haematologica 2002; 87:1009-1013
http://www.haematologica.org/2002_10/1009.htm

Optimal duration of oral anticoagulant therapy after a first episode of venous thromboembolism: where to go?

The issue of the optimal duration of secondary prophylaxis in patients with a first episode of venous thromboembolism (VTE) is far from being clarified. While oral anticoagulant treatment is effective in reducing the probability of recurrence by 80% or more, it exposes patients to an increased risk of bleeding, which may not be warranted in a significant proportion of them. In addition to a poor quality of laboratory monitoring of oral anticoagulant treatment,[1] the ISCOAT studies have identified age[2] and the presence of cancer[3] as significant risk factors for bleeding, but age and cancer are also both complicated by an increased risk of recurrence.[1-4] On the basis of the pioneering work of Coon and Willis,[5] who assessed the existence of an inverse relationship between the time elapsed from the index event and the risk of VTE recurrence, attention was mainly given to a moderate prolongation of the duration of oral anticoagulant treatment as a way to reduce the rate of recurrence without incurring an unacceptable bleeding risk.[6-10] Meanwhile, information was gained about the differential risk of recurrence of VTE in patients with circumstantial risk factors,[6,11] and in those in whom VTE was associated with cancer[12] or with thrombophilic states.[13,14] It is now clear that the risk of recurrence is lower in patients with associated transient risk factors,[6] while it is greater in patients with cancer[12,3] and in patients with thrombophilia.[13,14] However, in cancer patients there are no clear estimates of the probability of recurrence according to the type of cancer. More important, there is evidence of a different risk of recurrent events in patients with different types of thrombophilia,[13,14] who otherwise have a normal life expectancy. The issue is further confounded by the increased quality of laboratory monitoring of oral anticoagulant therapy - at least in European countries[1,4] - which may significantly affect the correct perception of the true bleeding risk of patients exposed to oral anticoagulant therapy after the initial 3-month period.

Current recommendations, albeit not universally accepted, suggest that patients with transient risk factors should be treated for 3 months or less, that patients with idiopathic VTE should be treated for 3 to 6 months according to the index event (deep vein thrombosis, DVT vs. pulmonary embolism, PE), and that prolonged, or life-long, treatment should be considered after VTE recurrence. Detection of a thrombophilic state should only encourage surveillance of patients, except for the presence of high titer anticardiolipin antibodies which may indicate the need for prolonged treatment – at even higher degrees of anticoagulation – or cancer, which is associated with recurrences occurring even during adequate oral anticoagulant treatment.[15] The milestone WODIT studies[10] have clearly shown no benefit in terms of VTE recurrence from extending secondary prophylaxis to one year over the 3 months in patients with a first episode of idiopathic venous thromboembolism. Thus, the conundrum of how long to continue treatment should be addressed by correct identification of individual patients actually requiring prolonged prophylaxis rather than by implementing strategies valid for the general population of patients with a first episode of VTE.[16] In this respect, four recent papers from Italian research groups have shown promising potential. The rate of compression ultrasonography (C-US) normalization was monitored in 283 patients with a first idiopathic, cancer-associated or post-operative asymptomatic DVT.[17] C-US normalization of popliteal and femoral venous segments was arbitrarily assigned when residual thrombus occupied, at maximum compressibility, less than 40% of the vein area in the absence of compression. In patients with no DVT recurrence or new thrombosis, C-US normalization was observed at 12 months in 100% of patients with post-operative DVT, in 59% of cancer-free symptomatic DVT outpatients and in 23.3% of symptomatic DVT outpatients with cancer. Independent negative effects on the probability of C-US normalization were observed for younger age, for the outpatient presentation of the index DVT, for DVT involving the entire femoro-popliteal axis, and for the presence of cancer. DVT recurrence or new thrombosis was observed at 12 months in 5 patients with post-operative DVT (4.8%), in 7 cancer-free patients with symptomatic DVT (5.0%) and in 8 patients with cancer (21.1%). Only 4 (20%) of these

