Introduction

After discontinuing anticoagulation a substantial proportion of patients with deep venous thrombosis (DVT) and/or pulmonary embolism (PE) will develop recurrent venous thromboembolic (VTE) events. According to the findings from prospective cohort studies conducted at our Institution\textsuperscript{1,2} and elsewhere\textsuperscript{3-7}, recurrent events are expected to develop in up to 40 per cent of all patients, this figure being considerably higher in patients with unprovoked than in those with provoked VTE, provided that factors accounting for the first episode are transitory.

Risk factors of recurrent thromboembolism

1. Persistent acquired risk factors

After stopping anticoagulation patients with active cancer, especially those with metastatic malignancy and those undergoing chemotherapy,
carry a particularly high risk of recurrent VTE, and so do patients with chronic medical diseases requiring prolonged immobilization. Although there is no conclusive evidence coming from randomized clinical trials, all such patients should be treated with long-term anticoagulation unless they have contraindications. According to the results of recent randomized clinical trials, low molecular weight heparins (LMWH) in full doses for the first month followed by approximately 75 per cent of the initial dosage for another 5 month period has the potential to halve the rate of recurrent events while not increasing the haemorrhagic risk. Conventional oral anticoagulants still represent the treatment of choice in medical conditions other than neoplastic diseases.

Indefinite treatment should also be considered in patients with multiple (especially if unprovoked) VTE episodes, the insertion of a permanent vena caval filter (whenever anticoagulation is not contraindicated) and the antiphospholipid antibody syndrome. Whether these subjects require anticoagulation regimens that are more intense than usual has long been debated. Based on the results of recent randomized studies, the latest international guidelines recommend also for these patients the adoption of conventional regimens.

2. Transient risk factors

Patients whose thrombosis is provoked by a major reversible risk factor, such as surgery or major trauma, have a low risk of recurrence, whereas this risk becomes higher when thrombosis is provoked by a minor reversible risk factor, such as minor leg trauma, estrogen therapy, pregnancy or puerperium, or prolonged air travel.

Accordingly, patients with major transient risk factors, such as major trauma or surgery, should be given 12 wk of anticoagulation. This period can be halved in those patients in whom DVT is confined to the calf vein system. In patients with minor transient risk factors, such as minor trauma, long air travel, hormonal therapy, a longer duration may be considered according to each individual case, after carefully considering the haemorrhagic risk and patients’ preferences.

When a thrombotic episode arises during pregnancy, it should be managed with LMWHs in full doses for at least three months, bearing in mind that the treatment should not be discontinued before the end of pregnancy, and should always be extended to cover the first six weeks after delivery.

3. Unprovoked VTE

After discontinuing anticoagulation, patients with the first episode of unprovoked VTE have a risk of recurrences that approaches 50 per cent of all such patients after 8-10 yr. This figure will not change after prolonging anticoagulation up to 6 or 12 months. Patients presenting with a first episode of unprovoked VTE should be offered at least 3 months of oral anticoagulant therapy, targeting an (INR) between 2.0 and 3.0. The decision as to go on or discontinue anticoagulation after this period should be individually tailored and balanced against the haemorrhagic risk. Indeed, the annual incidence of major bleeding from long-term anticoagulation is 1.5–2.0 per cent, and the ‘case-fatality rate’ of an episode of major bleeding is considerably higher that that of an episode of recurrent VTE.

Whether low-dose warfarin, that is a dose that produces a targeted INR between 1.5 and 2.0, may offer a suitable option for patients requiring longer periods of anticoagulation has long been debated. We believe that conventional warfarin regimen should be regarded as the first choice. However, a low-intensity regimen can be considered in particular situations depending on individual judgment, for example, in patients reputed to be at a higher haemorrhagic risk.

Several post-baseline parameters have the potential to identify subgroups of patients with unprovoked VTE in whom anticoagulation can be safely discontinued. In a few cohort studies, the ultrasound persistence of residual thrombosis after an episode of proximal DVT was found to be an independent risk factor for recurrent thromboembolism. In subsequent randomized clinical trials and systematic reviews of available studies it has been shown that adjusting the duration of anticoagulation according to the persistence of residual thrombosis reduces the risk of recurrent VTE by 40 per cent.

Following the demonstration that a marker of thrombotic tendency (D-dimer) can be helpful in the risk stratification, and thus ultimately therapeutic guidance, of individual patients with DVT, a randomized clinical trial showed that in patients who are left without anticoagulation as a consequence of a negative D-dimer – assessed one month after warfarin discontinuation – the rate of recurrent events is only slightly higher than in patients with positive D-dimer who continue anticoagulation. In addition, repeating D-dimer testing after anticoagulation suspension has the potential to identify a number of individuals in...
whom D-dimer reverts to be positive and are, therefore, candidate to resume anticoagulation in order to prevent VTE recurrences.

Another post-baseline factor potentially associated with an increased risk of recurrent VTE is the early development of post-thrombotic manifestations. In this regard, an example of how useful a few post-baseline parameters can be, alone or in combination with baseline variables, for the identification of patients at low risk of recurrent VTE, has recently been offered by the prospective study by Rodger et al. Indeed, women with unprovoked VTE and none or 1 of a number of parameters (early post-thrombotic manifestations, D-dimer positivity at time of discontinuing anticoagulation, obesity, and age older than 65) were found to exhibit a considerably lower risk of recurrent VTE than the remaining patients.

