to as a “bubble study”]), multiple cerebral infarcts/TIA, or Valsalva preceding the presenting event. Warfarin (goal international normalized ratio 3 to 4) was given to patients who were candidates for surgery but refused and in those patients without an alternative stroke etiology and one of the “high risk” characteristics listed. Aspirin (250 mg per day) was given to all other patients unless a potential alternative stroke etiology necessitated a different treatment (i.e., carotid endarterectomy for an ipsilateral severe carotid stenosis). A total of 66% of the patients received aspirin, 5% of patients received warfarin for 3 months and were then switched to aspirin (to treat deep vein thrombosis or pulmonary embolism), 21% were given warfarin, and 8% of patients underwent surgical closure of the PFO (most of these patients were given warfarin until surgery, which occurred within 12 weeks of the event). Medication compliance was assessed clinically and was described as good in 75% of the patients. There were no patients lost to follow-up and mean duration of follow-up was 36 months (with a range of 10 to 91 months).

A group of investigators at the University of Rome “La Sapienza” prospectively followed 86 cryptogenic stroke patients without atrial septal abnormalities (mean age 47 ± 14 years) and 74 cryptogenic stroke patients with a PFO found on TEE (mean age 53 ±

14 years).²¹ Patients received aspirin, warfarin, both, or neither at the discretion of the enrolling physician. Investigators were not blinded to treatment or to PFO status. Outcomes were not adjudicated by a blinded evaluator or committee. There was no difference in baseline clinical characteristics between the groups, although the data were not presented. Compared to a control group of 13 patients with PFO who did not have a history of stroke or TIA, the group with PFO and stroke were more likely to have a right-to-left shunt at rest ($p = 0.04$) and a greater degree of septal wall mobility ($p = 0.04$). The data concerning outcomes with regard to treatment were not presented. No patients were lost to follow-up and the median duration of follow-up was 31 months (with a range of 4 to 58 months).

The French PFO/ASA study prospectively followed 581 patients less than 55 years of age (mean 42.5 years) with a cryptogenic stroke.⁶ Of this cohort, 216 (37%) had a PFO, 10 (1.7%) had an ASA, and 51 (9%) had both. All patients received aspirin 300 mg per day except for those patients who had a deep vein thrombosis or pulmonary embolism who received 3 to 6 months of warfarin. Thus, investigators were not blinded to treatment. All outcomes were adjudicated by a blinded validation committee. Compared with the cohort of patients who did not have atrial septal abnormalities, the patients who did have them were younger, less likely to have hypertension or hypercholesterolemia, marginally less likely to be an active smoker, and more likely to have a history of migraines. Only two patients were lost to follow-up (neither of which had an atrial septal abnormality) and the mean duration of follow-up was 37.8 months \pm SD of 9.7 months.

The Patent Foramen Ovale in Cryptogenic Stroke Study (PICSS) prospectively enrolled 630 stroke patients who were participating in the Warfarin-Aspirin Recurrent Stroke Study (WARSS).³¹ All patients in WARSS who had received a TEE as part of their evaluation and those who had had a cryptogenic stroke and would agree to a TEE were eligible to participate in the PICSS trial. The average age of these patients was 59 years. A total of 312 (49.5%) were randomized to warfarin while 318 (50.5%) received aspirin. Patients and physicians were blinded to the type of medication used. Of this cohort, 265 patients (42%) had a cryptogenic stroke and 365 patients (58%) had a stroke from a known etiology. A PFO was found on TEE in 203 patients (33.8%), and an ASA was present in 69 (11.5%). In univariate analysis, patients with a PFO or ASA were more likely to have had a cryptogenic stroke, more likely to have no disability from their stroke, and less likely to have a history of hypertension, diabetes, and a sedentary lifestyle. Among cryptogenic stroke patients, 39% had a PFO, compared to 30% in patients with a known cause of stroke ($p < 0.02$). Large PFO were much more common in patients with cryptogenic stroke (20% versus 9.7%, $p < 0.001$). All clinical and radiologic endpoints were adjudicated by a

blinded panel, while all intracerebral hemorrhages were adjudicated by a single blinded radiologist. The duration of follow-up for all patients was 24 months and 10 patients (1.6%) were lost to follow-up at a mean of 13 months after randomization.

