What is the optimum duration of anticoagulation for the management of patients with idiopathic deep venous thrombosis and pulmonary embolism?

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The optimum duration of anticoagulation following idiopathic deep venous thrombosis and pulmonary embolism is controversial. The JRCPE is delighted to publish a debate written by three international experts. Dr Shetty and Dr Campbell recommend that three months' anticoagulation is sufficient, while Professor Hyers recommends anticoagulation for longer than three months.

KEYWORDS Anticoagulant therapy, idiopathic venous thromboembolism

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Three months of anticoagulation is sufficient

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Anticoagulant therapy is highly effective in preventing recurrent events in patients with venous thrombo-embolism (VTE). For patients with 'secondary' or 'provoked' VTE affecting isolated calf veins or upper limb, there is general agreement that six weeks to three months of anticoagulation is adequate. Those with 'provoked' iliofemoral deep vein thrombosis (DVT) or pulmonary embolism (PE) are usually treated for three or six months. The duration of treatment in patients with idiopathic VTE, however, is controversial. Some experts recommend long-term anticoagulation after the first episode of VTE, whereas others, including ourselves, advocate only three months of anticoagulation.[1,2] Although a recurrent event such as a massive PE can be fatal, haemorrhagic complications of anticoagulation can be equally dangerous. Therefore, a decision to continue anticoagulant therapy beyond three months should not be taken lightly. We believe that long-term treatment should not be considered universally for all patients with idiopathic VTE. For our contribution to this debate we have reviewed the literature and presented the evidence supporting our view.

THE HYPOTHESIS

Proponents of long-term anticoagulant therapy are assuming that every person who has had an idiopathic DVT or PE will have an ongoing thrombophilic tendency and therefore is highly likely to develop recurrent events once anticoagulation is discontinued. This is unlikely to be the case as the aetiology of idiopathic VTE is likely to be diverse and the risk for recurrence is also likely to be variable. Indiscriminate long-term anticoagulant treatment in every such person is clearly not a logical option.

RISK OF RECURRENT EVENTS

We randomised 369 patients with proximal DVT or PE (42% idiopathic) for three months and 380 patients (47% idiopathic) for six months of anticoagulant therapy. Fatal and non-fatal failures of resolution, extension or recurrence during and after three or six months of anticoagulation were similar between the two groups, at 8% each. Major haemorrhages during treatment occurred in 2% of the six months group and in none of the patients randomised to the three months group.[3]

A prospective cohort study has reported that the risk of any fatal PE and definite or probable fatal PE after discontinuation of anticoagulation is 0.49 events (95% confidence interval, CI, 0.36–0.64 events) per 100 person-years and 0.19 events (CI 0.12–0.30 events) per 100 person-years, respectively, and that the case-fatality rate for recurrence is 9.0% (CI 6.8–11.8%) for any fatal PE and 3.8% (CI 2.4–5.9%) for definite or probable fatal PE in patients with a first episode of symptomatic VTE who received anticoagulant therapy for a mean duration

of six months (range 3–39 months). In this study, following the first episode of symptomatic VTE, the annual risk of definite or probable fatal PE was 0.15 (CI 0.08–0.26) per 100 person-years after the first year. Only 12/1,138 patients with idiopathic VTE had definite or probable fatal PE after 4,844 person-years' follow-up.[4]

Another study randomised patients with a first episode of idiopathic proximal deep venous thrombosis who had completed three months of oral anticoagulant therapy to either discontinue oral anticoagulants or to continue for nine additional months. Both groups were followed up for an average of over 37 months. Primary intention-to-treat analysis showed that 21/134 (15.7%) patients assigned to continued oral anticoagulant therapy had a recurrent VTE, as compared with 21/133 (15.8%) patients who discontinued anticoagulant therapy (relative risk: 0.99; 95% CI, 0.57–1.73). The incidence of recurrence after the discontinuation of treatment was 5.1% per patient-year in patients in the three months group and 5.0% per patient-year in the extended treatment group. None of the recurrent VTEs was fatal. Non-fatal major bleeding occurred in 1.5% of patients in the three months group and in 3% of patients in the extended period group.[5] There were no fatalities due to bleeding in the extended treatment group. Thus, prolonged anti-coagulation did not reduce the risk of recurrent VTE but did increase the risk of major bleeding.