patients had shown normalization of their index DVT prior to the event. The presence of cancer was the only significant predictor of DVT recurrence and/or new thrombosis occurring within 3 months from the index DVT, while patients were still on anticoagulant treatment (OR = 4.90). The absence of previous C-US normalization was the only predictor of recurrence or new thrombosis occurring after 3 and 6 months from the index DVT (OR ≥ 5.26). With a similar objective, Prandoni *et al*. monitored the rate of C-US normalization in 313 patients with idiopathic, transient risk factor-associated or thrombophilia-associated DVT.[18] C-US normalization of popliteal and femoral venous segments was arbitrarily assigned as the maximum diameter of the vein segment being less than 2 mm at maximum compressibility. The cumulative incidence of normalization was 38.8% at 6 months and 58.1% at one year. Of 58 recurrences and/or new thromboses, 17 (29%) occurred in patients with previous C-US normalization. In a Cox model, the hazard ratio for recurrent events was 2.4 in patients with persistent residual thrombosis, 2.5 in those with idiopathic thrombosis and 3.1 for patients with thrombophilia. Taken together, these findings strongly suggest that absence of C-US normalization after a first episode of DVT is a factor favoring recurrence or new thrombosis and may be relevant to the optimal duration of oral anticoagulant treatment.

Another study demonstrated that after interruption of oral anticoagulation in 392 patients with VTE (idiopathic, associated with cancer, or with transient risk factors) increased D-dimer levels were associated with a 2.45-fold increased risk of recurrent events, occurring at a rate of 6.7% patient-years.[19] The negative predictive power of D-dimer levels lower than 0.5 mg/L was 91% when measured at interruption of oral anticoagulation and increased to 96% when measured 3 months after the interruption of anticoagulant treatment. These results applied to the entire series of patients, irrespectively of the type of VTE presentation. The authors used a quantitative D-dimer (VIDAS) adopting the same cut-off value suggested by the manufacturer to exclude VTE in patients with a clinical suspicion of either DVT or PE. Recurrences occurred in 16.2% of the patients with persistently increased D-dimer and in 3.9% of patients with consistently low D-dimer levels. These data suggest a role of D-dimer assays in devising strategies to optimize prevention of VTE recurrence, but it should be noted that 10 of the 40 recurrent events observed in this study occurred in the first 90 days after discontinuation of oral anticoagulant treatment.[19] Thus, Fattorini *et al*.[20] tested the hypothesis of whether D-dimer measurement performed during oral anticoagulant treatment might also be predictive of recurrent events. Plasma samples for quantitative D-dimer measurements (LPIA Mitsubishi) were collected in 139 consecutive patients with a first episode of proximal DVT of the lower limbs (31 with cancer), starting from at least one month after initiation of oral anticoagulant treatment and continuing throughout anticoagulant treatment for a follow-up of 99 patient-years. The occurrence of DVT recurrence was monitored for an additional 78.3 patient-years after the interruption of oral anticoagulation. The diagnosis of DVT recurrence and/or new thrombosis was based on serial C-US examinations. In the absence of previous C-US normalization, *in situ* DVT recurrence was diagnosed if a previously non-occlusive thrombus had changed to an occlusive thrombus, provided the vein area before compression had increased by more than 50%.[21] Eighteen patients (6 with cancer) suffered DVT recurrence or new thrombosis, occurring 1 to 33 months after the last D-dimer measurement (median 8.5 months), in 8 cases during oral anticoagulant treatment. A single D-dimer measurement was obtained in 61 patients, two D-dimer measurements in 45 patients and 3 or more measurements in 33 patients. Mean D-dimer levels were significantly higher in patients who later developed DVT recurrence than in the remaining patients, but not in patients with cancer than in patients without cancer. In a logistic regression model mean D-dimer levels and age, but not cancer or gender were independent predictors of DVT recurrence. Patients in the higher deciles of the distribution of D-dimer values had a greater probability of suffering DVT recurrence than patients in the lower deciles. This relationship was not significantly different for patients suffering recurrences on anticoagulant treatment or after interruption of oral anticoagulation. Using the 60th percentile of the patients' D-dimer distribution as a cut-off value (1.1 μg/mL), 4 of 84 patients with a mean D-dimer below the cut-off developed DVT recurrence vs. 14 of 55 patients with D-dimer levels above the cut-off, with a negative predictive value of 95.2%. Accordingly, the Mantel-Haenszel OR for DVT recurrence in patients with a mean D-dimer above the cut-off (adjusted for the presence of cancer) was 6.62, and the absolute probability of DVT recurrence was 3.1% patient-years in patients with a mean D-dimer below the cut-off and 21.5% patient-years in patients with a mean D-dimer

