Management Based on Residual Vein Thrombosis to Optimise the Duration of Oral Anticoagulants After Deep Vein Thrombosis

a report by

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In patients with a first episode of deep vein thrombosis (DVT) of the lower limbs, the standard for establishing the duration of oral anticoagulant therapy (OAT) is based on the nature of the DVT. It is currently three to six months for idiopathic DVT and three months for provoked thrombosis.[1] Long-term anticoagulant treatment is highly effective in preventing recurrent venous thromboembolism (VTE), but this is associated with an increased risk of major bleeding that may offset the benefits of anticoagulation.[2–6] The eighth edition of the American College of Chest Physicians (ACCP) clinical practice guidelines[7] on antithrombotic therapy for venous thromboembolic diseases stated that patients with a first episode of idiopathic DVT should be treated for at least three months and then evaluated for the risk–benefit ratio of prolonged anticoagulation. Most patients with idiopathic DVT will not require prolonged OAT, but their identification is difficult.[7] New parameters have been proposed to classify a patient's risk of recurrent thrombosis. Of these, D-dimer and residual vein thrombosis (RVT) have been more extensively evaluated.[8–10]

RVT expresses the persistence of venous thrombus over time. This parameter is usually detected by compression ultrasonography (C-US), which is the standard method for diagnosing proximal DVT of the lower limbs.[11] In earlier prospective studies conducted in patients with symptomatic DVT, the presence of a residual thrombus was associated with an increased risk of thrombotic recurrence in both idiopathic and provoked venous thrombosis.[9,10] Recurrent events occurred not only in the previously affected veins but also in other sites, suggesting that residual thrombus may indicate an underlying prothrombotic state.[9,10]

Based on these observations, D-dimer and RVT have been evaluated for optimising OAT duration.[12,13] Results from these investigations showed that patients with persistent RVT, or positive D-dimer, are clearly in need of long-term anticoagulation, while in those in whom such markers become normal OAT can be safely withdrawn after a few months.

The main advantage of using such markers relies on the possibility of assessing the patient's risk, thus allowing the duration of individual anticoagulation to be determined. Here we report and discuss the clinical utility of an RVT-based strategy to manage patients with a first episode following idiopathic or provoked DVT of the lower limbs.

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The experiences of two groups have been published.[13,14] Prandoni et al. evaluated 538 consecutive patients with acute proximal DVT who were randomised to receive either a flexible duration of OAT (up to one year in patients with secondary DVT and two years in those with idiopathic DVT) based on the persistence or regression of ultrasound-confirmed residual thrombi at regular follow-up visits, or a fixed duration (three months in patients with secondary DVT and six months in those with idiopathic DVT). All patients were followed up to three years to assess the development of recurrent VTE. During the three-year follow-up period, recurrent VTE developed in 32 of the 271 patients (11.8%) randomised to the flexible duration, and in 46 of the 267 (17.2%) randomised to the fixed duration. 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 randomised to the flexible duration of OAT compared with those allocated to the fixed duration of OAT was 0.62 (95% confidence interval [CI] 0.39–0.97; p=0.036). When the effect and the duration of OAT were included in the model, the hazard ratio became 0.79 (95% CI 0.5–1.26; p=0.32). During the period of anticoagulation, clinically relevant bleeding developed in four patients (1.5%) randomised to the flexible duration of OAT, and in two patients (0.7%) allocated to the fixed duration.
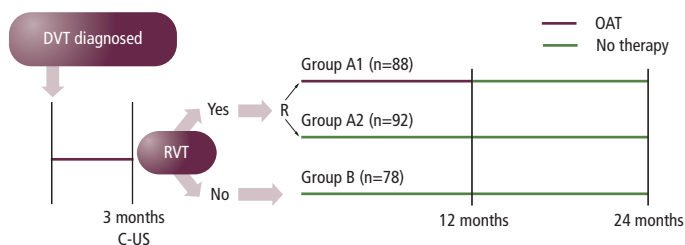
It is concluded that tailoring the duration of anticoagulation based on the persistence of residual thrombi reduces the rate of recurrent VTE without an appreciable increase in the haemorrhagic risk.

In our studies, we used a standard time of three months after the index DVT to assess RVT. *Figure 1* is the reported study design of the first randomised trial.[13] Patients with RVT were randomised to either stop or continue OAT (international normalised ratio [INR] 2.0–3.0) for nine additional months (groups A2 and A1). Those without RVT did not continue anticoagulation (group B). RVT detection is reported in *Figure 2*.

