thrombosis. It is surely in younger subjects, where the confounding presence of other risk factors is less likely, that the signif-
ance 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. 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),7 the authors concluded that the results "provide the strongest evidence to date that antiphos-
philip antibodies are an independent risk factor for stroke". Although accepting that there have been few, rigorously designed, epidemiological studies, Kittner and Gorlicher have concluded that the stroke risk associated with antiphospholipid anti-
bodies may be substantial, especially in young adults. Evidence is also accumulating for an extremely high recurrence rate of thrombo-
opulmonary embolism in APA-positive subjects, the work of Rosove and Brewer, quoted by Muir, Alwan, and Squire, being in agreement with this. To reiterate I believe that the results of APASS by appropriately validated laboratory methods, where persist-
ence 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.

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 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.

M GREAVES
Department of Haematology, Royal Hallamshire Hospital, Glossop Road, Sheffield S10 2JF, UK

4. McNeil HP, Simpson RJ, Chesterman CN, Krilis SA. Anti-phospholipid antibodies are directed against a complex antigen that includes a lipid binding inhibitor of coagula-
5. Bevers EM, Galli M, Barbui T, Comufuris P, Zoroni N, RRFA. Lupus anticoagulant IgG (LA) are not directed to phospholipids, but to a complex of lipid-bound prothrom-
6. Lindsey N, Henderson FI, Malia R, Milford-
7. Greaves M. Clinical associations and prognostic significance of antibodies to phospho-
8. Antiphospholipid Antibodies in Stroke Study Group (APASS). Thrombosis: clinical effects of anti-

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 pul-
monary embolism was observed in this study population and we think that the results did not reflect reality because, in the trial setting, the method of diagnosing DVT allowed very early detection and sub-
sequent aggressive treatment. This most probably resulted in a reduced incidence of pulmonary embolism, diagnosed on the basis of clinical suspicion and death, com-
pared with the routine, clinical situation.

Furthermore it is unclear why the authors concluded that "whilst heparin is promis-
ing, aspirin is equally, or perhaps even more promising as an antithrombotic regime" because, of the six trials of antiplatelet ther-
apy 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 misconception 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 cita-
tions to Orgaran are incorrect. (1) It should not be included under low molecular weight heparin trials. (2) The study published by Turpie" is an Orgaran trial. (3) TOAST is a continuing Orgaran trial. The administra-
tion 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 patients with stroke, it is unfair to compare it with heparin and the low molecular weight heparin. Indeed because of their different haemosta-
tic 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 haemor-
rhagic tendency between groups 7/102 and 8/106 as a "non-significant 12% increase"! Surely, such a conclusion is totally unjustifi-
ed in a scientific journal.

If such overviews are to have any value, then the authors could have applied the same criteria. We conclude that, overall, in patients with


SandercocK et al reply:

We feel that Magnani and Ruys have missed the point of our overview. Although eight of the 11 trials included in our review were specifically designed to assess the effect of early anti-
coagulant therapy on deep venous thrombosis (DVT), we felt that any assess-
ment 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 end-
points" of trivial importance, but major events. Deaths and haemorrhagic transforma-
tions are—fortunately and unfortunately—infrequent in clinical trials; lack of data does not mean that all available data, however, still did not provide clear answers to the following important questions: (1) Does early anti-
coagulant 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 compared with aspirin. Larger clini-
cal trials lacked sufficient power to provide reliable evidence on whether or not their occurrence was influenced by the use of anticoagulants. Finally, their analysis using all the available data, however, still did not provide clear answers to the following important questions: (1) Does early anti-
coagulant 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 compared with aspirin. Larger clini-
cal trials lacked sufficient power to provide reliable evidence on whether or not their occurrence was influenced by the use of anticoagulants. Finally, their analysis using all the available data, however, still did not provide clear answers to the following important questions: (1) Does early anti-
coagulant treatment reduce (or increase) mortality? (2) Does routine anticoagulant therapy increase the risk of haemorrhagic transformation moderately, substantially (or not at all)?