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)

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Stroke remains a common and costly problem worldwide, but substantial advances have been made in recent decades in understanding stroke mechanisms, risk factors, and therapies. Because thrombosis plays an important role in the pathogenesis of ischemic stroke, drugs that interfere with hemostasis and clot formation such as anticoagulants and platelet antiaggregants commonly are used in the management of cerebrovascular disease. Considerable evidence supports the use of certain antithrombotic drugs in stroke prevention. However, because of limited supportive data, the use of these agents in patients with acute ischemic stroke remains controversial.

In this report, we examine the published evidence relevant to the effects of anticoagulants and antiplatelet agents on acute ischemic stroke mortality, morbidity, and recurrence rates as well as associated ancillary benefits and risks of those treatments on the rates of deep vein thrombosis, pulmonary embolus, and cardiovascular complications. As part of these analyses, we also sought to determine whether there was evidence supporting differential efficacy of these drugs according to ischemic stroke subtypes.

Methods. To prepare this report, experienced neurologists with a special interest in stroke diagnosis and management were appointed by the Quality Standards Subcommittee (QSS) and the Therapeutics and Technology Assessment (TTA) Subcommittee of the American Academy of Neurology, and the Stroke Council and Science Advisory and Coordinating Committee (SACC) of the American Heart Association (AHA). The QSS, TTA, Stroke Council and SACC are each charged with the responsibility of preparing evidence-based reports pertaining to medical practice issues including stroke.

To facilitate the process of joint guideline development, a Steering Committee, chaired by representatives of the AAN and the American Stroke Association of the AHA, was appointed to discuss potential topics of wide interest to the stroke community. Choosing the role of anticoagulants and antiplatelet agents in acute ischemic stroke as the first topic, a Joint Writing Committee was appointed with equal representation from each organization.

The Joint Writing Committee first conducted a

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structured literature review with the assistance of a professional medical research librarian based at the University of Minnesota (see Acknowledgment). The literature review was based on MEDLINE searches from 1966 through February 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 (see Acknowledgment).

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 pentoxifylline were also excluded because they have major vascular effects other than antiplatelet actions. Case reports, studies of primary intracranial hemorrhages, studies that included only patients with 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 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 reported on a well defined subgroup of patients treated within 48 hours of symptom onset. A number of excellent and comprehensive articles on acute stroke management have been published recently, such as the recommendations from the European Stroke Initiative,[1] but these reports did not meet our criteria for inclusion because they were based on reviews of other studies and expert opinion rather than primary source clinical trials.

Each study considered was rated using the evidence classification system of the QSS and approved by the AAN and AHA (Appendix A). This evidence-based classification scheme excludes review articles,

Table 1 *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 DVT/PE?

5. What are the risks of hemorrhage associated with antithrombotic treatment?

6. Do antithrombotic agents alter acute cardiovascular complications?

DVT/PE = deep vein thrombosis/pulmonary emboli.

letters, comments, editorials, and articles based solely on 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 in table 1. 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 of A, B, or C based on the quality of evidence as outlined in Appendix A.

Results. The structured literature search yielded 2372 abstracts. There were no disagreements among the reviewers regarding inclusion or exclusion of individual studies. This review process yielded 310 articles to be read in full and reviewed by the committee members in detail. Of the total reviewed, only 10 articles satisfied all inclusion criteria.[2-11] Despite the apparently common use of anticoagulation for progressing stroke or vertebrobasilar stroke, we found no Class I or II evidence addressing these specific clinical situations. None of the included studies that fulfilled the prespecified inclusion criteria and addressed the review's key questions (see table 1) examined the use of hirudin, dipyridamole, ticlopidine, or clopidogrel in the setting of acute ischemic stroke. Table 2 summarizes the results.

Key questions

1. Do antithrombotic agents reduce stroke mortality and stroke-related morbidity?

Neither stroke-related mortality nor all-cause mortality was used as the primary endpoint in any of the studies included in this document. Stroke-related impairment was difficult to compare among the studies because different outcome scales were used and the interval after onset of the stroke at which stroke-related morbidity was assessed varied. The therapeutic agents used in the studies in which mortality

Table 2 *Summary of results*

Platelet antiaggregants and anticoagulants within 48 hours of acute ischemic stroke

