

stroke, Orgaran is superior to low-dose heparin.

Our main conclusion, that the available randomised trials included in our overview were wholly inadequate 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 contraindications 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, in 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 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 which, by testing 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 establish the true time window to treatment (12 hours), the effect of age (benefit at all ages) and that thrombolysis and aspirin together work better than either individually.^{2,3}

No wonder 95.5% of 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 (streptokinase in the past year), seven (warfarin treatment), two (?pregnant), 13 (bleeding tendency or DU), 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 reasons.

Who are we clinicians to decide, on the basis of no evidence whatsoever,⁴ 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 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 to continue, but also to expand 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)^{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 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 ischaemic stroke. Let us not make the mistake of equating trial eligibility with treatment eligibility, nor make assumptions about when promising, but largely untested, treatments^{4,5} 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 sensible manner possible by adopting 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 of patients without prior disability is aimed at maximising the chance of a statistically meaningful result.

Experimental evidence suggests that the therapeutic window for successful neuroprotection 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%.^{2,3} Haemorrhage was less common in patients treated within 90 minutes of stroke onset.⁴ Outcome after stroke is variable, but generally much better after lacunar or small cortical infarcts than after large MCA infarction. Inclusion of patients with inevitably bad outcome due to preexisting disability, 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 a better 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

other neuroprotective drugs, for every one given thrombolysis.

We agree with the need to discover if aspirin, heparin, or both, improve outcome after stroke and we have placed suitable patients in the pilot and main phases of IST at random. In practice, however, it is only patients in whom the benefits of aspirin/heparin are uncertain who are eligible for this trial. These are treatments for secondary prevention and for the avoidance of deep venous thrombosis, etc, not acute interventions. It has been predicted that 20 000 patients may be required for a clear result with this trial design; factorial randomisation within MAST would be an unnecessary complication to the design, and many clinicians are unhappy about withholding aspirin from a patient who recovers from a proven ischaemic stroke.

It is counterproductive to argue over the detail of the various trials that are in progress. Meta-analysis has already been agreed among the coordinators of the major randomised thrombolytic stroke trials. We should concentrate our efforts on increasing the proportion of stroke patients who are adequately assessed, investigated by CT scan and offered rational treatment.

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NOTICE

Guillain-Barré syndrome: the evolution of therapy.

In 1980, a new era in Guillain-Barré syndrome (GBS) research began. Before that year, most studies of GBS had been single-centre studies of various clinical, immunological, pathologic, or epidemiological aspects of the disease. Descriptions of the response to treatment also fell into that category, and no clearly proven treatments were available. Following a series of presentations at the annual meeting of the American Academy of Neurology on the use of plasma exchange in GBS, a distinguished group of senior investigators organised a multicentre, two-country study of plasma exchange in GBS.¹ At the same time, a four-centre Swedish study² and a

multicentre French study³ began. All three reached the same conclusion as regards the efficacy of plasma exchange in GBS—outcome improved more with plasma exchange than with no treatment.²⁻⁴ In the meantime, the Dutch GBS Study Group compared plasma exchange and human immune globulin, determining that the two treatments were at least equally efficacious and possibly that human immune globulin was even better than plasma exchange.⁵ A large multicentre European trial has suggested that a five-day course of intravenous methylprednisolone, when used alone or added to plasma exchange in the treatment of GBS, does not produce significant benefit.⁶

Where do we stand now? Both plasma exchange and human immune globulin have been proven to be effective in GBS, and one should be used in those individuals with clear diagnoses who are unable to walk. Both treatments require expertise in delivering them, due to known side effects. Despite these findings, many questions still remain. Should treatment be given to those with GBS still able to walk? How can clinically significant relapses, which occur following both treatments best be handled? Moreover, neither is perfect: a significant number of patients apparently do not respond at all, most still have prolonged disability, and some are left with significant permanent deficits.

These issues lead to the most important question: are there other treatments that might be better than plasma exchange and human immune globulin? In order to provide at least one answer to this question, an international group of investigators has met and designed a three-armed trial comparing plasma exchange, human immune globulin, and plasma exchange followed by human immune globulin in patients with GBS who are less than 14 days from onset of neuropathic symptoms. This trial is designed to confirm the results of the Dutch study showing equal efficacy of plasma exchange and human immune globulin and to discover whether plasma exchange followed by human immune globulin is even more effective. The study is currently underway in 41 centres in 10 countries, and plans to enroll 390 patients. The costs are being partly underwritten by Sandoz AG, and all subjects randomized to human immune globulin or plasma exchange plus human immune globulin receive Sandoglobulin at no cost. We are actively seeking patients for this study and would welcome referrals. The study centres and principal investigators are listed below. Another answer to the same question is being sought by the Dutch GBS Study Group, whose preliminary studies using historical controls suggest that human immune globulin plus steroids is better than human immune globulin alone for the treatment of GBS (F van der Meché, personal communication). A randomised controlled trial is planned. The results of both these trials will be eagerly awaited.

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