Residual Vein Thrombosis and D-Dimer for Optimizing Duration of Anticoagulation in Idiopathic Deep Vein Thrombosis

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Abstract: Long-term anticoagulant treatment is highly effective in preventing recurrent Venous Thrombo-Embolism (VTE) in patients with idiopathic Deep Vein Thrombosis (DVT) of the lower limbs, though associated with an increased risk for major bleeding that may offset the benefits of anticoagulation. Accordingly to recent guidelines, patients with idiopathic DVT should be treated for at least 3 months and then should be evaluated for the risk-benefit ratio of long-term therapy. However, such 'time for decision' is often unclear and the optimal duration of VKA remains debatable.

In recent studies, markers for the assessment of the individual risk for recurrent thrombosis have been proposed, which can be of help to establish the optimal duration of VKA treatment; among them, the D-dimer (D-d) assay and the Residual Vein Thrombosis (RVT) assessment by Compression Ultra-Sonography (CUS) were shown to be the most suitable. Studies' results showed that negative results of these parameters after 3 to 6 months of therapy, identify a group of patients at low-risk for recurrent thrombosis in whom VKA treatment can be withheld. In the present review we will discuss advantages and potential limits of using these individual markers for the management of patients with a first episode of DVT of the lower limbs.

Keywords: DVT, residual vein thrombosis, D-Dimer, anticoagulation.

RISK FOR RECURRENT THROMBOSIS ACCORDING TO THE NATURE OF THE INDEX EVENT

Long-term anticoagulant therapy of deep vein thrombosis (DVT) aims to complete the treatment of the acute episode and prevent further recurrence of venous thrombo-embolism (VTE) [1]; low-molecular weight-heparin (LMWH) and oral vitamin K antagonists (VKA) are the most commonly used effective drugs. The feasibility of long-term treatment with VKA is limited by the need for laboratory monitoring and dose adjustment, while parenteral administration is the main limitation for long-term therapy with LMWH; both these anticoagulants are associated with an increased risk of major bleeding [2]. Based on this assumption, it is reasonable to stop anticoagulant treatment when the benefit of reducing recurrent VTE no longer outweighs the risk of major bleeding. However, such 'time for decision' is often unclear and the optimal duration of VKA treatment in patients with VTE remains debatable.

When deciding how long patients with VTE should be treated, we have to consider the risk of recurrence related to the index episode and this risk when VKA treatment is discontinued. Some studies have compared different durations of anticoagulant treatment, while others looked at the incidence of major clinical events after VTE, with the objective to identify risk factors useful to tailor anticoagulation. A third group of studies assessed the clinical value of markers useful for establishing the individual risk for recurrent VTE and, consequently, the optimal VKA duration. This annotation will deal with the results and clinical impact of studies using these different strategies in patients with a first episode of DVT of the lower limbs and treated with VKA. DVT may be associated with temporary risk factors (surgery, trauma, immobilization), with persistent risk factors (cancer, paralysis, chronic diseases, etc.) or be unprovoked, occurring in the absence of any identifiable risk factors for thrombosis.

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The risk of recurrent VTE whilst on warfarin therapy is about 1-3%. The risk of recurrent VTE after stopping anticoagulant therapy markedly differs depending on whether the initial DVT was associated with one or more risk factors. In patients with a first episode of DVT, the estimated risk of recurrence after anticoagulant withdrawn is 8% if the index episode was idiopathic and 3% in case of provoked VTE [3-9]. Patients with cancer carry a higher rate of recurrence of up to 14·0% per year. In patients without transient risk factors, the risk for recurrent DVT persists for many years; the cumulative incidence of recurrent VTE is 17.5% after 2 years, 24.6% after 5 years and 30.3% after 8 years [4]. These data apply even in patients in whom pulmonary embolism is the main manifestation of VTE [8]. It is important to consider that, regardless of the nature of the index event, the risk of recurrence is higher early after discontinuation of anticoagulant therapy [4,5,10]. The specific risk for recurrent VTE associated with low-risk thrombophilia is unclear. Considering the specific role of the more common thrombophilic abnormalities with respect to the risk of recurrence, some evidence shows an increased odds for recurrent VTE of 1.72 (95% confidence interval [CI] 1.27-2.31) and of 1.41 (95% CI 1.14-1.75) for *F2* G20210A (Prothrombin G20210A) and *F5* R506Q (Factor V Leiden) respectively [11]. Others confirmed such results for *F5* R506Q only (relative risk [RR] 1·39; 95% CI 1·15-1·67) [12], while others did not [5,13,14]. At the present time, findings for low-risk thrombophilia do not justify the prolongation of anticoagulant and should remain an individual decision. Differently, in cases of high-risk thrombophilia (double heterozygous or homozygous for *F5* R506Q, moderate/severe deficiency of antithrombin, protein C and S or presence of lupus anticoagulant) prolonged anticoagulation is indicated [5].