above the cut-off. These data suggest that D-dimer levels recorded during and off oral anticoagulation may have a similar predictive power and raise the possibility of identifying subjects at greater risk of recurrence even within the population of patients with cancer-associated DVT.

These new insights warrant prospective management studies to test the potential for individual tailoring of the optimal duration of oral anticoagulant treatment after a first episode of DVT. Different options are available. A first option is to investigate recanalization as the main indicator of the risk of recurrent events. This option has advantages concerned with the reliability of the instrumental diagnosis. Two papers concluded similarly on failed recanalization as a risk factor for DVT recurrence even considering apparently different criteria for the occurrence of C-US normalization. In both studies, failed recanalization was a risk factor for both DVT recurrence and new thrombosis, indicating that the condition does not represent a local risk factor, but rather reflects a systemic abnormality.[17,18] A second option rests on the identification of critical D-dimer levels as an indicator of a higher probability of recurrent events. Although this is obviously less reliable in absolute terms than the instrumental evaluation of patients, it should not be overlooked for a number of reasons. First, it has been shown to be predictive using two different assays.[19,20] Second, attribution of the risk of recurrence can apparently be normalized, irrespective of the assay chosen, according to the assay-dependent distribution of D-dimer levels of patients who are still on oral anticoagulant treatment.[20] In the study by Palareti *et al.*,[19] patients with high D-dimer at the interruption of oral anticoagulant treatment still had increased D-dimer levels at 3 months (*personal communication*). Using the 60th percentile of the D-dimer distribution as a cut-off value would thus permit avoidance of the interruption of oral anticoagulant treatment, provided the distribution of D-dimer levels with whatever assay is known in advance. A third option is to investigate for thrombophilia defects as an indicator for prolonging treatment. Identification of all thrombophilia defects would, however, be difficult, if not in an *a propos* trial, in clinical practice. Disregarded markers may be independent risk factors for thrombosis.[22,23] In addition, there is no clear evidence from the WODIT studies that thrombophilic states may be aggravated by a much higher risk of recurrent events in the general population of patients with idiopathic VTE. In the WODIT studies,[24] thrombophilia was detected in 28.3% of the screened patients: recurrent VTE occurred in 25% of thrombophilia patients and 17% of non-thrombophilia patients (OR = 1.58, p = ns). Potential thrombophilia markers, such as factor VIII and lipoprotein (a) were not evaluated in these studies. Probably more important, D-dimer levels may be surrogate markers of thrombophilia. After interruption of oral anticoagulation, increased D-dimer levels are observed with a similar frequency in patients with and without thrombophilia (50.4% vs. 46.4%), but patients with thrombophilia and increased D-dimer have a 21.2 fold greater chance of VTE recurrence than patients with thrombophilia and normal D-dimer.[25] This finding is in agreement with the independent value of increased D-dimer levels as a risk factor for a first episode of VTE observed in the Leiden Thrombophilia Study.[26] In this study D-dimer levels above the 70th percentile of the combined distribution of patients and controls were 2.2 fold more frequent in VTE patients, independently of the presence of associated thrombophilia defects.

