Complete Summary

GUIDELINE TITLE

Anticoagulants and antiplatelet agents in acute ischemic stroke: report of the Joint Stroke Guideline Development Committee of the American Academy of Neurology and the American Stroke Association (a division of the American Heart Association).

BIBLIOGRAPHIC SOURCE(S)

Coull BM, Williams LS, Goldstein LB, Meschia JF, Heitzman D, Chaturvedi S, Johnston KC, Starkman S, Morgenstern LB, Wilterdink JL, Levine SR, Saver JL. Anticoagulants and antiplatelet agents in acute ischemic stroke: report of the Joint Stroke Guideline Development Committee of the American Academy of Neurology and the American Stroke Association (a division of the American Heart Association). Neurology 2002 Jul 9;59(1):13-22. [19 references] PubMed

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GUIDELINE STATUS

This is the current release of the guideline.

According to the guideline developer, this guideline has been reviewed and is still considered to be current as of October 2005. This review involved new literature searches of electronic databases followed by expert committee review of new evidence that has emerged since the original publication date.

**** 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.

- February 28, 2008, Heparin Sodium Injection: The U.S. Food and Drug Administration (FDA) informed the public that Baxter Healthcare Corporation has voluntarily recalled all of their multi-dose and single-use vials of heparin sodium for injection and their heparin lock flush solutions. Alternate heparin manufacturers are expected to be able to increase heparin production

sufficiently to supply the U.S. market. There have been reports of serious adverse events including allergic or hypersensitivity-type reactions, with symptoms of oral swelling, nausea, vomiting, sweating, shortness of breath, and cases of severe hypotension.

COMPLETE SUMMARY CONTENT

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SCOPE

DISEASE/CONDITION(S)

Acute ischemic stroke (cardioembolic, large vessel atherosclerotic, vertebrobasilar, or "progressing" stroke)

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Management
Prevention
Treatment

CLINICAL SPECIALTY

Critical Care
Emergency Medicine
Neurology

INTENDED USERS

Not stated

GUIDELINE OBJECTIVE(S)

- To examine the published evidence relevant to the effects of anticoagulants and antiplatelet agents on acute ischemic stroke mortality, morbidity, and recurrence rate as well as associated ancillary benefits and risks of those

treatments on the rate of deep vein thrombosis, pulmonary embolus, and cardiovascular complications
- To determine if there is evidence supporting the differential efficacy of anticoagulants and antiplatelet agents according to ischemic stroke subtype
- To offer evidence-based recommendations on the management of acute ischemic stroke

TARGET POPULATION

Patients with acute ischemic stroke

INTERVENTIONS AND PRACTICES CONSIDERED

1. Platelet antiaggregants (aspirin)
2. Unfractionated heparin (intravenously or subcutaneously)
3. Low molecular weight (LMW) heparin/heparinoids, such as ORG 10172, nadroparin calcium, danaparoid, dalteparin, certoparin, Fraxiparine

Notes:

- The platelet glycoprotein IIb/IIIa inhibitor abciximab was considered but data were insufficient to make any recommendations on its use in the setting of acute ischemic stroke.
- Guideline developers intended to consider hirudin, dipyridamole, ticlopidine, or clopidogrel but were unable to do so because none of the studies that fulfilled the prespecified inclusion criteria addressed the reviewer's key questions.
- Guideline developers did not consider prostacyclin and pentoxifylline because these agents have major vascular effects other than antiplatelet actions.

MAJOR OUTCOMES CONSIDERED

- Stroke-related morbidity and mortality
- Stroke recurrence
- Systemic thrombotic complications, such as deep vein thrombosis (DVT)/pulmonary embolism (PE)
- Risks of hemorrhage
- Acute cardiovascular 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

The literature review was based on MEDLINE searches from 1966 through Feb. 2001. In addition, Current Contents and International Pharmaceutical Abstracts

databases were searched from 1985 to February 2001. The search strategy, available online at www.aan.com, included controlled clinical trials and large-scale cohort studies.

