Atrial Fibrillation, Stroke, and Acute Antithrombotic Therapy
Analysis of Randomized Clinical Trials

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Background—Strokes in patients with atrial fibrillation (AF) are typically larger, are associated with higher early mortality, and occur in older patients versus strokes in patients with sinus rhythm. Until recently, the value of antithrombotic therapies for acute stroke management has been based on empiric evidence.

Summary of Review—We present a critical review of 3 randomized clinical trials testing aspirin, heparin/heparinoid, or both involving 5029 patients with AF and acute stroke. Early recurrent ischemic stroke occurred in about 5% of patients during the 2 to 4 weeks after initial stroke. Data conflict about whether early use of heparin/heparinoid reduced early recurrent ischemic stroke but are consistent regarding its lack of overall benefit on long-term functional outcome. Modest benefits for reduction of early recurrent stroke and functional outcome were associated with aspirin use, based largely on subgroup analysis from a single, large, unblinded trial.

Conclusions—No benefit of heparin has been demonstrated for acute stroke patients with AF; whether selected subgroups would respond differently remains to be proven. Aspirin followed by early initiation of warfarin for long-term secondary prevention is reasonable antithrombotic management. (Stroke. 2002;33:2722-2727.)

Key Words: aspirin ■ atrial fibrillation ■ heparin ■ stroke ■ thrombolysis

A lthough 1 of 6 ischemic strokes is associated with atrial fibrillation (AF), the value of early antithrombotic therapy for AF patients with acute stroke has only recently been clarified by randomized trials. Most ischemic strokes in AF patients are due to cardiogenic embolism of left atrial appendage thrombi. AF patients with stroke are typically older (averaging approximately 75 years) with large hemispheric strokes and with higher early mortality compared with ischemic stroke patients in sinus rhythm.1,2 These features, combined with the potential threat of early, recurrent cardiogenic embolism and frequent spontaneous lysis of cardioembolic occlusions, necessitate that the benefit versus risk of antithrombotic therapies for acute stroke be examined separately in AF patients.

In the 1980s and early 1990s, numerous case series and case-control studies assessed the value of early heparin anticoagulation in AF-associated stroke. Recent randomized trials provide higher-quality evidence that should supplant earlier observations as the basis for management decisions. Outcomes in >5000 patients with acute stroke and AF randomized to heparin, low-molecular-weight heparin, or aspirin in recent clinical trials are available (Table 1).2-5 Even so, no clinical trial is perfect or answers all questions about all issues, and relevant methodological aspects warrant scrutiny. Randomized clinical trials yield the most reliable information about treatment effects, but inclusion/exclusion criteria influence the external validity of their results and must be examined carefully.

We critically analyze the benefits and risks of antithrombotic/fibrinolytic agents for AF patients with acute stroke on the basis of data from all available randomized clinical trials (AF patients have been included in several other recent randomized trials in acute ischemic stroke, but outcomes in AF patients have not been reported separately6-11). The implications of the trials’ results for the management of AF patients with acute ischemic stroke are discussed.

Three Key Randomized Clinical Trials
In the International Stroke Trial (IST), 19 435 patients with suspected acute ischemic stroke within 48 hours (93% confirmed as ischemic by early CT) at 467 hospitals were randomly assigned to aspirin 300 mg/d versus no aspirin and, separately, to 1 of 2 dosages of subcutaneous heparin versus no heparin in a 2×3 factorial design (Table 1).1 Treatment was not masked (ie, it was unblinded), and there were no prespecified criteria for early recurrent stroke; both features augmented the potential for biased determination of early recurrent stroke. Functional outcomes after 6 months were assessed mainly by participant questionnaire. Results for the subgroup of 3169 participants (17%) with AF have been...
TABLE 1. Randomized Trials of Antithrombotic Therapy in Acute Stroke and AF

<table>
<thead>
<tr>
<th>Trial</th>
<th>Mean Time to Treatment</th>
<th>Interventions</th>
<th>% Patients With AF</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>IST²³ (1997)</td>
<td>17%/19 h</td>
<td>Heparin 12 500 SC BID</td>
<td>3169</td>
<td></td>
</tr>
<tr>
<td>CAST⁴ (1997)</td>
<td>7%/25 h</td>
<td>Aspirin 160 mg/d</td>
<td>1411</td>
<td></td>
</tr>
<tr>
<td>HAEST⁵ (2000)</td>
<td>100%/21 h</td>
<td>LMW heparin</td>
<td>449</td>
<td></td>
</tr>
</tbody>
</table>

LMW indicates low molecular weight.
*Other randomized trials included AF patients but did not report results separately for this subgroup.
†Half received aspirin.
‡Half received heparin.

reported: the mean age was 78 years, 56% were women, and the 14-day and 6-month mortality rates were 17% and 39%, respectively. Symptomatic hemorrhagic transformation was reported in 1% and was twice as frequent in AF participants as in those in sinus rhythm (P<0.05).