Treatment	Benefit data	Risk data
Aspirin	Prevention of early recurrent ischemic stroke (CAST, IST)* Small benefit in reducing death and dependence (CAST, IST, MAST)	Small increase in intracerebral hemorrhage or hemorrhagic transformation (CAST, IST, MAST)* Small increase in transfused or fatal extracranial hemorrhage (IST, CAST)*
IV unfractionated heparin	Inadequate data	Inadequate data
SQ unfractionated heparin	Small benefit in reducing early recurrent stroke outweighed by small increase in CNS hemorrhage (IST)† No benefit in reducing morbidity, mortality (IST)† Reduces PE and DVT (IST†, McCarthy and Turner[6])‡	Increase in symptomatic CNS hemorrhage (8/1000 treated, IST)† Increase in fatal or transfused systemic hemorrhage (9/1000 treated, IST)†
LMW heparins/heparinoids	Benefit in reducing 6-month morbidity (nadroparin, Kay et al[5])¶ No benefit in reducing 3-month morbidity (TOAST)¶ Reduces DVT (TOAST)¶	Variable increase in systemic and CNS hemorrhage across studies (Kay et al.,[5] TOAST,¶ Berge[10]§)

* Compared with placebo/no aspirin.
† Compared with no subcutaneous heparin (50% on ASA, 50% on no ASA).
‡ Compared with no subcutaneous heparin.
¶ Compared with placebo.
§ Compared with aspirin.

CAST = The Chinese Acute Stroke Trial; IST = The International Stroke Trial; MAST = The Multicentre Acute Stroke Trial–Italy; PE = pulmonary emboli; DVT = deep vein thrombosis; LMW = low molecular weight; TOAST = Trial of the Heparinoid ORG 10172 in Acute Stroke.

and/or stroke-related impairment could be assessed included platelet antiaggregants,[2,4,8] unfractionated heparin,[4,6,7] and LMW heparin/heparinoids.[3,5,10]

Platelet antiaggregants. Two large prospective, randomized, placebo-controlled trials included aspirin given within 48 hours of stroke onset.[2,4] The Chinese Acute Stroke Trial (CAST) was a randomized, double-blind, placebo-controlled trial of aspirin at 160 mg/day started within 48 hours of onset of suspected acute ischemic stroke[2] (Class I). A total of 21,106 patients were randomized at 413 hospitals at a mean of 25 hours after the onset of symptoms. Aspirin reduced early mortality rate (3.3 vs 3.9%; $p = 0.04$). However, the beneficial effects of aspirin did not reach significance for the primary endpoint of the combined proportion of patients who were dead or dependent at hospital discharge (30.5 vs 31.6%; $p = 0.08$).

The International Stroke Trial (IST) was another large prospective, randomized, but open-label trial of aspirin and unfractionated heparin (Class II).[4] A total of 19,436 patients were randomized at specialist and nonspecialist hospitals in 36 countries. Half of the patients were randomized to aspirin at 300 mg/day, and the remaining patients were randomized to a group instructed to avoid aspirin. In a factorial design, half of the patients in each group either received subcutaneous, unfractionated heparin or were instructed to avoid heparin. The treatment assignments persisted for up to 14 days, after which time the clinicians were encouraged to consider treating all patients with aspirin. Trends favoring aspirin in

the proportion of patients who were dead at 14 days were not significant (heparin 9%, aspirin 9%; no heparin 9.3%, no aspirin 9.4%). The differences in proportion dead or dependent at 6 months also did not reach statistical significance (heparin 62.9%, aspirin 62.1%; no heparin 62.9%, no aspirin 63.5%). A combined analysis of the results of these two trials shows that aspirin (160 mg or 325 mg daily) had a small but statistically significant reduction of 9 ($\pm$3) fewer deaths or nonfatal strokes per 1000 treated patients (absolute risk reduction = 0.9%; number needed to treat = 111).[12]

The Multicenter Acute Stroke Trial–Italy was a placebo-controlled, unblinded, randomized trial that included 465 patients who received either aspirin alone (n = 153), aspirin plus IV streptokinase (n = 156), or neither aspirin nor streptokinase (n = 156) within 6 hours of stroke onset (Class II). The streptokinase arm was associated with increased 10-day mortality. This study found no effect of aspirin (either alone or in combination with streptokinase) in reducing 10-day mortality rate (aspirin, 10% vs control, 13%), 6-month disability (aspirin, 42% vs control, 39%), or the combined endpoint.[8] However, because only 153 patients received aspirin alone, this study was likely underpowered to determine whether aspirin alone reduced mortality and morbidity rates after stroke.

