Articles

The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19 435 patients with acute ischaemic stroke

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Summary

Background Only a few small trials have compared antithrombotic therapy (antiplatelet or anticoagulant agents) versus control in acute ischaemic stroke, and none has been large enough to provide reliable evidence on safety or efficacy.

Methods The International Stroke Trial (IST) was a large, randomised, open trial of up to 14 days of antithrombotic therapy started as soon as possible after stroke onset. The aim was to provide reliable evidence on the safety and efficacy of aspirin and of subcutaneous heparin. Half the patients were allocated unfractionated heparin (5000 or 12 500 IU bd [twice daily]) and half were allocated "avoid heparin"; and, in a factorial design, half were allocated aspirin 300 mg daily and half "avoid aspirin". The primary outcomes were death within 14 days and death or dependency at 6 months. 19 435 patients with suspected acute ischaemic stroke entering 467 hospitals in 36 countries were randomised within 48 hours of symptom onset.

Results Among heparin-allocated patients, there were non-significantly fewer deaths within 14 days (876 [9·0%] heparin *vs* 905 [9·3%] no heparin), corresponding to 3 (SD 4) fewer deaths per 1000 patients. At 6 months the percentage dead or dependent was identical in both groups (62·9%). Patients allocated to heparin had significantly fewer recurrent ischaemic strokes within 14 days (2·9% *vs* 3·8%) but this was offset by a similar-sized increase in haemorrhagic strokes (1·2% *vs* 0·4%), so the difference in death or non-fatal recurrent stroke (11·7% *vs* 12·0%) was not significant. Heparin was associated with a significant excess of 9 (SD 1) transfused or fatal extracranial bleeds per 1000. Compared with 5000 IU bd heparin, 12 500 IU bd heparin was associated with significantly more transfused or fatal extracranial bleeds, more haemorrhagic strokes, and more deaths or non-fatal strokes within 14 days (12·6% *vs* 10·8%). Among aspirin-allocated patients there were non-significantly fewer deaths within 14 days (872 [9·0%] *vs* 909 [9·4%]), corresponding to 4 (SD 4) fewer deaths per 1000 patients. At 6 months there was a non-significant trend towards a smaller percentage of the aspirin group being dead or dependent (62·2% *vs* 63·5%, 2*p*=0·07), a difference of 13 (SD 7) per 1000; after adjustment for baseline prognosis the benefit from aspirin was significant (14 [SD 6] per 1000, 2p=0·03). Aspirin-allocated patients had significantly fewer recurrent ischaemic strokes within 14 days (2·8% *vs* 3·9%) with no significant excess of haemorrhagic strokes (0·9% *vs* 0·8%), so the reduction in death or non-fatal recurrent stroke with aspirin (11·3% *vs* 12·4%) was significant. Aspirin was associated with a significant excess of 5 (SD 1) transfused or fatal extracranial bleeds per 1000; in the absence of heparin the excess was 2 (SD 1) and was not significant. There was no interaction between aspirin and heparin in the main outcomes.

Interpretation Neither heparin regimen offered any clinical advantage at 6 months. The results suggest that if heparin is given in routine clinical practice, the dose should not exceed 5000 IU subcutaneously twice daily. For aspirin, the IST suggests a small but worthwhile improvement at 6 months. Taking the IST together with the comparably large Chinese Acute Stroke Trial, aspirin produces a small but real reduction of about 10 deaths or recurrent strokes per 1000 during the first few weeks. Both trials suggest that aspirin should be started as soon as possible after the onset of ischaemic stroke; previous trials have already shown that continuation of low-dose aspirin gives protection in the longer term.

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Introduction

Every year, several million people worldwide are treated for acute ischaemic stroke[1]. If some widely practicable therapies could be reliably shown to prevent death or dependence for "just" 10 or 20 of every 1000 patients, it would, for every million stroke patients so treated, ensure that an extra 10 000 were alive and independent. If such benefits exist, they must not, therefore, be overlooked. Reliable assessment of them may, however, require randomised trials with tens of thousands of patients.[2,3] Two such candidates are heparin and aspirin.

Most strokes are caused by acute occlusion of a cerebral artery. Anticoagulants are widely used,[4-6] to facilitate early clot lysis, to inhibit clot propagation in the cerebral arteries, and to prevent early arterial re-embolisation and venous thromboembolism originating in immobile limbs.[2] However, there is little randomised evidence on the balance of risks and benefits of heparin in acute ischaemic stroke. Low-dose regimens of around 5000 IU twice daily of subcutaneous unfractionated heparin (or equivalent low-molecular-weight heparins or heparinoids) do reduce the risk of deep venous thrombosis,[2,7] but the effects of these and higher-dose regimens on the cerebral arterial circulation and on the risk of intracranial haemorrhage are

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unclear.[2,7] A medium-dose regimen of 12 500 IU subcutaneous unfractionated heparin twice daily prevents left-ventricular wall thrombus in acute myocardial infarction (AMI),[8,9] and proved feasible in two large trials,[10,11] but has not been tested in acute stroke.[2,7]

Antiplatelet drugs such as aspirin can be effective in the secondary prevention of "serious vascular events" (stroke, AMI, and vascular death).[12] Taken for a few years after a myocardial infarction, ischaemic stroke, or transient ischaemic attack (TIA), antiplatelet therapy typically avoids about 40 serious vascular events per 1000 patients treated.[12] It also reduces the incidence of deep venous thrombosis and pulmonary embolism in high risk patients,[13] and is effective in the treatment of AMI, preventing about 40 serious vascular events per 1000 patients treated for just one month.[12] In acute ischaemic stroke there is substantial platelet activation, which can be inhibited by aspirin.[14,15] But there is no large-scale randomised evidence on aspirin in acute ischaemic stroke.[2,16]

Aspirin and heparin have different mechanisms of action, so the combination might be more effective than either alone, although this might be offset by a greater risk of bleeding. In AMI, the combination of aspirin and heparin was not significantly more effective than aspirin alone,[17,18] but no trials have made this comparison in acute stroke.[2,7,16]

Given the uncertain balance of risk and benefit for heparin and for aspirin in acute stroke,[2,7,12,16] the uncertainty of many physicians about the safety and efficacy of these drugs in this setting[4-6] and the wide variation in clinical practice,[4-6] the IST was designed to assess the separate and combined effects of subcutaneous heparin (in twice daily doses of 5000 IU or 12 500 IU) and of aspirin (300 mg daily). Large numbers of patients were included in order to provide a reliable estimate of their effects on death and other major clinical events during the first 14 days after acute ischaemic stroke, and on death and dependency in activities of daily living at 6 months, as well as any adverse effects on intracranial haemorrhage and on transfused (or fatal) extracranial bleeds.

Methods

Patients

Eligibility A patient was eligible if, in the view of the responsible physician, there was evidence of an acute stroke (irrespective of severity) with onset less than 48 h previously, no evidence of intracranial haemorrhage (see below), and no clear indications for, or contraindications to, heparin or aspirin. The fundamental criterion for eligibility was simply that the physician was uncertain whether or not to administer either or both of the trial treatments to that particular patient.

Exclusions Possible reasons not to include a patient were either only a small likelihood of worthwhile benefit (eg, the symptoms seemed likely to resolve completely within a few hours or the patient was severely disabled before the stroke) or a high risk of adverse effects (eg, hypersensitivity to aspirin, active peptic ulceration or recent gastrointestinal bleeding; or already on long-term oral anticoagulants).

Computed tomographic (CT) scanning All patients were to be CT scanned to exclude intracranial haemorrhage, before randomisation where possible, and in comatose patients a CT was mandatory. However, if there was likely to be a long delay in getting the CT scan and if, on clinical grounds, the physician considered the stroke very likely to be ischaemic, a non-comatose patient could be randomised before CT. For those allocated active treatment, the initial doses could be given while the CT was being arranged, but treatment was stopped if intracranial haemorrhage was found (which it rarely was).

Classification and predicted prognosis Neurological deficits recorded at telephone randomisation were used to classify the infarct as: total anterior circulation, partial anterior circulation, posterior circulation, lacunar, or other, by means of a computer algorithm.[19] Prognosis was predicted by a validated model,[20] using baseline data to calculate the probability of a poor outcome (see statistical methods).

Planned interventions and their timing

After informed consent had been obtained (the procedure varied to conform to local ethical committee requirements), patients were entered by telephoning the central randomisation service at the Clinical Trial Service Unit (CTSU), Oxford, UK. After the baseline data had been entered and checked for range and consistency, the computer allocated the study treatment(s) (a minimisation algorithm was used to reduce any imbalance in recorded prognostic features between treatment groups).[21] At that point the patient was irrevocably included in the study. Clinicians could depart from the randomly allocated treatment if a clear reason to do so had arisen, but they could not withdraw a patient from follow-up even if the patient turned out not to have had a stroke or did not receive the treatment allocated.

Heparin Half of the patients were randomly allocated to receive subcutaneous unfractionated heparin (one-quarter 5000 IU twice daily [low-dose] and one-quarter 12 500 IU twice daily [medium-dose]); and half were allocated to "avoid heparin". Heparin was supplied by the hospital, and sodium heparin could be used if calcium heparin was not available. In more than 30 000 patients with AMI (most of whom also received fibrinolytic therapy and aspirin) 12 500 IU twice daily had been fairly safe without routine monitoring of coagulation times,[10,11] so such monitoring was optional in the IST.

Aspirin Using a factorial design, half of all patients were allocated to 300 mg aspirin daily and half to "avoid aspirin". If a patient could not swallow safely, aspirin was to be given by nasogastric tube, per rectum (300 mg suppository), or intravenously (100 mg lysine salt in 100 mL normal saline over 60 min). Aspirin was supplied by each hospital. Patients could continue any prescribed nonsteroidal antiinflammatory drugs, but analgesics containing aspirin were to be avoided in patients allocated to "avoid aspirin", unless the physician considered that a clear indication for them had developed.

Timing Patients allocated active treatment (heparin, or aspirin, or both) were to receive the first dose(s) immediately after randomisation, and treatment was to continue for 14 days or until prior discharge. At discharge, clinicians were to consider giving all patients long-term aspirin.[12] All other aspects of treatment were determined by the responsible clinician.

Events and outcomes

Events in hospital A single-sided form was to be completed from the patient's medical records at 14 days or at hospital discharge or death, if sooner. This included contact details, final diagnosis of the index event, compliance with allocated treatment, use of other drugs, nature and timing of any clinical events in hospital, including the likely cause of death, and aspirin use at discharge. Patients allocated active treatment were considered compliant if they missed no more than two of their scheduled doses. Patients allocated to avoid heparin or to avoid aspirin were considered non-compliant if they received any heparin or any antiplatelet therapy respectively in hospital within 14 days of randomisation.