Male gender has also been associated with an increased risk of recurrent VTE [13,15]. Overall, men have a higher risk than women (RR 1.6; 95% CI 1.2-2.0) to develop recurrent thrombosis after stopping anticoagulation [16]. Although some additional risk factors for recurrent venous thrombosis have been postulated (such as post-thrombotic syndrome), these parameters should not influence the duration of VKA [17].

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RISK FOR RECURRENCE ASSESSED ON INDIVIDUAL RISK

Several studies evaluated length of VKA treatment after DVT, all had differences in the diagnostic strategies, agents and regimens as well as risk stratification of patients. Some randomized trials were designed to evaluate whether the duration of anticoagulant treatment could be shortened to less than 3 months [3,18,19]; for this purpose, 4-6 weeks courses of anticoagulant treatment were compared with 3-6 months of therapy. During the follow-up, ranging between 6 months and 1 year, the increase of the absolute risk with the shorter duration was approximately 8%; thus, the studies concluded that anticoagulant treatment should be continued for at least 3 months after an episode of DVT.

In recent studies, markers for the assessment of the individual risk for recurrent thrombosis have been proposed, which can be of help to establish the optimal duration of VKA treatment; among them, the D-dimer (D-d) assay and the RVT assessment by CUS were shown to be the most suitable [21-23]; In the DACUS study [24], patients with a first episode of deep vein thrombosis, treated with OAT for 3 months, were managed according to RVT findings. Those with RVT were randomized to either stop or continue anticoagulants for 9 additional months, whereas in those without RVT, OAT was stopped. Of the 78 (30.2%) patients without RVT, only 1 (1.3%; 0.63% person-years) had a recurrence. The adjusted HR of patients with RVT versus those without was 24.9 (95% CI, 3.4-183.6; $P = .002$). Absence of RVT was used to identify a substantial subset of patients (at least 30% of patients with unprovoked DVT) characterized by a low risk of recurrent VTE who require a short-term antithrombotic treatment.

In the Aesopus study [26], authors evaluated 538 consecutive patients with acute proximal DVT who were randomized to receive either a flexible duration of VKA (up to 1 year in patients with secondary DVT, up to 2 years in those with idiopathic DVT) based on persistence or regression of ultrasound confirmed residual thrombi at regular follow-up visits, or a fixed duration (3 months in patients with secondary DVT, 6 months in those with idiopathic DVT). All patients were followed up to 3 years to assess the development of recurrent VTE. During the 3-year follow-up period, recurrent VTE developed in 32 of the 271 patients (11.8%) randomized to the flexible duration, and in 46 of the 267 (17.2%) randomized to the fixed duration of VKA. In a multivariate analysis including age, gender, type of DVT, clinical symptoms of pulmonary embolism, and thrombophilia, the hazard ratio of developing recurrent VTE in patients randomized to the flexible as compared to those allocated to the fixed duration of VKA was 0.62 (95% CI, 0.39 to 0.97; p = 0.036). When the effect and the duration of VKA was included in the model, the hazard ratio became 0.79 (95% CI, 0.50 to 1.26; p = 0.32). During the period of anticoagulation, clinically relevant bleeding developed in 4 patients (1.5%) randomized to the flexible duration of warfarin and in 2 (0.7%) allocated to the fixed duration. The Author's conclusion were that tailoring the duration of anticoagulation based on the persistence of residual thrombi reduces the rate of recurrent VTE without an appreciable increase in the hemorrhagic risk.

