Complete Summary

GUIDELINE TITLE

Practice parameter: recurrent stroke with patent foramen ovale and atrial septal aneurysm: report of the Quality Standards Subcommittee of the American Academy of Neurology.

BIBLIOGRAPHIC SOURCE(S)

Messe SR, Silverman IE, Kizer JR, Homma S, Zahn C, Gronseth G, Kasner SE. Practice parameter: recurrent stroke with patent foramen ovale and atrial septal aneurysm: report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2004 Apr 13;62(7):1042-50. [37 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- August 16, 2007, Coumadin (Warfarin): Updates to the labeling for Coumadin to include pharmacogenomics information to explain that people's genetic makeup may influence how they respond to the drug.
- October 6, 2006, Coumadin (warfarin sodium): Revisions to the labeling for Coumadin to include a new patient Medication Guide as well as a reorganization and highlighting of the current safety information to better inform providers and patients.

COMPLETE SUMMARY CONTENT

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CATEGORIES
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SCOPE

DISEASE/CONDITION(S)

- Stroke
- Patent foramen ovale (PFO)
- Atrial septal aneurysm (ASA)

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Prevention
Risk Assessment
Treatment

CLINICAL SPECIALTY

Cardiology
Neurology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- 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
- To establish the optimal method of stroke prevention in this population of patients

TARGET POPULATION

Patients with a cryptogenic stroke and a patent foramen ovale (PFO), atrial septal aneurysm (ASA), or both

INTERVENTIONS AND PRACTICES CONSIDERED

Prevention/Treatment

1. Aspirin
2. Warfarin

Note: There is insufficient evidence regarding the effectiveness of either surgical or percutaneous closure of patent foramen ovale (PFO).

MAJOR OUTCOMES CONSIDERED

- Incidence of recurrent stroke
- Death
- Incidences of major and minor bleeding complications

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

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.

The resulting articles and their references were screened using the inclusion and exclusion criteria described in a table in the original guideline document. Specifically, the Quality Standards Subcommittee (QSS) 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

The QSS chose to limit their 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, the QSS used the strictest, most conservative criteria for inclusion in their analysis in order to make the most valid recommendation possible.

NUMBER OF SOURCE DOCUMENTS

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

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Rating of Therapeutic Article

Class I: Prospective, randomized, controlled clinical trial (RCT) 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 dropouts and crossovers 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 II: Prospective matched group cohort study in a representative population with masked outcome assessment that meets a–d above OR an RCT in a representative population that lacks one criteria a–d.

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 IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion.

Note: 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).

Rating of Prognostic Article

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.

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.

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.

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.

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis of Randomized Controlled Trials
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

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 above in the "Rating Scheme for the Strength of the Evidence in Appendix" field (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 of the original guideline document).

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 the Quality Standards Subcommittee (QSS) 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. The QSS then calculated the relative risks (RR) 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, the QSS compared the RR of stroke or death for each of the available therapies using aspirin as the reference. When appropriate, the QSS selectively pooled the data from comparable studies using general variance-based meta-analytic techniques. The QSS determined 95% confidence intervals for all calculations. Final recommendations are graded according to the scheme described below in the "Rating Scheme for the Strength of the Recommendations" field.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Other

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

When formulating the recommendations the guideline developers considered the *magnitude* of the effect (benefit or harm of therapy, accuracy of tests, yield of studies) and the relative *value* of various outcomes. Under most circumstances, there is a direct link between the level of evidence used to formulate conclusions and the strength of the recommendation. This linkage is illustrated in Appendix 9 of the 2004 AAN Guideline Process Manual (see Companion Documents field). Thus, an "established as" (two class I) conclusion supports a "should be done" (level A) recommendation; a "probably effective" (two class II) conclusion supports a "should be considered" (level B) recommendation; a "possibly effective" (two class III) conclusion supports a "may be considered" recommendation. In those circumstances where the evidence indicates that the intervention is not effective or useful, wording was modified. For example, if multiple adequately powered class I studies demonstrated that an intervention is not effective, the recommendation read, "should not be done."

There are important exceptions to the rule of having a direct linkage between the level of evidence and the strength of recommendations. Some situations where it may be necessary to break this linkage are listed below:

- A statistically significant but marginally important benefit of the intervention is observed
- The intervention is exorbitantly costly
- Superior and established alternative interventions are available
- There are competing outcomes (both beneficial and harmful) that cannot be reconciled

Under such circumstances the guideline developers may have downgraded the level of the recommendation.

Edlund W, Gronseth G, So Y, Franklin G. Clinical practice guideline process manual. St. Paul (MN): American Academy of Neurology (AAN); 2004. 49 p.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Rating of Recommendations

A = Established as effective, ineffective, or harmful for the given condition in the specified population.

B = Probably effective, ineffective, or harmful for the given condition in the specified population.

C = Possibly effective, ineffective, or harmful for the given condition in the specified population.

U = Data inadequate or conflicting. Given current knowledge, treatment (test, predictor) is unproven.

Translation of Evidence to Recommendation

Level A rating requires at least two consistent Class I studies*.

Level B rating requires at least one Class I study or two consistent Class II studies.

Level C rating requires at least one Class II study or two consistent class III studies.

