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Risk of Early Death and Recurrent Stroke and Effect of Heparin in 3169 Patients With Acute Ischemic Stroke and Atrial Fibrillation in the International Stroke Trial

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Background and Purpose—We sought to investigate the apparently high risk of early death after an ischemic stroke among patients with atrial fibrillation (AF), identify the main factors associated with early death, and assess the effect of treatment with different doses of subcutaneous unfractionated heparin (UFH) given within 48 hours.

Methods—We studied the occurrence of major clinical events within 14 days among 18 451 patients from the International Stroke Trial, first for all treatment groups combined. Then, among patients with AF, we examined the effects of treatment with subcutaneous UFH started within 48 hours and continued until 14 days after stroke onset.

Results—A total of 3169 patients (17%) had AF. Seven hundred eighty-four patients were allocated to UFH 12 500 IU SC BID, 773 to UFH 5000 IU SC BID, and 1612 to no heparin. Within each of these groups, half of the patients were randomly assigned to aspirin 300 mg once daily. Compared with patients without AF, patients with AF were more likely to be female (56% versus 45%), to be old (mean age, 78 versus 71 years), to have an infarct on prerandomization CT (57% versus 47%), and to have impaired consciousness (37% versus 20%). The initial ischemic stroke type was more often a large-artery infarct (36% versus 21%). A lacunar stroke syndrome was less common (13% versus 26%). Death within 14 days was more common in patients with AF (17% versus 8%) and more often attributed to neurological damage from the initial stroke (10% versus 4%). The frequency of recurrent ischemic or undefined stroke was not significantly different (3.9% versus 3.3%). The proportion of AF patients with further events within 14 days allocated to UFH 12 500 IU ($n=784$), UFH 5000 IU ($n=773$), and to no-heparin ($n=1612$) groups were as follows: ischemic stroke, 2.3%, 3.4%, 4.9% ($P=0.001$); hemorrhagic stroke, 2.8%, 1.3%, 0.4% ($P<0.0001$); and any stroke or death, 18.8%, 19.4% and 20.7% ($P=0.3$), respectively. No effect of heparin on the proportion of patients dead or dependent at 6 months was apparent.

Conclusions—Acute ischemic stroke patients with AF have a higher risk of early death, which can be explained by older age and larger infarcts but not by a higher risk of early recurrent ischemic stroke, although slightly more patients with AF died from a fatal recurrent stroke of ischemic or unknown type (1.3% versus 0.9%). In patients with AF the absolute risk of early recurrent stroke is low, and there is no net advantage to treatment with heparin. These data do not support the widespread use of intensive heparin regimens in the acute phase of ischemic stroke associated with AF. (*Stroke*. 2001;32:2333-2337.)

Key Words: atrial fibrillation ■ heparin ■ mortality ■ randomized controlled trials ■ recurrence ■ stroke

Atrial fibrillation (AF) is found in 6% to 20% of patients with acute stroke.¹⁻⁸ The reported risk of recurrent stroke varies between 10% and 20% during the first year.⁹⁻¹³ The risk of very early recurrence has been investigated in several studies^{4-6,10,11,14-17} and varies between 0.1% and 1.3% per day during the first 2 weeks after the initial event.^{6,10,14,15} The striking variation between studies can be explained partly by differences in study design (some studies were retrospective and others prospective) and by differences in the study populations

(some studies included AF patients with coexistent cardiac abnormalities and others only patients with “lone” AF). Several studies have reported higher case fatality and morbidity after an ischemic stroke among AF patients compared with patients in sinus rhythm.^{5,6,11,18-20} The underlying cause of this high case fatality is unclear. Possible factors include a higher frequency of large, especially cortical, infarcts,^{11,17,19,21} the presence of concomitant ischemic heart disease,¹⁵ and a high frequency of early recurrent stroke.