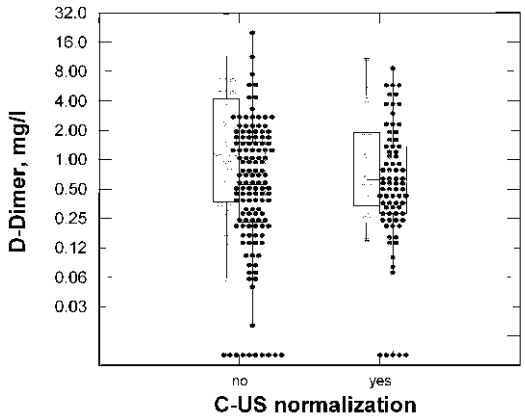

Figure 1. D-dimer levels (log scale) in patients with cancer (open circles) and without cancer (closed circles) on oral anticoagulant treatment after a first episode of deep vein thrombosis according to the occurrence of C-US normalization (defined as in ref. 17) at the time of blood sampling. Data are taken from ref 20. A significant effect of age (p = 0.0001), a borderline effect of cancer (p = 0.054), but no effect of C-US normalization on D-dimer levels were observed by analysis of variance.

Are increased D-dimer levels and failed C-US normalization independent risk factors for DVT recurrence ? No study has formally approached this issue. Interestingly, persistence of thrombosis, idiopathic DVT and thrombophilia were independent risk factors for VTE recurrence in one study,[18] suggesting the possibility of largely independent effects of increased D-dimer and absent C-US normalization as predictors of recurrent VTE. Additional analysis of the data reported[20] does not reveal a significant dif-

ference in D-dimer levels measured during oral anticoagulation in patients with and without C-US normalization, with a borderline significance of the effect of cancer on D-dimer levels (Figure 1). A similar independence of the effects of C-US normalization and D-dimer levels on the risk of VTE recurrence was very recently reported also in the series of patients evaluated in Bologna.[27]

As suggested by Prins and Marchiori,[16] "*the future perspective to establish the optimal duration of secondary prevention in an individual patient may well rely on the improvement of the assessment of his/her risk of recurrence, that involves... also results of laboratory assays of a thrombotic tendency (e.g. D-dimer) and results of tests to evaluate the reduction of thrombotic burden (e.g. serial compression ultrasound)*". The hypothesis of the combined use of serial C-US and D-dimer levels to establish the optimal duration of oral anticoagulation after a first episode of deep vein thrombosis awaits testing in future prospective management studies.

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Funding

This work was partially supported by a grant from the Italian Ministry of Health (progetto Ricerca Finalizzata '99, Contratto ICS 160.3/RF99.88).

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Inside Haematologica. Inherited thrombophilia: the impact of our increasing understanding of molecular mechanisms on clinical practice

The chapter of genetic thrombophilia was opened in this journal by a landmark article by Bjorn Dahlback.[1] Four years later, Dahlback *et al*.[2] introduced the concept of *thrombophilia as a multigenic disease*. At that time they wrote: "*The realization that thrombophilia is a multifactorial disease, with both circumstantial and genetic risk factors being involved in its pathogenesis, is presumably going to influence the future management of the thrombophilic patient. However, available data are not sufficient for calculation of the thrombosis risk associated with combinations of genetic defects. As most studies are made on selected populations, while accurate prevalence numbers of the different defects in the general population are still lacking, it can only be concluded that individuals with combined defects have higher thrombosis risk than those with individual defects*."

In subsequent years, Haematologica has published several papers on the subject of genetic thrombophilia.[3-16] In this issue of Haematologica, two reports deal with genetic predisposition to thromboembolism.[17,18] In particular, De Stefano *et al*.[18] have carefully analyzed the available evidence in order to establish simple guidelines for the management of patients with inherited thrombophilia.

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