D-dimer assay has been proven to be effective in similar clinical settings. In the Prolong study [20], authors performed D-dimer testing 1 month after the discontinuation of anticoagulation in patients with a first unprovoked proximal deep-vein thrombosis or pulmonary embolism who had received a vitamin K antagonist for at least 3 months. Patients with a normal D-dimer level did not resume anticoagulation, whereas those with an abnormal D-dimer level were randomly assigned either to resume or to discontinue treatment. Patients with an abnormal D-dimer level 1 month after the discontinuation of anticoagulation have a significant incidence of recurrent venous thromboembolism, which is reduced by the resumption of anticoagulation. However, it is unknown whether D-d changes subsequently. Therefore, the aim of Prolong study II [25] was to assess D-d time course and its relation with late recurrences in patients with normal D-d 1 month after anticoagulation suspension for a first episode of unprovoked VTE. Patients with a normal D-d 1 month after stopping anticoagulation repeated D-d testing every 2 months for 1 year. D-d was normal in 68% (243/355) of patients 1 month after anticoagulation suspension. Patients in whom D-d became abnormal at the third month and remained abnormal afterward had a higher risk of recurrence (7/31; 27% patient years; 95% confidence interval [CI]: 12-48) than patients in whom D-d remained normal at the third month and afterward (4/149; 2.9% patient years; 95% CI: 1-7; adjusted hazard ratio: 7.9; 95% CI: 2.1-30; P = .002).

However, these trials had some drawbacks: in the PROLONG study, D-d assay was performed after VKA interruption [20] and in RVT investigations [21,22] study cohorts comprised also provoked DVT patients. As a matter of fact, none of these studies has offered clear-cut results useful to assess the optimal duration of VKA treatment.

For addressing these issues, we conducted a prospective management study (the Extended-DACUS) [27] where was investigated the risk-benefit ratio of an RVT-based VKA duration approach in patients with a first episode of idiopathic DVT of the lower limbs. Briefly, in patients without RVT, VKA was suspended after 3 months while in those with RVT, VKA was continued for additional 15 or 21 months. Among 548 patients, 29.9% did not have RVT and VKA was stopped; the remaining patients continued anticoagulants up to 18 or 2 years. During treatment, the rate of recurrent VTE was 0% in RVT-negative and 7.4% and 6.5% in RVT-positive groups, treated for 18 and 24 months respectively. Rate of major bleeding was 0%, 0.9% and 1.2% among the above reported groups. After VKA suspension, rate of recurrent events growth up to 1.2% in RVT-negative and up to 14.5% and 10% in RVT-positive group treated for 18 and 24 months. These results indicate that in patients without RVT, a short VKA treatment is sufficient; in those with persisting RVT, treatment duration extended to 2 years substantially reduces, but not abolishes, the risk of thrombosis recurrence.

DIFFERENT STRATEGIES FOR SECONDARY PREVENTION

In order to avoid the risk for bleeding complications and the inconvenience of extended or indefinite VKA treatment, some investigators looked at low-intensity VKA for secondary prevention of recurrent VTE. Two trials evaluated the opportunity to extend oral anticoagulation with low-intensity warfarin (INR 1.5-2.0) after an initial treatment of 3-6 months of conventional-intensity anticoagulation (INR 2·0-3·0) [27, 28]. The first study showed superior efficacy of a low-intensity anticoagulant regimen compared to placebo in the prevention of recurrent VTE, but the second investigation, which compared a conventional regimen to less-intensive therapy, showed that the latter approach was less effective without reducing major bleeding. At the present, extending anticoagulant treatment with reduced level of anticoagulation does not seems to be a worthy approach.

