thrombosis. It is surely in younger subjects, where the confounding presence of other risk factors is less likely, that the significance of the finding of APA is likely to be revealed. In a UK survey of results of screening for APA, 109 subjects with detectable APA have been registered in an uncontrolled setting. An outstanding feature of this group is the relatively high incidence of miscarriage (n = 18, mean age 32 years) with thrombotic cerebrovascular events. Muir, Alwan, and Squire will no doubt be aware of the large, multicentre, case-control study performed in the UK, the Anti-Phospholipid Antibodies in Stroke Study Group (APASS); the authors concluded that the results provide the strongest evidence to date that antiphospholip antibodies are an independent risk factor for stroke. Although accepting that there have been few, rigorously designed, epidemiological studies, Kittner and Gorlick have concluded that the stroke risk associated with antiphospholipid antibodies may be substantial, especially in young adults. Evidence is also accumulating for an extremely high recurrence rate of thrombosis in APA-positive subjects, the work of Rosove and Brewer,16 quoted by Muir, Alwan, and Squire, being in agreement with this. To reiterate I believe that the data of Alwan by appropriately validated laboratory methods, where persistence of the abnormality is demonstrated, and when consideration is given to the clinical situation, especially the presence of other evidence of primary antiphospholipid syndrome, such as history of recurrent miscarriage or thrombocytopaenia and the absence of other risk factors, may be of clinical significance.

This is no doubt that, as I stated, prospective studies are required. Against the background of current knowledge, however, clinicians are likely to prescribe aspirin or warfarin in APA-positive subjects with occlusive cerebrovascular events in an attempt to reduce the perceived risk of further thrombosis. I agree, and stated, that the use of immunosuppressive therapy is generally inappropriate.

The nihilistic approach to this area adopted by Muir, Alwan, and Squire will not, I fear, help in the further understanding of the significance of APA in thrombotic disease.

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4 McNeil HP, Simpson RJ, Chesterton CN, Krilis SA. Anti-phospholipid antibodies are directed against complex phosphatidylserine, which includes a lipid binding inhibitor of coagulation: B-glycoprotein I (apolipoprotein H). Blood 1990;76:874-8.

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

The primary goal of these studies1 was to assess the efficacy and safety of antithrombotic drugs for prevention of deep venous thrombosis (DVT). We therefore disagree with the authors, who extrapolated major conclusions on the effect of antithrombotic drugs on a secondary endpoint such as death. In addition, the incidence of pulmonary embolism in this study population probably did not reflect reality because, in the trial setting, the method of diagnosing DVT allowed very early detection and subsequent aggressive treatment.1 This most probably resulted in a reduced incidence of pulmonary embolism, diagnosed on the basis of clinical suspicion and death, compared with the routine, clinical situation.

Furthermore it is unclear why the authors concluded that "whilst heparin is promising, aspirin is equally, or perhaps even more promising as an antithrombotic regime" because, of the six trials of antiplatelet therapy described, the three largest have not been completed, two did not provide data on clinical events, and the third was too small to be informative.

We would also like to correct some misconceptions about Org 10172 (Orgaran).

Firstly, it is a low molecular weight heparin not a low molecular weight heparin. It contains no heparin or heparin derivatives.

Secondly, in table 1 the following citations to Orgaran are incorrect. (1) It should not be included under low molecular weight heparin trials. (2) The study published by Turpie17 is an Orgaran trial. (3) TOAST is a continuing Orgaran trial. The administration route is intravenous and the drug is administered for seven days by continuous infusion. (4) U.K Orgaran17 is the research code for the heparinoid marketed as Orgaran.

Thirdly, as Orgaran is superior to heparin for DVT prophylaxis in patients with stroke, it is unfair to compare with the former and the low molecular weight heparin.4 Indeed because of their different haemostatic activities it is confusing to combine under "All trials" the effects of these three types of anticoagulant.

Finally, Sandercroock et al emphasise in their abstract the difference in haemorrhagic transformation between DVT and ICH. 7/102 and 8/106 as a "non-significant 12% increase"! Surely, such a conclusion is totally unjustified in a scientific journal.

If such overviews are to have any value, then the authors should apply the same standards and then draw general conclusions about the effect of fruit. Had James Lind done the same he would not have found a cure for scurvy.


