Antithrombotic therapy in acute ischaemic stroke: an overview of the completed randomised trials

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Abstract

A formal statistical overview of all truly randomised trials was undertaken to determine whether antithrombotic therapy is effective and safe in the early treatment of patients with acute stroke. There were 15 completed randomised controlled trials of the value of early antithrombotic treatment in patients with acute stroke. The regimes tested in acute presumed or confirmed ischaemic stroke were: heparin, 10 trials with 1047 patients: oral anticoagulants, one trial with 51 patients: antiplatelet therapy, three trials with 103 patients. Heparin was tested in one trial with 46 patients with acute haemorrhagic stroke. Outcome measures were deep venous thrombosis (confirmed by I¹²⁵ scanning or venography), pulmonary embolism, death from all causes, haemorrhagic transformation of cerebral infarction, level of disability in survivors. In patients with acute ischaemic stroke, allocation to heparin was associated with a highly significant 81% (SD 8, 2p < 0.00001) reduction in deep venous thrombosis detected by I¹²⁵ fibrinogen scanning or venogram. Only three trials systematically identified pulmonary emboli, which occurred in 6/106 (5.7%) allocated control vs 3/132 (2.3%) allocated heparin, a non-significant 58% reduction (SD 45.7, 2p > 0.1). There were relatively few deaths in the trials in patients with presumed ischaemic stroke: 94/485 (19.4%) among patients allocated to the control group vs 79/497 (15.9%) among patients who were allocated heparin. The observed 18% (SD 16) reduction in the odds of death was not statistically significant. The least biased estimate of the effect of treatment on haemorrhagic transformation of the cerebral infarct (HTI) comes from trials where all patients were scanned at the end of treatment, irrespective of clinical deterioration; using this analysis, haemorrhagic transformation occurred in 7/102 (6.9%) control vs 8/106 (7.5%) treated, a non-significant 12% increase (SD 56, 2p > 0.1). These data cannot exclude the possibility that heparin substantially increases the risk of HTI. No data on disability in survivors could be obtained. Early heparin treatment might be associated with substantial reductions in deep venous thrombosis (and probably also pulmonary embolism) and possibly a one fifth reduction in mortality (equivalent to

the avoidance of 20-40 early deaths per thousand patients treated). However, the data were wholly inadequate on safety, particularly on the risk of haemorrhagic transformation of the infarct and on the hazards of heparin therapy in patients with known intracerebral haemorrhage. The trials of oral anticoagulants (15 deaths among 57 patients) and antiplatelet therapy (two deaths among 103 patients) were too small to be informative. Much larger randomised trials—comparing aspirin, heparin and the combination of both drugs against control—in patients with acute ischaemic stroke are justified (and several are now planned or underway).

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Each year, there are about 1.5 million new strokes per year in the USA and in the European Community.¹⁻³ Eighty five per cent of strokes are ischaemic,³ so over the next decade, there will be some 12.8 million patients with acute ischaemic stroke, for whom antithrombotic treatment might be considered. Of these patients, about 1.5 million will be dead within two weeks of their stroke. Many will survive, but be dependent on other people for help with activities of daily living. Aspirin and heparin are simple, practicable antithrombotic regimes which could be given to almost every patient with acute ischaemic stroke. If these two treatments were proven to be effective and safe, the potential scale of their use is enormous.