The Committee also searched the Cochrane Database for pertinent randomized clinical trials and systematic reviews. Cochrane Reviews typically consist of formal meta-analyses of published and unpublished trials, not all of which are indexed in MEDLINE. These reviews were used to identify any relevant studies that may not have been found in the other searches. In addition, to help ensure that all pertinent studies were considered, a letter requesting relevant articles was sent to an international group of stroke experts who, in the opinion of the Joint Writing Committee, were considered authorities in the field of antithrombotic treatment of acute ischemic stroke.

Inclusion/Exclusion Criteria

The treatments selected by the Joint Writing Committee for review included unfractionated heparin, low molecular weight (LMW) heparin, heparinoids, aspirin, ticlopidine, clopidogrel, dipyridamole, hirudin, and glycoprotein IIb/IIIa antagonists. Reports of thrombolytics and fibrinogenolytics identified in the search were excluded because they are neither antiplatelet agents nor anticoagulants. Prostacyclin and pentoxyfylline were also excluded because they have major vascular effects other than antiplatelet actions. Case reports, studies of primary intracranial hemorrhages, studies that included only subjects with transient ischemic attack (TIA), and studies of dural sinus or cerebral vein thrombosis were also excluded.

To be considered for analysis, a study had to be a controlled clinical trial that tested an anticoagulant or antiplatelet agent in patients with an ischemic stroke. In addition, the drug must have been given within 48 hours of symptom onset. Clinical endpoints had to be clearly defined before the study started. Studies that included patients in whom treatment could be delayed after 48 hours were considered only if results were also separately on a well-defined subgroup of patients treated within 48 hours of symptom onset. A number of excellent and comprehensive papers on acute stroke management have been published recently, such as the recommendations from the European Stroke Initiative, but these reports did not meet criteria for inclusion since they were based upon reviews of other studies and expert opinion rather than primary source clinical trials.

NUMBER OF SOURCE DOCUMENTS

- 2372 abstracts found
- 310 articles read in full and reviewed by the committee members in detail
- 10 articles satisfied all of the inclusion 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

The following evidence classification system of the Quality Standards Subcommittee (QSS) was approved by the American Academy of Neurology (AAN) and the American Heart Association (AHA).

Levels of Evidence

Class I: Evidence provided by a prospective, randomized, controlled clinical trial with masked outcome assessment, in a representative population. The following are required:

- Primary outcome(s) is/are clearly defined.
- Exclusion/inclusion criteria are clearly defined.
- Adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias.
- Relevant baseline characteristics are presented and substantially equivalent among treatment groups, or there is appropriate statistical adjustment for differences.

Class II: Evidence provided by a prospective, matched cohort study in a representative population with masked outcome assessment that meets all of the above OR a randomized controlled trial in a representative population that lacks one of the above criteria.

Class III: Evidence provided by all other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, in which outcome assessment is independent of patient treatment.

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

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Each study that was considered was rated using the evidence classification system of the Quality Standards Subcommittee (QSS) and approved by the American Academy of Neurology (AAN) and the American Heart Association (AHA). This evidence-based classification scheme excludes review articles, letters, comments, editorials, and articles based solely upon expert opinion.

Abstracts of all identified articles were independently reviewed by two members of the committee, and accepted articles were read and independently abstracted by two committee members according to the Data Abstraction Form, available online at www.aan.com. This form was designed to address the key questions listed below. These key questions were designed to critically assess the major issues involved in the efficacy of anticoagulants and antiplatelet agents in the outcome of patients with acute ischemic stroke. For each of these questions, the quality of the

evidence was rated and recommendations formulated and assigned a grade based on the quality of evidence.

Key Questions

1. Do antithrombotic agents reduce stroke-related morbidity and mortality?
2. Do antithrombotic agents reduce early stroke recurrence?
3. Do antithrombotic agents vary in efficacy according to stroke subtype?
4. Do antithrombotic agents reduce systemic thrombotic complications, such as deep vein thrombosis/pulmonary emboli (DVT/PE)?
5. What are the risks of hemorrhage associated with antithrombotic treatment?
6. Do antithrombotic agents alter acute cardiovascular complications?