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Analysis of primary prevention studies in patients with AF has shown that oral anticoagulant therapy reduces the risk of stroke by 60% to 70%.^{22,23} In the European Atrial Fibrillation Trial (EAFT),¹³ a secondary prevention study, the relative risk reduction with oral anticoagulation was of similar magnitude, but the best time to start anticoagulant therapy was not clear. In the EAFT, half of the patients were randomized >2 weeks after stroke onset, and effective anticoagulation was not obtained within the first weeks, when the risks (hemorrhagic transformation of the infarct) and benefits (prevention of recurrent ischemic stroke) are probably highest. Only 2 studies have focused on treatment with anticoagulants in the acute phase of stroke, but they showed no evidence of benefit of heparin compared with aspirin²⁴ or no antithrombotic treatment.²⁵

The data from the International Stroke Trial (IST),²⁶ a large, randomized, controlled trial of heparin, aspirin, both, or neither in patients with acute ischemic stroke, provided an opportunity to study these questions further. In the main phase of the trial, data on the presence or absence of AF at baseline were recorded, and >3000 patients with this arrhythmia were included. The aim of this report was to compare the early case fatality in patients with AF and those without AF and to examine whether any difference in case fatality was chiefly related to clinical features at baseline or to difference in the frequency of recurrent stroke in the acute phase. We also wanted to study the effect of different heparin doses on the risk of recurrent ischemic stroke and intracranial hemorrhage (ICH) in patients with AF.

Subjects and Methods

Patients and Treatment

We studied data available for the 18 451 patients entered during the main phase of the IST between March 1993 and May 1996. (AF status at baseline was not recorded in the 984 patients entered during the pilot phase.) The IST was a multicenter, multinational, randomized open trial that sought to assess the effectiveness of early antithrombotic treatment in patients with acute stroke.²⁶ Patients with mild, moderate, and severe deficits presenting within 48 hours of the onset of suspected acute ischemic stroke were eligible for the study, provided that the responsible physician did not initially consider there to be any clear indications for, or clear contraindications to, any one of the trial treatments (aspirin or heparin). Patients were randomized in a 3×2 factorial design, ie, to subcutaneous unfractionated heparin (UFH) (5000 IU BID or 12 500 IU BID), aspirin 300 mg, both, or neither. Coagulation times were monitored at the discretion of the treating physician. Treatment was given for 14 days or until prior hospital discharge. CT scan to exclude ICH was to be performed before randomization when possible and was mandatory in comatose patients. A noncomatose patient could be randomized before CT scan only if there was likely to be a long delay in getting the CT scan and the physician considered the stroke most likely to be ischemic. For those allocated to active treatment, the initial doses could be given while CT was being arranged, but treatment was stopped if ICH was found.

Classification

On the basis of neurological symptoms at study entry, patients were categorized by means of a computer algorithm according to the criteria of Bamford et al²⁷ into 1 of the following clinical syndromes: total anterior circulation stroke (TACS), partial anterior circulation stroke (PACS), posterior circulation stroke (POCS), lacunar anterior circulation stroke (LACS), or other.

Outcome Measures

Protocol-specified primary outcomes were death from any cause within 14 days and death or dependency at 6 months. Protocol-specified secondary outcomes were as follows: symptomatic ICH within 14 days (including symptomatic hemorrhagic transformation of the original infarct) as confirmed by CT, MRI, or necropsy; ischemic stroke (including any recurrent stroke of ischemic or unknown type); major extracranial hemorrhage; and other major clinical event, such as pulmonary embolism, within 14 days. There were no specific criteria to define a recurrent ischemic stroke, so that the decision of whether or not recurrent stroke had occurred was left to the judgment of the responsible physician.

Analysis and Statistical Methods

The protocol specified 2 main analyses for the primary outcomes, namely, "immediate heparin" (low or medium dose) versus "avoid heparin" and "immediate aspirin" versus "avoid aspirin." In these analyses we have also compared medium- versus low-dose heparin versus no heparin. In the factorial design, half of the heparin and control patients were allocated aspirin, and since there was no interaction between aspirin and heparin,²⁶ we combined the aspirin and no-aspirin groups for the purpose of these analyses. All analyses were "intention-to-treat," and thus patients were included in the analysis in the group to which they were allocated, irrespective of their compliance with trial treatment. Analysis of total numbers of patients affected was done by χ^2 tests and χ^2 tests for trend.