A secondary analysis of a Phase II, randomized, double-blind, placebo-controlled, dose-escalation trial of abciximab, a platelet glycoprotein IIb/IIIa inhibitor, was relevant to the above question. This drug was given within 24 hours of acute ischemic stroke

(abciximab-treated patients, n = 54; placebo-treated patients, n = 20). The study found a trend toward a higher rate of excellent recovery among patients who received abciximab (modified Rankin scale <1: 35% vs 20%; Barthel >98: 50% vs 40%), but the trial was not powered to detect clinically relevant differences in functional outcome assessments (Class I).[9] Three-month mortality rate was not statistically different between the groups (placebo, 15% and abciximab, 17%).

Unfractionated heparin. Available data demonstrate no reduction in mortality or morbidity rates with unfractionated heparin given subcutaneously to patients with acute stroke.[4,6] In the IST trial,[4] one-fourth of the patients were randomized to subcutaneous unfractionated heparin at 5000 IU twice daily and another one-fourth to 12,500 IU twice daily, whereas the remaining half were instructed to avoid unfractionated heparin. Thus, in the factorial design, half of the patients in each group either received aspirin or were instructed to avoid aspirin (Class II).

Randomized, controlled trials of dose-adjusted IV unfractionated heparin in acute stroke that specifically address long-term, stroke-related morbidity and mortality have not been reported. One study published in 1986 reported a prospective, double-blind trial of dose-adjusted IV unfractionated heparin (Class I) in 225 patients with partial stable carotid and vertebrobasilar distribution stroke.[7] This trial showed that there was no difference in death at 7 days between patients who were treated with unfractionated heparin (1/112 [0.89%]) and those treated with placebo (2/113 [1.77%]). Functional activity at 7 days, 3 months, and 1 year also was not significantly different between groups. At 6 months, the proportion of patients who were dead or dependent was identical for the group that received unfractionated heparin and the group that avoided heparin (62.9% in each). Mortality at one year was significantly increased in the unfractionated heparin-treated group compared with the placebo group (heparin, 17 vs control, 8; p <0.05).[7]

Low molecular weight heparins/heparinoids. LMW heparins or heparinoids have antifactor Xa activity and a decreased tendency to induce thrombocytopenia compared with unfractionated heparin. A double-blind trial randomized 308 patients from four Hong Kong hospitals into three groups: placebo, nadroparin calcium at 4100 anti-Xa IU once daily, or 4100 anti-Xa IU twice daily (Class I).[5] There was no reduction in death (7, 8, and 8 in the high, low, and placebo groups) or dependence at 3 months between the groups given nadroparin as compared with those given placebo (53% in high, 60% in low, and 64% in placebo groups). After 6 months, there was a significant, dose-dependent benefit in the drug-treated patients, with good outcomes in 55% of those treated with high-dose nadroparin vs only 45% in those given placebo. However, this result was not replicated in a preliminary report of a large multicenter, randomized trial in a European population (Fraxi-

parine in Ischemic Stroke Study).[13] Thus, results for anti-Xa agents in acute ischemic stroke have not been consistent.

The Trial of the Heparinoid ORG 10172 (danaparoid) in Acute Stroke (TOAST) was a randomized, double-blind, placebo-controlled trial in which 1281 patients were enrolled at 36 US centers (Class I).[3] The active treatment arm received IV, dose-adjusted danaparoid. There was no significant difference in overall favorable outcomes at 3 months, although at 7 days, 34% of treated patients and only 28% of control subjects had very favorable outcomes ($p = 0.01$).

The Heparin in Acute Embolic Stroke Trial (HAEST)[10] is a prospective study that compared dalteparin, an LMW heparin, with aspirin given within 30 hours of atrial fibrillation-associated stroke (Class I). There were no statistically significant differences between treatment groups in death and physical dependency at 3 months (66.1% in treated vs 64.8% in control participants).

A prospective, randomized, nonplacebo-controlled trial of the LMW heparin, certoparin, given within 12 hours of acute ischemic stroke involved 400 patients (the Therapy of Patients with Acute Stroke [TOPAS] trial). There were four treatment groups: 3000 U daily, 3000 U twice daily, 5000 U twice daily, and 8000 U twice daily. No benefit was shown in the short term or at 3 months in stroke outcome between low and higher doses of certoparin.[11] Those with a Barthel Index >90 at 3 months included 61.5% in Group 1, 60.8% in Group 2, 63.3% in Group 3, and 56.3% in Group 4.

