of symptomatic intracranial or major extracranial bleeding when low-dose unfractionated heparin was added to aspirin for 14 days in IST was six cases per 1000; so that a net beneficial effect might, on balance, be anticipated. We therefore concur with Bath and colleagues that the combination of low-dose low-molecular-weight heparin (which may have a more favourable risk-benefit profile than unfractionated heparin) and aspirin still warrants assessment. Given that the risk of deep vein thrombosis is highly correlated to the degree of paralysis, such a study could focus on patients with more severe stroke, with the duration of treatment guided by ambulatory status, and, ideally, a rigorous assessment for clinical venous thromboembolism as events are frequently overlooked or misdiagnosed in this population.

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Authors’ reply

Sir—Angel Chamorro suggests that low-molecular-weight heparins have only theoretical advantages over unfractionated heparin. However, in trials of the prevention and treatment of venous thromboembolism, low-molecular-weight heparins are at least as good as, if not better than, unfractionated heparin for safety and efficacy. Even in acute stroke, low-molecular-weight heparins were better at preventing deep vein thrombosis in a meta-analysis.1

Second, Chamorro suggests that unfractionated heparin has properties, such as being anti-inflammatory, that low-molecular-weight heparins do not possess. However, low-molecular-weight heparins are anti-inflammatory, for example by lessening neutrophil adhesion, chemotaxis, migration, and production of nitric oxide.

Third, he implies that only unfractionated heparin has data suggesting beneficial effects on lesion size in experimental stroke; similar data also exist for low-molecular-weight heparins. We therefore agree that low-molecular-weight and unfractionated heparins differ, but disagree on which is better. Taking the above information together with the mildly negative results for unfractionated heparin in the International Stroke Trial1 was the rationale for running TAIST.

Our concern about future trials of anticoagulation is what questions are left? Most design variables have been covered in the existing trials: which drug, dose, recruitment time-window, comparator, and stroke subtype.1 Apart from IST, no trial has had the size to assess whether anticoagulation can improve functional outcome by a small amount rather than the 10% or more assumed in TAIST and earlier studies; for example, a sample size of around 14 000 would be needed to detect a small absolute reduction in death or dependency of 2% from a control rate of 50% (assuming significance 5% and power 90%). Additionally, to test a neuroprotection mechanism for unfractionated heparin would require recruitment within 3–6 h, a challenging project for thousands of patients.

An alternative outcome that could be studied in a future trial is venous thromboembolism, as we, and now J Kelly and colleagues, point out. They report preliminary data on the rate of venous thromboembolism after stroke in the modern era and assess use of magnetic resonance thrombus-imaging. Their rates for deep vein thrombosis and pulmonary embolism are, unsurprisingly, much higher than those of symptomatic events in the aspirin group of TAIST. A pragmatic trial comparing combined heparin and aspirin with aspirin alone would need to study symptomatic, not total, venous thromboembolism in patients with leg paresis, with a sample size of at least 2500 assuming a rate of 2·6% in the aspirin group and a relative reduction of 50% with heparin. Since heparin-related symptomatic intracranial haemorrhage is largely a feature of treatment within 24 h of stroke onset,1 delay of randomisation until after this period would be worthwhile.

The need for such a trial is debated. Nevertheless, the combined nursing, monitoring, and drug costs (as relevant) of administering heparin are high and a cost-benefit analysis done within a trial might find against anticoagulation, which suggests that the trial should be done to remove this doubt. In the meantime, the use of heparin should be restricted, in most patients, to the confines of a clinical trial.1

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Antimalarial agents in pregnancy

Sir—Gil Klinger and colleagues (Sept 8, p 813)1 report the favourable risk to benefit ratio of hydroxychloroquine (4-aminquinoline) treatment during pregnancy to control symptoms of rheumatic diseases. The use of hydroxychloroquine during pregnancy, in animal studies, causes retinopathy in fetuses.1 No major birth defects have been reported in human beings for low doses (once weekly) given to prevent malaria during pregnancy.2

Discontinuation of the drug might not prevent side-effects in fetuses because of its long half-life, and can precipitate a relapse or induce pregnancy failure.3 For these reasons we generally continue treatment with hydroxychloroquine during pregnancy in patients with rheumatic diseases. Our experience of use of antimalarial drugs in these circumstances may provide additional support to the conclusions reached by Klinger and colleagues.