Results

At study entry, a total of 3169 patients (17%) were in AF and 15 282 were not in AF. The mean delay between the stroke and randomization was 18.7 hours in patients with AF versus 20.4 hours in those without (difference in means, 1.7 hours; 95% CI, 1.2 to 2.2).

Compliance with the allocated treatment was good; only 6% of patients with AF and 8% of patients without AF received heparin despite being allocated to the no-heparin group. Compliance with aspirin allocation was equally good across all treatment groups.

Table 1 summarizes the principal baseline characteristics of the patients. Compared with patients without AF, patients with AF were more likely to be female (56% versus 45%), to be old (mean age, 78 versus 71 years), and to have impaired consciousness (37% versus 20%). The initial stroke was more often a large infarct with the clinical deficits suggesting involvement of the entire territory of the middle cerebral artery (TACS) (36% versus 21%). Lacunar stroke was less common among patients with AF (13% versus 26%). Correspondingly, infarction on the prerandomization CT scan was more often seen in patients with AF (57% versus 47%). Since the study design permitted randomization while CT was being arranged, inevitably, in a few patients, it was discovered that the event leading to randomization was a hemorrhagic stroke (AF 2%, not AF 3%). Treatment was stopped after the CT scan in such cases.

The risk of recurrent ischemic stroke within 14 days was low and not significantly altered by the presence or absence of AF (Table 2): 123 (3.9%) and 500 (3.3%) in patients with and without AF, respectively. Symptomatic ICH within 14 days occurred significantly more often in AF patients: 39 (1.2%) versus 109 (0.7%). A total of 534 AF patients (17%) died within 14 days compared with 1149 patients (8%) without AF (odds ratio, 2.5; 95% CI, 2.2 to 2.8). Table 3 shows that AF patients were more likely to die from neuro-

TABLE 1. Baseline Characteristics in Stroke Patients With and Without AF, Recorded at Time of Randomization

Characteristics	AF (n=3169)	No AF (n=15 282)	OR (95% CI)*
Age, mean, y	77.8	70.6	7.2 (6.9–7.6)‡
Female sex	1779 (56%)	6823 (45%)	1.6 (1.5–1.7)
Symptoms noticed on waking	854 (27%)	4552 (30%)	0.9 (0.8–1.0)
Impaired consciousness	1166 (37%)	3039 (20%)	2.4 (2.2–2.6)
Subtype of stroke			
TACS	1155 (36%)	3252 (21%)	2.1 (2.0–2.3)
PACS	1310 (41%)	6166 (40%)	1.0 (1.0–1.1)
LACS	409 (13%)	4014 (26%)	0.4 (0.4–0.5)
POCS	289 (9%)	1809 (12%)	0.8 (0.7–0.9)
Other	6 (0.2%)	41 (0.3%)	0.7 (0.3–1.7)
Had prerandomization CT scan	1968 (62%)	10 434 (68%)	0.8 (0.7–0.8)
Infarct on prerandomization CT scan†	1127 (57%)	4915 (47%)	1.5 (1.4–1.7)
Final diagnosis of initial event leading to randomization			
Ischemic stroke	2865 (90%)	13 813 (90%)	1.0 (0.9–1.1)
Hemorrhagic stroke	79 (2%)	490 (3%)	0.8 (0.6–1.0)
Stroke of unknown type	172 (5%)	592 (4%)	1.4 (1.2–1.7)
Not a stroke/unknown	53 (2%)	387 (3%)	0.7 (0.5–0.9)

*An odds ratio (OR) >1 indicates that the characteristic is more common in patients with AF. If the 95% CI does not include unity, the result is significant at the $\geq 5\%$ level.

†Among those who had a prerandomization CT scan.

‡This is the difference between the 2 means with 95% CIs, not an OR.

logical damage from the initial stroke or from pneumonia, coronary heart disease, pulmonary embolism, or early recurrent stroke.

