Antiphospholipid syndrome (APS) is the association of antiphospholipid antibodies with thrombosis and/or pregnancy morbidity and mortality [1]. APS, unlike the hereditary thrombophilias, which tends to only affect the venous system can and does affect any vascular bed. Thrombosis can occur in arteries, veins and microvasculature or even multiple sites simultaneously. The latter is known as catastrophic APS and carries a high mortality [2].

Retrospective studies in the 1990s suggested that APS should be managed by high-intensity (INR target 3.0–4.0) oral anticoagulation, but the more recent prospective studies of Crowther et al. [3] and WAPS study published in this journal strongly suggest only an INR of 2.0–3.0 is required. While we applaud these studies, we remain guarded about their implications for the management of patients with arterial APS. We have a major concern that the majority of patients included in these two studies had venous not arterial thrombosis. Furthermore, neither achieved the expected size: both excluded large numbers of patients because they had already had recurrent events on oral anticoagulation; and in the Crowther’s study patients with recent stroke were excluded so that in the final study 76% of the patients had previous venous thrombosis only; also in Crowther’s study review of the high-intensity arm showed that the patients were below the therapeutic range for 43% of the time.

The literature and our clinical practice suggest that APS affecting the arterial system is reflective of a potent antibody that requires more intensive anticoagulation, with a high recurrence rate. Cerebrovascular disease in APS carries high mortality and morbidity, with important and often disabling sequelae. Thus, preventing recurring thrombotic stroke is one of the main therapeutic goals in such patients [4]. Anecdotally, the initiation of adequate anticoagulant therapy coincides with rapid, often dramatic, amelioration of symptoms. It is not uncommon for patients with cerebral APS to ‘know’ precisely when their INR has fallen – the headaches, dysarthria, memory disturbance and neurological features predictably returning when the INR drops, for example, below 3.0 [5].

While future investigation must better define homogeneous subsets of patients with APS, current secondary prophylaxis of thrombosis in these patients must be tailored according to individual estimated risks of recurrence, risk of hemorrhage and severity of potential recurrent events. Our current management of patients with APS is shown in Fig. 1. We agree with the prospective studies that patients with APS and previous venous thromboembolism should have a target INR of 2.0–3.0. However, if patients have recurrent events or arterial events at presentation, we set the target INR at 3.0–4.0.

Published data show that the frequency and severity of bleeding complications are not high in patients with APS treated with oral anticoagulation, even at target INR >3.0 [3,6], maybe due in part to the lower age of this population as compared with, for example, patients with chronic atrial fibrillation. Certainly, in APS patients with previous arterial events, the dangers of thrombosis and stroke far outweigh the risk of anticoagulant-induced bleeding. The traditional fear of cerebral hemorrhage has almost certainly resulted in the undertreatment of many patients with cerebral APS.

There are a few caveats. Firstly, in the patients who have concurrent systemic lupus erythematosus, changing polypharmacy is common, and so care needs to be taken at the time of changing medication. We recommend that all our patients
should have an INR check within 3 days of changing a drug that may affect warfarin control. Secondly, many patients with APS have moderate thrombocytopenia. It should be emphasized that thrombocytopenia does not protect the patient against further thromboses. Our policy is not to change the INR target unless the platelet count falls below $50 \times 10^9 \text{L}^{-1}$.

Lastly, many women with cerebral APS are fertile and the teratogenicity of vitamin K antagonists is well established in pregnancy. We counsel these patients preconceptually about switching to low molecular weight heparin (LMWH) and aspirin when a pregnancy test is positive (before 6 weeks of pregnancy), although our experience has been that there is a definite risk of recurrent cerebral events in pregnancy with LMWH and they may need to return to vitamin K antagonists later in pregnancy [7].

In conclusion, we agree that APS patients with previous venous thrombotic events should have moderate-intensity (INR 2.0–3.0) anticoagulation. However, those with previous arterial events merit high intensity (INR 3.0–4.0) until there is evidence to the contrary. The sadness we feel on writing this article is that despite the new millennium, we have only one type of anticoagulant – the vitamin K antagonists – licensed for long-term use. Many of our patients regard attending anticoagulant clinics with trepidation. Like many other practising physicians, we await with great passion, the appearance of new oral anticoagulants that do not require monitoring and has a wider therapeutic window without an overlapping bleeding risk. Finally, we would urge that a separate prospective study of two intensities of oral anticoagulation is required in those with APS and previous arterial events.

References
5 Letellier E, Hughes GRV. “Listen to the patient” – anticoagulation is critical in the antiphospholipid (Hughes) syndrome. *J Rheumatol* 2003; 30: 897.