RISK OF BLEEDING

One of the major considerations in prescribing anticoagulants is the risk of bleeding associated with their use. A meta-analysis, aimed at estimating the clinical impact of anticoagulant-related bleeding, included 33 randomised controlled trials and prospective cohort studies which investigated patients with VTE, and reported major bleeding and death as primary study outcomes. The patients received 4,374 patient-years of oral anticoagulant therapy (target international normalised ratio, INR, 2.0–3.0) for at least three months. The meta-analysis found that around one in seven bleeding episodes with oral anticoagulant therapy is fatal or intracranial.[6] The overall case fatality was around 13.4%, with a major bleeding and intracranial bleeding rate of 1.15 per 100 patient-years. These risks persisted beyond three months of anticoagulation. The case fatality rate of major bleeding was 9.1% and the rate of intracranial bleeding was 0.65 per 100 patient-years for anticoagu-lation beyond three months.[6]

It has been estimated that 80 recurrent PEs and two to ten deaths per 1,000 patients can be prevented after one year by continuing anticoagulation beyond six months. However, there will be 20 to 60 major bleeds and two to six deaths with this approach.[7] Thus, we can not recommend giving long-term anticoagulation treatment to all idiopathic VTE patients as benefits do not clearly outweigh risks.

With any long-term drug therapy, the most important issue is one of compliance. This is particularly important when the drug concerned can cause potentially life-threatening adverse effects if taken in a higher than recommended dose. Many of the patients with VTE are older adults who are more likely to have haemorrhagic complications.[8] Poor compliance may be an important issue with them. They are more sensitive to the effect of warfarin[9] and are likely to be on multiple drugs which may interact with warfarin. They are also more likely to bleed with anticoagulant therapy because of their underlying medical and surgical problems.

COST AND INCONVENIENCE

Taking oral anticoagulant therapy with warfarin and other vitamin K antagonists requires careful monitoring and regular INR checks. Patients living in remote areas may have to travel long distances at regular intervals for these tests. It can be argued that near-patient testing and the use of new oral anticoagulants which do not need routine monitoring can overcome these inconveniences. At present the primary care cost of anticoagulation per patient is estimated to be around £322 per year in the UK.[10] With rational and evidence-based decision-making, this cost can potentially be avoided in a large number of patients with idiopathic VTE.

CONCLUSIONS

When planning the management of any medical condition, the important considerations are the safety and efficacy of the proposed treatment. 'First do no harm' is one of the key ethical principles. Evidence suggests that in patients with idiopathic VTE the risk of recurrent events is relatively low. Any benefit such patients may gain by anticoagulation beyond three months is negated by the risk of serious haemorrhages, which may even be fatal. Therefore, we believe that there is a need to develop methods to identify patients with idiopathic VTE who are at a high risk of developing recurrent events. Some have thrombophilia or ongoing risk factors such as cancer, which makes it easier to decide about long-term anticoagulation.

In patients who do not have such obvious indications, the decision can be more difficult and controversial. Attempts have been made by some studies to identify high-risk patients. A meta-analysis has shown that elevated D-dimer levels measured one month after discontinuation of anticoagulation in patients with idiopathic VTE identifies those who are at higher risk of recurrence.[11] Another study has reported that, after adjustment for clinical risk factors, an elevated D-dimer level (between one and two months) after completion of six months' anticoagulation is significantly associated with an increased risk of unprovoked recurrent thrombosis (hazard ratio 2.0, 95% CI 1.01–3.9). This study suggests a 10% annual risk of recurrence after

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stopping anticoagulant therapy in a male with an unprovoked first episode of VTE and a positive D-dimer.[12] Such a patient may benefit from long-term anticoagulation. On the other hand, a female patient with provoked or unprovoked VTE and a negative D-dimer has around 2% annual risk of recurrence and, therefore, may not benefit from long-term anticoagulation.[12] Further refinements in predicting recurrence will help us to make a rational choice of anticoagulant regime.

We have presented the evidence that the incidence of recurrent VTE is relatively low and the benefits of longer duration of anticoagulant therapy are clearly outweighed by the risk of serious, including fatal, bleeding. Should duration of anticoagulation be 'fixed and evidence-based, or flexible and personalised?' asks one author.[13] We feel that, ideally, it should be both evidence-based and personalised.

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Anticoagulation for idiopathic venous thromboembolism should be given for longer than three months

TM Hyers

Venous thromboembolism (VTE) is usually treated with 5–10 days of a heparin-related product, followed by oral anticoagulation with a vitamin K antagonist.[1] The duration of oral anticoagulation is often tailored to the perceived risk of recurrent VTE. Three months of anticoagulation is recommended for patients with a first VTE and transient or reversible risk factors such as trauma, surgery, immobilisation or oestrogen use. Prolonged or indefinite anticoagulation is recommended for patients with recurrent VTE, cancer or anti-phospholipid antibodies.