Conclusion. 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.[12] Abciximab, unfractionated heparin, LMW heparins, and heparinoids have not been shown to reduce mortality or stroke-related morbidity when used within 48 hours of onset in patients with acute ischemic stroke.

2. Do antithrombotic agents reduce early stroke recurrence?
Even if an antithrombotic agent given to patients with acute ischemic stroke fails to reduce neurologic impairment, the agent might still be useful in preventing early stroke recurrence. The definition of "early" is variable among studies, ranging from the duration of hospitalization to 4-weeks poststroke. As a result, combining the results of individual trials is not possible.

Platelet antiaggregants. Results of CAST[2] suggested that aspirin lowered the risk of recurrent ischemic stroke from 2.1 to 1.6%, but the risk of all recurrent strokes (hemorrhagic or ischemic) was not significantly reduced (Class I). Similarly, IST[4] suggested that aspirin significantly reduced the rate of recurrent ischemic stroke from 3.9 to 2.8%. Aspirin also reduced the combined rate of ischemic and hemorrhagic stroke from 4.7 to 3.7%.

Unfractionated heparin. There is no reliable evidence that dose-adjusted, IV, unfractionated heparin reduces the risk of early recurrent stroke. In the randomized study of patients with carotid-distribution, partial stable stroke, dose-adjusted IV unfractionated heparin did not prevent stroke progression within 7 days of treatment as compared with placebo (9/112 [17%] treated vs 22/113 [19.5%] placebo) (Class I).[7] In IST,[4] subcutaneous unfractionated heparin treatment reduced the rate of recurrent ischemic stroke from 3.8 to 2.9%. However, the benefit was balanced by an increased frequency of hemorrhagic stroke in the patients treated with heparin (heparin, 1.3% vs nonheparin, 0.4%). It should be noted that pretreatment CT scan was not required and, therefore, some hemorrhages may have been classified as ischemic stroke.

Low molecular weight heparins/heparinoids. In a study of 449 patients, it was found that, compared with aspirin, the LMW heparin, dalteparin, did not prevent early stroke progression (dalteparin, 10.7% vs aspirin, 7.6%; $p = 0.26$) or stroke recurrence (dalteparin, 8.5% vs aspirin, 7.5%; $p = 0.26$) in patients with atrial fibrillation[10] (Class I). In TOAST, reduction in recurrent stroke in patients treated with danaparoid did not reach statistical significance[3] (Class I). Similarly, administration of nadroparin was associated with a nonsignificant reduction in early stroke recurrence (three patients on nadroparin compared with one on placebo at 6 months).[5]

Conclusion. Aspirin reduces the risk of early recurrent ischemic stroke when given within 48 hours of stroke onset but increases the risk of hemorrhagic stroke (absolute risk reduction = 0.7%; number needed to treat = 143). Overall, for aspirin there is a slight but statistically significant benefit in reducing recurrent stroke. Conversely, unfractionated heparin and LMW heparin/heparinoids, when used within 48 hours of onset in patients with acute ischemic stroke, have not been shown to reduce the rate of stroke recurrence.

3. Do antithrombotic agents vary in efficacy by stroke subtype?

Platelet antiaggregants. Both CAST and IST used the Oxfordshire Community Stroke Project Classification System to examine the effect of aspirin on specific ischemic stroke subtypes. The Oxfordshire Community Stroke Project Classification system divides strokes into four main categories: total anterior circulation infarction, partial anterior circulation infarction, posterior infarction, and lacunar infarction. The benefits of aspirin therapy in reducing death in nonfatal acute ischemic stroke were not altered in a statistically significant fashion in any Oxfordshire Stroke subtype in CAST.[2] Similarly, the benefits of aspirin for the whole trial were not significantly altered by the presence of atrial fibrillation at baseline in either CAST[2] or IST.[4]

Unfractionated heparin. Although patients with atrial fibrillation do benefit from long-term anticoagulation for secondary stroke prevention,[14] there are limited data addressing the optimal time for beginning anticoagulation after an acute ischemic stroke. Subcutaneous unfractionated heparin reduced acute recurrent cardioembolic stroke in the IST trial, but increased the intracerebral hemorrhage rate to a similar degree.[4] However, the level of anticoagulation was not routinely measured during follow-up, and the study did not address the use of IV, dose-adjusted heparin. Sixteen percent (n = 3109) of the patients randomized in IST[4] had atrial fibrillation at baseline. In this subgroup, there were 21 fewer recurrent ischemic strokes per 1000 patients treated with unfractionated heparin, but this was offset by 16 more hemorrhagic strokes.