Antithrombotic drugs yield substantial clinical benefits in the early treatment of unstable angina and acute myocardial infarction.⁴⁻¹⁰ For example, in acute myocardial infarction, one month's oral aspirin reduces early mortality by one fifth⁴ and one or two weeks' heparin can reduce one month mortality by about one tenth.⁵⁻¹¹ If the widespread early use of these treatments in patients with acute ischaemic stroke (cerebral infarction) were associated with similar benefits, perhaps 300 000 early deaths would be avoided over the next decade in Europe and USA. In addition to improving survival, early antithrombotic treatment with aspirin or heparin, by reducing the volume of infarcted cerebral tissue, avoiding early recurrence of thromboembolic stroke and reducing venous thromboembolic complications might reduce neurological disability in survivors.¹²⁻¹⁴

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This paper is a formal statistical overview of all the randomised trials of antithrombotic treatment in patients with acute ischaemic stroke. Our aim was to determine whether there is clear evidence that treatment is beneficial and, if not, whether a very large scale trial is justifiable.¹⁵⁻¹⁷

Methods

We sought to identify all truly randomised trials of early treatment with antithrombotic agents in patients with acute stroke. Thus trials in which allocation to treatment or control group was not truly randomised (that is, alternating, or based on date of birth or hospital number) were not included, since foreknowledge of treatment allocation might lead to biased treatment allocation. Trials which randomised patients more than seven days after onset of the stroke, and trials in patients with only transient ischaemic attacks were excluded, because this review was confined to early treatment of acute stroke. The anticoagulant agents considered were: standard unfractionated heparin, low molecular weight (LMW) heparin, and oral anticoagulants. We sought trials of the antiplatelet agents: aspirin, ticlopidine, sulphinyprazole, suloctidil, dipyridamole, indobufen, flurbiprofen and the combination of aspirin and dipyridamole. Relevant randomised trials were identified by computer aided search (MEDLINE), by conversation with colleagues (particularly those who had coordinated such studies), by scrutiny of the reference lists of trials and review articles, by inquiry of various manufacturers of anticoagulants and by searching the trials register held by the Antiplatelet Trialists' Collaboration (APT).¹⁷ We aimed to extract from each trial the number of patients originally allocated to each treatment group, and in each treatment group, the number of patients: a) with objective evidence of the occurrence of deep venous thrombosis (DVT) detected by systematic 125-I-fibrinogen scanning or systematic radiograph contrast venography during the scheduled treatment period; b) with at least one confirmed pulmonary embolus; c) who died from any cause during the scheduled follow up period (generally longer than the scheduled period of drug treatment); d) who died from any cause during the scheduled treatment period; e) with haemorrhagic transformation confirmed by routine CT scanning; f) with recurrent stroke by the end of the scheduled study follow up period; g) who were dead or dependent on help from other people in activities of daily living at 6 months after the stroke. Data on the number of patients with each outcome event, by allocated treated group, irrespective of compliance, and whether or not the patient was subsequently considered ineligible or otherwise excluded from treatment or follow up were sought to allow an "intention to treat" analysis.

If these data were not available in publications, further data were sought by correspondence with the authors. Data on whether CT scanning was performed before randomisation were also sought.

Statistical analysis

The statistical overview was performed by the standard method described by Yusuf and Peto.¹⁶⁻¹⁸ For each trial, the number of subjects in whom a particular adverse event was observed in the treatment group (O) is contrasted with the number that, if treatment really had no effect, would have been expected (E) on the basis of the overall experience in the treatment and control groups combined. If treatment were effective, the grand total (GT) should be negative. If, however, treatment were wholly without effect, the GT would differ only randomly from zero (with variance total [VT] equal to the sum of the individual variances in the separate O - E values, and with the standard deviation [SD] equal to the square root of the total variance). Formal statistical tests assessing whether treatment is without effect involve the calculation of Z, the number of standard deviations by which the GT differs from zero ($Z = GT/SD$), and comparison of Z with tables of the standard normal distribution. (Thus, for example, a favourable result with $Z = -1.96$ suggests a P value of about 0.05.) (All P values are two-sided.) An estimate of the typical percentage reduction in the odds (R) of an adverse event occurring among treated patients compared with controls can be calculated with use of the approximate formula $R = 100 - 100 \text{ expected } (Z/SD)$, with 95% confidence limits $100 - 100 \text{ expected } (Z/SD \pm 1.96/SD)$, and the standard deviation of R may be estimated by $-R/Z$. Tests for heterogeneity of the effects of treatment between several different trials (or categories of trial) can also be performed. For each trial in which the variance, V, of O - E is not zero, the quantity $(O - E)^2/V$ can be calculated, and all such quantities, one per trial, added up. Subtraction of $(GT)^2/VT$ from this total provides an approximate chi-square test statistic, with one fewer degree of freedom than the number of such trials. An overview of many trial results assumes not that the real effects of treatment are all exactly the same size in the different trials but merely that most or all of the real effects probably point in the same general direction.