We followed up 35 infants born to 34 women who received hydroxychloroquine during pregnancy for systemic lupus erythematosus (19), scleroderma (three), undifferentiated connective tissue disease (two), mixed connective tissue disease (four),
under strict clinical observation.5

breastfeeding, our experience, in deliveries is probably related to relatively high incidence of preterm confirm the safety of hydroxychloro-

1 month. No baby had ocular haemorrhages at birth that resolved at

Schepens' indirect ophthalmoscopic and retinal vessels were assessed by tropicamide and 1% phenylephrine, size, and reaction to light. After assessment of ocular motility, papillary inspection of anterior segment, done at birth and again at 1 year in assessed infants showed a normal circumference measurements and development tests to assess gross and fine motility were done in 16 babies at ages 6, and 12 months.1 All the assessed infants showed a normal growth and development ratio.

An ophthalmological assessment was done at birth and again at 1 year in 16 infants, including those who were breastfed. Eye examination consisted of inspection of anterior segment, assessment of ocular motility, papillary size, and reaction to light. After midriasis was achieved with 1% tropicamide and 1% phenylephrine, refraction and optic-nerve head, retina, and retinal vessels were assessed by Schepens6 indirect ophthalmoscopic method. Two infants showed retinal haemorrhages at birth that resolved at 1 month. No baby had ocular symptoms or complications because of maternal treatment.

Our preliminary data seem to confirm the safety of hydroxychloroquine treatment during pregnancy. The relatively high incidence of preterm deliveries is probably related to maternal disease. Since there are no absolute contraindications to breastfeeding, our experience, in accordance with previous reports, suggest the feasibility of breast-feeding, under strict clinical observation.1

Sir—Iqbal Malik and co-workers (Sept 22, p 971)5 investigate the association between soluble adhesion molecules and incident coronary heart disease (CHD) events. Unfortunately, the study, the meta-analysis, and the interpretation are seriously flawed. The data presented in the meta-analysis, which show the odds ratios for soluble intercellular adhesion molecule 1 (sICAM-1) in the top 33% compared with the bottom third, is incorrect. Hwang and colleagues7 and Ridker and colleagues3 used quartile analyses, which showed that only the upper quartile of sICAM-1 was associated with an increased odds ratio for incidence of CHD. Indeed, why would Malik and colleagues do a prespecified tertile analysis when both the initial reports showed that only the upper quartile was associated with an increased risk for CHD events? The value for the upper tertile of sICAM-1 was substantially higher than the cut-off points of the upper quartile of the two original reports, and these differences may have been due to issues in the methods, such as measurement in serum stored for 20 years at –20°C compared with plasma stored at –80°C. Despite the above concerns, increased concentrations of sICAM-1 in the upper tertile were associated with an odds ratio of 1–51 (95% CI 1–10–2–08) after adjusting for all traditional risk factors. The observation that this relation was reduced after adjustment for socioeconomic status may be statistically important but is clinically irrelevant. The measurements of socioeconomic status used by Malik and colleagues never been nor ever will be used by any national guidelines to identify individuals at risk for CHD.

The investigators have shown that measurement of sICAM-1 in 20-year-old serum was still helpful in identifying individuals with a 50% greater risk for myocardial infarction after adjustment for all risk factors currently recommended for risk stratification. Thus, they have confirmed the hypothesis that novel blood tests such as measuring sICAM-1 may have a clinical role in primary prevention in identifying individuals who are at a high enough risk to justify potentially expensive pharmacological therapy for risk reduction.

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Sir—Iqbal Malik and colleagues’ essential conclusions1 are that measurement of sICAM-1, soluble vascular adhesion cell molecule-1 (sVCAM-1), soluble E-selectin, and soluble P-selectin in serum are unlikely to add much predictive information in addition to that provided by conventional risk factors such as age, von Willebrand factor, and plasma fibro-nectin.

However, by contrast we have noted that raised plasma soluble P-selectin predicts adverse outcome in coronary atherosclerosis.2 We believe that one likely reason for this discrepancy is that we, in common with almost all other workers, used citrated plasma, whereas Malik and colleagues measure soluble P-selectin in serum.

Until recently, the source of soluble P selectin was in doubt. Many groups have supported our original hypothesis3 that the great proportion, if not all, of soluble P-selectin arises from platelets, not the endothelium. Evidence for this view comes from diverse sources. For example, endothelial cell stimulant DDAVP induces raised concentrations of von Willebrand factor but not soluble P-selectin in vivo.4 Furthermore, we have been unable to detect P-selectin in human umbilical vein endothelial cell lysates or tissue culture supernatants, whereas it is easy to detect in platelet lysates (unpublished data). However, the most pertinent data arise from measurement of soluble P-selectin in paired serum or plasma. Increased levels in serum