Outcome at 6 months (death, dependency, and incomplete recovery) In a few countries, the randomising physician collected 6-month follow-up data in an outpatient clinic. Elsewhere, the country coordinating centre mailed a validated questionnaire[22,23] to the patient (or relative or other proxy) or

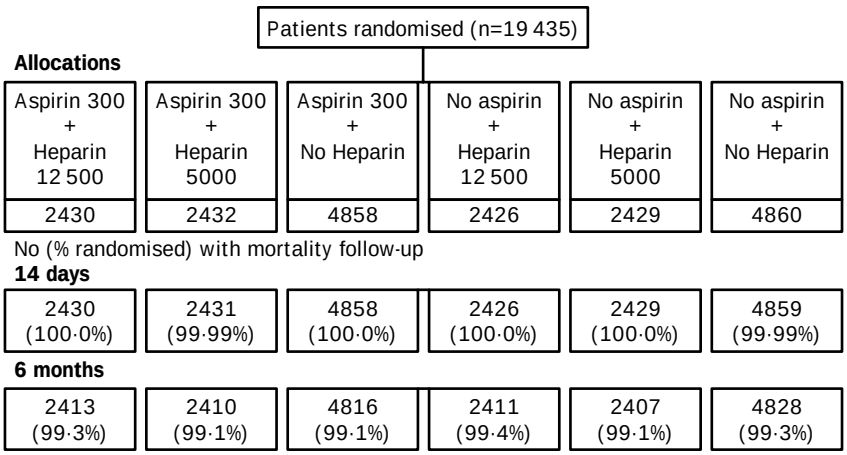

Figure 1: **Trial randomisation flow chart**

interviewed them on the telephone. The different methods of follow-up were valid.[3] Where it was done centrally, follow-up was blind to treatment allocation.

Protocol-specified primary outcomes These were: (*a*) death from any cause within 14 days and (*b*) death or dependency (ie, needing help from another person with daily activities) at 6 months.[22,23]

Protocol-specified secondary outcomes These were: (*a*) symptomatic intracranial haemorrhage (haemorrhagic stroke) within 14 days (including any recurrent stroke definitely due to haemorrhage or symptomatic haemorrhagic transformation of the original infarct) that was confirmed by CT, magnetic resonance imaging, or necropsy; (*b*) ischaemic stroke within 14 days (including any recurrent stroke of ischaemic or unknown type); (*c*) major extracranial haemorrhage (including any bleed that required transfusion or caused death within 14 days); (*d*) other major events within 14 days such as pulmonary embolism; (*e*) death from any cause by 6 months; and (*f*) dependence in activities of daily living, or incomplete recovery from the stroke, at 6 months. Only events in hospital within 14 days of randomisation in patients who went on to survive at least 14 days were considered "non-fatal".

Planned study size The protocol considered, as an example, the situation where 10% would die without treatment and where 15% of those deaths could be avoided by treatment. Even if treatment really did reduce the risk by 15%, chance could make the observed difference in a trial of 10 000 patients not conventionally significant (eg, 440 *vs* 490 deaths). This chance of failing to recognise a treatment that really does reduce mortality by 15% did not seem a reasonable risk to take so the protocol specified that the aim in the IST was "at least 20 000 patients to ensure that the risk of such a false negative trial is negligible". A secondary aim of the IST was a reliable assessment of the safety of early antithrombotic therapy. Since the most important complication is fatal or disabling haemorrhagic transformation, the study "must have sufficient statistical power to detect even moderate increases in this rare but often serious event".

Analyses

Main analyses The protocol specified two main analyses for the primary outcomes—namely, "immediate heparin" (low or medium dose) *vs* "avoid heparin" and "immediate aspirin" *vs* "avoid aspirin".

Subsidiary analyses For the primary outcomes, the main subsidiary analyses were: medium *vs* low dose heparin; aspirin *vs* "avoid aspirin", subdivided by aspirin use in the previous 3 days, recorded at randomisation; heparin *vs* "avoid heparin", subdivided by heparin use in the previous 24 h, recorded at randomisation; subdivision of the main analyses by whether CT was first done before or after randomisation and by the number of hours between symptom onset and randomisation (0-3, 3-6, 6-12, 12-24, 24-48 h); and whether any effects of aspirin and of heparin were additive. These comparisons were also to be made for the secondary outcomes. It was prospectively planned to consider the IST results with those of the only comparably large trial, the 20 000 patient Chinese Acute Stroke Trial of aspirin.[24]

Statistical methods

Most comparisons involved simple analyses of total numbers of patients affected.[12] Proportional reductions were expressed as odds reductions (with 95% CI for main analyses and 99% CI for subgroup analyses). Absolute differences were calculated as benefits per 1000 patients treated, and were generally given together with their SD.

Estimates of treatment effects adjusted for severity of initial stroke were calculated as follows. The prognosis was estimated using a model which predicted the probability of death or dependency at 6 months from data recorded at randomisation.[20] For each stratum of severity (see footnote, figure 2) the observed (O) minus expected (E) value and its variance (V) were calculated and these were summed to give the overall (O−E) and V. The statistic k was defined as $1000(T + C)/(TC)$, where T and C are the total numbers of treated and control patients: both for heparin and for aspirin k = 0.207. The adjusted benefit per 1000 is then $k(O-E)$, with standard deviation $k\sqrt{V}$.

Two-sided p values (2*p*) are cited throughout.

The independent data monitoring committee reviewed interim analyses of major outcome events about once a year during the recruitment phase, and allowed the study to run its full course.

Characteristic		Characteristic	
Delay (h from symptoms)	**No (%)**	**Systolic BP (mm Hg)**	**No (%)**
0–3	843 (4%)	<140	3590 (18%)
4–6	2322 (12%)	140–59	5402 (28%)
7–12	4114 (21%)	160–79	5035 (26%)
13–24	5568 (29%)	>180	5408 (28%)
25–48	6588 (34%)	**Stroke syndrome**	
Age (yr)		Total anterior	4638 (24%)
<50	986 (5%)	Partial anterior	7912 (40%)
50–59	2029 (11%)	Posterior circulation	2228 (12%)
60–69	4487 (23%)	Lacunar	4657 (24%)
70–79	6808 (35%)	**Leg weakness**	
>80	5125 (26%)	Present	14 678 (76%)
Sex		Absent	4502 (23%)
F	9028 (46%)	Not assessable	255 (1%)
M	10 407 (54%)	**CT scan**	
Onset		Before randomisation	13 020 (67%)
Awake	13 750 (71%)	After randomisation	5569 (29%)
During sleep	5685 (29%)	Not done/not known	846 (4%)
Conscious level		**Appearance of pre-randomisation CT**	
Unconscious	260 (1%)	Infarct visible	6415 (49%)
Drowsy	4254 (22%)	No infarct visible	6605 (51%)
Alert	14 921 (77%)	**Pre-randomisation antithrombotic therapy**	
Cardiac rhythm		Aspirin within previous 3 days	3940 (20%)
Sinus rhythm, not AF*	16 266 (84%)	Heparin within previous 24 hours	436 (2%)
Atrial fibrillation (AF)	3169 (16%)		

*Information on presence of atrial fibrillation at entry not sought during pilot phase, so cardiac rhythm at entry not known for 984 patients.

Table 1: **Characteristics at randomisation for all treatment groups combined**

Results

Recruitment and follow-up

In the pilot phase 984 patients were recruited between January, 1991, and February, 1993,[3] with 18 456 recruited between March, 1993, and May, 1996, in the main trial. 5 were entered in error, so no data were collected on these patients. Thus 19 435 patients were randomised, by 467 hospitals in 36 countries. Outcome data were 99.99% complete for 14-day outcome and 99.2% complete for 6-month outcome (figure 1).

Characteristics of patients

Large numbers and central randomisation (with minimisation[21]) ensured good balance between the six treatment groups for the main recorded (and, presumably, unrecorded) prognostic factors. Table 1 shows baseline characteristics for all treatment groups combined.† The median time to randomisation was 19 h (4% within 3 h, 16% within 6 h, 37% within 12 h, and 66% within 24 h). At randomisation, 61% were aged over 70, 23% had impaired consciousness and 16% were known to be in atrial fibrillation. 67% had had a CT scan before randomisation (49% of these scans showed an infarction, no infarct lesion being visible in the remainder); a further 29% were scanned after randomisation; and 4% never had a CT scan.

†A breakdown by treatment group is obtainable from *The Lancet*

Compliance

Compliance was good. Low-dose heparin was received throughout the scheduled treatment period by 90% and medium-dose heparin by 88% of those allocated it; no heparin was received by 94% of those allocated to avoid it. Aspirin was taken throughout the scheduled treatment period by 92%, and no antiplatelet therapy was taken by 93% of those allocated to avoid it. For compliant patients, the mean duration of active treatment was 11 days both for heparin and for aspirin. The chief reason for stopping treatment before 14 days was early discharge from hospital.

Heparin versus avoid heparin

Deaths within 14 days (upper left, table 2) Among heparin-allocated patients there were non-significantly fewer deaths within 14 days (9·0% *vs* 9·3%, corresponding to an absolute reduction of 3 [SD 4] per 1000 patients). When causes of death were examined separately, the only significant difference was the increased numbers, with heparin, of deaths attributed to haemorrhagic stroke (28 *vs* 15, $2p=0{\cdot}04$) and to extracranial bleeding (12 *vs* 3, $2p=0{\cdot}02$).

Fatal or non-fatal events within 14 days (lower left, table 2) Heparin-allocated patients had significantly fewer recurrent ischaemic strokes within 14 days (2·9% *vs* 3·8%, $2p=0{\cdot}005$) but this benefit was completely offset by a similar-sized increase in haemorrhagic stroke

Outcome	Heparin *vs* no heparin			Aspirin *vs* no aspirin		
	Heparin	No heparin	Events prevented per 1000 (SD)	Aspirin	No aspirin	Events prevented per 1000 (SD)
No randomised	9717	9718		9720	9715	
No with 14 day data	9716 (99·99%)	9717 (99·99%)		9719 (99·99%)	9714 (99·99%)	
Deaths and likely causes						
Initial stroke	584(6·0%)	613 (6·3%)	3 (3)	592 (6·1%)	605 (6·2%)	1 (3)
Recurrent ischaemic stroke	79 (0·8%)	98 (1·0%)	2 (1)	88 (0·9%)	89 (0·9%)	0 (1)
Haemorrhagic stroke	28 (0·3%)	15 (0·2%)	−1 (1)*	23 (0·2%)	20 (0·2%)	0 (1)
Coronary heart disease	64 (0·7%)	79 (0·8%)	2 (1)	72 (0·7%)	71(0·7%)	0 (1)
Pulmonary embolism	36 (0·4%)	39 (0·4%)	0 (1)	31 (0·3%)	44(0·5%)	1 (1)
Extracranial haemorrhage	12 (0·1%)	3 (0·0%)	−1 (0)*	9 (0·1%)	6 (0·1%)	0 (0)
Other vascular	57 (0·6%)	44 (0·5%)	−1 (1)	40 (0·4%)	61 (0·6%)	2 (1)*
Non-vascular	16 (0·2%)	14 (0·1%)	0 (1)	17 (0·2%)	13 (0·1%)	0 (1)
Total (any cause)	876 (9·0%)	905 (9·3%)	3 (4)	872 (9·0%)	909 (9·4%)	4 (4)
Fatal and non-fatal events						
Recurrent ischaemic stroke	283 (2·9%)	370 (3·8%)	9 (3)**	275 (2·8%)	378 (3·9%)	11 (3)***
Haemorrhagic stroke (HS)	120 (1·2%)	41 (0·4%)	−8 (1)****	87 (0·9%)	74 (0·8%)	−1 (1)
Recurrent ischaemic stroke or HS	396 (4·1%)	411 (4·2%)	2 (3)	361 (3·7%)	446 (4·6%)	9 (3)**
Death or non-fatal stroke	1136 (11·7%)	1171 (12·0%)	4 (5)	1099 (11·3%)	1208 (12·4%)	11 (5)*
Pulmonary embolism	53 (0·5%)	81 (0·8%)	3 (1)*	57 (0·6%)	77 (0·8%)	2 (1)
Transfused or fatal extracranial haemorrhage	129 (1·3%)	37 (0·4%)	−9 (1)****	109 (1·1%)	57 (0·6%)	−5 (1)•••

HS=haemorrhagic stroke (ie, symptomatic intracranial haemorrhage or symptomatic haemorrhagic transformation or infarct) confirmed by CT scan, MRI, or necropsy. Negative numbers indicate that more events of this type occurred in patients allocated to receive active treatment. SD=standard deviation.
*$2p<0{\cdot}05$, **$2p<0{\cdot}01$, ***$2p<0{\cdot}001$, ****$2p<0{\cdot}00001$. Selected exact p values given in text.