Results

Twenty one trials were identified (tables 1 and 2). Six trials are either planned or are still in progress and results are not expected to be available for some time. This review is of the remaining fifteen¹⁹⁻³³ completed trials.

Trials of heparin and oral anticoagulant drugs in acute stroke

We have identified 11 controlled trials of anticoagulant drugs in patients with acute ischaemic stroke which compared anticoagulant effects with control. The agents were: standard heparin (six trials), LMW heparin (four trials), oral anticoagulants (one trial). One trial in patients with haemorrhagic stroke compared standard heparin with control. Details of the regimes are in the tables. The scheduled period of acute antithrombotic

Table 1 Randomised trials of heparin or oral anticoagulants in acute stroke

Study Author/trial name	Number of patients	Start of treatment within (hrs) of stroke onset	CT scan before trial entry (%)	Scheduled duration of treatment (days)	Scheduled duration of clinical follow up (months/days)	Active treatment	Control treatment	Route	Dose	Dose interval
Acute presumed ischaemic stroke: completed trials										
<i>Standard Heparin Trials</i>										
Duke ¹⁹	225	48	100	7	12 months	Heparin	P	iv	adjusted ^a	cont inf
CESG ²⁰	45	48	100	10	14 days	Heparin	N	iv	adjusted ^b	cont inf
McCarthy ²¹	305	48	0	14	3 months	Heparin	N	sc	5000U	8 hrs
McCarthy ²²	32	48	0	14	1 month	Heparin	N	sc	5000U	8 hrs
Czechanowski ²³	107	120	0	14	14 days	H-DHE	P	sc	5000U+0.5mg	12 hrs
Duke ²⁴	65	48	81 ^a	7	12 months	Heparin	P	sc	5000U	8 hrs
<i>LMWH Heparin Trials</i>										
Turpie ²⁵	75	168	100	14	3 months	LMWH	P	sc	750aXaU	12 hrs
Prins ²⁶	60	72	100	14	14 days	LMWH	P	sc	2500aXaU	12 hrs
Sandset ²⁷	103	72	100	14	1 month	LMWH	P	sc	3000–5500aXaU	24 hrs
Elias ²⁸	30	48	100 ^a	14	14 days	LMWH	N	sc	15,000aXaU	24 hrs
<i>Oral Anticoagulants</i>										
Marshall ²⁹	51	72	0	21	6 months	Phen +24 hrs H	N	o	adjusted ^c	24 hrs
Acute Presumed Ischaemic Stroke: planned/in progress										
TOAST ^d	1300 ^d	24	100	7	3 months	LMWH	P	sc	Adjusted ^e	24 hrs
UK ORG10172	180 ^d	120	100	8–10	12 weeks	LMWH	P	sc	750aXaU	12 hrs
International Stroke Trial ^f	20 000 ^d	48	100 ^h	14	6 months	Heparin	N	sc	1250aXaU	24 hrs
						Heparin	N	sc	5000U	12 hrs
						Heparin+	N	sc	12 500U	12 hrs
						Aspirin	N	o/pr	5000U	12 hrs
						Heparin+	N	sc	300mg	24 hrs
						Aspirin	N	sc	12 500U	12 hrs
Kay	200 ^d	48	100	7	12 months	Aspirin	N	o/pr	300mg	24 hrs
Acute Haemorrhagic Stroke: completed trial						LMWH	P	sc	300mg	24 hrs
Dickman ³⁰	46	4 days	100	6	ns	H	N	sc	7500aXaU	12 hrs
									5000U	8 hrs

H: standard heparin; H-DHE: standard heparin + Dihydroergotamine; LMWH: low molecular weight heparin; Phen: Phenindione; aXaU: anti-factor Xa units; P: placebo; N: No treatment; iv: intravenous; cont inf: continuous infusion; sc: subcutaneous; ns: not stated.