"Stroke in progression" is another clinical situation often considered as a potential indication for anticoagulation. Studying this condition has been difficult because of the variability in its definition. Moreover, different time frames are considered in the various studies and, therefore, the distinction between progression of the old stroke and onset of a new stroke is frequently unclear. It is also true that a patient with stroke may worsen from conditions not directly related to the stroke, e.g., hyperglycemia, congestive heart failure, or renal failure.

The double-blind, placebo-controlled trial of the effects of dose-adjusted, IV, unfractionated heparin in patients with carotid-distribution partial stable stroke also attempted to determine whether IV unfractionated heparin can prevent stroke progression.[7] Patients with noncardioembolic stroke were treated within 48 hours of symptom onset with either continuous IV, unfractionated heparin (n = 112) or placebo (n = 113) for 7 days. Stroke impairment and progression of impairment was defined and assessed using the United Kingdom's Medical Research Council scale. This scale is a system for grading motor impairment and was part, but not all, of the assessment. No significant difference was noted in the proportion of patients with progression (19.5% in the placebo-treated group and 17% in the heparin-treated group). It should be noted that patients with progressing stroke and those with threatened basilar artery occlusion were specifically excluded from the study. Moreover, the relatively low rate of progression in the placebo patients limited the ability of the study to detect a small but potentially meaningful effect of unfractionated heparin (Type II error). Worsening attributable to cerebral hemorrhage or hemorrhagic transformation did not occur in any patient.

Low molecular weight heparins/heparinoids. In a prespecified secondary analysis of TOAST data unadjusted for multiple comparisons, a potential beneficial effect of the heparinoid, danaparoid, was suggested in the subgroup of patients with large artery atherosclerosis, whereas no suggestion of efficacy was detected in cardioembolic and lacunar

subgroups.[3] In the Heparin in Acute Embolic Stroke Trial,[10] LMW heparin was not more effective than aspirin in patients with cardioembolic stroke caused by atrial fibrillation (Class I).

Conclusion. The slight, beneficial effect of aspirin in acute ischemic stroke appears not to be influenced by stroke subtype. There is no convincing evidence that anticoagulants are effective for any particular stroke subtype. The finding that danaparoid was of possible benefit in patients with a large artery stroke was based on a prespecified secondary analysis unadjusted for multiple comparisons; therefore, the observation awaits prospective validation before it can be given any weight.

4. Do antithrombotic agents reduce systemic thrombotic complications such as deep vein thrombosis and pulmonary emboli?

Very few of the studies of acute ischemic stroke that address deep vein thrombosis (DVT) and pulmonary emboli (PE) met the inclusion criteria for this review. However, in general there were more data on reduction of DVT, detected by radiolabeled fibrinogen and venography, than on PE. Moreover, the low number of PE in the patients with stroke limited the statistical power to detect an effect of the treatment in reducing these events (Type II error).

Platelet antiaggregants. Aspirin therapy did not significantly reduce the rate of PE (aspirin, 0.1% vs placebo, 0.2%) in CAST[2] (Class I). Aspirin also failed to reduce PE in IST[4] (aspirin, 0.6% vs avoiding aspirin, 0.8%) (Class II).

Unfractionated heparin. Subcutaneous unfractionated heparin reduces the risk of PE[4,6] and DVT.[6] However, no randomized clinical trial has examined whether IV unfractionated heparin prevents DVT or PE in patients with acute ischemic stroke. In IST,[4] patients randomized to 12,500 IU subcutaneous heparin had fewer PE recorded within 14 days than those on aspirin (0.5% vs 0.8%; $p = 0.02$) (Class II). However, 5000 IU subcutaneous heparin was not more effective than aspirin in preventing PE.[4]

A randomized, unblinded trial evaluated the effect of 5000 units of unfractionated calcium heparin administered subcutaneously every 8 hours for 2 weeks in preventing DVT and PE. That study also found that with heparin use, there was a statistically significant reduction in PE from 33/161 (20%) to 7/144 (5%) and in DVT, as detected by radiolabeled fibrinogen leg scans, from 117/161 (73%) to 32/144 (22%) (Class II).[6] The unfractionated heparin-treated group also had a lower 3-month mortality rate (53/161 [33%] vs 31/144 [21%]).

