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 unselected manner. An outstanding feature is a cohort of young women ($n = 18$, mean age 32 years) with thrombotic cerebrovascular events.⁷ Muir, Alwan, and Squire will no doubt be aware of the large, multicentre, case-control study performed by the Antiphospholipid Antibodies in Stroke Study Group (APASS)⁸; the authors concluded that the results "provide the strongest evidence to date that anticardiolipin antibodies are an independent risk factor for stroke". Although accepting that there have been few, rigorously designed, epidemiological studies, Kittner and Gorelick⁹ 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 thrombotic events in APA-positive subjects, the work of Rosove and Brewer,¹⁰ quoted by Muir, Alwan, and Squire, being in agreement with this. To reiterate I believe that the finding of APA by appropriate and 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 thrombocytopenia and the absence of other risk factors, may be of clinical significance.

There 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 rather 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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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.² 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.²

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 Turpie³ 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 10172⁴ 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 classify it 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 between 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 must not mix apples with lemons 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.

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Sandercock *et al* reply:

We feel that Magnani and Ruys have missed the point of our overview.¹ Although eight of the 11 trials included 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 on haemorrhagic transformation of cerebral infarction,² as these are not "secondary endpoints" of trivial importance, but major events. Deaths and haemorrhagic transformations are—fortunately—rare, so individual trials lacked sufficient power to provide reliable evidence on whether or not their occurrence was influenced by the use of anticoagulants. Even an 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) mortality? (2) Does routine anticoagulant therapy increase the risk of haemorrhagic transformation moderately, substantially (or not at all)?

We accept Drs Magnani and Ruys' 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, when compared with low dose heparin.³ 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, compared with low-dose heparin, 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 moderate excess 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 haemorrhagic transformation into account) to conclude that, overall, in patients with