Prognosis: In patients who have had a cryptogenic stroke (or TIA), does a PFO or ASA increase the risk of recurrent stroke? For this question the Lausanne study is class IV because it lacks comparison with a control group of patients who did not have an atrial septal abnormality. The La Sapienza study is designated as class II because outcome determination was not blinded to the presence or absence of an atrial abnormality. Both PICSS and the French PFO/ASA study attain class I prognostic study grades.

In the French PFO/ASA study of 581 patients, the average annual rate of subsequent stroke or death in PFO patients compared to non-PFO patients was 1.5% versus 1.8% (RR = 0.90, 95% CI 0.46 to 1.82). In this study, PFO shunt size was not significantly associated with the risk of recurrent cerebrovascular events. Compared to patients without PFO, the hazard ratio associated with a small PFO shunt was 1.01 (95% CI 0.23 to 4.52) and for a large shunt was 1.10 (95% CI 0.39 to 3.11).

In PICSS, the average annual risk of subsequent stroke or death was 7.4% among patients with PFO and 7.7% among those without PFO (RR = 0.96, 95% CI 0.64 to 1.44) in the entire study cohort of 630 patients. In the cryptogenic stroke subset of 265 patients, the average annual risk was 7.15% and 6.35%, respectively (RR = 1.14, 95% CI 0.60 to 2.17). Like prior retrospective studies, PICSS found a higher prevalence of large PFO in cryptogenic stroke patients compared to patients with a known stroke subtype. However, similar to the French PFO/ASA study, there was no increased risk of recurrent stroke based upon PFO size. Compared to patients without PFO, the hazard ratio associated with a small PFO shunt was 1.23 (95% CI 0.76 to 2.0, $p = 0.41$) and for a large shunt was 0.59 (95% CI 0.28 to 1.24, $p = 0.16$).

Combining the cryptogenic stroke populations from these two class I studies in a meta-analysis results in a homogeneous pooled relative risk of stroke or death in PFO patients compared to non-PFO patients of 0.96 (95% CI 0.59 to 1.55).

The class II La Sapienza study similarly found no difference between the average annual risk of stroke or death in the PFO group (3.7%) compared to those patients in the cryptogenic stroke group (4.5%), RR = 0.74 (95% CI 0.30 to 1.81). Inclusion of this class II study into the above pooled analysis has little effect, with a homogeneous pooled relative risk of 0.95 (95% CI 0.62 to 1.44).

There are insufficient data in any of the studies to accurately estimate the relative risk associated with ASA alone. The French PFO/ASA study included 10 patients with a lone ASA, none of whom reached an endpoint during the study period, while PICSS did not provide data on patients who had an ASA exclusively.

In the French PFO/ASA study, the average annual risk of the composite of subsequent stroke and death in patients with both PFO and ASA compared to those without interatrial septal abnormalities demonstrated a trend, but was not significantly elevated (3.8% versus 1.8% per year; RR = 2.10, 95% CI 0.86 to 5.06). However, there was a significantly increased risk of stroke recurrence alone (not death) with both PFO and ASA (3.8% versus 1.1% per year; RR = 2.98, 95% CI 1.17 to 7.58). In PICSS, among patients with any stroke subtype, the annual risk of patients with both a PFO and ASA compared to those without an interatrial septal abnormality was not significantly elevated (8.0% versus 7.7%; RR = 1.04, 95% CI 0.51 to 2.12). These data were not available for the cryptogenic stroke cohort alone. Consequently, a combined analysis of the role of PFO and ASA in cryptogenic stroke could not be performed.