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Grades of Recommendation

Grade A. At least one convincing Class I study or at least two consistent, convincing Class II studies.

Grade B. At least one convincing Class II study or at least three convincing Class III studies.

Grade C. At least two convincing and consistent Class III studies.

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

Draft guidelines were reviewed for accuracy, quality, and thoroughness by the American Academy of Neurology (AAN) members, topic experts, and pertinent physician organizations.

Final guidelines were approved by the American Academy of Neurology Quality Standards Subcommittee on December 8, 2001, the American Academy of Neurology Practice Committee on January 31, 2002, and the American Academy of Neurology Board of Directors on February 23, 2002. A report was published in *Neurology* 2002;59:13-22.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Definitions of the levels of evidence (Class I-IV) and grades of recommendation (Grade A-C) are provided at the end of the Major Recommendations field.

1. Patients with acute ischemic stroke presenting within 48 hours of symptom onset should be given aspirin (160 to 325 mg/day) to reduce stroke mortality and decrease morbidity, provided contraindications such as allergy and gastrointestinal bleeding are absent, and the patient has not been or will not be treated with recombinant tissue type plasminogen activator (***Grade A***). The data are insufficient at this time to recommend the use of any other platelet antiaggregant in the setting of acute ischemic stroke.
2. Subcutaneous unfractionated heparin, low molecular weight (LMW) heparins, and heparinoids may be considered for deep vein thrombosis (DVT) prophylaxis in at-risk patients with acute ischemic stroke, recognizing that nonpharmacologic treatments for DVT prevention also exist (***Grade A***). A benefit in reducing the incidence of pulmonary embolism (PE) has not been demonstrated. The relative benefits of these agents must be weighed against the risk of systemic and intracerebral hemorrhage.
3. Although there is some evidence that fixed-dose, subcutaneous, unfractionated heparin reduces early recurrent ischemic stroke, this benefit is negated by a concomitant increase in the occurrence of hemorrhage. Therefore, use of subcutaneous unfractionated heparin is not recommended for decreasing the risk of death or stroke-related morbidity or for preventing early stroke recurrence (***Grade A***).
4. **A**. Dose-adjusted, unfractionated heparin is not recommended for reducing morbidity, mortality, or early recurrent stroke in patients with acute stroke (i.e., in the first 48 hours) because the evidence indicates it is not efficacious and may be associated with increased bleeding complications (***Grade B***).

4. **B**. High-dose LMW heparin/heparinoids have not been associated with either benefit or harm in reducing morbidity, mortality, or early recurrent stroke in patients with acute stroke and are, therefore, not recommended for these goals (***Grade A***).
5. Intravenous (IV), unfractionated heparin or high dose LMW heparin/heparinoids are not recommended for any specific subgroup of patients with acute ischemic stroke that is based on any presumed stroke mechanism or location (e.g., cardioembolic, large vessel atherosclerotic, vertebrobasilar, or "progressing" stroke) because data are insufficient (***Grade U***). Although the LMW heparin dalteparin at high doses may be efficacious in patients with atrial fibrillation, it is not more efficacious than aspirin in this setting. Because aspirin is easier to administer, it, rather than dalteparin, is recommended for the various stroke subgroups (***Grade A***).

<u>Definitions</u>:

Levels of Evidence

Class I: Evidence provided by a prospective, randomized, controlled clinical trial with masked outcome assessment, in a representative population. The following are required:

- Primary outcome(s) is/are clearly defined.
- Exclusion/inclusion criteria are clearly defined.
- Adequate accounting for drop outs and crossovers with numbers sufficiently low to have minimal potential for bias.
- Relevant baseline characteristics are presented and substantially equivalent among treatment groups, or there is appropriate statistical adjustment for differences.

Class II: Evidence provided by a prospective, matched cohort study in a representative population with masked outcome assessment that meets all of the above OR a randomized controlled trial in a representative population that lacks one of the above criteria.

Class III: Evidence provided by all other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, in which outcome assessment is independent of patient treatment.