^aAdjusted dose to keep partial thromboplastin time 50–70 seconds

^bAdjusted dose to keep partial thromboplastin ratio 1.5–2.5x pretreatment level.

^cAdjusted dose to keep prothrombin ratio 2–3x control

^dPlanned numbers of patients

^eTreatment of acute stroke trial (TOAST). Adjusted dose therapy

^fThis trial has a 3x2 factorial design

^gPercentage with CT scan within 48 hours of trial entry

^hCT scan not mandatory before randomisation, but should be obtained quickly thereafter if possible.

Table 2 Randomised trials of antiplatelet agents in acute ischaemic stroke

Study Author/trial name	Number of patients	Start of treatment within (hrs) of stroke onset	Scheduled duration of treatment (days)	Scheduled duration of clinical follow up (months/days)	Active treatment	Control treatment	Route	Dose	Dose interval
<i>Completed Trials</i>									
Utsumi ³¹	29	ns	ns	N/A	Ticl	P	o	300mg	ns
Joseph ³²	44	240	ns	N/A	Asp+dip	N	o	± 330mg Asp ± 180mg Dip	ns
Ciuffetti ³³	30	12	21	N/A	Ticl	P	o	250mg	12 hrs
<i>Planned/In Progress</i>									
Britton	300 ^a	ns	ns	ns	Aspirin	P	o	325mg	24 hrs
MAST Italy ^b	1500 ^a	6	10	6 months	Aspirin	N	o/or iv	350mg 100mg	24 hrs
International Stroke Trial National Study, China	20 000	See table 1 for details			Str	iv	1.5MU	One dose only	
	20 000 ^d	48	100	35 days	Aspirin	P	o	325mg	24 hrs

Ticl: Ticlopidine; Dip: Dipyridamole; P: Placebo; N: No treatment; o: oral; iv: intravenous; ns: not stated; N/A: not available; Str: Streptokinase

^aPlanned number of patients

^bPatients are allocated to one of four treatment groups in a 2 × 2 factorial design: placebo, aspirin, streptokinase, and aspirin and streptokinase.

treatment ranged from six to 21 days (mean 12 days). The scheduled period of clinical follow up varied from 1–12 months. Six trials routinely performed CT in all patients before randomisation,^{19 20 25–28} one trial performed CT in most patients,²⁴ three trials performed CT in almost none^{21–23} and one trial was undertaken before CT scanning was introduced.²⁹

a) Effect of heparin on deep venous thrombosis

Two trials did not report data on deep venous thrombosis (DVT).^{19 29} Nine trials, all comparing heparin with placebo or open control, systematically sought to determine the effect of treatment on the occurrence of (DVT) detected by systematic I¹²⁵ fibrinogen scanning or

systematic radiographic contrast venography; eight trials were in patients with ischaemic stroke^{21–28} and one was in patients with haemorrhagic stroke.³⁰ In trials of heparin in ischaemic and haemorrhagic stroke, treatment was associated with a highly significant 79% (SD 8) 2p < 0.00001 reduction in the odds of confirmed DVT in the scheduled treatment period (fig 1).

There was no clear evidence that reductions in confirmed DVT were importantly different between: patients with ischaemic stroke and patients with haemorrhagic stroke; patients with adjusted dose intravenous heparin, low dose subcutaneous heparin or LMW heparin; when DVT was detected by venography and I¹²⁵ fibrinogen scanning (fig 1).