ROLE OF RVT IN THE TREATMENT OF CANCER-RELATED DEEP VEIN THROMBOSIS

Patients with cancer have a substantial risk for VTE recurrence as well as for bleeding complications while on long-term VKA [29], thus making LMWH the best therapeutic option in the acute and long-term treatment of cancer-related DVT [30-32]. Current guidelines suggest that such patients should be treated for at least 6 months or longer if cancer is active [32]

However, the major limitation of the available information on cancer-related DVT is that it does not enable thrombotic risk stratification according to type and tumor burden. Therefore, even in cancer patients, the possibility of an individual assessment for VTE

Table 1. Proposed Duration of VKA Therapy Following VTE According to 8th ACCP Guideline and Presence of Individual Markers

Indication	8th ACCP	Indication based on RVT or D-Dimer
First episode of VTE secondary to a transient risk factor	3 months	Patients with persistent RVT may need of prolonged VKA
First episode of unprovoked VTE (even if case of low-risk thrombophilia*)	At least 3 months, then evaluation of risk-benefit ratio for prolonged anticoagulation. If favourable, continue VKA indefinitely	Assessment of D-dimer or RVT after 3 months. Negative D-dimer or absence of RVT allow suspension of VKA
First episode of unprovoked VTE		If RVT present, periodic re-assessment of risk-benefit ratio or continue VKA for up 2 years
Cancer-related VTE	At least 6 months or indefinite in case of active cancer	RVT-based duration of LMWH is under investigation

* Heterozygous Factor V Leiden or Prothrombin G20210A

risk is highly recommended. For this purpose, the role of an RVT-based strategy in patients with cancer-related DVT has been recently evaluated [personal communication, interim analysis of the Cancer-DACUS]. Patients received LMWH for 6 months, administered at therapeutic dosage for the first month and then reduced by 25% in the next 5 months [21]. At this time, patients with RVT were randomized to continue anticoagulants for 6 additional months (Group A1) or to stop (Group A2), while patients without RVT stopped LMWH (Group B). Outcomes were recurrent VTE and/or major bleeding. Over a period of 24 months, 227 patients were evaluated across 12 centres in Italy; RVT was detected in 162 (71.3%) patients; 79 patients were randomized to continue anticoagulation while the remaining 83 were randomized to stop it. RVT was absent in 65 patients. Recurrent events occurred in 22.8% (31.6% person-year) of those who discontinued and 13.9% (20.6% person-year) of those who continued LMWH. In patients without RVT, recurrent VTE occurred in 3% (4.1% person-year) of patients. The adjusted HR for age and sex for Group A2 *versus* A1 and Group B versus A1 was 1.58 (95% CI 0.85-2.93; $P = .145$) and 4.54 (CI 2.3-6.66; $P = 0.028$), respectively. One major bleeding event occurred in each group of patients who stopped (Group A2 [1.5%] and B [2.1%]) and 3 (3.8%) in those who continued anticoagulation. Overall, 31 (23·1%) patients died due to cancer progression after a median follow-up of 13·2 months after randomization.

CONCLUSIONS

The long-term duration of VKA after a first episode of DVT of the lower limbs is still debated. The estimation of the risk of recurrent DVT is essential for establishing length of anticoagulants; this risk can be related to the index episode or to the intrinsic patient's risk for recurrent VTE and/or for bleeding complications. Accordingly to the first consideration, patients with idiopathic DVT should receive at least 3 months of anticoagulants while those with transient risk factor 3 months or less. Based on intrinsic patient's risk, treatment with a VKA should be tailored on the results of markers assessing individual thrombotic risk at the end of conventional treatment. Such markers are now available: absence of RVT or persistently negative D-dimer allow the withdrawn of VKA, no matter the type of the index DVT. In contrast, presence of RVT at the end of minimum period of anticoagulation (3 months of VKA in case of idiopathic DVT or 6 month of LMWH in case of cancer-related thrombosis) require at least 2 years of anticoagulation (Table **1**).

In conclusion, after 3 months of VKA physicians have to establish the risk-benefit ratio of continuing long-term anticoagulation. Detection of individual parameters may help in this decision but scheduled periodic re-assessment of the benefit from extending anticoagulation is needed.

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