The Chinese Acute Stroke Trial (CAST) compared aspirin 160 mg/d with placebo (double-blind) in 21 106 patients with suspected acute ischemic stroke within 48 hours (94% confirmed as ischemic by early CT) at 413 hospitals in China, assessing outcomes after 4 weeks. There were apparently no prespecified criteria for recurrent stroke. AF was present in only 7% (n=1411) of participants (probably reflecting the relatively low mean age of the stroke cohort). Limited data about the subgroup of AF patients from the CAST have been published, with additional outcome data available combining AF patients assigned to aspirin in the CAST with those from the IST (Appendix 1).

The Heparin in Acute Embolic Stroke Trial (HAEST) randomly assigned 449 AF patients with acute ischemic stroke (all confirmed by CT) within 30 hours of stroke onset from 45 Norwegian centers to a low-molecular-weight heparin (dalteparin 100 IU/kg SC twice daily) or aspirin 160 mg/d in a double-blind design, with the main outcomes of recurrent stroke during the first 14 days and functional status or death after 3 months. Criteria for recurrent stroke included persistent worsening of the original deficit after the first 48 hours; progressive stroke was defined similarly except that it occurred within 48 hours of stroke onset and was more frequent than recurrent stroke. The mean patient age was 80 years, and 55% were women, with an 8% 14-day mortality rate and a 17% 3-month mortality rate. Extracranial bleeding was significantly increased in those assigned dalteparin, confirming an in vivo antithrombotic effect by the dosage used.

Frequency of Early Recurrent Ischemic Stroke

Early recurrent ischemic stroke appears to be slightly more frequent in acute stroke patients with AF than in those in sinus rhythm. In the IST, the reported rate of recurrent ischemic stroke was 5% over 14 days among 1612 AF participants not receiving heparin (half received aspirin). With allowance for a 20% reduction in early ischemic stroke recurrence by aspirin (see below), the rate of recurrent ischemic stroke in the absence of aspirin from the IST results is estimated as 6% over 2 weeks. The HAEST reported recurrent ischemic stroke within 2 weeks in 8% of 224 AF patients with acute stroke given aspirin (although some portion of these recurrences may have been nonthrombotic worsening of the original deficit). The CAST found a 5% frequency of recurrent ischemic stroke over 4 weeks among 696 AF patients given aspirin. When the results from participants receiving aspirin in these 3 clinical trials were combined, the rate of recurrent ischemic stroke within 2 weeks in AF patients was approximately 5%.

None of these 3 trials attempted to distinguish recurrent ischemic stroke due to cardiogenic embolism from those due to other mechanisms. When those with AF versus sinus rhythm in the IST were compared, the frequency of recurrent ischemic strokes was only slightly higher in AF patients, and the relative risk reduction by aspirin was similar, suggesting that many recurrences could have been noncardioembolic.

Aspirin for Acute AF-Associated Stroke: IST and CAST

Aspirin reduced early recurrent ischemic/unknown strokes by approximately 25% in AF participants in the unblinded IST, with a smaller effect (5% reduction) in the double-blinded CAST, yielding a combined relative risk reduction of 21% (95% CI, −5 to 41) (Table 2). Analysis confined to the smaller number of CT-proven ischemic recurrent strokes yielded a relative risk reduction of 30% (95% CI, −4 to 53*) (Appendix 2). Hemorrhagic stroke (including symptomatic hemorrhagic transformation) occurred with nearly equal frequency in those receiving aspirin versus no aspirin/placebo (relative risk=1.0) (Table 2). The number of AF patients who would need to be treated with aspirin to prevent 1 recurrent stroke over 2 to 4 weeks is approximately 100 on the basis of the combined analysis of the IST and the CAST. The effect of aspirin on recurrent ischemic stroke among AF participants in the IST and the CAST closely paralleled that for the larger number in sinus rhythm, suggesting that the observed reduction in AF patients may not necessarily have been due to prevention of recurrent cardiogenic embolism.