Table 2: **Main outcome events within 14 days**

Outcome	Heparin *vs* no heparin			Aspirin *vs* no aspirin		
	Heparin	No heparin	Events prevented per 1000 (SD)	Aspirin	No aspirin	Events prevented per 1000 (SD)
No randomised	9717	9718		9720	9715	
No with 6 month data	9641 (99·2%)	9644 (99·2%)		9639 (99·2%)	9646 (99·3%)	
Fully recovered, independent	1655 (17·2%)	1641 (17·0%)	−2 (5)	1694 (17·6%)	1602 (16·6%)	−10 (5)
Not recovered, but independent	1923 (19·9%)	1941 (20·1%)	2 (6)	1945 (20·2%)	1919 (19·9%)	−3 (6)
Dependent	3898 (40·4%)	3986 (41·3%)	9 (7)	3927 (40·7%)	3957 (41·0%)	3 (7)
Dead from any cause	2165 (22·5%)	2076 (21·5%)	−9 (6)	2073 (21·5%)	2168(22·5%)	10 (6)
Dead or dependent	6063 (62·9%)	6062 (62·9%)	0 (7)†	6000 (61·2%)	6125(63·5%)	13 (7)‡

†After adjustment for prognosis predicted at baseline, the benefit from heparin was 0 (SD 6), NS. ‡After adjustment for baseline stroke severity, the benefit from aspirin was 14 (SD 6), ($2p=0{\cdot}03$). Negative numbers; same conventions as in table 2.
*$2p<0{\cdot}05$, **$2p<0{\cdot}01$, ***$2p<0{\cdot}001$, ****$2p<0{\cdot}00001$.

Table 3: **Outcome at 6 months**

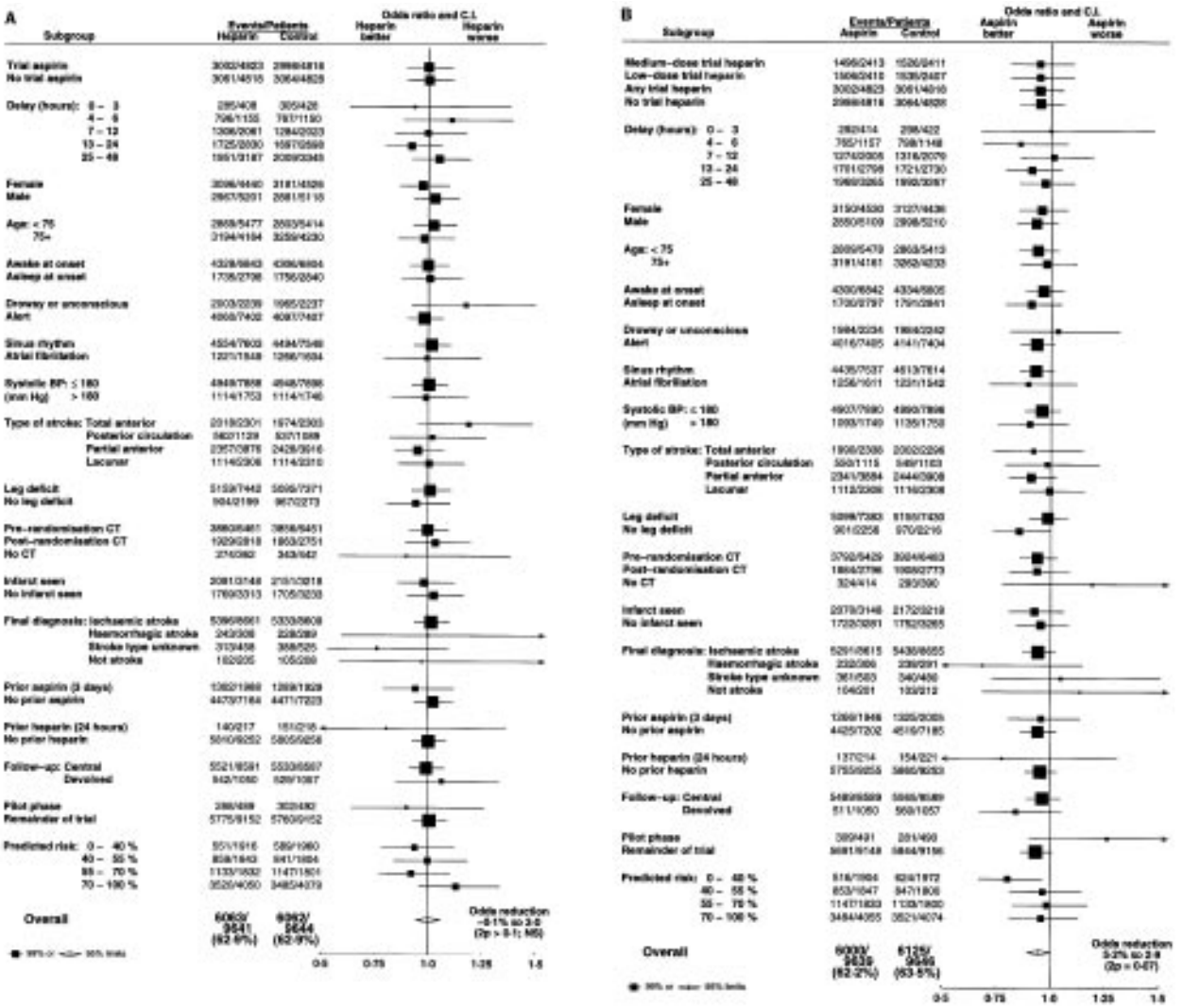

Figure 2: **Reductions in odds of being dead or dependent at six months for (a) heparin versus no heparin, and (b) aspirin versus no aspirin, subdivided by various clinical features present at randomisation**

Squares indicate odds ratios within each subgroup with sizes denoting amount of information available[12] and 99% confidence intervals are represented by horizontal lines. "Delay" refers to numbers of hours between time symptoms were first noted (counted from time of waking if onset during sleep) and randomisation. SBP=systolic blood pressure (mm Hg) at randomisation. "Infarct seen" refers to the presence or absence of infarction on a pre-randomisation CT scan. "Final diagnosis" refers to final diagnosis made in relation to initial event leading to randomisation and not to any post-randomisation event. "Pilot phase" indicates that patient was randomised during pilot phase of trial. "Predicted risk" indicates probability of poor outcome, calculated from baseline clinical data (see statistical methods).

(1·2% *vs* 0·4%, $2p<0·00001$). There was no significant difference in the combined outcome of death or any non-fatal recurrent stroke, but there was a highly significant excess of 9 (SD 1) transfused or fatal extracranial bleeds per 1000 patients allocated heparin (1·3% *vs* 0·4%, $2p<0·00001$). Heparin-allocated patients had fewer pulmonary emboli recorded within 14 days (0·5% *vs* 0·8%, $2p=0·02$).

Outcome at 6 months (left, table 3) At 6 months, there were more deaths among patients allocated heparin than among controls but the absolute increase of 9 (SD 6) per 1000 was not significant. Moreover, it was offset by a non-significant reduction in the number alive but dependent of 9 (SD 7) per 1000. At 6 months, the percentage dead or dependent was identical (62·9%) for both heparin and no heparin. After adjustment for predicted prognosis, the estimate of treatment effect remained zero.

Subgroup analyses (figure 2) Once allowance is made for the multiplicity of comparisons, there is no clear evidence of any beneficial effect from heparin in any of the prespecified subgroups or in subgroups defined by other factors (such as whether or not symptoms were first noted on waking or whether or not leg weakness was present). This was also true for the primary outcome of death at 14 days and for secondary outcomes (not shown). Analyses of effects subdivided by the score for predicted probability of death or dependency at 6 months indicated a non-significant trend towards an adverse treatment effect with heparin among patients with the worst predicted prognosis. Analyses of the main benefit (reduction in recurrent ischaemic stroke) and risks (haemorrhagic stroke and other major bleeds) did reveal subgroups of patients for whom the benefits of heparin seemed to be greater than average. In those subgroups, however, the risks also appeared to be higher than average, and there was no net benefit. For example, table 4 shows that among patients with atrial fibrillation at entry there were 21 fewer recurrent ischaemic strokes

	Heparin *vs* no heparin			Aspirin *vs* no aspirin		
	Heparin	No heparin	Events prevented per 1000 (SD)	Aspirin	No aspirin	Events prevented per 1000 (SD)
Without atrial fibrillation						
No randomised	8159	8105		8097	8167	
Recurrent ischaemic stroke	239 (2·9%)	291 (3·6%)	7 (3)*	222 (2·7%)	308 (3·8%)	10 (3)***
Haemorrhagic stroke (HS)	88 (1·1%)	34 (0·4%)	−7 (1)****	65 (0·8%)	57 (0·7%)	−1 (1)
Recurrent ischaemic stroke or HS	327 (4·0%)	325 (4·0%)	0 (3)	287 (3·5%)	365 (4·5%)	9 (3)**
Death or non-fatal stroke	838 (10·3%)	836 (10·3%)	0 (5)	776 (9·6%)	898 (11·0%)	14 (5)**
With atrial fibrillation						
No randomised	1557	1612		1622	1547	
Recurrent ischaemic stroke	44 (2·8%)	79 (4·9%)	21 (7)**	53 (3·3%)	70 (4·5%)	13 (7)
Haemorrhagic stroke (HS)	32 (2·1%)	7 (0·4%)	−16 (4)***	22 (1·4%)	17 (1·1%)	−3 (4)
Recurrent ischaemic stroke or HS	76 (4·9%)	86 (5·3%)	5 (8)	75 (4·6%)	87 (5·6%)	10 (8)
Death or non-fatal stroke	297 (19·1%)	333 (20·7%)	16 (14)	322 (19·8%)	308 (19·9%)	−2 (3)

*$2p$<0·05, **$2p$<0·01, ***$2p$<0·001, ****$2p$<·00001. Negative numbers; same conventions as in table 2.

Table 4: **Effect of heparin and aspirin on recurrent stroke within 14 days among patients with and without atrial fibrillation**

per 1000 treated with heparin, but this was offset by 16 more haemorrhagic strokes.

Medium versus low dose heparin (table 5) The medium-dose regimen caused more transfused or fatal extracranial bleeds (2·0% *vs* 0·6%), more haemorrhagic strokes (1·8% *vs* 0·7%), and no reduction in other strokes, hence a significantly higher risk of death or non-fatal stroke within 14 days (12·6% *vs* 10·8%, $2p$=0·007). This adverse effect on 14-day outcome had no clear net effect on death or dependency at 6 months. When these heparin doses were compared, not with each other, but with the "avoid heparin" controls, medium-dose heparin was associated with a non-significant 5 (SD 6) per 1000 increase in early death or recurrent stroke and with a definite 16 (SD 8) per 1000 excess of transfused or fatal extracranial bleeds (not shown). By contrast, low-dose heparin was associated with a significant reduction in early death or stroke (10·8% *vs* 12·0%, $2p$=0·03), corresponding to 12 (SD 6) fewer per 1000, with only a slight and non-significant excess of transfused or fatal extracranial bleeds (0·6% *vs* 0·4%; table 6).