Figure 1 Apparent effect on deep venous thrombosis detected by systematic I^{125} fibrinogen scanning or by systematic venography in trials among patients with ischaemic stroke and one trial in haemorrhagic stroke. The stratified ratio of the odds of an event in the treatment group to that in the control group it is plotted for each trial (black square: area proportional to the amount of information contributed); with its 99% confidence interval (horizontal line). The presence of a black square to the left of the solid vertical line suggests benefit (but this benefit is significant at the level of $2p < 0.01$) only if the entire confidence interval is to the left of the solid vertical line. An overview of all of the trial results (and its 95% confidence limit) is represented by a black diamond beside which is the reduction in the overall incidence in those trials.

Figure 2 Apparent effect on pulmonary embolism. For explanation of symbols and conventions, see legend to fig 1.

Figure 3 Apparent effect on mortality of heparin or warfarin on trials in patients with ischaemic or haemorrhagic stroke. For explanation of symbols and conventions, see legend to fig 1.

b) Effect of heparin on pulmonary embolism

The data on pulmonary embolism (fatal or non-fatal) are given in fig 2. The 58% reduction in pulmonary embolism, though substantial, is not conventionally significant.

c) Effect of heparin or warfarin on death from all causes by the end of study period

Allocation to treatment with any type of anticoagulant therapy in acute ischaemic or haemorrhagic stroke was associated with a non-significant 14% reduction in the odds of death (SD 15, $2p > 0.1$) from all causes by the end of scheduled follow up period¹⁹⁻³⁰ (fig 3). Because of the relatively few deaths, the 95% confidence intervals were wide and included the possibilities that treatment could be associated with a reduction of perhaps one third or with an increase of about one sixth in the odds

of death. Analysis of the heparin trials in acute ischaemic stroke¹⁹⁻²⁸ showed that treatment was associated with a non-significant 18% reduction (SD 16, $2p > 0.1$) in the odds of death by the end of scheduled follow up period (fig 3). The trial in haemorrhagic stroke³⁰ showed a non-significant 31% increase in the odds of death (SD 84, $2p > 0.1$, NS). These results are shown in fig 3. Mortality results were not significantly different in trials where heparin was given to patients with CT-confirmed cerebral infarction and in trials where heparin was given without CT. However, the data were wholly inadequate to determine the effect on mortality of a policy of "heparinization without CT".

A separate analysis of the numbers of deaths from all causes during the scheduled treatment period was reported in eight trials.^{19 20 23 25-29}

Figure 4 Apparent effect of heparin on haemorrhagic transformation of the infarct. For explanation of symbols and conventions, see legend to fig 1.

The numbers of deaths were small; 28/333 allocated control vs 32/363 allocated anti-coagulants. There was a non-significant 10% increase in the odds of death (SD 29, 2p > 0.1, NS) with a very wide confidence interval; consistent with either evidence of a beneficial effect, a harmful effect or no effect at all. Data on cause specific mortality in each treatment group, on recurrent stroke and on disability at six months were not available from the published reports or from the trialists' personal records.

d) Effect of heparin on haemorrhagic transformation of the cerebral infarct

A relatively unbiased assessment of the effect of antithrombotic treatment on the occurrence of haemorrhagic transformation of the infarct (HTI) would come from studies where all surviving patients have a CT scan at the end of the scheduled treatment period, irrespective of any clinical deterioration. The least biased assessment would be of the effect of treatment on the composite event "HTI detected on routine CT scanning at the end of the scheduled treatment period or fatal haemorrhagic stroke during the scheduled treatment period" (no trials had this as a prespecified analysis). Five trials^{19 20 25-27} reported data on HTI detected by CT scan: CT scan was performed because of clinical deterioration and the results of these trials showed that treatment was associated with a 198% excess of HTI (SD 165%, 2p > 0.1, NS) (fig 4). Analysis restricted to "haemorrhagic transformation on routine scans performed at the end of the scheduled treatment period or fatal haemorrhagic stroke"

showed that treatment was associated with a 12% increase in HTI (SD 56, 2p > 0.1, NS) (fig 4).