Although the authors did not distinguish symptomatic from asymptomatic DVT, the finding of fewer PE and a lower proportion of deaths in the unfractionated heparin-treated group is evidence that heparin given as either 5000 IU subcutaneously every 8 hours or 12,500 IU subcutaneously BID was beneficial. Patients treated with unfractionated heparin were less likely to have PE (7 of 24 patients

with autopsy-verified PE) than were control patients (33 of 47 patients). However, the proportion of patients with nonfatal PE was not reported. Moreover, the number of hemorrhagic strokes in the two groups was similar, with four heparin and three control patients having hemorrhagic transformation of the initial stroke. However, these data should be interpreted with caution because this study, reported in 1986, reported no neuroimaging data.[6]

Low molecular weight heparins/heparinoids. A study involving 203 patients on nadroparin and 105 on placebo found no decrease in DVT incidence at 10 days, but there was only one event in the entire cohort, a frequency so low as to make it difficult to exclude a Type II error.[5] In TOAST,[3] there were 2/638 with DVT (0.3%) on danaparoid vs 10/628 (1.6%) with placebo ($p < 0.05$), but there was no significant reduction in frequency of PE (2/238 [0.3%] with danaparoid vs 4/628 [0.6%] with placebo).

Conclusion. The frequency of DVT in acute stroke is reduced by anticoagulants but not by antiplatelet agents. It is unclear whether frequency of PE is also decreased because too few PE occurred in the cohorts studied to exclude the possibility of a Type II error.

5. What are the risks of hemorrhage associated with antithrombotic agents?

Platelet antiaggregants. Based on CAST[2] and IST,[4] aspirin increases the risk of systemic and CNS hemorrhage. In CAST,[2] the risk of hemorrhage large enough to require transfusion or a fatal systemic hemorrhage was 0.8% in aspirin-treated patients vs 0.6% in nonaspirin-treated patients ($p = 0.02$) (Class I). In IST,[4] the risk of hemorrhage requiring transfusion or fatal systemic hemorrhage was 1.1% in aspirin-treated patients compared with 0.6% in nonaspirin-treated patients ($p = 0.0004$) (Class II).

There were no cases of symptomatic major intracerebral hemorrhage through day 5 or even to 3 months in any treatment group in the abciximab trial.[9] There were also no cases of nonintracranial bleeding through day 5. In the aspirin-alone group in the Multicenter Acute Stroke Trial–Italy,[8] the rates of symptomatic cerebral hemorrhage (3/153 [2%]), CT scan-verified intracerebral hemorrhage (1/153 [0.7%]) and hemorrhagic infarction (7%) were similar to or lower than those in the group given no study drug.

Unfractionated heparin. In the IST study,[4] subcutaneous unfractionated heparin (5000 U BID or 12,500 IU BID) increased the risk of both systemic and CNS hemorrhage (Class II). A higher rate of hemorrhage occurred with the higher dose. In that study, 1.2% of patients given subcutaneous heparin had a hemorrhagic stroke compared with 0.4% of control participants ($p < 0.0001$); 1.3% had fatal or systemic hemorrhage requiring transfusion compared with 0.4% for control participants ($p < 0.00001$).

One randomized, double-blind, placebo-controlled

study of IV unfractionated heparin in partial stable carotid and vertebrobasilar distribution stroke excluded patients with presumed cardioembolic stroke.[7] A total of 112 patients were treated with IV heparin for 7 days and compared with 113 on placebo (Class I). No patients had symptomatic intracerebral hemorrhage, although follow-up head CT was only performed in the 19 patients who met the study's criteria for progressing stroke.

Given the paucity of controlled clinical trials to assess hemorrhagic complications in acute ischemic stroke, data currently are not adequate to determine the magnitude of the risk of IV administration of unfractionated heparin in a heterogeneous group of patients treated within 48 hours of onset.