Aspirin versus avoid aspirin

Deaths within 14 days (upper right, table 2) Among aspirin-allocated patients there were non-significantly fewer deaths within 14 days (9·0% *vs* 9·4%), corresponding to an absolute reduction of 4 (SD 4) per 1000 patients, with no significant reduction in any specific causes except "other vascular" (40 *vs* 61, $2p$=0·04).

Fatal or non-fatal events within 14 days (lower right, table 2) Aspirin-allocated patients had significantly fewer recurrent ischaemic strokes within 14 days (2·8% *vs* 3·9%, $2p$<0·001) and this benefit was not offset by any significant excess of haemorrhagic strokes (0·9% *vs* 0·8%). There was a significant reduction in the likelihood of death or any non-fatal recurrent stroke (11·3% *vs* 12·4%, $2p$=0·02), corresponding to 11 (SD 5) fewer per 1000 treated. There was a significant excess of 5 (SD 1) transfused or fatal extracranial bleeds per 1000 patients allocated aspirin (1·1% *vs* 0·6%, $2p$=0·0004). Fewer pulmonary emboli were recorded within 14 days with aspirin (0·6% *vs* 0·8%), but this difference was not significant ($2p$=0·08).

Outcome at 6 months (right, table 3) At 6 months, there were fewer deaths among aspirin-allocated patients but the absolute decrease of 10 (SD 6) per 1000 was not significant. There was little difference in the percentages alive but dependent, and the unadjusted 13 (SD 7) reduction per 1000 in death or dependency was not significant ($2p$=0·06). After adjustment for predicted prognosis, the reduction was similar but the effect was significant (14 [SD 6] fewer dead or dependent per 1000, $2p$=0·03). More aspirin-allocated patients reported complete recovery from their stroke (17·6% *vs* 16·6%, $2p$=0·07).

Subgroup analyses (figure 2) Once allowance is made for the multiplicity of comparisons, there is no good evidence of heterogeneity of effect in any of these subdivisions. Analysis of the effect of aspirin subdivided by the prognostic score indicated greater benefit among good-prognosis patients but the trend was not significant. There was also a slightly greater excess of haemorrhagic stroke associated with aspirin among

Outcome	Medium dose (12 500 IU twice daily)	Low dose (5000 IU twice daily)	Events (SD) prevented per 1000 allocated medium dose
No with 14 day data	4856 (100·0%)	4860 (100·0%)	
No with 6 month data	4824 (99·3%)	4817 (99·1%)	
Events within 14 days			
Deaths and likely cause			
Initial stroke	300 (6·2%)	284 (5·8%)	−3 (5)
Recurrent ischaemic stroke	43 (0·9%)	36 (0·7%)	−1 (2)
Haemorrhagic stroke	17 (0·4%)	11 (0·2%)	−1 (1)
Coronary heart disease	31 (0·6%)	33 (0·7%)	0 (2)
Pulmonary embolism	12 (0·2%)	25 (0·5%)	2 (1)*
Extracranial haemorrhage	5 (0·1%)	7 (0·1%)	0 (1)
Other vascular	33 (0·7%)	24 (0·5%)	−2 (2)
Non-vascular	11 (0·2%)	5 (0·1%)	−1 (1)
Death from any cause within 14 days	452 (9·3%)	424 (8·7%)	−6 (6)
All fatal and non-fatal events			
Recurrent ischaemic stroke	155 (3·2%)	128 (2·6%)	−6 (3)
Haemorrhagic stroke (HS)	85 (1·8%)	35 (0·7%)	−10 (2)****
Recurrent ischaemic stroke or HS	234 (4·8%)	162 (3·3%)	−15 (4)***
Death or non-fatal stroke	610 (12·6%)	526 (10·8%)	−17 (7)**
Pulmonary embolism	20 (0·4%)	33 (0·7%)	3 (1)
Transfused or fatal extracranial haemorrhage	99 (2·0%)	30 (0·6%)	−14 (2)****
At 6 months			
Fully recovered, independent	824 (17·1%)	831 (17·3%)	2 (8)
Not recovered, but independent	978 (20·3%)	945 (19·6%)	−7 (8)
Dependent	1919 (39·8%)	1979 (41·1%)	13 (10)
Dead from any cause	1103 (22·9%)	1062 (22·0%)	−8 (8)
Dead or dependent	3022 (62·6%)	·3041 (63·1%)	5 (10)

*$2p$<0·05, **$2p$<0·01, ***$2p$<0·001, ****$2p$<0·00001. A negative number indicates more events of this type occurring in patients allocated 12 500 IU than in patients allocated 5000 IU sc bd.

Table 5: **Direct randomised comparison of effects of subcutaneous heparin 12 500 and 5000 IU twice daily**

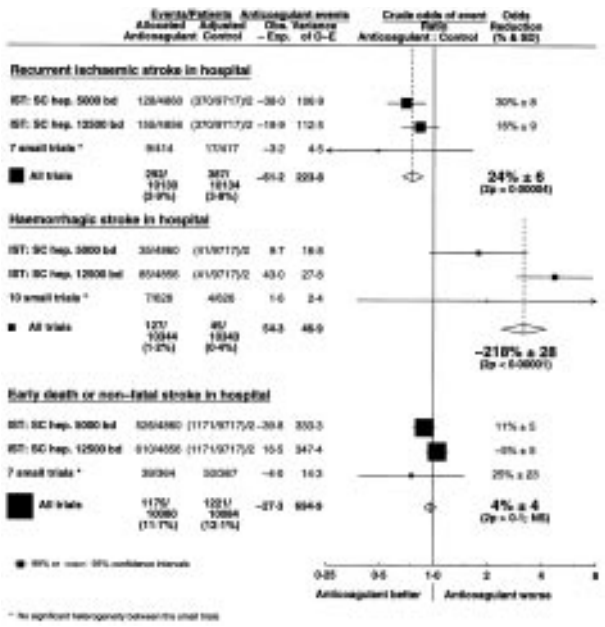

Figure 3: **Short-term effects of early anticoagulant therapy**
Systematic review[7] of effects of anticoagulants during the scheduled treatment period (mostly about 14 days) in completed unconfounded randomised trials in acute ischaemic stroke on: (a) recurrent ischaemic stroke, (b) haemorrhagic stroke, (c) death from any cause or non-fatal stroke (non-fatal stroke includes non-fatal recurrent strokes of ischaemic or unknown type and haemorrhagic strokes).[7] Conventions as in figure 2. Overall results in all available trials, and their 95% CIs, are represented by diamonds. Note: numbers of patients allocated control have been adjusted to take account of deliberately unequal randomisation in some trials. Full details of trials included are available in published systematic review.[7]

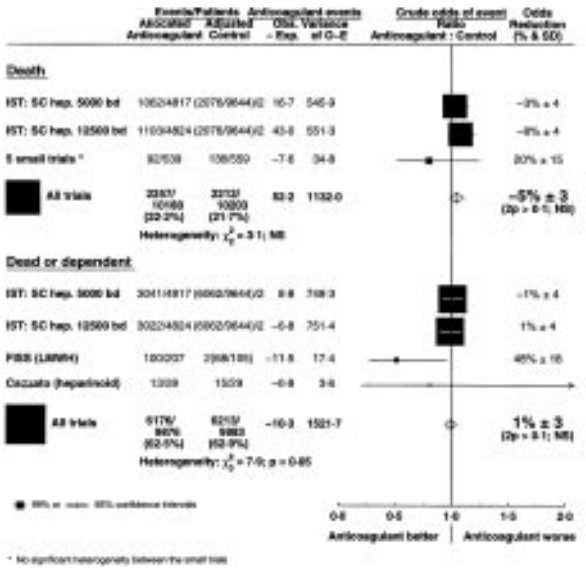

Figure 4: **Long-term effects of early anticoagulant therapy**
Systematic review[7] of effects of anticoagulants at end of scheduled follow-up period (generally 3, or as in the IST, 6 months) in completed unconfounded randomised trials in acute ischaemic stroke on: (a) death from any cause, and (b) death or dependency in activities of daily living. Conventions as in figure 2. Note: numbers of patients allocated control have been adjusted to take account of deliberately unequal randomisation in some trials. Full details of trials included are available in systematic review.[7]

patients who, before randomisation, had the least severe strokes, although even in them this excess was small (5 per 1000) and not significant (not shown).

Non-trial treatments

The use of most non-trial treatments in hospital (eg, corticosteroids, glycerol, haemodilution, carotid surgery and thrombolysis) were well balanced between the treatment arms. Calcium antagonists were used slightly more often in patients allocated to avoid heparin (10·5% *vs* 11·5%, p=0·05) and in patients allocated to avoid aspirin (10·6% *vs* 11·4%, NS). There were, of course, definite differences in the use of non-trial heparin between those allocated heparin and those not and in non-trial aspirin between those allocated aspirin and those not. Controls were slightly more likely to get these non-trial treatments, tending to reduce any positive treatment effect in the trial. However, the largest difference was in the use of non-trial aspirin between those allocated aspirin and those not (2·2% *vs* 5·8%) and even this would have had little effect on the overall outcome of the study.

Discussion

Heparin

Heparin (low and medium dose combined) did not significantly affect deaths at 14 days or death or dependency at 6 months. These results are consistent with overviews[2,7] of the short-term effects in other anticoagulant trials (figure 3). The 15 previous trials were small, and even in aggregate included only 1599 patients, so they contribute little information. 13 trials have not published results on death or dependency at final follow-up; of the two that did (figure 4), only one indicated a significant benefit at 6 months.[25] In the light of the IST, this result may well (despite its statistical significance) be due to chance, especially since there was no significant difference in outcome at 3 months. However, other explanations are plausible (eg, different types of heparin and different types of patient). Trials in progress of anticoagulants in different categories of patients with acute stroke[7,26] may help to clarify whether differences between anticoagulant regimens are real or not.

A more or less consistent pattern for the effects of heparin was evident across many categories of patient, a reduction in recurrent ischaemic strokes being generally offset by a similar-sized increase in haemorrhagic stroke. In 1994 the Stroke Council of the American Heart Association concluded that there was insufficient evidence to make any recommendation about the use of heparin in acute cardioembolic stroke,[27] yet heparin is still widely used in this setting.[4–6] Atrial fibrillation (AF) is the commonest potential source of embolism in acute stroke,[28] and over 3000 patients in the IST were in AF at the time of randomisation. The average risk of recurrent ischaemic stroke within 14 days was slightly higher among control patients with AF (4·9%) than among those without it (3·6%) but, although heparin was associated with a larger than average reduction in recurrent ischaemic stroke among those with AF, this was offset by a larger than average increase in haemorrhagic stroke. This does not support the routine use of subcutaneous heparin in acute cardioembolic stroke, and current studies with other anticoagulants may be too small to modify that view. Some clinicians favour anticoagulants in vertebrobasilar territory ischaemic stroke.[29] In the IST, however, the 2000 patients with a posterior circulation syndrome had, if

Outcome	Events (SD) prevented per 1000 patients allocated to	
	Heparin (5000 IU bd)†	Aspirin (300 mg daily)‡
Deaths from any cause within 14 days	6 (5)	4 (4)
All events (fatal or non-fatal) within 14 days		
Recurrent ischaemic stroke	12 (3)***	11 (3)***
Haemorrhagic stroke (HS)	−3 (1)*	−1 (1)
Recurrent ischaemic stroke or HS	9 (3)**	9 (3)**
Death or non-fatal stroke	12 (6)*	11 (5)*
Pulmonary embolism	2 (1)	2 (1)
Major extracranial haemorrhage	−2 (1)	−5 (1)***§
At 6 months		
Fully recovered, independent	−2 (7)	−10 (5)
Not recovered, but independent	5 (7)	−3 (6)
Dependent	3 (9)	3 (7)
Dead from any cause	−5 (7)	10 (6)
Dead or dependent	−2 (9)	13 (7)

*2p<0·05, **2p<0·01, ***2p<0·001, ****2p<0·00001. Exact p values in text. Negative numbers indicate more events of this type occurred in patients allocated to antithrombotic treatment than in patients allocated to avoid it. SD=standard deviation. †Comparing low-dose sc heparin with avoid low-dose heparin (half of both groups of patients were allocated aspirin). ‡Comparing aspirin with avoid aspirin (half of both groups of patients were allocated sc heparin). §2 per 1000 in aspirin vs no aspirin in the absence of heparin (2p=NS).

