Long term anticoagulant treatment in the antiphospholipid syndrome

The interesting paper recently published by Derksen et al.1 in the Annals1 on the need for a long term anticoagulant treatment in patients with antiphospholipid antibodies and venous thrombosis prompts several observations.

1. Anticoagulants cannot be used at that time, where the risk of thrombosis is obviously high, so pregnancy-associated thrombosis should probably be excluded from analysis. This also applies to carrying out by Rosove et al., which included three subsequent thromboses occurring during pregnancy or in the immediate postpartum period. To make their conclusion more valid, could the authors specify if pregnancy-associated events were initial or recurrent thrombosis?

2. Oral anticoagulants were not used in all of the 19 patients at the time of 1/3 venous thromboembolic episodes. It is not clear if the pill was stopped after the initial episode, as recommended by most authors.2 If it was not, the risk of recurrent thrombosis was overestimated in patients still receiving the pill.

3. For clinicians, the problem is to avoid recurrent thrombotic events, irrespective of their site, venous or arterial. In the study by Derksen et al., myocardial infarction in two patients despite 'adequate' anticoagulation, which demonstrates that the vascular protection provided by anticoagulants is not absolute.

4. During the past 8 years, growing evidence has emerged favouring the long or very long term use of anticoagulants in patients with antiphospholipid syndrome. A major problem is to determine the duration of this treatment, since it is recognised as carrying a serious risk especially at an international normalised ratio of three or more.3,4 It is assumed that anticoagulants are required as long as antiphospholipid antibodies are present.5 To test the validity of this recommendation, could Derksen et al. mention the sequential determinations of antiphospholipid antibodies in their patients, with and without relapse?

At present, the prevention of recurrent thrombotic events in the antiphospholipid syndrome is still a matter of debate. Two retrospective studies favour the use of oral anticoagulants6,7 Conversely, antiplatelet agents have been said to be effective in patients with focal cerebral ischaemia and antiphospholipid antibodies.8 Prompt relapses may occur after a "pill" or aspirin withdrawal. A clear and definitive answer, if any, requires prospective controlled trials such as the recently undertaken French cooperative study comparing aspirin to warfarin (AWAPS).9

Authors' Reply: We read with great interest the letter from Drs Piette and Wechsler concerning our recent paper in the Annals on anticoagulant treatment in patients with antiphospholipid antibodies and venous thrombosis.1 We wish to make the following comments:

1) In our series four thrombotic episodes were pregnancy related. These were initial thrombosis in two patients (numbers 5 and 12) and a recurrent thrombosis in patient number 6 and 10. In 10 patients low-dose oestrogen containing pills were taken at the time of the first episode. These pills were stopped in all but one (number 17). Our data are insufficient to answer the question whether patients with antiphospholipid antibodies are at more risk for thrombosis in the presence of other risk factors (such as oestrogen-containing pills, pregnancy, immobilisation, cigarette smoking or hypercholesterolaemia). However, our observation that antiphospholipid antibodies were absent in 17/34 venous thromboses and in at least one of the episodes in 10/12 patients with recurrent thrombosis indicates that antiphospholipid antibodies are not a risk factor. The generalisation to the universal need for a 'second hit' for thrombosis to occur.

2) Myocardial infarction that occurred in two patients during treatment with oral anticoagulants suggested that antiplatelet therapy does not prevent arterial thrombosis in all patients. In both patients we added low-dose aspirin to treatment with oral anticoagulants.

3) Our patients were re-tested at least every six months and all but one remained positive. The exception was patient number 4. He became negative for antiphospholipid antibodies six months before myocardial infarction and is still negative two years later. This suggests that disappearance of antiphospholipid antibodies (defined as lupus anticoagulants and anticardiolipin antibodies) does not imply disappearance of the risk for thrombosis, and agrees with data showing that antibodies causing positive tests for antiphospholipid antibodies may differ from those causing thrombosis.9

We agree that the optimal therapy for patients with the antiphospholipid syndrome still has to be established. All clinical data that have been previously reported may suffer from selection bias. We need data from prospective trials on unselected patients and adequate control groups. Such trials should stratify for any other underlying disease, type and titre of antiphospholipid antibodies, other risk factors for thrombosis, and type of initial event. Due to the large number of patients required and the expected rate of (re-)thrombosis they should be multicentre and have many years of follow-up. Such treatment trials are complex, expensive and in the end probably easy to combat. Furthermore, in each trial only a limited number of the many possible strategies for antithrombotic treatment in patients with the antiphospholipid syndrome can be tested.

We very much applaud the initiatives taken by our French colleagues collaborating in AWAPS and hope that their study will result in a safe and effective therapy of patients with antiphospholipid syndrome. In the meantime, we advise long-term treatment with oral anticoagulants in all patients with antiphospholipid antibodies and venous thrombosis because these patients have a very high risk of recurrent venous thrombosis, and oral anticoagulants in contrast to acetylsalicylic acid, effectively prevent the recurrence of venous thrombosis.