Sandercock et al reply: We feel that Magnani and Ryus have missed the point of our overview. Although eight of the 11 trials included in our paper were primarily designed to assess the effect of early anticoagulant therapy on deep venous thrombosis (DVT), we felt that any assessment of safety must include an analysis of the effect of treatment on deaths and other haemorrhagic transformation of cerebral infarction, as these are not "secondary endpoints" of trivial importance, but major events. Deaths and haemorrhagic transformation are of course fortunate events and individual trials lacked sufficient power to provide reliable evidence on whether or not their occurrence was influenced by the use of anticoagulants. Turpie et al. in their meta-analysis using all the available data, however, still did not provide clear answers to the following important questions. (1) Does early anticoagulant treatment reduce (or increase) morality? (2) Does routine anticoagulant therapy increase the risk of haemorrhagic transformation moderately, substantially (or not at all)?

We accept Drs Magnani and Ryus' comments on the nomenclature of the low molecular weight heparinoid (Orgaran). We agree that Turpie's relatively small study suggested that Orgaran reduced the risk of DVT in patients without low-dose heparin.17 In this study, however, four patients (8.9%) in the Orgaran group and two patients (4.8%) in the standard heparin group developed haemorrhagic transformation of cerebral infarction (odds ratio 1.95: 95% confidence interval 0.34 to 11.3) and this observed excess of haemorrhagic transformation of cerebral infarction with Orgaran was compared with low-dose heparin.17 This is consistent with the hypothesis that Orgaran is indeed a more potent antithrombotic agent. Only nine patients in each group died (9/45 Orgaran versus 9/42 heparin: odds ratio 0.92, 95% CI 0.3 to 2.6). Thus, although benefit for DVT may be greater with Orgaran compared with low-dose heparin, the data on safety are insufficient to exclude a modest risk of haemorrhagic transformations or death, or both, with Orgaran. As the data are so limited, we feel it is premature (taking important events such as death and haemorrhage into account) to conclude that, overall, in patients with...
stroke, Orgaran is superior to low-dose heparin.

Our main conclusion, that the available randomised trials included in our overview were not designed to determine whether or not antithrombotic therapy with aspirin, heparin, or other agents are safe and effective when used in patients with acute stroke, is unaltered and will remain so until the large trials in progress (IST, TOAST, National Study of Stroke in China, MAST-I) are completed.

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Mast trials

The study by Morris et al1 on recruitment for acute stroke treatment trials of patients with stroke admitted to hospital illustrates, not treatment eligibility, should these treatments be proven to work, but simply how an artificially restrictive selection process can hinder trial recruitment.

In their study, the two trials compared had very different exclusion criteria, not dictated simply by the standard contra-indications to the treatments being tested, and are addressing very different questions. In the International Stroke Trial (IST) all types of acute ischaemic stroke are eligible up to 48 hours after onset unless severely disabled or there is a clear contraindication to aspirin or heparin, such as active duodenal ulcer. The aim of the IST is to answer the simple question, Do aspirin or heparin, or both improve outcome after acute ischaemic stroke? The trial was designed to include as heterogeneous a group of patients with acute stroke as possible, so that in future, physicians would know accurately the risks and benefits of aspirin and heparin treatment when treating almost any such patient.

In contrast, the Multicentre Acute Stroke Trial (MAST), to which Morris et al referred, a very restricted question is being asked: “Does streptokinase improve outcome after major middle cerebral artery (MCA) territory ischaemic stroke if started within six hours?” Consequently the result of this trial will only apply to a very restricted group of patients with acute stroke—those with major MCA occlusions reaching hospital in time to be examined, investigated and treatment started within six hours. In other words, the trial design pres-supposes that streptokinase will not work after six hours, or in small cortical, or lacunar, or posterior circulation strokes. It will not yield any information on whether aspirin should be used as well as streptokinase, or avoided. These presuppositions are foolish, especially as we already have the example of the large myocardial infarction trials in determining thrombolysis and aspirin beyond six hours from symptom onset, and in a very heterogeneous group of patients with acute myocardial infarction, it was possible to demonstrate a true window to treatment (12 hours), the effect of age (benefit at all ages) and that thrombolysis and aspirin together work better than either individually.2

