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

The primary goal of these studies 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.

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 heparinoid, 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 Torpie 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) UK Org 10172 is the research code for the heparinoid marketed as Orgaran.

Thirdly, as Orgaran is superior to heparin for DVT prophylaxis in the patient with stroke, it is unfair to compare with heparin 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, Sandercock et al emphasise in their abstract the difference in haemorrhagic transformation and the results of 7/10 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 need to apply more care 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.


4 McNiel HP, Simpson RJ, Chesterman CN, Kritis SA. Anti-phospholipid antibodies are directed against complexes that include a lipid binding inhibitor of coagula-
5 Bevers EM, Galli M, Barbui T, Comurarius P, Zoccoli P. RFA: Lupus anticoagulant IgG's (LA) are not directed to phospholipids, but to a complex of lipid-bound prothrom-
7 Greaves M. Clinical associations and prognostic significance of antibodies to phos-
8 Antiphospholipid Antibodies in Stroke Study Group (APASS); inclusion of anticalci-

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stroke, Orgaran is superior to low-dose heparin.

Our main conclusion, that the available randomised trials included in our overview were insufficient 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 al.1 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 have 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 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 occlusion reaching hospital in time to be examined, investigated and treatment started within six hours. In other words, the trial design presupposes 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 draw that 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, then, that 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 clinical 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 (strepokinase in the past year), seven (warfarin treatment), two (pregnancy), 13 (bleeding tendency or DII1), nine (transient ischaemic attack), 12 (not clinical stroke) had true contraindication to streptokinase and most of these were potentially-ineligible for the IST for the same reasons.

Who are we clinicians to decide, on the basis of no evidence however,1 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 to date, with more than 440 patients randomised (most in Italy but some in the United Kingdom) and strong encourage-
ment from its Data Monitoring Committee not only to aspirin but also streptokinase or heparin to enhance recruitment. MAST-I is testing streptokinase, aspirin, both or neither (like the Italian Group Studying Streptokinase in myocardial infarction (GISSI) and ISIS-2)3 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 after 6 hours 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 such as acute stroke. Let us not make the mistake of equating trial eligibility with treatment eligibility, nor make assumptions about when promising, but larger trials34 are 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 adopting wide entry criteria and avoiding presupposi-
tions about the effects of treatment.

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1 Morris AD, Grosset DG, Squire IB, Lees KR,

2 ISIS-2 Collaborative Group: Randomised trial of intravenous streptokinase, oral aspirin, both or neither among 17187 cases of acute myocardial infarction. Lancet 1988;ii:349-60.


Dr Les 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 severe 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 haematomas 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. Outcome after stroke is variable, but generally much better after lacunar or small cortical infarcts than after large MCA infarction. Inclusion of patients with ineligibility to outcome possible by adoption of disability, or a high probability of good out-
come 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 treat-
maments that have a possible safety profile may be tested in wider groups of patients; in our Acute Stroke Unit at the Western Infirmary we give 10 patients at random