Table 6: **Absolute benefits observed in the IST of low-dose heparin or aspirin compared with control**

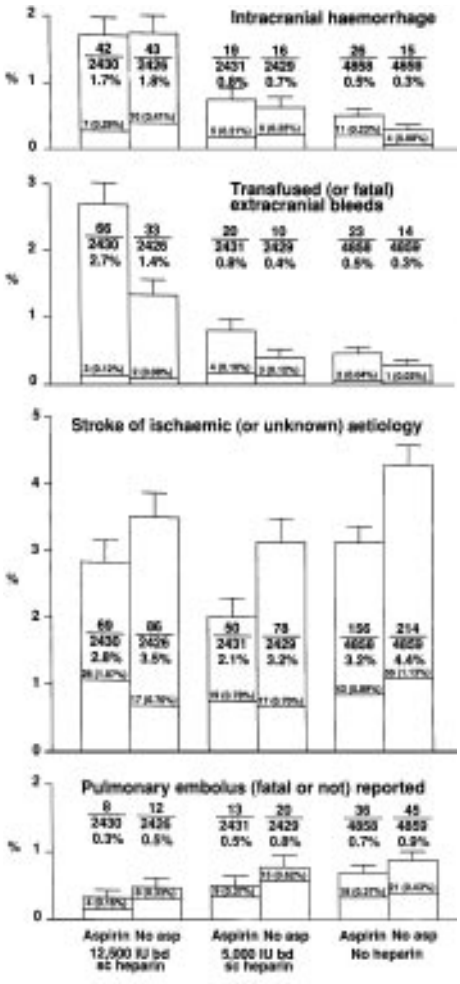

Figure 5: **Effects subdivided by heparin and aspirin allocation on:**
absolute risk of symptomatic intracranial haemorrhage;
absolute risk of transfused or fatal extracranial haemorrhage;
absolute risk of recurrent ischaemic stroke;
absolute risk of pulmonary embolism reported (with possibility of substantial under-reporting)
Error bars plot one standard error for percentage. For each bar, lower part gives number and percentage of fatal events.

anything, a slightly higher than average risk of haemorrhagic stroke with heparin, and no beneficial effect was observed on death or dependency at 6 months (figure 2a), although the CI was wide.

Recent guidelines have recommended low-dose heparin as prophylaxis against venous thromboembolism for stroke patients (chiefly for those at higher risk due to having a paralysed leg or not being able to walk for some other reason).[27] In the IST the recorded rate of pulmonary embolism was low (0·8%) among patients allocated to avoid heparin. The low rate of non-fatal pulmonary embolism recorded in all of these groups may, however, reflect under-reporting. There was only a marginally significant reduction in pulmonary embolism with heparin, which appeared more marked with medium-dose heparin (table 5) and was not conventionally significant with low-dose heparin (table 6).

Might bleeding have been lessened by monitoring coagulation times? Recent research confirms that the different reagents used for testing of activated partial thromboplastin times (APTT) in different centres yield different results, making it difficult to define an internationally agreed therapeutic range for heparin therapy.[30] Moreover, the medium-dose heparin regimen studied in the IST had been used without monitoring in very large trials in AMI patients who had also generally received thrombolytic therapy and aspirin, and the observed bleeding rates with this fixed-dose approach had been low[10,11] (although the absolute bleeding risks in stroke were somewhat higher than in AMI). By contrast, despite repeated monitoring of APTT, adjusted dose intravenous heparin regimens have been associated with significant increases in major bleeding.[17,18]

Aspirin

The effects of immediate aspirin use in acute ischaemic stroke on the unadjusted primary outcomes in the IST were not significant. There was, however, a significant reduction of 11 (SD 5) deaths or non-fatal recurrent strokes within 14 days per 1000 patients allocated aspirin. The unadjusted 13 (SD 7) per 1000 reduction in death or dependency at 6 months approached conventional significance and, after adjustment for baseline stroke severity, became conventionally significant (reduction of 14 [SD 6] per 1000). These results are consistent with the small MAST-I study, which is the only previous trial of aspirin in acute stroke,[16] and, more importantly, with the results of the large Chinese Acute Stroke Trial,[24] in which about 10 early deaths or non-fatal strokes were avoided per 1000 allocated aspirin. Since most patients with acute ischaemic stroke are likely to benefit from long-term antiplatelet therapy,[12] the IST and CAST results for the safety (and slight additional benefit) of giving aspirin immediately in acute ischaemic stroke are reassuring. In IST and CAST combined, aspirin was associated with an excess of about 2 (SD 1) haemorrhagic strokes per 1000. The effects of aspirin and of heparin on intracranial haemorrhage are largely independent of each other (figure 5a), but the effects on other bleeds are

not (figure 5b). This means that, in the absence of heparin, aspirin produces only 2 (SD 1) transfused or fatal extracranial bleeds per 1000. The effects of aspirin in the presence and absence of the different heparin regimens on early recurrent stroke and pulmonary embolism are shown in figures 5c and d.

Internal validity

The chief strengths of this study are the strict randomisation of large numbers with good compliance and minimal loss to follow-up. Lack of placebo control and the unblinded assessment of in-hospital events could, at least in principle, allow some bias to be introduced. To minimise bias in the assessment of the 6 month outcome the assessors in most countries were "blind" to treatment allocation. Moreover, the pilot phase of the study indicated that most patients could not recall their treatment allocation at 6 months,[3] so they too were effectively "blinded". Estimates of treatment effects among those with central follow-up (which is likely to be largely blinded) and those without were not significantly different (figure 2). Thus, lack of blinding probably did not materially affect the main findings for the primary outcomes. Clinicians might, however, have been more likely to arrange repeat CT scanning in patients on active treatment who worsened clinically, detecting more intracranial haemorrhages, so the open design may have introduced some bias in the assessment of the secondary outcomes. However, the apparent effects of aspirin in the open IST were similar to those in CAST, which was placebo-controlled, and the short-term effects with heparin in the IST were similar to those seen in the placebo-controlled trials.[7]

Generalisability

The IST was done in a wide variety of specialist and non-specialist hospitals in 36 countries, but the average frequency of different outcomes, overall and in specific subgroups, was similar to that seen in Oxfordshire, UK,[28,31–33] and the frequency of early recurrent stroke was similar to that in a review of epidemiological studies and randomised trials in acute stroke.[34] However, pulmonary embolism was reported much less frequently (0·7%) than in a recent review (3-39%),[35] so the generalisability of the IST result may be reduced by the likely underascertainment of this secondary event. On the other hand the IST was very large so that even in subgroups of patients the results are based on substantial numbers, and this helps in the interpretation.

Clinical implications

The IST results apply chiefly to patients who have already been CT scanned to exclude intracranial haemorrhage or in whom intracranial haemorrhage is unlikely and are due to be CT scanned soon.

These results provide evidence against the routine use, in patients with acute ischaemic stroke, of any heparin regimen as intensive as the subcutaneous "medium-dose" regimen, and provide no indication for the selective use of such a regimen even for the immediate treatment of particular types of patient (such as those with cardioembolic or vertebrobasilar ischaemic stroke). By contrast, with low-dose heparin there was evidence of modest short-term benefit and less evidence of hazard. It would, therefore, be prudent to avoid regimens more intensive than low-dose subcutaneous heparin during the first week or two after stroke onset when the risks of cerebral bleeding are highest. The combination of low-dose subcutaneous heparin and aspirin looked as if it might be better in the short term than aspirin alone (with more favourable differences in early death, 8·0% *vs* 9·3%, and early recurrent stroke or intracranial haemorrhage, 2·8% *vs* 3·7%, with little additional risk of major extracranial haemorrhage, figure 5). However, these analyses were based on a relatively small number of patients (6000) and were from a large number of subgroup analyses. The hypothesis that aspirin plus low-dose heparin is better than aspirin alone (which, incidentally, is not supported by the results at 6 months) needs to be tested by a further trial. At least 20 000 patients would be required to confirm the apparent early benefit and exclude any comparable-sized hazards of adding low-dose heparin to aspirin.

Because the evidence on aspirin is based on 40 000 randomised patients (IST and CAST), it is more reliable than that for heparin. The benefit from the IST and CAST, of about 10 deaths or recurrent strokes avoided per 1000 patients treated with aspirin in the first few weeks is about the same size as the benefit per year from long-term aspirin treatment in stroke survivors.[12] Unless there are clear contraindications, immediate use of aspirin (with an initial dose of about 300 mg, though a lower maintenance dose might then suffice[12]) should be considered in all patients with acute ischaemic stroke, especially if a CT has excluded intracerebral haemorrhage. Long-term low-dose aspirin, continued for some years after the ischaemic stroke, will improve the prognosis for many patients,[12] and IST and CAST now show a slight further improvement in the prognosis if aspirin starts at the beginning rather than at the end of the hospital stay.

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France (2) (C) (Grenoble) CHU de Grenoble: †Hommel M

Greece (152) (C) (Aigion) Aigion General Hospital: Dialoupis K, (Athens) 3rd Hospital I.S.S. of Athens: Georgious P, Kalliakmanis A, Korovinis M, Michailidis A, University of Athens School of Medicine: †Vemmos K, (Crete) University General Hospital of Crete: Papadakis J

Hong Kong (115) (C) (Chaiwan) Pamela Youde Nethersole Eastern Hospital: Cheung CM, Tsoi TH, Wan WY, Yam Y, (Hong Kong) Kwong Wah Hospital: Alexander LCB, Ko K, Law A, Princess Margaret Hospital: Kong TK, Lau KK, Tong BC, The Prince of Wales Hospital: †Wong LKS, (Kowloon) Queen Elizabeth Hospital: Chan J, Li PCK., Ng PKK, Wong C-K, Yeung JHM, United Christian Hospital: Chui TY, Ng P

Hungary (105) (C) (Debrecen) University of Debrecen Medical School: Bereczki D, †Csiba L, Fekete I, Csepany T, (Miskolc) B.A.Z. County Hospital: Boszormenyi I, Csolto M, Sagi I, Sipos G

India (229) (D)(Bangalore) Nimhans: Nagaraja D, St Johns Medical College Hospital: Rangan G, Jacob M, Chandramouli C (Hyderabad) Nizam's Institute of Medical Sciences: Meena AK, Murthy JMK, (Madras) Voluntary Health Services Centre: Ramachandran V, Saikumar M, Srinivas K, Sashikala K, (New Delhi) All India Institute of Medical Sciences: †Prasad K, Antonio DP, Desai P, Gaekwad S, Raghavan S