In the class II La Sapienza study, ASA was not defined, but patients with right-to-left interatrial shunt at rest combined with increased septal mobility of more than 6.5 mm appeared to be at greater risk of recurrent stroke than patients without these features (RR and CI not provided nor calculable given available data). However, the risk of recurrence among this apparent higher risk group remained lower than the risk of recurrence among cryptogenic stroke patients without PFO.

There are no studies that examined the risk of subsequent stroke or death among cryptogenic stroke patients with PFO or ASA on no therapy.

Summary. Among patients who have had a cryptogenic stroke and are treated medically, the data from two class I studies and one class II study, analyzed separately and in combination, indicate that PFO alone does not portend a meaningfully increased risk of subsequent stroke or death. However, a small increase or decrease in risk cannot be excluded by the current data. There were inadequate data to make conclusions about isolated ASA. The results regarding patients with PFO and ASA are somewhat inconsistent. The French PFO/ASA study indicated that cryptogenic stroke patients with both PFO and ASA carry an increased risk of stroke recurrence when treated medically, although the association with combined stroke and death only demonstrated a trend in that direction and was not significant. In contrast, PICSS found no association between the presence of PFO and ASA with stroke or death. However, the study did not provide the data to address the effect of PFO and ASA specifically in the population with cryptogenic strokes. Further, both studies had limited power to fully characterize the impact of combined PFO and ASA.

There were meaningful differences in the patient populations included in the two class I studies. Patients in PICSS were much older than those in the French PFO/ASA study (59.0 years versus 42.5 years). While both of these studies found that patients with PFO or ASA were less likely to have traditional vascular risk factors compared to those

without any atrial abnormalities, these risk factors were much more prevalent in the PICSS patient population: 60.1% of patients in PICSS had hypertension, compared to 15.5% of patients in the French PFO/ASA study; diabetes was present in 28.4% in PICSS and 4.1% in the French PFO/ASA study; and history of prior stroke was found in 14.7% of the PICSS subjects and only 2.8% of patients in the French PFO/ASA trial. Given that the risk of stroke from more common etiologies increases with age, interatrial septal abnormalities found in older patients with stroke are less likely to have been the proximate cause and consequently less likely to be associated with the risk for subsequent stroke or death. Overall, it is clear that patients followed in the PICSS trial had drastically higher recurrence rates than any of the other studies.

As noted earlier, numerous case-control trials have found an association between cryptogenic stroke and the presence of PFO and ASA. Our conclusions appear to conflict with these previous findings; however, there are important distinctions between these studies. First, the case-control trials used different control groups, either normal healthy subjects or patients with strokes of known causes, compared to the cohort studies that used cryptogenic stroke patients without atrial abnormalities. Further, the case-control studies evaluated first stroke, while the prospective cohort studies reviewed here examined the risk of recurrent stroke. While case-control studies are useful for determining associations with outcomes that are relatively rare, such as a possible relationship between PFO/ASA and stroke, they are unable to determine the incidence of these rare events. Prospective cohort studies require larger numbers of patients and longer follow-up, particularly when the outcome of interest is relatively rare, but they are able to estimate the incidence of the outcome of interest. These studies have shown that the risk of recurrent stroke or death in these patients ranges from 1 to 8% per year which is, in fact, not much different from other age-matched cryptogenic stroke patients.

There were a number of potential limitations in the interpretation of the existing prospective data. In all studies, patients with cryptogenic strokes without PFO or ASA served as controls, but these patients may be at increased risk of subsequent stroke or death compared to the general population as they may harbor other undefined abnormalities or risk factors for stroke. If this conjecture is true, then such a comparison may inaccurately lead to the conclusion that there is no attributable risk associated with PFO. At present, no other suitable prospective control population exists, since comparison with normal healthy subjects would be inappropriate. Finally, there were relatively few endpoints in these studies, which limited the power to reveal associations if they exist.

Therapy: Is warfarin superior to aspirin in preventing recurrent stroke or death for patients with a stroke or TIA and an atrial septal abnormality?