The frequency of various events, subdivided by heparin allocation, is shown in Table 4. The 3 treatment groups were comparable with respect to baseline characteristics (data not shown), and, within each group, half of the patients were randomly allocated to aspirin. However, there was no evidence of an interaction effect between aspirin and heparin, and patients receiving aspirin are therefore not excluded from the analysis. The proportions of AF patients with fatal or nonfatal events within 14 days allocated to UFH 12 500 IU, UFH 5000 IU, and no heparin were as follows: stroke of ischemic or unknown type, 2.3%, 3.4%, 4.9% ($P=0.001$); symptomatic ICH, 2.8%, 1.3%, 0.4% ($P<0.001$); and any recurrent stroke or death, 18.8%, 19.4%, and 20.7% ($P=0.3$), respectively. Therefore, despite a clear and dose-dependent reduction in ischemic strokes among patients allocated to heparin, this advantage was offset by a similarly sized increase in hemorrhagic strokes in the heparin-allocated

groups. Consequently, there was no net difference in death or the event “death or dependency 6 months after the stroke.”

We found that a small proportion (3%) of patients included (among those first scanned after randomization) had experienced an ICH. We therefore repeated the analysis restricted to patients known to have nonhemorrhagic stroke. The results of this analysis were remarkably similar to those in Table 4 (data available on request).

Discussion

These data from the IST confirm the findings from other studies that patients with AF have a case fatality that is approximately twice as high as the case fatality in patients without AF (17% versus 8% after 2 weeks). In IST, patients with AF, compared with those without AF, were on average older, had more comorbidity, and had more severe strokes, and these factors are likely to have contributed to the higher case fatality in AF. On the other hand, recurrent stroke (ischemic/unknown or hemorrhagic) occurred equally often in patients with and without AF, and although slightly more

TABLE 2. Events Within 14 Days in Patients With and Without AF, All Treatment Groups Combined

	AF (n=3169)	No AF (n=15 282)	OR (95% CI)
Fatal or nonfatal recurrent ischemic stroke	123 (3.9%)	500 (3.3%)	1.2 (1.0–1.5)
Fatal or nonfatal symptomatic ICH	39 (1.2%)	109 (0.7%)	1.7 (1.2–2.5)
Fatal or nonfatal recurrent ischemic stroke or symptomatic ICH	161 (5.1%)	603 (4.0%)	1.3 (1.1–1.6)
Fatal or nonfatal recurrent ischemic stroke, symptomatic ICH, or death	630 (19.9%)	1548 (10.1%)	2.2 (2.0–2.4)
Death from any cause	534 (16.9%)	1149 (7.5%)	2.5 (2.2–2.8)

OR indicates odds ratio.

TABLE 3. Causes of Death Within 14 Days in Stroke Patients With and Without AF, All Treatment Groups Combined

	AF (n=3169)	No AF (n=15 282)	OR (95% CI)*
Neurological damage from initial stroke	305 (9.6%)	557 (3.6%)	2.9 (2.5–3.4)
Recurrent stroke, ischemic or unknown	42 (1.3%)	131 (0.9%)	1.7 (1.2–2.4)
Recurrent stroke, hemorrhagic	6 (0.2%)	32 (0.2%)	1.0 (0.4–2.4)
Pneumonia	85 (2.7%)	180 (1.2%)	2.5 (2.0–3.3)
Coronary heart disease	44 (1.4%)	92 (0.6%)	2.6 (1.8–3.7)
Pulmonary embolism	21 (0.7%)	50 (0.3%)	2.3 (1.4–3.8)
Other vascular or unknown	26 (0.8%)	84 (0.5%)	1.7 (1.1–2.6)
Nonvascular	5 (0.2%)	23 (0.2%)	1.2 (0.4–3.1)
Total	534 (16.9%)	1149 (7.5%)	

*Odds ratio (OR) calculated with those not dying as a comparator.

patients with AF died from a fatal recurrent stroke of ischemic or unknown type, early recurrences could not explain the worse outcome in patients with AF. The most common cause of early death in patients with AF was neurological damage from the initial stroke, as might be anticipated, since they had more severe strokes with a predominantly cortical localization.^{11,17,19,21,28}