Trials of antiplatelet agents in acute stroke

Of the six trials of antiplatelet therapy in patients with acute ischaemic stroke, the three largest have not been completed. Two of the completed trials did not systematically record data on clinical events^{31 32} (they studied laboratory coagulation factors only) and the third was too small to be informative.³³

Discussion

Current use of antithrombotic drugs in acute stroke

There is considerable variation in the use of antithrombotic drugs (aspirin or heparin) to treat patients with acute ischaemic stroke.³⁴ In a survey of the current treatment of patients with ischaemic stroke, 83% of US neurologists reported that they had used heparin in such patients over the previous year.³⁴ However, only 6% of the physicians felt that, based on their understanding of the literature, heparin had clearly been shown to be effective in the treatment of patients with acute cerebral infarction. Furthermore, 59% thought it had not been shown to be effective.³⁴ Despite these apparently conflicting opinions, approximately 22% of patients with ischaemic stroke seen by USA neurologists in the survey were given heparin within the first 24 hours of stroke.³⁴ In the Stroke Data Bank,^{35 36} a multicentre project which prospectively collected data on patients with stroke admitted to academic hospitals in the USA, 538 of 1273 patients

Deep vein thrombosis, pulmonary embolism, death and haemorrhagic transformation of the infarct in randomised trials of heparin in acute ischaemic stroke.

Proportional reduction :	81 % (8)	58 % (46)	18 % (16)	-12% (57)
2p :	<0.00001	NS	NS	NS
Events prevented per 1000 :	369 (96)	34 (86)	35 (142)	-7 (64)

Figure 5 Absolute rates of DVT, pulmonary embolism, death and haemorrhagic transformation of the infarct in patients with presumed or confirmed cerebral infarction. Figures in brackets are standard deviations.

with cerebral infarction (42%) were given heparin during their admission to hospital. Thus in the USA, heparin is used, but without a clear consensus on whether it is effective or not; clinical practice in other western countries is probably similar. Similar variations in the use of aspirin in the acute treatment of stroke have been found in a survey of physicians in Yorkshire, UK (Bamford J, personal communication).

Heparin in acute myocardial infarction

As the underlying pathophysiology of acute cerebral infarction and acute myocardial infarction have many features in common, it is useful to review the effects of heparin in acute myocardial infarction. A formal review of twenty four trials of heparin in patients with an acute myocardial infarction by MacMahon *et al*³⁷ provided clear evidence of benefit; allocation to heparin was associated with a significant 10% reduction in mortality. In these trials, heparin significantly reduced reinfarction by one fifth and stroke by one half. The heparin regimes tested in about 90% of patients involved doses of 20 000 IU or more daily, given subcutaneously in about half the patients. An overview of two large trials published after McMahon's review (ISIS-3 and GISSI-2) showed that, when subcutaneous heparin is given to patients with acute myocardial infarction who have already received aspirin and a fibrinolytic drug, the benefits of adding heparin may be rather more modest.³⁸

Heparin or warfarin in acute stroke; are they effective?

There has been no formal overview of the studies in acute stroke which we have identi-