PICSS is classified as a class II study for addressing this question. It was a prospective cohort study that was built into the larger WARSS randomized clinical trial, but patients were randomized to therapy without regard to whether they participated in PICSS. Further, the report of PICSS did not enumerate the baseline characteristics of the patients receiving warfarin compared to the patients receiving aspirin. The Lausanne article is a prospective cohort study, but therapies were selected for patients based on their physicians' estimates of their subsequent risk. This may have led to substantial confounding by indication and designates the Lausanne study as class III. The French PFO/ASA study is class IV for this question as all patients were initially placed on aspirin for secondary prevention. Therefore, it is not used in the following analysis. The La Sapienza article provides no information regarding outcomes related to treatment.

The Lausanne study reported that the type of treatment (all patients received antiplatelet medication, anticoagulation, or surgical closure of the PFO) did not significantly affect the risk of stroke recurrence. However, very few events occurred in this cohort (8 strokes and 5 deaths among 140 patients) and there was insufficient detail to calculate the relative risk of any treatment relative to aspirin antiplatelet therapy.

PICSS demonstrated that among patients with any stroke subtype and a PFO, there was no difference in the average annual rate of subsequent stroke or death between treatment with warfarin relative to aspirin, 8.25% versus 6.6% (RR = 1.25, 95% CI 0.64 to 2.42). Similarly, among the cryptogenic cohort with PFO, there was again no difference in average annual rate of stroke or death in warfarin-treated patients relative to aspirin-treated patients, 4.75% versus 8.95% (RR = 0.53, 95% CI 0.18 to 1.58). The point estimate from this analysis suggested a possible benefit of warfarin but the CI is extremely wide. Thus, PICSS was unable to conclude that there is a benefit or harm of warfarin over aspirin. Insufficient data were available from PICSS to compare these therapies specifically among patients with both PFO and ASA, but as there were only 7 strokes or deaths among these 44 patients, it is unlikely that any significant differences would have been discerned.

Both the Lausanne study and PICSS provided some data on adverse outcomes related to treatment. The Lausanne study reported no major bleeding events in the aspirin-treated or warfarin-treated cohorts (although major bleeding was not explicitly defined), but the latter group had a minor bleeding rate of 2.4 events/100 patient-years. PICSS reported significantly higher rates of adverse events. The rate of major hemorrhage (intracranial, intraspinal, or requiring transfusion) in the warfarin-treated group was 1.78 events/100 patient-years and in the aspirin-treated group was 1.91 events/100 patient-years (rate ratio = 0.93, $p = 1.0$). Minor bleeding complications were more common in the warfarin cohort (22.9 events/100 patient-years) compared to the aspirin co-

hort (8.66 events/100 patient-years) (rate ratio = 2.64, $p < 0.001$). The French PFO/ASA study did not provide sufficient information on the risk of bleeding events.

No controlled studies have been published comparing the efficacy of surgical or percutaneous PFO closure with medical therapy.

Summary. The available quantitative data regarding therapy are limited to a single class II study, which failed to demonstrate a difference between the effects of warfarin and aspirin on the risk of subsequent stroke or death among patients with cryptogenic strokes and atrial septal abnormalities. PICSS was principally designed as a prognostic study and was underpowered to determine an effect of therapy. Thus, the confidence intervals associated with this finding do not rule out superiority of either drug and the results are inconclusive. Further, one class II and one class III study demonstrated an increased risk of minor bleeding with warfarin compared to aspirin. It is important to note that there is a subset of patients that should always be treated with anticoagulation. If there is a concomitant deep vein thrombosis or pulmonary embolism, current recommendations call for at least 3 months of anticoagulation therapy.³³

Practice recommendations. For patients who have had a cryptogenic stroke and have a PFO, the evidence indicates that the risk of subsequent stroke or death is no different from other cryptogenic stroke patients without PFO when treated medically with antiplatelet agents or anticoagulants. Therefore, in persons with a cryptogenic stroke receiving such therapy, neurologists should communicate to patients and their families that presence of PFO does not confer an increased risk for subsequent stroke compared to other cryptogenic stroke patients without atrial abnormalities (Level A). However, it is possible that the combination of PFO and ASA confers an increased risk of subsequent stroke in medically treated patients who are less than 55 years of age. Therefore, in younger stroke patients, studies that can identify PFO or ASA may be considered for prognostic purposes (Level C).