No wonder all the patients in the study by Morris et al were excluded from their streptokinase trial: 50% presented after six hours; 23% had a previous cerebrovascular accident with residual cognitive deficit; 15-5% had a lacunar infarct; 5-5% had posterior circulation ischaemia; 22-5% had other serious systemic illness (nature not specified). In fact only 32 (haemorrhage on CT), two (tumour on CT), one (streptokinase in the past year), seven (warfarin treatment), two (pregnant), 13 (bleeding tendency or DI), nine (transient ischaemic attack), 12 (not clinical stroke) had true contraindications to streptokinase and most of these were potentially-ineligible for the IST for the same reason.

Who are we clinicians to decide, on the basis of no evidence whatever, that patients with a previous cerebrovascular accident, or who reach hospital after six hours (most patients with stroke in the United Kingdom) or who have a lacunar or mild cortical infarct, etc, are unlikely to benefit from a particular acute stroke treatment, never mind thrombolysis? If treatments are not tested in a practical manner in a representative group of patients, then the trial result will never be applicable to the generality of patients who suffer an acute ischaemic stroke, and important benefits may be missed.

It is important to understand that the MAST trial described by Morris et al is not the same as the Multicentre Acute Stroke Trial—Italy (MAST-I). MAST-I is the largest randomised controlled trial of thrombolysis in acute ischaemic stroke that has gone so far, with more than 440 patients randomised (most in Italy but some in the United Kingdom) and strong encouragement from its Data Monitoring Committee not only as a recruitment effort to expand the trial and enhance recruitment. MAST-I is testing streptokinase, aspirin, both or neither (like the Italian Group Studying Streptokinase in myocardial infarction (GISSI) and ISIS-2)1 in all types and severities of acute ischaemic stroke. It has a six-hour time window to treatment which is likely to be extended in the near future. At the end of MAST-I, a physician faced with a patient with stroke will have useful information on the risks and benefits of streptokinase and aspirin, together and separately, applicable to that individual patient.

Clinical trials should be designed to answer practical questions on the risks and benefits of treatment for as many patients as possible, especially for conditions as common as acute stroke. Let us not make the mistake of equating trial eligibility with treatment eligibility, nor make assumptions about when promising, but large-scale work1 is likely to work. The lessons from the acute myocardial infarction trials of thrombolytic and antithrombotic drugs should not be ignored. Until a treatment is found that works, acute ischaemic stroke treatment trials should proceed in the most practical and feasible manner possible, by addressing wide entry criteria and avoiding presuppositions about the effects of treatment.

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Dr Lees et al reply:

We thank Dr Wardlaw, who is the United Kingdom representative of MAST-I, for her letter. Despite her criticism of the cautious entry criteria for the international version of MAST, more patients have been randomised to MAST than to MAST-I in the United Kingdom.

We agree that stroke trials should adopt wide entry criteria without prejudging the results. We also believe, however, in restricting exposure to potentially dangerous treatments to patients in whom the risk/benefit ratio justifies intervention. We are not prepared to disregard evidence regarding treatment from experimental studies, large clinical studies of thrombolysis after acute myocardial infarction and pilot studies after stroke. The selection of a homogeneous group with good prior disability is aimed at maximising the chance of a statistically meaningful result.

Experimental evidence suggests that the therapeutic window for successful neuro-protection through reperfusion is under six hours.1 Although the ISIS-3 study reported intracerebral haemorrhage in under 1% of patients treated with thrombolysis after myocardial infarction, the incidence of fatal intracranial haematoma in pilot studies of thrombolysis after stroke has been up to 10%.2 Haemorrhage was less common in patients treated within 90 minutes of stroke onset.3 Outcomes after MAST-I are variable, but generally much better after lacunar or small cortical infarcts than after large MCA infarction. Inclusion of patients with ineligibility after outcome is possible by ad hoc disabling, or a high probability of good outcome due to minor stroke, would confound assessment of outcome.

We consider that it is responsible to await evidence that thrombolysis is of benefit under optimal conditions before progressing to milder forms of stroke, treated late. This is not prejudice; it is caution. Other treatments that have been shown to improve outcome may be tested in wider groups of patients: in our Acute Stroke Unit at the Western Infirmary we give 10 patients at random