Level U rating for studies not meeting criteria for class I– class III.

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

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Guidelines were approved by the Quality Standards Subcommittee in July 2003, the American Academy of Neurology (AAN) in October 2003, and the AAN Board of Directors in January 2004.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Definitions of the strength of the recommendations (A, B, C, U) and classification of the evidence (Class I through Class IV) are provided at the end of the "Major Recommendations" field.

Practice Recommendations

For patients who have had a cryptogenic stroke and have a patent foramen ovale (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 atrial septal aneurysm (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 atrial septal aneurysm (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**).

Definitions:

Rating of Recommendations

A = Established as effective, ineffective, or harmful for the given condition in the specified population.

B = Probably effective, ineffective, or harmful for the given condition in the specified population.

C = Possibly effective, ineffective, or harmful for the given condition in the specified population.

U = Data inadequate or conflicting. Given current knowledge, treatment (test, predictor) is unproven.

Translation of Evidence to Recommendation

Level A rating requires at least two consistent Class I studies*.

Level B rating requires at least one Class I study or two consistent Class II studies.

Level C rating requires at least one Class II study or two consistent class III studies.

Level U rating for studies not meeting criteria for class I– class III.

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

Rating of Therapeutic Article

Class I: Prospective, randomized, controlled clinical trial (RCT) 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 dropouts and crossovers 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 II: Prospective matched group cohort study in a representative population with masked outcome assessment that meets a–d above OR an RCT in a representative population that lacks one criteria a–d.

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 IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion.

Note: 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).

Rating of Prognostic Article

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.

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definition. The risk factor is measured in an evaluation that is masked to the outcome.

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.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Optimal management of patients who have an atrial septal abnormality and have already had a stroke

POTENTIAL HARMS

One class II and one class III study demonstrated an increased risk of minor bleeding with warfarin compared to aspirin.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- There were a number of potential limitations in the interpretation of the existing prospective data. In all studies, patients with cryptogenic strokes without patent foramen ovale (PFO) or atrial septal aneurysm (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 patent foramen ovale (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.
- This statement is provided as an educational service of the American Academy of Neurology (AAN). 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.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Personal Digital Assistant (PDA) Downloads
Quick Reference Guides/Physician Guides
Slide Presentation

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Messe SR, Silverman IE, Kizer JR, Homma S, Zahn C, Gronseth G, Kasner SE. Practice parameter: recurrent stroke with patent foramen ovale and atrial septal aneurysm: report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2004 Apr 13;62(7):1042-50. [37 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2004 Apr 13

GUIDELINE DEVELOPER(S)

American Academy of Neurology - Medical Specialty Society

SOURCE(S) OF FUNDING

American Academy of Neurology (AAN)

GUIDELINE COMMITTEE

Quality Standards Subcommittee of the American Academy of Neurology

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

AAN Quality Standards Subcommittee Members: Gary Franklin, MD, MPH (*co-chair*); Gary Gronseth, MD (*co-chair*); Charles Argoff, MD; Christopher Bever, Jr., MD; Jody Corey-Bloom, MD, PhD; John England, MD; Gary Friday, MD; Michael Glantz, MD; Deborah Hirtz, MD; Donald Iverson, MD; David Thurman, MD; Samuel Weibe, MD; William Weiner, MD; Stephen Ashwal, MD (*ex-officio*); Jacqueline French, MD (*ex-officio*); Catherine Zahn, MD (*ex-officio*)

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: A list of American Academy of Neurology (AAN) guidelines, along with a link to a Portable Document Format (PDF) file for this guideline, is available at the AAN Web site.

Print copies: Available from the AAN Member Services Center, (800) 879-1960, or from AAN, 1080 Montreal Avenue, St. Paul, MN 55116.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Recurrent stroke in patients with patent foramen ovale and atrial septal aneurysm. AAN guideline summary for clinicians. St. Paul (MN): American Academy of Neurology. 2. p. Available in Portable Document Format (PDF) from the American Academy of Neurology (AAN) Web site.
- Practice parameter: recurrent stroke with patent foramen ovale and atrial septal aneurysm. St. Paul (MN): American Academy of Neurology. 2004. 13 p. Available for personal digital assistant (PDA) download from the AAN Web site.

- Slide presentation: practice parameter: risk of recurrent stroke and secondary stroke prevention in patients with interatrial septal abnormalities (an evidence-based review). St. Paul (MN): American Academy of Neurology. 2004. Available in Power Point from the AAN Web site.
- AAN guideline development process [online]. St. Paul (MN): American Academy of Neurology (AAN). Available from the AAN Web site.
- Edlund W, Gronseth G, So Y, Franklin G. Clinical practice guideline process manual. St. Paul (MN): American Academy of Neurology (AAN); 2004. 49 p. Electronic copies available in Portable Document Format (PDF) from the AAN Web site.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on August 17, 2004. The information was verified by the guideline developer on September 9, 2004. This summary was updated by ECRI on March 6, 2007 following the U.S. Food and Drug Administration (FDA) advisory on Coumadin (warfarin sodium). This summary was updated by ECRI Institute on September 7, 2007 following the revised U.S. Food and Drug Administration (FDA) advisory on Coumadin (warfarin).

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