Among patients with a cryptogenic stroke and atrial septal abnormalities, there is insufficient evidence to determine the superiority of aspirin or warfarin for prevention of recurrent stroke or death (Level U), but the risks of minor bleeding are possibly greater with warfarin (Level C). There is insufficient evidence regarding the effectiveness of either surgical or percutaneous closure of PFO (Level U).

Recommendations for future research. This review reveals a paucity of methodologically sound evidence regarding the implications of PFO and ASA in cryptogenic stroke and the optimal management of these patients. The actual mechanisms by which atrial septal abnormalities cause stroke are still being debated and must be more fully elucidated, since the prognosis and treatment may be different for

paradoxical thromboembolic strokes than for those related to atrial arrhythmias.

Further research is needed to better characterize the natural history of patients with these abnormalities, especially those with both PFO and ASA. Retrospective analyses have suggested that certain anatomic and pathophysiologic features may raise the risk of stroke, including increased area of patency, increased amount of shunting, degree of overlap of the septum primum and secundum, presence of a Chiari network, Valsalva prior to the first event, and stroke in multiple vascular territories.^{18,19,34-37} Neither the prospective French PFO/ASA or PICSS studies found an association between degree of shunting and risk of stroke recurrence, but this may be due in part to limited statistical power. Thus, future investigations should address the clinical and anatomic features that may impact the risk of subsequent stroke in patients with atrial septal abnormalities and evaluate the risks of alternative interventions.

Future studies of prognosis and therapy should be done with well-defined cohorts and large numbers of relatively young patients (e.g., under 55 years) with a

recent cryptogenic stroke who appear to be at particularly increased risk, including those with a large PFO or those with both a PFO and an ASA. Studies that compare percutaneous closure with medical management have begun enrolling patients. As there does not appear to be a clear benefit of one specific medical therapy, such trials could compare closure to either aspirin or warfarin. Additionally, these studies should employ a stratified randomization to equally distribute subgroups based on age, PFO size, and other factors that may influence the risk of subsequent events.

Clinicians who encounter patients with cryptogenic stroke and PFO (and/or ASA) should encourage them to consider participating in research protocols.

Disclaimer

This statement is provided as an educational service of the American Academy of Neurology. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved.

Appendix 1: Description of classification-of-evidence and level-of-recommendation schema

Rating of recommendations	Translation of evidence to recommendation	Rating of therapeutic article	Rating of prognostic article
Level A = Established as effective, ineffective, or harmful for the given condition in the specified population	Level A rating requires at least two consistent Class I studies*	Class I: Prospective, randomized, controlled clinical trial with masked outcome assessment, in a representative population. The following are required: a) Primary outcome(s) is/are clearly defined b) Exclusion/inclusion criteria are clearly defined c) Adequate accounting for drop-outs and cross-overs with numbers sufficiently low to have minimal potential for bias d) Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.	Class I: Evidence provided by a prospective study of a broad spectrum of persons who may be at risk for developing the outcome (e.g., target disease, work status). The study measures the predictive ability using an independent gold standard for case definition. The predictor is measured in an evaluation that is masked to clinical presentation and the outcome is measured in an evaluation that is masked to the presence of the predictor.
Level B = Probably effective, ineffective, or harmful for the given condition in the specified population	Level B rating requires at least one Class I study or two consistent Class II studies	Class II: Prospective matched group cohort study in a representative population with masked outcome assessment that meets a–d above OR a RCT in a representative population that lacks one criteria a–d.	Class II: Evidence provided by a prospective study of a narrow spectrum of persons at risk for having the condition, or by a retrospective study of a broad spectrum of persons with the condition compared to a broad spectrum of controls. The study measures the prognostic accuracy of the risk factor using an acceptable independent gold standard for case definition. The risk factor is measured in an evaluation that is masked to the outcome.
Level C = Possibly effective, ineffective, or harmful for the given condition in the specified population	Level C rating requires at least one Class II study or two consistent class III studies	Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.†	Class III: Evidence provided by a retrospective study where either the persons with the condition or the controls are of a narrow spectrum. The study measures the predictive ability using an acceptable independent gold standard for case definition. The risk factor is measured in an evaluation that is masked to the outcome.
Level U = Data inadequate or conflicting. Given current knowledge, treatment (test, predictor) is unproven	Studies not meeting criteria for class I–class III	Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion.	Class IV: Any design where the predictor is not applied in a masked evaluation OR evidence provided by expert opinion or case series without controls.