All-cause mortality during the 2 to 4 weeks after stroke was not reduced by aspirin versus control in the combined analysis of the 2 trials (13%; relative risk=1.0; 95% CI, 0.8 to 1.2*) (Appendix 2), nor was the composite outcome of recurrent stroke or death reduced (relative risk=1.0; 95% CI, 0.8 to 1.1). A small favorable trend by aspirin for reducing death or dependency at 6 months among AF patients was reported in the IST (22% of those treated with aspirin versus 20% of controls were alive and independent; relative risk of good outcome=1.1; 95% CI, 0.9 to 1.3; P=0.20) (Table 2).
Heparin and Heparinoids for Acute AF-Associated Stroke: IST and HAEST

Does the use of heparin/heparinoids reduce early recurrent ischemic stroke in AF patients? Data from the 2 relevant randomized clinical trials conflict. The double-blind HAEST found no reduction in early recurrent ischemic stroke among AF patients randomized to receive a low-molecular-weight heparin versus aspirin (Table 2).5 In contrast, the IST found “a clear and dose-dependent reduction in recurrent ischemic stroke among patients allocated to heparin (P/H11005 0.001) given subcutaneously. 2 The overall rates of recurrent ischemic stroke in the control arms (5% in IST, 8% in HAEST) and of secondary brain hemorrhage (2% in IST, 3% in HAEST) among those given heparin/heparinoid were similar in the 2 trials. Potential explanations for the discrepant effects of heparin/heparinoid on recurrent ischemic stroke include biased detection of events in the unblinded IST, a different effect of the 2 specific agents, inclusion of nonthrombotic causes of worsening among events in HAEST, the play of chance, or a combination of these reasons. Taken at face value, the trend toward a substantially larger reduction in recurrent ischemic strokes by heparin among IST participants with AF (44%) versus those in sinus rhythm (19%; P=0.09 for heterogeneity of odds ratio) supports an effect on early recurrent cardiogenic embolism in AF patients.3

However, the reduction in early recurrent ischemic stroke by heparin in the IST was almost entirely offset by increased symptomatic brain hemorrhage: the frequency of recurrent ischemic stroke combined with hemorrhagic stroke was approximately 5% in both heparin arms and in those not receiving heparin (risk reduction by heparin 10%; 95% CI, −20 to 40). Neither the IST nor the HAEST showed a benefit of anticoagulation on functional outcome 3 to 6 months later, nor have other randomized trials of low-molecular-weight heparins in patients with mixed cardioembolic sources shown such benefit.7,8,15

Table 2 summarizes the results of randomized trials of heparin or aspirin in acute stroke with AF.2–5,7,12,15,16

Thrombolytic Therapy for Acute AF-Associated Stroke

AF patients have been modestly overrepresented in case series and clinical trials of acute stroke patients treated with
thrombolytic therapy: 20% to 30% of patients receiving intravenous thrombolytic agents and almost half of those undergoing intra-arterial thrombolysis have had AF.\textsuperscript{6,11,17–19} This increased prevalence is likely explained by the abrupt, often dramatic, onset of major hemispheric deficits with AF-associated stroke, prompting urgent evaluation within the restricted time limits for thrombolytic therapy. Hypothetically, “old” thrombi from the left atrial appendage that subsequently embolize could be relatively refractory to thrombolysis; however, recanalization rates after tissue plasminogen activator (tPA) use appear to be high in AF patients.\textsuperscript{18–20} Given the generally larger volume of brain infarction in AF patients with stroke, thrombolytic therapy has been predictably associated with a higher likelihood of symptomatic brain hemorrhage.\textsuperscript{18,21–24} By multivariate analysis with adjustment for extent and severity of ischemia, AF was not independently associated with secondary brain hemorrhage after thrombolysis.\textsuperscript{21–24}

While a recent case-control study reported improved outcomes in AF patients with acute stroke treated with intravenous tPA,\textsuperscript{20} stronger evidence is from subgroup analysis of the randomized National Institute of Neurological Disorders and Stroke (NINDS) tPA trial. The trial included 115 AF patients with acute ischemic stroke (all confirmed by CT) randomized to receive either intravenous tPA (0.9 mg/kg up to 100 mg maximum) or placebo within 3 hours of stroke onset, given double-blind, with the primary outcome functional status assessed 6 months after stroke.\textsuperscript{6} The use of tPA within 3 hours of stroke doubled the likelihood of a favorable outcome among all trial participants, but specific results for the subgroup of AF patients have not been reported separately.\textsuperscript{25} There was no evident treatment interaction ($P=0.96$) between a history of AF and benefit from tPA, but statistical power to detect an interaction was limited.\textsuperscript{25} The focus of this trial was on recovery from the initial ischemic deficit, and effects on early recurrent ischemic stroke are not available.