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

Grade of Recommendation

Grade A. At least one convincing Class I study or at least two consistent, convincing Class II studies.

Grade B. At least one convincing Class II study or at least three convincing Class III studies.

Grade C. At least two convincing and consistent Class III studies.

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

Potential Overall Benefits:

- These guidelines may assist physicians in making appropriate clinical decisions regarding the use of anticoagulant and antiplatelet agents in the management of patients with acute ischemic stroke.

Potential Specific Benefits:

- Aspirin (160 mg or 325 mg daily) results in a small but statistically significant reduction in death and disability when given within 48 hours after ischemic stroke, as indicated by a combined analysis of available studies.
- Anticoagulants (but not antiplatelet agents) reduce the frequency of deep vein thrombosis (DVT) in acute stroke.

POTENTIAL HARMS

There is an increase in both systemic and central nervous system (CNS) hemorrhage in patients treated with aspirin, subcutaneous unfractionated heparin, or low molecular weight (LMW) heparin/heparinoids.

CONTRAINDICATIONS

CONTRAINDICATIONS

Contraindications to aspirin include allergy, gastrointestinal bleeding, and plans to be treated with recombinant tissue type plasminogen activator.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- None of the studies included for review by the guideline developers that fulfilled the prespecified inclusion criteria and addressed the review´s key questions examined the use of hirudin, dipyridamole, ticlopidine or clopidogrel in the setting of acute ischemic stroke.
- This statement is provided as an educational service of the American Stroke Association of the American Heart Association (AHA) and 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 neurological problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative method of care. The American Academy of Neurology and American Heart Association recognize 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
Tool Kits

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

Getting Better
Staying Healthy

IOM DOMAIN

Effectiveness
Safety
Timeliness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Coull BM, Williams LS, Goldstein LB, Meschia JF, Heitzman D, Chaturvedi S, Johnston KC, Starkman S, Morgenstern LB, Wilterdink JL, Levine SR, Saver JL. Anticoagulants and antiplatelet agents in acute ischemic stroke: report of the Joint Stroke Guideline Development Committee of the American Academy of Neurology and the American Stroke Association (a division of the American Heart Association). Neurology 2002 Jul 9;59(1):13-22. [19 references] PubMed

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ADAPTATION

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

DATE RELEASED

2002 Jul (reviewed 2005 Oct)

GUIDELINE DEVELOPER(S)

American Academy of Neurology - Medical Specialty Society
American Stroke Association - Disease Specific Society

SOURCE(S) OF FUNDING

American Academy of Neurology (AAN)

GUIDELINE COMMITTEE

Joint Stroke Guideline Development Committee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Joint Stroke Guideline Development Committee: Milton Alter, MD, PhD (Co-Chair, American Academy of Neurology); George J. Hademenos, PhD (Co-Chair, American Heart Association); Larry B. Goldstein, MD; Philip B. Gorelick, MD, MPH; Chung Y. Hsu, MD, PhD; Jose Biller, MD; and Wendy Edlund

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

According to the guideline developer, this guideline has been reviewed and is still considered to be current as of October 2005. This review involved new literature searches of electronic databases followed by expert committee review of new evidence that has emerged since the original publication date.

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 is available:

- AAN guideline development process [online]. St. Paul (MN): American Academy of Neurology. Electronic copies: Available from the American Academy of Neurology (AAN) Web site.
- Anticoagulants and antiplatelet agents in acute ischemic stroke. St. Paul (MN): American Academy of Neurology. 2002. 13 p. Available for personal digital assistant (PDA) download from the AAN Web site.

Get With the Guidelines (GWTG) provides disease-specific process documents and tools for in-house quality improvement. See the American Heart Association Web site for more information. See the related QualityTool summary on the Health Care Innovations Exchange Web site for this related tool set.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on February 6, 2004. This summary was updated by ECRI Institute on June 22, 2007 following the U.S. Food and Drug Administration (FDA) advisory on heparin sodium injection. This summary was updated by ECRI Institute on March 13, 2008 following the updated FDA advisory on heparin sodium injection.

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