* In exceptional cases, one *convincing* Class I study may suffice for an “A” recommendation if 1) all criteria met, 2) magnitude of effect ≥ 5 , and 3) narrow confidence intervals (lower limit >2).

† Objective outcome measurement—an outcome measure that is unlikely to be affected by an observer’s (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).

RCT = randomized controlled trial.

Appendix 2: Data extraction table

Study characteristics	Lausanne study (Bogousslavsky et al., 1996 ²⁷)	La Sapienza study (De Castro et al., 2000 ²¹)	French PFO/ASA study (Mas et al., 2001 ⁶)	PICSS (Homma et al., 2002 ³¹) cryptogenic strokes	PICSS (Homma et al., 2002 ³¹) all stroke subtypes
Study design	Prospective cohort	Prospective case control	Prospective cohort	RCT	RCT
Blinded to treatment?	No	No	No	Yes	Yes
Adjudicated endpoints?	No	No	Yes	Yes	Yes
Baseline clinical characteristics available?	No	No	Yes	No, but the author stated there were no significant differences	Yes
No. (%) of patients lost to follow-up	0	0	2 (0.3)	NA	10 (1.6)
Follow-up duration, mo (range)	36 (10 to 91)	31 (4 to 58)	37.8 ± SD 9.7	24	24
Total number of patients	340	160	581	265	630
Mean age ± SD, y	44 ± 14	49.8 ± NA	42.5 ± NA	NA	59.0 ± 12.2
No. (%) of patients with no atrial septal abnormality	200 (58.8)	86 (53.8)	304 (52.3)	153 (61.2)	398 (66.2)
Annual risk of stroke or death, %	NA	4.5	1.8	6.3	7.7
No. (%) of patients with a PFO (with or without an ASA)	140 (41)	74 (46.3)	216 (37)	98 (39.2)	203 (33.8)
Annual risk of stroke or death, %	3.1	3.7	1.5	7.2	7.4
No. (%) of patients with a lone ASA	0	NA	10 (1.7)	NA	25 (4.0)
Annual risk of stroke or death	NA	NA	0	NA	NA
No. (%) of patients with a PFO and an ASA	35 (10.3)	NA	51 (8.7)	NA	44 (7.0)
Annual risk of stroke or death, %	NA	NA	3.7	NA	8.0
Annual risk of stroke or death on aspirin for patients with an atrial septal abnormality, %	NA	NA	1.6	9.0	6.6
Annual risk of stroke or death on warfarin for patients with an atrial septal abnormality, %	NA	NA	NA	4.8	8.3
Major bleeding complications on warfarin, events/100 pt-years	0	NA	NA	NA	1.78
Minor bleeding complications on warfarin, events/100 pt-years	2.4	NA	NA	NA	22.9
Major bleeding complications on aspirin, events/100 pt- years	0	NA	NA	NA	1.9
Minor bleeding complications on aspirin, events/100 pt- years	0	NA	NA	NA	8.6

PFO = patent foramen ovale; ASA = atrial septal aneurysm; PICSS = Patent foramen Ovale in Cryptogenic Stroke Study; RCT = randomized controlled trial; NA = not available.

Appendix 3

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