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Evaluating new physical treatments

I am grateful for the opportunity to respond to your Leader article Evaluating new physical treatments.1

Let me start by describing myself as one of the author's electrotherapy "cynics", being extremely sceptical of claims made for these modalities and rarely use them. In this context, a controversial area of research, results are required from a series of well designed, controlled trials, such as the excellent study by Heusler et al.,2 so that a measured judgment on the efficacy of the treatment can be taken. Pre-empting these studies and making inferences from results of a single study would be unscientific. Moreover, electrotherapy modalities are usually performed as an adjunctive therapy with an aim to increase strength and range of movement, and here their production of "analgesia through a powerful placebo effect"3 may be extremely useful.

It is somewhat strange that the author readily advocates massage by manipulators and nurses, even though massage is poorly evaluated. Furthermore, citation of the trial performed by a chiropractic was superior to physiotherapy in the treatment of low back pain,4 demonstrates the danger of attaching too great a significance to results of isolated trials. Critical assessment of the chiropractic study's design, execution and data analysis suggests it was seriously flawed, and its exaggerated and misleading conclusions have been widely challenged.4,5 It therefore seems unwise for the author to suggest NHS...
purchasers might consider "buying" inadequately evaluated therapies, on the same basis that physiotherapy was derided for accepting electrotherapy by "... giving credence to unscientific hype".1 Caveat emptor.

I fully endorse the author's call for more research into the efficacy of physiotherapy, and already many of the obstacles that impeded physiotherapy research are being addressed. In a recent letter in the British Journal of Rheumatology I explained that through the creation of university departments, the expertise and career structure exists to enable us to advance research in physiotherapy. We are now successfully competing for funding to critically evaluate our treatments, so that we can deliver the most effective treatment to our patients with the optimal use of resources.

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AUTHOR'S REPLY: I am delighted that Dr Hurley agrees with me that much physiotherapy requires proper evaluation. This does not, however, imply repeating experiments indefinitely until the answer to researchers' wishes has been obtained. One well conducted piece of research may well be all that is necessary to answer a question, and at the very least it requires an equally scientific reply rather than prejudice hidden behind words such as "measured judgments".

Had Dr Hurley read my editorial carefully he would have realised that I nowhere advocated the use of massage. He must accept, though, that massage and other complementary therapies are already high on the list of purchasers' wishes. A recent survey by the National Association of Health Authorities and Trusts showed that 65% of District Health Authorities and Trusts favoured purchasing such therapies as part of their NHS provision.1 Probably many of them act only by a placebo effect, but few are likely to be purchased purely to advocate, as Dr Hurley does for physiotherapy, the use of complex pieces of electrical equipment such as lasers as placebos.

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Distinction between initiation and progression of the osteoarthritis process

I read with positive interest but negative feelings the article by Cumming et al.1 Their conclusion that arthritis of the hip should be included in the list of factors that protect against hip fracture, is in line with our previous observation on the inverse relationship between osteoarthritis and osteoporosis, and in particular with the recent epidemiological evidence revealed in the MEDOS Study.4 The MEDOS study is also based on self-reported osteoarthritis in a large series of controls and hip fracture cases. In both studies the inverse relationship between osteoarthritis and osteoporosis is independent of body weight, which supports the hypothesis that there is a direct causal relationship between osteoporosis and osteoarthritis.

A disturbing element in the paper by Cumming and Klíneberg is the confusing terminology used throughout the paper. The term 'arthritis' is used interchangeably with 'osteoarthritis'. We do not agree that this interchangeable terminology should be used in an international rheumatology journal. The term arthritis is so bound to many other forms of arthritis, in particular rheumatoid arthritis, gout and pelvispondylitis, that this will inevitably lead to confusion in later citations. Although the term osteoarthritis is also not the best one, this term is now well accepted as an alternative to osteoarthritis. According to our opinion and to many others, such as, Radin, clear distinction should be made between initiation of the osteoarthritis process and progression. That secondary inflammation might be involved in the progression of osteoarthrosis is well accepted, but whether inflammation is the primary trigger of osteoarthritis is doubtful. A number of studies on the initiation of the osteoarthritis process support the possibility that the increased bone density reduces the mechanical ability of subchondral bone to deform under impact loads with resulting damage to the articular cartilage and osteoarthritis.4

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AUTHORS' REPLY: We regret that the use of the terms 'arthritis' and 'osteoarthritis' appear to have been used interchangeably in our recent paper. We can assure Drs Dequeker and Westhovens that we gave careful thought to the use of these two terms. We tried to use the term 'osteoartrosis' whenever possible (particularly in the Introduction and Discussion sections of our paper). However, our data were based on self-reported joint symptoms; we did not ask subjects about osteoarthritis specifically. Thus we tried to use the term 'arthritis' whenever we were referring to the data from our study (particularly in the Results section and in the tables). We thought it would be misleading to readers if, for example, we wrote about 'self-reported osteoarthritis of the hip'.
Evaluating new physical treatments.

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