A first episode of idiopathic VTE, also known as primary or unprovoked VTE, is associated with a higher rate of recurrent VTE than that associated with provoked VTE (VTE associated with an identified risk factor). This difference in risk (two- to three-fold) is particularly notable when the identified risk factor is reversible or transient. The degree of increased risk with idiopathic

disease is difficult to predict in individual cases, and often remains so even after an exhaustive and expensive search for a risk factor. Because of the increased risk associated with idiopathic VTE, many physicians believe that anticoagulation should be given for longer than three months. This approach immediately raises two questions: How long should anticoagulation be given to these patients? And how do we value the competing risks of recurrent VTE and haemorrhage when giving prolonged anticoagulation? The answer to the first question can be sought in the medical literature. The answer to the second question is ultimately a decision made by informed patients after weighing the competing risks and the personal burden of continuing prolonged anticoagulation.

Clinical trials that have examined the duration of anticoagulation have been admirably summarised in a recent exhaustive review, but the trials provide only

partial answers.[1] In assessing these trials, several cautions are necessary. Many of the trials were not powered to detect small differences in bleeding rates, included not only patients with idiopathic disease but also those with known risk factors, had variable follow-up periods (up to one year) after anticoagulation was stopped and used suboptimal diagnostic criteria for recurrent VTE (the method of diagnosis was not always specified). However, the trials taken together indicate that prolonged anticoagulation does reduce the risk of recurrence after a first idiopathic VTE, albeit with possibly an increased bleeding rate. Shorter durations of treatment did not produce much difference. In comparison to three months of anticoagulation, six months seemed to offer little additional benefit.[2,3]

Twelve months of anticoagulation reduced the risk of recurrence during the period of anticoagulation.[4] However, during extended follow-up after stopping 12 months of therapy, the rate of recurrence seemed to catch up to the rate seen with three months of therapy.[4] Thus, 12 months of anticoagulation may only postpone a seemingly inevitable recurrence.

What about even longer periods of anticoagulation? This anticoagulation regimen has been called prolonged or indefinite, meaning there is no set length of treatment. These studies not only included patients with a first idiopathic VTE but also some patients with recurrent disease and patients with idiopathic disease whose serum D-dimer was elevated one month after stopping an initial course of therapy.[5–8] The three trials with an anticoagulation target international normalised ratio (INR) of 2.5 (range 2.0–3.0) showed a 90% risk reduction with prolonged treatment. The trial with an INR range of 1.5–2.0 showed a 60% risk reduction.[8] The risk of serious bleeding varied between 1–3% yearly, and more recent trials indicate that an annual serious bleeding rate of around 1% can be attained with standard intensity anticoagulation.[8,9] It may be that any duration of treatment of idiopathic VTE only postpones a recurrence. However, the trials hint that recurrence rates of VTE begin to reach a plateau after two years of anticoagulation.[5–8]

The answer to the second question is a value judgement and requires the active participation of the patient. I think the authors of the recent review recognised this fact when they recommended three months of anticoagulation for patients with a first idiopathic event, followed by an evaluation of the risk–benefit ratio of longer-term therapy.[1]

They recommended longer-term therapy for those with low bleeding risk and when good anticoagulant monitoring is available. The authors acknowledge that their recommendation favoured the prevention of recurrent VTE over the burden of long-term anticoagulation. The informed patient must decide what are acceptable risks for both recurrent VTE and bleeding. In my experience, many patients are more concerned with bleeding risk and the burden of therapy than with recurrent disease, particularly after one or two years of treatment. In fact, patients in the studies of indefinite periods of anticoagulation usually stopped treatment after a serious haemorrhage or after deciding that continuing treatment with a vitamin K antagonist was too burdensome.

In my practice, after reviewing the risks and benefits of treatment of a first idiopathic VTE, I recommend at least one year of anticoagulation unless patients are at high bleeding risk or proper anticoagulant monitoring is unavailable. I make it clear that, in my opinion, optimum therapy should be for two years. However, I also stress that the decision must be collaborative and that a patient may stop treatment at any time when the burden of continued therapy is perceived to be too large.

Recently, regimens have been studied that use a flexible duration of anticoagulation that is tied to an objective study of residual thrombus or a laboratory test. Investigators used venous ultrasonography before stopping anticoagulation or serum D-dimer testing one month after stopping anticoagulation in an attempt to identify patients at higher risk of VTE recurrence.[7,10] Patients with positive ultrasound findings or increased D-dimer levels were found to have higher recurrence rates if anticoagulation was stopped. The obvious inference from the studies is that a recommendation should be made for further anticoagulation if the test is positive. This approach looks promising, but these studies had relatively small numbers of patients. Confirmatory studies tailoring duration of therapy based on results of the test are needed before firm recommendations can be made.

The current debate may change in the near future when new oral anticoagulants that require no monitoring become available. Patients may perceive these drugs to be less burdensome than a vitamin K antagonist. However, new oral anticoagulants will be associated with bleeding, and patients and clinicians will still have to balance this risk with that of recurrent VTE.

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