Low molecular weight heparins/heparinoids. In TOAST,[3] serious systemic hemorrhage occurred in 5.3% of danaparoid-treated patients vs 2.7% of control participants. Serious CNS hemorrhage occurred in 14/638 (2.2%) of danaparoid-treated patients vs 7/628 (1.1%) of control participants (Class I). In the Heparin in Acute Embolic Stroke Trial,[10] there was no difference in CNS hemorrhage between aspirin and dalteparin treatments, but systemic hemorrhage was more common in the LMW heparin-treated group (5.8%) compared with the aspirin-treated group (1.8%) (Class I). A study performed in Hong Kong found that both systemic and CNS hemorrhagic transformations were rare and not significantly different in those treated with nadroparin compared with placebo (10/203 [4.9%] vs 9/105 [8.6%]) (Class I).[5] In TOPAS, certoparin therapy was associated with a parenchymal hemorrhage on CT scan in 2.2% of participants. More intracranial and extracranial bleeding complications were observed in patients receiving the highest dose of certoparin (Class II).[11]

Conclusion. There is an increase in both systemic and CNS hemorrhage in patients treated with aspirin, subcutaneous unfractionated heparin, or LMW heparin/heparinoids.

6. Do antithrombotic agents alter acute cardiovascular complications?

Cardiovascular complications considered in this review included acute myocardial infarction, acute congestive heart failure, clinically significant cardiac arrhythmia, systemic embolism, anaphylaxis, and related hypotensive crisis. Aside from myocardial infarction, data addressing these cardiovascular complications are lacking. In the TOAST study (Class I),[3] there were only 18 myocardial infarctions—11 in the active treatment group (three fatal) and seven in the placebo group (two fatal) during the 3 months after stroke. That difference was not statistically significant. In IST,[4] no differences were observed in the frequency of deaths from coronary artery disease among the treatment groups.

Conclusion. The available data suggest that the incidence of acute cardiovascular complications is low, and none of the available studies had sufficient power to detect a modest treatment effect on these endpoints.

Discussion. Despite decades of use of anticoagulation in the treatment of acute stroke and a plausible pathophysiologic rationale for such use, there were surprisingly few randomized trials that addressed the effects of anticoagulants given within a few hours of onset of symptoms. The time frame of 48 hours from stroke onset selected for this review excluded many studies from consideration, but this interval is justified by considerable new experimental and neuroimaging evidence on the pathogenesis of stroke.

IST included 843 patients treated within 0 to 3 hours of symptom onset and 2322 patients treated within 4 to 6 hours. However, the study found no significant differences in the odds of death or dependency at 6 months for the group receiving subcutaneous unfractionated heparin compared with the group that did not receive unfractionated heparin in either treatment time window. In TOAST,[3] an IV heparinoid had no overall benefit, even though the mean time to treatment was slightly more than 15 hours. Therefore, there is no evidence that early treatment with anticoagulants decreases mortality after an acute stroke. The available evidence does suggest a small benefit for use of aspirin in the first 48 hours. It remains possible that delaying initiation of anticoagulation until after this time period could decrease the risks of hemorrhage while still improving outcomes.

High-quality data regarding the relative risks and benefits of anticoagulant and antiplatelet drugs in specific subgroups of patients with ischemic stroke are limited because most of the available clinical trials were not specifically powered to examine efficacy by subtype. There is no clear benefit for anticoagulants in any particular subgroup. Although patients with atrial fibrillation do benefit from long-term anticoagulation,[14] the optimal time for instituting anticoagulation in such patients remains unclear. Only three trials of aspirin (160 to 325 mg/day) were identified for this review. The two large studies (CAST[2] and IST[4]) demonstrated a small but statistically significant benefit for aspirin in reducing stroke morbidity and recurrence.

Three Cochrane Reviews are relevant to these guidelines.[15-17] One meta-analysis of data from 23,427 subjects enrolled in 21 trials (last searched, March 1999) concluded that immediate anticoagulation of patients with acute ischemic stroke was not associated with a statistically significant reduction in the odds of death or dependency at final follow-up (OR: 0.99; 95% CI: 0.94 to 1.05).[15] A second meta-analysis of data from 705 subjects enrolled in 5 trials (last searched, April 1999) concluded that danaparoid and enoxaparin were more effective in reducing the risk of DVT than unfractionated heparin in patients with acute ischemic stroke (OR: 0.52; 95% CI: 0.56 to 0.79).[16] However, the data were insufficient to determine whether LMW heparins or hepari-

noids were more effective than unfractionated heparin in reducing the risk of major adverse clinical events such as PE or intracranial hemorrhage.