The stakes are higher for thrombolytic treatment of AF patients with stroke: the inherently worse prognosis of AF-associated stroke accentuates both the risks and potential benefits of intravenous tPA. Many AF patients with stroke are elderly, but age alone does not appear to be a contraindication for the use of intravenous tPA.\textsuperscript{26} Additional data about the efficacy and safety of thrombolysis in larger numbers of AF patients with acute stroke, and particularly those aged >75 years with large strokes, would be reassuring.\textsuperscript{27} The value of intra-arterial thrombolysis specifically in AF patients cannot be determined from the published literature.

**Subgroups of AF Patients Defined by Mechanism, Stroke Size, Presence of Left Atrial Thrombi, or Other Factors**

On the basis of current concepts of ischemic stroke mechanisms in AF, predictors of early recurrent embolism, and risk factors for hemorrhagic worsening during anticoagulation, subgroups of AF patients who could respond differently to acute antithrombotic therapy can be postulated. Perhaps 25% of ischemic strokes in AF patients are noncardioembolic, and the effects of acute antithrombotic therapy may differ in this subset (which tends to suffer smaller, less disabling strokes).\textsuperscript{28} Transesophageal echocardiography demonstrates left atrial appendage thrombus in approximately 25% of AF patients with prior stroke and in 10% of those without prior clinical stroke, but the prognostic value for proximate embolization has not been defined (the observation that AF patients without clinical embolism demonstrate appendage thrombi suggests that thrombi visualized by transesophageal echocardiography do not always pose an immediate threat). Hemostatic abnormalities may predict early recurrent strokes.\textsuperscript{29}

Larger infarcts are more prone to symptomatic hemorrhagic worsening caused by antithrombotic and fibrinolytic therapies; small infarcts could favorably shift the balance of benefit and risk of heparin on the basis of the IST results (but are of no consequence on the basis of the HAEST results). The interval from stroke onset to treatment with heparin/heparinoid averaged approximately 20 hours in the available randomized trials; early initiation of heparin within 6 hours has been associated with improved outcome in a clinical case series.\textsuperscript{30} No subgroup data from existing randomized trials are available, and hence the relevance of these AF subgroups to immediate antithrombotic management remains speculative.

**Are the Key Randomized Trials Applicable to Clinical Practice?**

Recent multicenter surveys of AF patients hospitalized for acute ischemic stroke in Europe and in the United States reported mean patient ages of 75 to 77 years, percentages of women of 50% to 60%, inpatient mortality rates of 18% to 19%, and a mortality rate of 33% after 3 months.\textsuperscript{1,3} In a large clinical case series of AF patients treated with intravenous heparin, the mean age was >70 years and early mortality was 9%, with rates of recurrent ischemic stroke of 2% and symptomatic hemorrhagic stroke of 3%.\textsuperscript{3} Overall, these are similar to the features of AF participants in the IST and the HAEST. No specific data are available for AF participants in the CAST, although the estimated early mortality among AF patients appears to be relatively low (10% to 12% during the first month).\textsuperscript{12} In summary, AF patients enrolled in the IST and the HAEST appear generally representative of AF patients with stroke from hospital-based surveys; no information is available about AF participants in the CAST.

**Summary and Conclusions**

Early recurrent ischemic stroke occurred in approximately 5% of AF patients during the initial 2 weeks in recent randomized trials, but it is unclear whether most were cardioembolic. This analysis began with the premise that AF patients with acute ischemic stroke may respond differently to antithrombotic therapies. However, when randomized trials that included both patients with AF and patients with sinus rhythm (IST and CAST) were considered, the relative effects of antithrombotic therapy were not importantly different between AF patients and the larger number of patients in sinus rhythm. The mechanistic implications of this observation are undetermined because of the aforementioned vagaries of the trial designs, but the clinical implications are more clear.