Israel (114) (D) (Haifa) Carmel Hospital: Gross B, (Holon) Wolfson Hospital: Eshel Y, Sarova I, (Jerusalem) Shaare Zedek Medical Center: Barazouski S, Rosin A, (Tel Aviv) Ichilov Hospital: Aronovich B, †Bornstein NM, Bova I, Gur A, Karepov V

Italy (3113) (C) (Acquapendente) Ospedale di Acquapendente: Pisanti P, Rollo F, (Ancona) Ospedale Geriatrico: Del Gobbo M, Guidi M, Pelliccioni G, Scarpino O, Ospedale Torrette: Ceravolo MG, Pelonara S, Provinciali L, Reginelli R, (Assisi) Ospedale di Assisi: Bondi L, (Bari) Policlinico di Bari: Federico F, Inchingolo V, Insabato R, Laddomeda G, Lucivero V, (Belluno) Ospedale di Belluno: Fassetta G, Gentile M, Giuseppe G, Tournier B, (Bergamo) Neurologia 1, Ospedale Riuniti: Defanti CA, De Marco R, Neurologia 2, Ospedale Riuniti: Belloni G, Camerlingo M, Casto L, Censori B, Mamoli A, (Bologna) Ospedale S.Orsola Malpighi: Azzimondi G, Bacci M, D'Alessandro R, Fiorani L, Naldi S, Nonino F, Peta G, Pugliese S, (Brescia) OSpedale di Brescia: Anzola P, Mangoni M, (Cagliari) Ospedale San Michele: Melis M, Spissu A, (Camposampiero) Ospedale Civile P Cosma: Chiavinato GL, (Carpi) Ospedale Ramazzini: Lolli V, Lugli ML, Miele V, Santangelo M, (Cascia) Ospedale di Cascia Norcia: Buccolieri A, Cozzari M, (Catania) Policlinico Universita: Giammona G, Giuffrida S, Le Pira F, Nicoletti F, Saponara R, (Cento) Ospedale di Cento, USL 30: Sarti G, (Cesena) Ospedale Bufalini, Cesena: Mazzini G, Pagliarani G, Pretolani E, Pretolani M, Rasi F, Tonti D, (Chiaravalle) Ospedale Civile: Lopresti, (Chioggia) Ospedale Civile di Chioggia: Zotti S, (Citta di Castello) Ospedale Civile: Arcelli G, (Como) Ospedale Valduce: Guidotti M, (Cortona) Ospedale di Cortona: Aimi M, Conti G, Corbacelli C, Migliacci R, Mollaioli M, (Firenze) Ospedale S.M.annunziata Medicina 2: Landini G, Manetti F, Ospedale S.M.Annunziata Medicina 3: Bartolozzi A, Bellesi R, (Foligno) Medicina, Ospedale di Foligno: Massi-Benedetti M, Maremmani AM, Neurologia, Ospedale di Foligno: Bacchi O, Brustenghi P, Stefanucci S, (Forli) Ospedale di Forli: Cirrillo G, Pedone V, (Galatina) Azienda USL LE/1 Galatina: Marzo A, (Genova) Dipartimento di Scienze Neurologiche: Bruzzone G, Del Sette M, Finocchi C, Gandolfo C, (Imola) Ospedale di Imola: Ballotta A, Bertuzzi D, Chioma V, Fini C, Masina M, Matacena C, Marzara G, Michelini M, Pirazzoli G, Sacchet C, (Isernia) Instituto Sanatrix: Aloj F, Buzzi MG, Castellano AE, Gatta A, Minotta S, Rossi F, (L'Aquila) Ospedale Collemaggio: Carolei A, Marini C, (Latisana) Medicina, Latisana: Gavardi M, (Lavagna) Ospedale di Lavagna: Caneva E, Canevari E, Colombo R, Giunchedi M, Ratto S, Rocca I, Sivori D, (Mede) Ospedale San Martino: Gallotti P, Garbagnoli P, Rossanigo PL, Tardani F, Zaccone MT, (Messina) Ospedale Piemonte: Arena A, Policlinico Universitario Messina: Musolino R, Rosario G, (Mestre-Venezia) Ospedale "Umberto I" Mestre: Haefele M, Pistollato G, (Milano) Ospedale Niguarda: Bottini G, Brucato A, De Juli E, Ferraro G, Thiella G, Rinaldi M, Santilli I, Sterzi R, Ospedale San Raffaele: Comola LM, Franceschi M, Volonte LMA, Ospedale Sesto San Giovanni: Cavestri R, Longhini E, Mazza P, (Modena) Ospedale di Modena: Bernardi C, Malferrari G, (Moncalieri) Moncalieri Santa Croce: Curti A, Fogliati M, Frediani R, Pecorari L, (Monselice) Ospedale di Monselice: Conforto L, Turrin M, (Negrar) Ospedale Don Calabria: Cacace C, Rimondi B, (Nuoro) Ospedale S Francesco: Murgia SB, (Offida) Ospedale di Offida: Cipollini F, (Olbia) Ospedale Civile Olbia-San Giovanni di Dio: Mura G, Pirisi A, Secchi G, (Orvieto) Ospedale di Orvieto: Franciosini MF, (Osimo) Ospedale di Osimo S.Benvenuto E Rocco: Pellegrini F, (Padova) Universita di Padova: Meneghetti G, (Parma) Ospedale Maggiore: Catahmo A, Finzi G, Ponari O, Tonelli C, (Pavia) Fondazione Mondino: Bosone D, Cavallini A, Micieli G, Nappi G, Poli M, Zappoli F, (Perugia) Istituto di Gerontologia E Geriatria: Aisa G, Cherubini A, Polidori MC, Romano G, Savastano V, Senin U, Ospedale Silvestrini: *Cantisani AT, Caselli P, Floridi P, Tiacci C, Policlinico: Benemio C, *Celani MG, Ciorba E, Comparato E, *Duca E, *†Ricci S, *Righetti E, *Zampolini M (Piacenza) Ospedale Civile Piacenza: Bionda E, Cammarata S, Debenedictis M, Gala B, Poli V, Vignola A, (Pistoia) Ospedale di Pistoia: Sita D, Volpi G, (Potenza) Ospedale di Potenza, San Carlo: Paciello , Peluso D, Sica U, (Putignano) San Michele in Monte

Laureto: lbaDellarosa A, (Salerno) Ospedale Riuniti: Iuliano G, (Sarnico) OSpedale di Sarnico,P.A.Faccanoni: Casella G, Mascaretti L, Scatena L, Spadaro C, (Sassari) Ospedale di Sassari: Casu G, Marras FA, Pirisi A, Spanu MA, Zuddas M, (Spoleto) Ospedale di Spoleto: Cenciarelli S, Grasselli S, Nazzareno M, (Terni) Ospedale Geriatria di Terni: Carnevali P, Consalvi G, Finistauri D, Grilli G, Maragoni M, Ospedale S.maria Neurologia: Bartocci A, Costantini F, De Santis L, Iannone G, Lancia G, Moschini E, Paci A, Sensidoni A, Trenta A, (Todi) Ospedale di Todi: Alunni G, Biscottini B, Boccali A, Cruciani M, Ibba R, Pacini M, (Tredabissi) Ospedale di Melegnano: Amodeo M, Colombo A, Marsile C, Pontrelli V, Sasanelli F, (Trieste) Ospedale Maggiore: Antonutti L, Boniccioli B, Chiarandini G, Chiodo-Grandi F, Gregori M, Guerrini N, Koscica N, Musco G, Nider G, Polo S, Relta G, Valli R, (Tronto) Ospedale S.Benedetto Del Tronto: Carboni R, Coccia G, Curatola L, Gobbato R, Infriccioli P, Sabatini D, Sfrappini M, (Valdarno) Ospedale di San Giovanni Valdarno: Cuccuini A, (Vibo Valentia) Presidio Ospedaliero "G.iazzolino": Consoli D, Vecchio A, (Vicenza) Ospedale San Bortolo: Dudine P, Morra M, Toso V, (Vimercate) Ospedale di Vimercate: Casati G, Ciccone A, Marmiroli P, (Zingonia) Policlinico San Marco: Chia F, Mauro A, Munari L, Perretti A

Japan (9) (C) (Tokyo) Tokyo Women's Medical College: Hayakawa I, Honma Y, Takagi M, Tei H, †Uchiyama S

Netherlands (728)(C) (Alkmaar) Medisch Centrum Alkmaar: Staatman HJS, Ten Houten R, Veering MM, (Amsterdam) Academisch Medisch Centrum: Horn J, Kwa VIH, Limburg M, Stam J, (Bergen Op Zoom) St Ziekenhuis Lievensberg: Berntsen Pjim, (Enschede) Medisch Centrum Twente: Brouwers Pjam, (Goes) Oosterschelde Ziekenhuis: Boon AM, Lieuwens WHG, Visscher F, (Leiden) Diaconessenhuis: Briet PE, Van Rossum J, (Maastricht) Academisch Ziekenhuis Maastricht: Boiten J, Lodder J, (Nijmegen) Ziekenhuis CAnisius Wilhelmina: Bernsen HJJA, Frenken CWGM, Poels EFJ, Prick MJJ, Verhagen WIN, (Rotterdam) Academisch Ziekenhuis Rotterdam: Bakker SLM, Dippel DWJ, Koudstaal PJ, Van Gemert HMA, (Utrecht) Academisch Ziekenhuis Utrecht: vd Worp HB, Kappelle J

New Zealand (453) (C) (Auckland) Auckland Hospital: †Anderson NE, Charleston A, Rodgers A, Roberts LA, (Nelson) Nelson Hospital: Clark M, (Tauranga) Tauranga Hospital: Chancellor AM, (Wellington) Wellington Hospital: Abernethy D, Baldey A, Duignan M, Feltham R, Fitzjohn T, Kelly R, (Whangarei) Whangarei Area Hospital: Orpin MJ

Norway (526) (C) (Aalesund) Sentralsjukehuset I More OG Romsdal: Skogen OR, (Baerum) Baerum Sykehus: Lofsnes I-L, Normann A, (Bergen) Haukeland Hospital: Naess H, Rissoen H, Thomassen L, (Bodo) Nordland SentralSykehus: Kristiansen MG, (Gjovik) Gjovik Fylkessykehus: Stubhaug O, (Hamar) Hamar Sykehus: Kydland H, (Harstad) Harstad Sykehus: Hensrud S, (Haugesund) Fylkessykekuset I Haugesund: Berentsen S, Ofstad R, (Honefoss) Ringerike Sykehus: Ljones F, (Kristiansand) Vest-Agder Sentralsykehus: Friis P., (Kristiansund N) Fylkessjukehuset I Kristiansund N: Blix I, (Lillehammer) Lillehammer Fylkessykehus: Brandt E, (Molde) Fylkessjukehuset I Molde: Sorum Y, (Narvik) Narvik Sykehus: Pedersen T, (Notodden) Notodden Sykehus: Erichsen KE, Flaaten B, Lid N, Solheim SB, Sukke SU, (Oslo) Aker University Hospital: Dahl T, Diakonhjemmet Sykehus: Eika C, Ullevaal Hospital: †Sandset PM, Rygh J, (Sarpsborg) Ostfold Sentralsykehus AVD.Sarpsborg: Hauge T, Torjussen B, (Tonsberg) Vestfold Sentralsykehus: Skogen P, (Tromso) Regionsykehuset I Tromso Nevrologisk: Mathiesen EB, Selseth BJ