fied. Previous reviews have either been informal, with no statistical estimation of typical treatment effects,³⁹⁻⁴¹ or did not use accepted statistical methods⁴² or pooled data from trials of acute treatment with trials of long-term secondary prevention.⁴² In the present overview in patients with acute, presumed ischaemic stroke, allocation to heparin therapy was associated with a highly significant 81% reduction in the odds of DVT. Proportional reductions in DVT were similar with standard heparin, LMW heparin, fixed low-dose regimes and adjusted full-dose regimes. Reductions were similar in patients with acute CT confirmed ischaemic stroke, with presumed ischaemic stroke and with acute haemorrhagic stroke. Heparin had similar effects on DVT in stroke patients as in patients experiencing different types of surgery¹³ and in patients with acute MI.³⁷ In the present overview, the reductions in the absolute risk of DVT were substantial: heparin therapy reduced DVT from 57% among controls to 15% among treated patients. There were insufficient events in the present overview to determine whether the reduction in DVT would lead to a reduction in pulmonary embolism (PE) in stroke patients. However, the observed 58% reduction in PE with heparin prophylaxis for stroke patients was similar to the results of heparin prophylaxis in surgical patients (47% reduction in PE)¹³ and in patients with acute MI (54% reduction in PE).³⁷ The reduction in non-fatal pulmonary embolism with heparin (5.7% reduced to 2.3%) would suggest that routine heparin thromboprophylaxis for patients with acute stroke might avoid three or four hundred DVTs and perhaps 30-40 pulmonary emboli for every thousand patients treated (fig 5). Should therefore all patients with ischaemic (or, indeed, haemorrhagic) stroke now be given heparin routinely to prevent DVT (and probably pulmonary embolism)? Our conclusion is that they should not because of lack of good data on safety.

Is heparin safe in acute stroke?

There is considerable uncertainty about the effect of therapy on the risk of death; therapy was associated with an 18% reduction in the odds of death (equivalent to the avoidance of perhaps 20 to 40 deaths per 1000 patients treated), but the upper 95% confidence interval was compatible with heparin leading to an increase in the odds of death by one sixth. Thus the present data cannot exclude the possibility that routine heparin therapy might cause an excess of perhaps 40 deaths for every 1000 patients treated. The second reason is that the data were wholly inadequate to assess the effect of heparin on the risk of disabling or fatal haemorrhagic transformation of cerebral infarction.

Heparin dosage

There is also uncertainty about the optimum dose of heparin. Whilst low dose subcutaneous heparin is effective in the prevention of venous thromboembolism,¹³ higher dose subcutaneous heparin regimes, such as 12 500 units 12 hourly, are more effective in the prevention of

thrombi in the arterial circulation, as assessed by the effects on left ventricular thrombus formation in acute myocardial infarction.^{9,10} Inhibition of formation or propagation of thrombi in cerebral arteries holds the promise of preventing stroke progression, and possibly even reducing cerebral infarct size, with a reduction in the subsequent neurological impairment and disability. However, several studies have suggested a higher risk of bleeding complications with the higher dose heparin regimes.^{10,11} A study by Turpie directly compared 12 500 units of heparin subcutaneously twice a day with 5000 units subcutaneously in patients with acute myocardial infarction,⁹ the risk of serious bleeding in the two treatment groups was very similar (1/112 for high dose heparin, 1/109 for low dose heparin). Whilst the observed effect (a 3% reduction in serious bleeds) was not conventionally significant, confidence intervals were very wide and included the possibility that the higher dose was associated with a 15-fold excess of serious bleeds. These data are wholly inadequate to assess any excess bleeding risk associated with the higher heparin dose. In acute ischaemic stroke, when haemorrhagic transformation or frank intracerebral bleeding can often be fatal or disabling, a randomised trial is clearly needed, not just to determine whether heparin is effective, but also to determine the relative safety and efficacy of the two doses: the balance of risks and benefits may be quite different for different doses.

Antiplatelet therapy in acute ischaemic stroke

If a policy of routine early aspirin therapy was shown to be equally effective and safe in the treatment of acute cerebral infarction as it is in the treatment of acute myocardial infarction,⁴ such a policy might lead to the avoidance of perhaps 20 to 40 deaths for every thousand acute ischaemic stroke patients treated. Widespread use of immediate aspirin therapy for patients with acute ischaemic stroke in the USA and the European Community might therefore avoid several thousand early deaths from stroke each year; perhaps 300 000 deaths over the next decade. If aspirin were to be used on this scale, it would need to be supported by particularly reliable evidence of safety and efficacy from large trials. No such trials exist. Whilst heparin is promising, aspirin is equally, or perhaps even more promising as an anti-thrombotic regime, as it is even cheaper and simpler to administer than fixed-dose subcutaneous heparin.