An interesting prediction model for the development of recurrent VTE has recently been published by a group of Austrian investigators, which enables identification of the recurrence risk based on the combination of two baseline factors (sex and type of clinical presentation) and one post-baseline factor (D-dimer). This observation is interesting, but requires confirmation in settings other than that where the model has been developed.

4. Inherited thrombophilia

While inherited thrombophilia does not increase the risk of recurrent thromboembolism while on warfarin, whether and to which extent carriers of inherited thrombophilia exhibit a higher risk of recurrent VTE after discontinuing anticoagulation is controversial. It is generally accepted, although not conclusively demonstrated, that carriers of antithrombin (AT), protein C and S, carriers of hyperhomocysteinemia, and carriers of increased levels of factor VIII or IX, have a recurrence risk that is higher than that of control subjects.

Whether carriers factor V Leiden or prothrombin G20210A variant - including homozygous carriers and carriers of double heterozygosity have a higher risk of recurrence as well is controversial, as there are data in favour and against this association. Discrepancies among studies may be related to different selection of inception cohort, length of follow up, initial treatment of the acute thrombotic disorder, duration of treatment, and changes in general management of thrombotic patients. As a consequence, whether detection of these abnormalities, which are highly prevalent in western countries, has the potential to identify a subgroup of patients who might benefit from the adoption of individually adjusted prevention strategies following their first thrombotic episode, is virtually unknown. Recent studies suggest that prolonging anticoagulation for one year following the qualifying episode of VTE has the potential to reduce the risk of recurrent events in comparison to conventional 3-month anticoagulation.

According to the results of a controlled, randomized clinical trial, homocysteine lowering by B-vitamin supplementation does not help prevent recurrent venous thrombosis.

5. Other factors

Following the observation that males exhibit a higher recurrence risk than females, a few meta-analyses of several studies confirmed the somewhat unexpected association between male sex and recurrent VTE. Whether this finding is accounted for by sex-specific risk factors at time of first venous thrombosis is controversial.

Patients with a first symptomatic unprovoked DVT are at higher risk of recurrent VTE than patients with a first unprovoked PE. In addition, patients with clinically symptomatic PE have consistently been found to be at a higher risk of recurrent PE than those with DVT alone. These findings have recently been confirmed by a patient-level meta-analysis.

Old age, which has long been regarded as a risk factor of venous thrombosis, has recently been identified as a predictive factor of recurrent VTE. Thus, the common practice of administering old patients lower regimens or shorter periods of anticoagulation because of the fear of haemorrhagic complications should be reconsidered. Likewise, excess body weight was recently found to be a powerful and independent risk factor of recurrent VTE. Obese patients should therefore, be carefully educated, as decrease in body weight is likely to play a key role in reducing the risk of recurrent events.

Finally, it has recently been reported that a number of simple laboratory tests, such as the activated partial thromboplastin time and global coagulation assays measuring thrombin generation can help identify patients at a lower or higher risk of recurrent VTE. These observations show potential, but need confirmation.
Recurrent VTE in the fertile age

Women who had their first episode in fertile age are at a higher risk of experiencing recurrent thromboembolism when they are given hormonal treatment or become pregnant. This risk is particularly high in women in whom the first episode had been triggered by hormonal compounds or had developed during pregnancy[^66-69]. Accordingly, hormonal treatment should be strongly discouraged in women with previous VTE. Whenever hormonal treatment is reputed to be necessary, the contemporary administration of oral anticoagulants should be considered. Postpartum anticoagulation is recommended in all women with previous VTE[^70].

While the systematical adoption of compression elastic stockings is recommended in all women with previous VTE throughout pregnancy, antenatal thromboprophylaxis with LMWH should be offered whenever the previous episode was unprovoked or was pregnancy- or estrogen-related, in carriers of thrombophilia, if there is a family history of thrombosis, if there are additional risk factors (such as obesity), and in women with multiple previous VTE episodes[^70].

New perspectives for the long-term treatment of patients with VTE

Finally, new categories of oral antithrombotic drugs are emerging, which have the potential to simplify the long-term treatment of patients with VTE by obviating the need for periodic laboratory monitoring, while being associated with a favourable benefit-to-risk ratio. They include compounds that inhibit factor Xa, such as rivaroxaban, and compounds that inhibit thrombin, such as dabigatran etexilate. Recently, the results of the Recover[^71] and those of the Einstein[^72] randomized clinical trials, dealing with the initial and long-term treatment of VTE patients with dabigatran etexilate and rivaroxaban, respectively, have been reported. In the former study, the administration of dabigatran etexilate at the dose of 150 mg twice daily for 6 months in patients with acute VTE was found to be as effective as warfarin in patients who had all been treated with heparins or fondaparinux for the initial 7 to 10 days, and was associated with a statistically significant reduction in the incidence of major or clinically relevant bleeding complications[^71]. In the latter, the administration of rivaroxaban from the beginning at the dose of 15 mg twice daily for three weeks followed by 20 mg once daily for 3 to 12 months in patients with acute DVT was found to be at least as effective and safe as conventional enoxaparin-warfarin treatment[^72]. Of interest, rivaroxaban was found to be significantly more effective than comparators for the achievement of the combined end-point recurrent VTE plus major bleeding. In addition, prolonging rivaroxaban at the dose of 20 mg once daily for an additional 6 to 12-month period in patients who had received at least three months of rivaroxaban or warfarin achieved an 82 per cent reduction in the risk of recurrent events over placebo while being associated with less than 1 per cent of major bleeding complications[^72].

References


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