Poland (759)(D) (Gdansk) Department of Neurology: Dobrzynska L, Krzeaniak-Bohdan M, (Gdansk) Specjalistyczny Szpital: Fryze W, (Katowice) Klinika Neurologiczna AM: Kazibutowska Z, (Lodz) Koperink Hospital: Klimek A, Stankiewicz M, Sktodowski P, (Siedlce) Dept of Neurology : Lyczywek-Zwierz T, Wlodek A, (Warsaw) Institute of Psychiatry & Neurology: †Czlonkowska A, Kuczynska-Zardzewialy A, Mendel T, (Zabrze) Klinika Neurologiczna AM: Rosciszewska D, Slusarczyk R

Portugal (380) (C) (Coimbra) Centro Hospitalar Coimbra: Cardoso M, Dias M, Dionisio A, Goncalves G, Palmeiro J, Hospitais DA Universidade de Coimbra: Cunha L, Ferro MA, Goncalves F, Mestre AG, (Lisboa) Egas Monis/S.F.Xavier: Breia P, Dos Santos V, Guia J, Guimaraes J, Leal A, Leitao AA, Santos L, Hospital Santa Maria: Crespo M, Ferro J, Melo T, Hospital Sao Jose: Arauijo C, Candido J, Duarte AP, Ramirez I, (Porto) Hospital de S Joao: Coelho F, Martins R, Rio EP, Silva A, Hospital De St Antonio: Correia C, (Correia M, Gabriela Lopes M, Lopes C, Silva MR, (Santo Tirso) Conde de S Bento: Azevedo E, Batista P, Carrondo J, Coelho MJ, Marques F, Rosa F, Santos LA

Romania (18) (D) (Bucharest) GH MarinesCU Hospital: †Popa C, Nistorescu A, Voiculescu D, Geana IV

Singapore (140) (C) (Singapore) Singapore General Hospital: †Chen CPL-H, Wong MC, Tan Tock Seng Hospital: Chua HC, Umapathi T, Venketasubramanian N

Slovak Republic (86) (C) (Banska Bystrica) F.D.Roosevelt Hospital: †Pelikan F, Paluchova J

Slovenia (53) (D) (Ljubljana) Medical Centre Ljubljana: †Grad A, Meglic B, Sviggelj V, (Maribor) Teaching Hospital Maribor: Hojs T

South Africa (69) (C) (Durban) Entabeni Hospital: †Hoffmann M, (Johannesburg) Johannesburg Hospital: Connor M, Fritz V, Morningside Clinic: Rosman K

Spain (478) (C) (Barcelona) Consorcio Sanitario de Mataro: Fossas Felip P, Moreno AT, Majo CC, Hospital de Bellvitge: Rubio F, Hospital Del Mar: Oliveras C, Hospital General de Cataluna: Balaguer E, Soler L, Hospital Mutua de Terrassa: Aguilar M, (Burgos) Hospital General Yague: Trejo Gabriel y Galan J, (Girona) Hospital Josep Trueta: Davalos A, Serena J, Camafort M, (Madrid) Hospital Clinico San Carlos: Egido Herrero JA, Gonzalez Gutierrez JL, Hospital de Getafe: Martinez Martin P, Hospital General Gregorio Maranon: Ariztegui NL, Herrera A, Villanueva JA, Hospital la Paz: Alonso de Lecinana M, Frank A, Diez Tejedor E, (Malaga) Hospital Clinico Universitario: Garcia PA, Marquez Martinez M, Moreno FP, (Mallorca) Hospital Son Dureta: Amer G, (Oviedo) Hospital Central Asturias: Llaneza M, Navarro R, Terrero JM, (Santander) Hospital Marques de Valdecilla: Rebollo M, (Sevilla) Hospital Universitario Valme: Fernandez Bolanos R, Jimenez M, Hospital Virgen del Rocio: Gil Peralta A, Jarrin S, (Vizcaya) Hospital de Cruces: Larraceochea J, (Zaragoza) Hospital Clinico Universitario: Mostacero E

Sri Lanka (20) (C) (Peradeniya) Peradeniya: †Sanmuganathan PS

Sweden (636) (C) (Alingsas) Alingsas Lasarett: Eklund B, (Bollnas) Bollnas Sjukhus: Astrom L, Press R, (Enkoping) Enkoping Hospital: Asberg KH, (Halmstad) Lanssjukhuset Halmstad: Ramstromer B, Skarfors E, Thomasson P, Thorin B, (Harnosand) Harnosands Sjukhus: Holmberg B-H, Olofsson J, (Hassleholm) Hassleholms Sjukhus: Ekberg M, Timberg I, (Huddinge) Huddinge University Hospital: Crisby M, Kostulas V, (Koping) Kopings Lasarett: Arcini N, Kobosko J, Kolesar T, Malmros B, Nicol P, Saaf J, (Kristianstad) Centralsjukhuset Kristianstad: Torstensson I, (Kristinehamn) Sjukhuset Kristinehamn: Johansson R, (Kungaln) Kungaln Sjukhus: Larsson G, Stromblad G, (Lindesberg) Lindesbergs Lasarett: Ahlkvist P, (Ljungby) Ljungby Lasarett: Holmer OS, Svensson K-A, (Motala) Lasarett Motala: Larsson L-I, Rosenquist U, (Nacka) Nacka Sjukhus: Forsberg E, Sjoblom N, (Norrtalje) Norrtalje sjukhus: Unden R, (Oskarshamn) Oskarshamns Sjukhus: Danielsson O, Hackell J, (Pitea) Pitea Alvdals Sjukhus: Marklund S-E, Nordstrom I, (Sandviken) Sandviken Hospital: Nordgren A, (Stockholm) Karolinska Sjukhuset: †Wahlgren NG, Wahlberg J, Soder Hospital: Carlstrom C, Zetterling M, (Sundsvall) Sundsvalls Sjukhus: Lindmark I, (Varnamo) Varnamo Hospital: Engquist L, Rustscheff S

Switzerland (1631) (C) (Aarau) Kantonsspital Neurologie: Hungerbuhler H-J, (Basel) Kantonsspital: Lyrer P, Steck A, (Bellinzona) Ospedale San Giovanni: Crivelli A, (Bern) Inselspital Med Klinik: Brabetz M, Koltai E, Straub PW, Studer H, Inselspital Med Klinik ASH: Weiss M, Inselspital Neurologie: Bassetti C, Eicher Vella E, Hess W, †Mattle H, (Biel) Regionalspital: Aepli R, Ulrich M, (Brig) Spital Brig: Escher J, Fischer J, (Bulach) Kreisspital Bulach: Nauer D, (Burgdorf) Regionalspital Burgdorf: Buri A, Gerber A, Rabaglio M, Stettler R, (Chur) Kantonsspital: Reinhart WH, (Frauenfeld) Kantonsspital: Bianchetti M, Nussbaumer P, Wick A, (Frutigen) Spital Frutigen: Moser S, Negri M, (Grenchen) Spital Grenchen: Schlup P, Wey B, (Heiden) Kantonales Spital Heiden: Kehl O, Waldburger R, (Interlaken) Regionalspital: Sula P, Wegmuller E, (Langenthal) Regional Spital: Trumpler U, (Liestal) Kantonsspital Liestal: Caliezi C, (Locarno) Ospedale Regionale la Carita: Mombelli G, Stricker H, (Luzern) Kantonsspital: Briner V, Burch T, Hub P, Joss R, Nager F, Truniger B, Z'Brun A, (Mannedorf) Kreisspital: Knoblauch M, Lippmann S, Muhlethaler K, (Mendrisio) Ospedale Beata Vergine M*: Balestra B, Noseda G, (Munsterlingen) Kantonsspital Muensterlingen: Muller F, (Olten) Kantonsspital: Butikofer K, Christen R, Pirovino M, (Schiers) Regionalspital Prattigau: Huber Th, (Solothurn) Burgerspital: Burgi H, Egger Th, Iff E, Ruegger S, (St.Gallen) Burgerspital St.Gallen: Grundler B, Kantonsspital: Emmenegger M, Ludin HP, (Sumiswald) Bezirksspital: Braunschweig J, (Thun) Regionalspital Thun: Stoller U, (Uster) Spital Uster: Eichhorn P, Spiegel M., (Uznach) Kantonales Spital Uznach: Weber A, (Visp) Regionalspital Sta Maria: Charvat J, Imoberdorf R, Nanzer A, (Wadenswil) Spital: Holy D, Mohr P, (Winterthur) Spital: Hany A, Horst A, Stoffel G, (Zurich) Spital Pflegi: Graetz G, Morell B, Stadtspital Triemli: Luthy R, Oelz D, Universitatsspital: Wyss P, (Zweisimmen) Bezirksspital Obersimmental: Marty H

Turkey (286) (C) (Eskisehir) Osmangazi Universitesi: Ozdemir G, Uzuner N, (Istanbul) Bakirkoy Ruh Ve Sinir Hastaliklari: Bakac G, Kirbas D, IstanbuL Medical Faculty: †Bahar S, Coban O, Krespi Y, Marmara University Hospital: Aktan S, Tekin S

UK (5789) (C) (Aberdeen) Aberdeen Royal Infirmary: Coleman RJ, Woodend Hospital: Hamilton SJC, (Ashford) Ashford Hospital: Kluth D, Marsh J, Wilkinson P, The William Harvey Hospital: Colchester ACF, Patel N, Travis S, (Aylesbury) Stoke Mandeville Hospital: Al-Hillawi AHS, Brockwell F, (Ballymena) Antrim/Braid Valley Hospital: Flanagan PG, (Bebington) Clatterbridge Hospital: Barrett JA, (Belfast) Belfast City Hospital: Fullerton KJ, Passmore AP, Stout RW, Royal Victoria Hospital: Beringer TRO, Gilmore DH, Urquhart D, (Birmingham) Selly Oak/Queen Elizabeth Hospital: Heafield MTE, Main A, Shinton R, (Bishop Auckland) Bishop Auckland General Hospital: Mehrzad AA, (Blackburn) Queens Park Hospital: Roberts NA, (Blackpool) Blackpool Victoria Hospital: O'Donnell M, Guirguis A, (Bolton) Bolton General Hospital: Adams KRH, Sammon R, (Boston) Pilgrim Hospital: Gatnash AA, (Brechin) Stracathro Hospital: Fulton J, (Brecon) Bronllys Hospital:

Davies A, Dunn AM, Harvey K, Millward M, Robinson D, Twyford SR, (Brighton) Royal Sussex County Hospital: Nurick S, Timeyin J, (Bristol) Frenchay Hospital: Burns-Cox CJ, Dow L, (Builth) Builth Hospital: Dunn AM, Riley M, Roberts SE, (Burnley) Burnley General Hospital: Sharma SC, (Canterbury) Kent & Canterbury Hospital NHS Trust: Britton M, Heller A, McCormack P, Potter JM, Roberts CI, Sturgess I, (Cardiff) Llandough Hospital NHS Trust: Bayer AJ, (Carlisle) Cumberland Infirmary: Athey G, Bennett-Jones DN, Billet J, Bleasdale S, Burke D, Chin PL, George J, Jennings P, Large DM, Mustchin CP, Robson RH, (Cheadle) Barnes Hospital: Bannister P, (Chester) Countess of Chester Hospital: Fitzroy Smith WD, Keeping IM, Worth RC, Youngs GR, (Cottingham) Castle Hill Hospital: Arnold AG, Beardsworth SF, Greenstone M, Haworth E, McGivern DV, Nanda BS, Tomlinson I, (Derby) Derby City General Hospital: Muhiddin K, (Dewsbury) Dewsbury & District Hospital: Kemp TM, (Doncaster) Doncaster Royal/Montague Hospital: Chadha D, Rajathurai A, (Dorchester) Dorset County Hospital: Williams RKT, (Dover) Buckland Hospital: Colchester ACF, (Dumbarton) Vale of Leven District General Hospital: Carmichael HA, (Dumfries) Dumfries & Galloway Royal Infirmary: Hay IFC, (Dundonald) The Ulster Hospital: Power MJP, (Edinburgh) Royal Infirmary: Chapman B, Royal Victoria Hospital: Smith R, Western General Hospital: Counsell C, Dennis M, Dorman P, Lindley R, †Sandercock P, Waddell F, Wardlaw J, Warlow CP, (Ellesmere Port) Ellesmere Port Cottage Hospital: Choudhury S, (Enniskillen) Erne Hospital: Kelly JF, (Exeter) Royal Devon & Exeter Hospital (Wonford): Hardie RJ, (Falkirk) Falkirk & District Royal Infirmary: Murdoch PS, Gibson H, Lenton RJ, Taylor J, (Glasgow) The Victoria Infirmary: MacIntyre D, Khand A, Western Infirmary: Colquhoun M, Lees KR, (Harlow) Princess Alexandra Hospital: Barrie MA, Walker R, (Hartlepool) General Hospital: Bruce DW, (Haverford West) Withybush General Hospital: James CM, (Hereford) Hereford General Hospital: Overstall P, (Hertford) Queen Elizabeth II Hospital: Voke J, (Hull) Hull Royal Infirmary: Clarke CE, (Inverness) Raigmore Hospital NHS Trust: Steven MM, (Ipswich) Ipswich Hospital: Grimmer M, (Keighley) Airedale General Hospital: Howe JG, The Junior Staff of Airedale Hospital (Leeds) St James Hospital: Bamford JM, Blundell S, Hayes J, (Leicester) Leicester Royal Infirmary: Ardron ME, Martin PJ, Pye IF, (Leigh) Leigh Infirmary: Khan AN, (Liverpool) Fazakerley Hospital: Harper N, McDowell DK, Sharma A, Turner JJ, Watkins C, Royal Liverpool Hospital: Barer D, Ellul J, Walton Centre for Neurology & Neurosurgery: Humphrey P, (Livingston) St John's Hospital: Farquhar D, Gray RS, Irving J, Middleton W, Wilson J, Williams A, (Llandrindod) Llandrindod Hospital: Asver MA, Dunn AM, Ellis M, Hallam J, (London) Central Middlesex Hospital: Bhatia R, Greenwich District Hospital: Ali MS, Al-Allaf AWYS, Habib M, Ibrahim Y, Rahman A, Sulch D, Guy's Hospital: Colchester ACF, King's College Hospital: Bath P, Butterworth R, King's College Hospital (Dulwich): Blackburn AM, St Andrew's Hospital: Gill MW, St Georges Hospital: Bateman K, Brown MM, Pereira AC, Saunders DE, The Homerton Hospital NHS Trust: Lehmann AB, Whipps Cross Hospital: Kafetz KM, McElligult GMF, Rossiter BD, Whittington Hospital: Hoffbrand B, Snow J, (Lurgan) Lurgan Hospital: Bannave K, Lee J, McCaffrey P, Ritchie K, Robinson J, (Macclesfield) Macclesfield District General Hospital: Davies ETL, Davison CE, Foster PN, Loughran CR, Stead RJ, Taylor MAR, Walker DJ, (Manchester) Trafford General Hospital: Musgrave SR, (Newark) Hawtonville Hospital: Sharma JC, Newark General Hospital: Sharma JC, (Newcastle) Freeman Hospital: Curless R, Davies P, Ford GA, Massey A, Newcastle General HospitaL: Ackroyd M, Barer D, Davis M, Royal Victoria Infirmary: Bates D, Burridge A, Cartlidge NEF, Gilroy J, Murdy J, Owen JP, Rodgers H, Sudlow M, (North Shields) Preston Hospital: Curless R, Walker 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References

1 Murray CJL, Lopez AD. Mortality by cause for eight regions of the world: Global Burden of Disease Study. *Lancet* 1997; **349:** 1269–76.

2 Sandercock PAG, van der Belt A, Lindley R, Slattery J. Antithrombotic therapy in acute ischaemic stroke: an overview of the completed randomised trials. *J Neurol Neurosurg Psychiatry* 1993; **56:** 17–25.

3 International Stroke Trial Pilot Study Collaborative Group. Study design of the International Stroke Trial (IST), baseline data and outcome in 984 randomised patients in the pilot study. *J Neurol, Neurosurg Psychiatry* 1996; **60:** 371-76.

4 Marsh EF, Adams HP, Biller J, et al. Use of antithrombotic drugs in the treatment of acute ischemic stroke. *Neurology* 1989; **39:** 1631-34.

5 Lindley RI, Amayo E, Marshall J, Sandercock P, Dennis M, Warlow C. Acute stroke treatment in UK hospitals: the Stroke Association survey of consultant opinion. *J R Coll Physicians Lond* 1995; **29:** 479-84.

6 Chen ZM, Xie JX, Collins R, Peto R, Liu LS. Survey of hospital care of patients with acute stroke in China. *Cerebrovasc Dis* 1995; **5:** 228.

7 Counsell C, Sandercock P. The efficacy and safety of anticoagulant therapy in patients with acute presumed ischaemic stroke: a systematic review of the randomised trials comparing anticoagulants with control. In: Warlow C, Van Gijn J, Sandercock P, eds. The Cochrane Database of Systematic Reviews (updated Dec 2, 1996). Available in the Cochrane Library [database on disk and CDROM]. Cochrane Collaboration; issue 1. Oxford: Update Software, 1997.

8 Turpie AGG, Robinson JG, Doyle DJ, et al. Comparison of high-dose with low-dose subcutaneous heparin to prevent left ventricular mural thrombosis in patients with acute transmural anterior myocardial infarction. *N Engl J Med* 1989; **320:** 352-57.

9 The SCATI (Studio sulla Calciparina nell 'Angina e nella Trombosi ventricolare nell' Infarto) group. Randomised controlled trial of subcutaneous calcium-heparin in acute myocardial infarction. *Lancet* 1989; ii: 182-86.

10 Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico GISSI-2: a factorial randomised trial of alteplase versus streptokinase and heparin versus no heparin among 12,490 patients with acute myocardial infarction. *Lancet* 1990; **336:** 65-71.

11 ISIS-3 (Third International Study of Infarct Survival) Collaborative Group. ISIS-3: a randomised comparison of streptokinase vs tissue plasminogen activator vs anistreplase and of aspirin plus heparin vs aspirin alone among 41,299 cases of suspected acute myocardial infarction. *Lancet* 1992; **339:** 753-70.

12 Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy. I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994; **308:** 81-106.

13 Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy. III: reduction in venous thrombosis and pulmonary embolism by antiplatelet prophylaxis among surgical and medical patients. *BMJ* 1994; **308:** 235-46.
14 van Kooten F, Ciabattoni G, Patrono C, Schmitz P, van Gijn J, Koudstaal P. Evidence for episodic platelet activation in acute ischemic stroke. *Stroke* 1994; **25:** 278-81.
15 Koudstaal P, Ciabattoni G, van Gijn J, et al. Increased thromboxane biosynthesis in patients with acute cerebral ischemia. *Stroke* 1993; **24:** 219-23.
16 Counsell C, Sandercock P. The efficacy and safety of antiplatelet therapy in patients with acute presumed ischaemic stroke: a systematic review of the randomised trials comparing immediate antiplatelet therapy with control. In: Warlow C, Van Gijn J, Sandercock P, eds. Stroke module of the Cochrane Database of Systematic Reviews [updated Dec 2, 1996). Available in the Cochrane Library [database on disk and CDROM). Cochrane Collaboration; issue 1. Oxford: Update Software, 1997.
17 Collins R, MacMahon S, Flather M, et al. Clinical effects of anticoagulant therapy in suspected acute myocardial infarction: systematic overview of randomised trials. *BMJ* 1996; **313:** 652-59.
18 Collins R, Peto R, Baigent C, Sleight P. Aspirin, heparin and fibrinolytic therapy in suspected acute myocardial infarction. *N Engl J Med* 1997; **336:** 847-60.
19 Lindley R. Are very large trials of promising treatments for acute stroke feasible? MD thesis. University of Newcastle-upon-Tyne 1993, 98-108.
20 Slattery J, Sandercock P. Prediction of death or dependency at six months in International Stroke Trial patients using data collected at randomisation. *Cerebrovasc Dis* 1996; **6** (suppl 2): 8.
21 White SJ, Freedman LS. Allocation of patients to treatment groups in a controlled clinical study. *Br J Cancer* 1978; **37:** 849-57.
22 Dennis M, Wellwood I, Warlow C. Are simple questions a valid measure of outcome after stroke? *Cerebrovasc Dis* 1997; **7:** 22-27.
23 Dennis M, Wellwood I, O'Rourke S, MacHale S, Warlow C. How reliable are simple questions in assessing outcome after stroke? *Cerebrovasc Dis* 1997; **7:** 19-21.
24 Chinese Acute Stroke Trial collaborative group. CAST: a randomised placebo controlled trial of early aspirin use in 21106 patients with acute ischaemic stroke. *Lancet* (in press).
25 Kay R, Wong KS, Lu YL, et al. Low-molecular-weight heparin for the treatment of acute ischemic stroke. *N Eng J Med* 1995; **333:** 1588-93.
26 Adams J. Trial of Org 10172 in Acute Stroke Treatment (TOAST). *Stroke* 1994; **25:** 545.
27 Adams Jr HP, Brott TG, Crowell RM, et al. Guidelines for the management of patients with acute ischemic stroke. A statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. *Stroke* 1994; **25:** 1901-13.
28 Sandercock P, Bamford J, Dennis M, et al. Atrial fibrillation and stroke: prevalence in different types of stroke and influence on early and long-term prognosis: Oxfordshire Community Stroke Project. *BMJ* 1992; **305:** 1460-5.
29 Amarenco P. Cerebellar stroke syndromes. In: Bogousslavsky J, Caplan R, eds. Stroke syndromes. Cambridge: Cambridge University Press, 1995: 344-357.
30 Kitchen S, Preston FE. The therapeutic range for heparin therapy: relationship between six activated partial thromboplastin time reagents and two heparin assays. *Thromb Haemost* 1996: **75:** 734-739
31 Bamford J, Dennis M, Sandercock P, Burn J, Warlow C. The frequency, causes and timing of death within 30 days of a first stroke: the Oxfordshire Community Stroke Project. *J Neurol Neurosurg Psychiatry* 1990; 53: 824-9.
32 Bamford J, Sanderock P, Dennis M, Burn J, Warlow C. A prospective study of acute cerebrovascular disease in the community: the Oxfordshire Community Stroke Project 1981-86. 2. Incidence, case fatality rates and overall outcome at one year of cerebral infarction, primary intracerebral haemorrhage and subarachnoid haemorrhage. *J Neurol Neurosurg Psychiatry* 1990; **53:** 16-22
33 Burn J, Dennis M, Bamford J, Sandercock P, Wade D, Warlow C. Long-term risk of recurrent stroke after a first-ever stroke: the Oxfordshire Community Stroke Project. *Stroke* 1994; **25:** 333-37.
34 Sandercock P, Tangkanakul C. Very early prevention of stroke recurrence. *Cerebrovasc Dis* 1997; **7** (suppl 1): 10-15.
35 Davenport R, Dennis M, Wellwood I, Warlow C. Complications after acute stroke. *Stroke* 1996; **27:** 415-20.