A third meta-analysis of data from 41,325 subjects enrolled in 8 trials (last searched, March 1999) concluded that antiplatelet agents have a net beneficial effect in acute ischemic stroke.[17] It was estimated that 13 more patients (95% CI: 4 to 22) were alive and independent for every 1000 patients treated with antiplatelet agents. There were two more intracranial hemorrhages (95% CI: 0 to 4) and seven fewer recurrent ischemic strokes (95% CI: 4 to 10) for every 1000 patients treated acutely with antiplatelet agents.

Future studies. The 48-hour time frame was chosen for this review in response to the concept that early therapeutic intervention would be more likely to decrease early recurrent events or clinical worsening. Unfortunately, the number of high quality studies with such early treatments that addressed the key questions for this review were extremely limited. Clearly, if future prospective trials of platelet antiaggregant or anticoagulant treatments in acute stroke are contemplated, consideration must be given to the need for very early institution of treatment. The strategy of delayed initiation of anticoagulation until after the first 24 to 48 hours have elapsed also merits attention if additional prospective trials of antithrombotics in acute stroke are undertaken, because such delay could reduce frequency of hemorrhage.

Whether other oral antiplatelet agents are as safe and effective as aspirin is unknown. Comparison trials of aspirin vs other antiplatelet regimens are warranted in patients with acute stroke who are not candidates for thrombolysis. During the course of our review, we noted one study that described the use of ticlopidine as a treatment for acute cerebral infarction.[18] However, this was a pilot study that did not have a clinically relevant endpoint and focused primarily on factors involving rheology. Thus, it failed to meet the criteria for inclusion in this review. Additional clinical trials should be carried out to assess the efficacy of potent, rapidly acting antiplatelet therapies such as IV glycoprotein IIb/IIIa antagonists either alone or in combination with thrombolytic agents.

Currently, no well designed, well executed trial of IV, dose-adjusted, unfractionated heparin has been completed in ischemic stroke using a time window of only a few hours. Previously, it was widely believed that acute IV anticoagulation would be efficacious in patients with cardioembolic stroke. This presumption was, in part, based on the overwhelming evidence for efficacy of oral anticoagulation in primary and secondary prevention of stroke in patients with atrial fibrillation. However, because the risk of early recurrent cardioembolic stroke appears low, the benefit of immediate anticoagulation may be outweighed by the risk of bleeding. Early anticoagulation with subcutaneous, unfractionated or low molecular weight heparins or IV heparinoid has not been demonstrated to be efficacious in patients with probable cardioembolism, but such agents have not been adequately studied. Assuming that the risk of intracerebral hemorrhage will be low, both the cellular and proteinaceous components of clot may be appropriate pharmacotherapeutic targets for reperfusion therapies after an acute ischemic stroke.

The secondary TOAST[3] analysis suggested that patients with large vessel atherothrombotic stroke fared better with IV heparinoid than patients receiving placebo; however, a well designed, prospective study especially targeting such patients is required. Now that techniques such as CT and magnetic resonance angiography permit rapid assessment of the cervicocephalic vasculature, it may be possible to design such a study. The question of whether IV, unfractionated heparin is efficacious in the treatment of acute ischemic stroke, either in all strokes or a specific subtype, will require additional well designed, randomized trials.

Recommendations

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 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, LMW heparins, and heparinoids may be considered for 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 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).

4A. 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).

4B. 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. 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).

Addendum. After completion of the literature review and formulation of this report, another relevant article was published by a group of investigators in Europe and one in Canada and is summarized here; the results are consistent with the recommendations cited above. This Class I double-blind study involved 1486 patients with acute ischemic stroke treated daily within 48 hours of onset for up to 10 days with tinzaparin, an anti-Xa LMW heparin.[19] Patients were randomized to high dose (175 IU anti-Xa IU/kg), low dose (100 anti-Xa IU/kg), or aspirin (300 mg). At 6 months follow-up, the proportions independent were 194/468 (41.5%), 206/486 (42.4%), and 205/482 (42.5%). Disability, case fatality, and neurologic deterioration rates were also similar among the treatment groups. No symptomatic DVT occurred in those on high-dose tinzaparin whereas in the group on aspirin, nine were recorded. Seven patients on high-dose tinzaparin and one patient on aspirin had a symptomatic intracranial hemorrhage.

Disclaimer. This statement is provided as an educational service of the American Stroke Association of the 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 neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methods of care. The AAN and AHA recognize that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all the circumstances involved.

Appendix A

Levels of evidence and recommendation grade classification scheme.

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 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.

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.

Appendix B

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This information is current as of July 9, 2002

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