Whether heparin/heparinoids reduce recurrent ischemic stroke (and recurrent cardiogenic embolism) in AF patients is
uncertain because of the conflicting results of the HAEST and the IST, but overall rates of recurrent stroke (ie, ischemic and hemorrhagic combined) and functional outcome are not improved by the use of these agents. Some have argued that early treatment with intravenous, adjusted-dose heparin (not yet tested in randomized trials) would be more efficacious, but this remains to be established.

With the caveat of potentially biased event detection in IST, analysis of 4551 AF patients randomized to aspirin versus control in the IST and the CAST treated a mean of approximately 20 hours after stroke onset shows trends toward modest reduction in early recurrent stroke and toward improved 6-month functional outcome. Given these trends combined with the safety and ease of use of aspirin, early aspirin therapy is sensible for AF patients with acute ischemic stroke (combined with low-dose subcutaneous heparin for prevention of venous thrombosis if substantial leg weakness is present).

The fraction of AF patients with good outcomes 6 months after stroke is distressingly small, emphasizing the importance of stroke prevention and the need for more efficacious acute interventions. Intravenous tPA given within 3 hours of stroke onset appears to offer the most potential benefit for AF patients with acute ischemic stroke; however, this is based on limited information about 115 AF patients in the NINDS tPA trial, and more data are needed to be confident of the effect in AF patients.

When should warfarin be initiated for secondary prevention? Warfarin anticoagulation is highly efficacious for long-term secondary prevention in AF patients, but there is a paucity of data addressing when warfarin can be safely initiated after stroke. In the European Atrial Fibrillation Trial, approximately 100 AF patients commenced oral anticoagulation within 2 weeks of ischemic stroke or transient ischemic attack, and there was no reported secondary hemorrhagic worsening (however, AF patients with large, disabling strokes that are prone to hemorrhagic transformation were underrepresented in this trial). On the basis of the usual timing of secondary hemorrhagic transformation between 12 hours and 4 days after stroke onset, it seems reasonable to begin warfarin as soon as the patient is medically and neurologically stable, often 2 to 3 days after stroke, to achieve therapeutic anticoagulation 7 to 10 days after stroke onset. Some experts routinely repeat a CT scan before initiating warfarin and delay warfarin therapy if hemorrhagic transformation is evident. Minor degrees of hemorrhagic transformation are frequent (particularly on MRI), and the clinical significance regarding initiation of warfarin is unclear and controversial. Empirically, we repeat a CT scan before initiating warfarin if there is clinical worsening, if the infarct is large, or in the presence of undue headache, delaying initiation of warfarin for 1 week if substantial hemorrhage is evident.

Appendix 1

Data on Recurrent Stroke From CAST

The main CAST results publication reported only the number of patients with death or nonfatal (confirmed) ischemic strokes in AF participants assigned to aspirin versus placebo (99 versus 111, respectively). In a subsequent combined analysis that pooled patients from IST and CAST, the number of AF patients with recurrent ischemic stroke was given as 46 versus 64 on aspirin versus no aspirin/placebo, but this was restricted to CT-confirmed recurrent ischemic strokes. Dr Z.M. Chen of the CAST reanalyzed the data and reported that when CT-confirmed and unknown strokes were combined (to be comparable with the IST report), recurrent ischemic strokes among AF participants occurred in 35 versus 38 on aspirin versus placebo, respectively (Z.M. Chen, written personal communication, January 2, 2002). The number of hemorrhagic strokes in the CAST was obtained by subtracting the IST patients from the combined total.

Appendix 2

Statistical Methods

Meta-analyses of the trials are presented as relative risk reductions for treatment groups compared with control groups. To estimate the relative risk reduction, the combined odds ratio estimate computed with the use of the modified Mantel-Haenszel (Peto) method was subtracted from 1. Before risk reduction was estimated, the assumption of statistical homogeneity of treatment effect (across trials and within a specific scenario) was tested with the use of the Q statistic for the relative odds scale, with lack of homogeneity precluding estimation of overall treatment effect (probability values are reported only if <0.2). Estimates of relative risk reduction in individual trials were computed by subtracting the estimated odds ratio from 1. Meta-analysis results to estimate relative risk reduction in which only combined data were reported (ie, individual trial data were not available) are indicated by an asterisk (*), and relative risk reduction was calculated as if data were from a single trial.

References


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