Absolute Risk of Early Recurrent Stroke in AF

The overall risk of early recurrent stroke of ischemic or unknown type in patients with AF was lower than reported in earlier studies and not significantly different from the group without AF, which is in agreement with some previous studies^{3–5,16,17,24} but disagrees with several others.^{6,10,11,14} One explanation for the different estimates might be different selection of patients. However, approximately one sixth of the patients in IST were in AF, which is very similar to that found in community-based incidence studies of stroke. This suggests that our patients are likely to be reasonably representative of patients with acute ischemic stroke and AF, and therefore factors related to patient selection may not be the explanation. Other explanations for the low estimate of the incidence of recurrent ischemic stroke among AF patients could be methodological: recurrent stroke was not a primary measure of outcome in the trial, or the trial did not apply a rigid definition of recurrent ischemic stroke but relied on the clinical judgment of local investigators. The effect of this

may have been to count only severe recurrent strokes, and hence we may have underascertained mild recurrent strokes. The high early case fatality (approximately 30%) after recurrent stroke tends to confirm the hypothesis that only severe recurrences were reported. Furthermore, since patients could be randomized up until 48 hours after onset of symptoms, some very early recurrences may have been missed.

Effect of Different Heparin Doses on Risk of Recurrence

We found that, although the higher heparin dose was associated with the fewest recurrent ischemic strokes, the clear dose-related trend to benefit was offset by a significant and dose-dependent increase in the risk of hemorrhagic stroke. These trends were also seen after exclusion of the small number of patients with ICH at randomization (who were first scanned after randomization), and there was no evidence of benefit from heparin on death or disability at 6 months.

Part of the apparent effects of heparin on recurrent ischemic stroke and symptomatic hemorrhage could be due to an observer bias. Since the trial was open, there may have been systematic bias operating against heparin by an increased attention to bleeding in patients allocated to heparin, especially the higher dose. However, this does not apply to outcome at 6 months, since this was effectively blinded. Additionally, the short-term effects of heparin were similar to those in other placebo-controlled trials, such as the Trial of Org 10172 in Acute Stroke

TABLE 4. Effect of Heparin in Different Doses on Events Within 14 Days and Outcome at 6 Months in Patients With AF*

	Heparin 12 500 IU (n=784)	Heparin 5000 IU (n=773)	No Heparin (n=1612)	P, Overall χ^2	P, χ^2 Trend
Events within 14 days					
Recurrent stroke of ischemic or unknown type	18 (2.3%)	26 (3.4%)	79 (4.9%)	0.006	0.001
Symptomatic ICH	22 (2.8%)	10 (1.3%)	7 (0.4%)	<0.0001	<0.0001
Recurrent stroke or symptomatic ICH	39 (5.0%)	36 (4.7%)	86 (5.3%)	0.8	0.6
Recurrent stroke, symptomatic ICH, or death	147 (18.8%)	150 (19.4%)	333 (20.7%)	0.5	0.3
Outcome at 6 months					
Dead from any cause	305 (38.9%)	292 (37.8%)	630 (39.1%)	0.8	0.8
Dead or dependent	612 (78.1%)	609 (78.8%)	1266 (78.5%)	0.9	0.8

*Within each of these groups, half of the patients were randomly assigned to aspirin 300 mg once daily.

Treatment (TOAST) study, a placebo-controlled trial of intravenous heparinoid in acute ischemic stroke, in which the subgroup of patients with cardioembolic stroke also showed no evidence of benefit from anticoagulation.²⁹

Implications for Practice

What then are the consequences of these analyses for the treatment of patients with AF in the acute phase of ischemic stroke? First, the risk of major recurrent stroke is lower than many clinicians fear. Second, the risk of bleeding complications with the higher heparin dose is a concern. A recent combined analysis of the 40 000 randomized patients in the IST and Chinese Acute Stroke Trial (CAST) showed that treatment with aspirin reduces the risk of recurrent ischemic stroke within 14 days by 30%, and the effect is similar in the presence or absence of AF.³⁰ For many patients presenting with acute ischemic stroke and AF, aspirin offers a safe and effective option for preventing early recurrent stroke in the first week or 2 after stroke onset. For patients who remain in AF and have no contraindications, oral anticoagulation with a target international normalized ratio of 2.0 to 3.0 is likely to be the most effective secondary prevention.¹³

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