Design considerations for trials capable of confirming or refuting the effects of antithrombotic therapy in acute ischaemic stroke suggested by present review

Firstly, the trial should be large: ISIS-2 was able to provide particularly clear evidence on the efficacy and safety of two widely practicable treatments for acute myocardial infarction because of its size: 1820 deaths occurred in the randomised 17 187 patients.⁴ The results were statistically reliable and allowed the analysis of clinically important subgroups, thus it was

possible to determine whether or not treatment was effective, but also for whom treatment was most likely to be effective. For example, stratified analyses clearly demonstrated that increasing delay in the start of fibrinolytic therapy was associated with progressive reduction in efficacy. The strength of evidence provided by the trial persuaded many clinicians to change their clinical practice and so both aspirin and streptokinase are now part of the routine care of patients with acute MI.^{4,3} The use of a 2 × 2 factorial design allowed each agent (aspirin and streptokinase) to be compared separately, and in combination, against control with the same sample size that would be required to compare one agent against control; the factorial design is statistically efficient and allows "two questions to be answered for the price of one". The trial was extremely simple in design, involving clinicians in little extra work, and thus enabled busy clinicians in district general hospitals to collaborate in the trial. The treatment was tested on a scale appropriate to its future use (ie in millions of patients with acute myocardial infarction worldwide). Similar, large, simple trials of aspirin and subcutaneous heparin which recruit the number of patients appropriate to the likely scale of their future use (millions of stroke patients worldwide) are now needed. In this context, trials which enroll a few tens of thousands of patients with acute ischaemic stroke seem appropriate. For example, a study which recruited just 20 000 patients with acute ischaemic stroke (that is, about half the size of ISIS-3), in which two week mortality was 12% in patients allocated control and 10% in patients allocated heparin could provide reliable evidence on the mortality effects: if an 18% (SD4) reduction in the odds of death were observed, it would be highly statistically significant and the 95% confidence intervals would be fairly precise (11–25% reduction). Perhaps more importantly, reliable analyses of medically important subgroups would also be possible (for example, whether benefit was substantially different in: patients started on treatment within six hours of onset, compared with those started later, in patients with cerebral infarction due to major cerebral vessel occlusion, compared with small vessel lacunar strokes, in patients aged over 75 compared with younger patients). Such analyses would give useful guidance to clinicians on whether treatment is particularly beneficial (or particularly hazardous) in certain categories of patient.

Trials in acute ischaemic stroke must also measure outcome in terms of survival free of severe disability (as in the Italian haemodilution trial⁴⁴) to ensure that treatment does not increase the proportion of patients surviving in a disabled state. No data on survival free of severe disability were available for the present review. Several trials conforming to these requirements are now planned or in progress (tables 1 and 2).

Conclusion

For patients with acute ischaemic stroke there

is therefore uncertainty about the balance of risks (disabling or fatal haemorrhagic transformation of cerebral infarcts and other bleeds) and potential benefits (reductions in cerebral infarct size, reduction in DVT and pulmonary embolism, all contributing to reduced early mortality and reduced disability in long-term survivors) from early antithrombotic therapy with either heparin or aspirin. On present evidence therefore a policy of routine antithrombotic therapy in the acute phase of stroke cannot be justified until the results of current large trials are available.

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The International Stroke Trial (co-principal investigators Dr Peter Sandercock and Professor Charles Warlow) will begin in early 1993. Anyone who would like to collaborate in the trial should write to Dr Peter Sandercock, Neurosciences Trials Unit, Western General Hospital, Edinburgh EH4 2XU, UK (telephone UK(44)-(0)31-343-6639, Fax UK(44)-(0)31-332-5150).

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