C-US of the affected leg was performed and images were obtained in transverse section only. Lumen compressibility was then evaluated by gentle pressure of the probe. The RVT diameter was taken by measuring the distance between the anterior and posterior walls of the vein on freeze-frame B-mode images during compression with the ultrasound probe.[11] Measurements were taken at the common femoral vein 1cm below the inguinal ligament and the popliteal vein, at the most prominent crease in the mid-popliteal fossa. RVT was arbitrarily scored as 'absent' when the figure was less than or equal to 40% of the vein diameter.[9] A patient was considered as having RVT when a persisting thrombus was shown to be present in at least one of the two examined vein segments.

Figure 1: Study Design of the Randomised Investigation

DVT = deep vein thrombosis; RVT = residual vein thrombosis; C-US = compression ultrasonography; OAT = oral anticoagulation.
• Group A1 indicates patients with RVT randomised to continue OAT for an additional nine months (one year in total);
• Group A2 indicates patients with RVT randomised to stop OAT; and
• Group B indicates patients without RVT who stop OAT after three months.

This approach was applied in 258 patients with idiopathic (166) or provoked (92) DVT. Presented in *Tables 1* and *2* are the major clinical characteristics of patients and study outcomes.

The hazard ratios (HRs) for recurrent events, adjusted for age and sex, were:

• A1 versus A2 = 1.58 (95% CI 0.85–2.93; p=0.145);
• A1 versus B =15.7 (95% CI 2.1–118.0; p=0.007); and
• A2 versus B = 24.9 (95% CI 3.4–183.6; p=0.002).

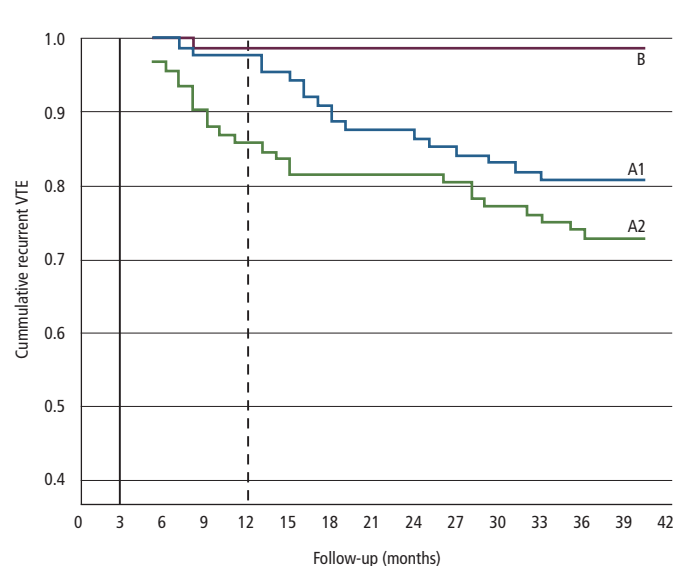The HRs for recurrent events, adjusted for idiopathic versus provoked DVT, were:

• A1 versus A2 = 1.58 (95% CI 0.86–2.94; p=0.141);
• A1 versus B = 15.2 (95% CI 1.9–121.8; p=0.01); and
• A2 versus B = 19.3 (95% CI 2.5–147.2; p=0.004).

As the results of the DACUS study showed a high risk of recurrent thrombosis after short-term anticoagulation, we decided to treat patients with RVT for at least 18 months or indefinitely, according to physician and patient preference. We prospectively followed 548 patients with idiopathic DVT who had at least one year of follow-up after OAT was withdrawn. These patients were managed according to RVT findings and continued OAT for at least 18 months if RVT was present (after three months from the index DVT). Those patients without RVT stopped OAT after three months. This approach showed that the cumulative rate of recurrent VTE in patients without RVT remains low (<2%), even after a long follow-up.

In patients with RVT the interruption of OAT carries a high risk of recurrent thrombosis. A separate analysis looking at recurrent thrombosis and major bleeding in patients who received mid-term (median 14 months) or long-term anticoagulation (median 28 months) highlighted a recurrence rate of 7.8 and 2.9%, respectively (see *Figure 3*). No differences were found in terms of major bleeding.
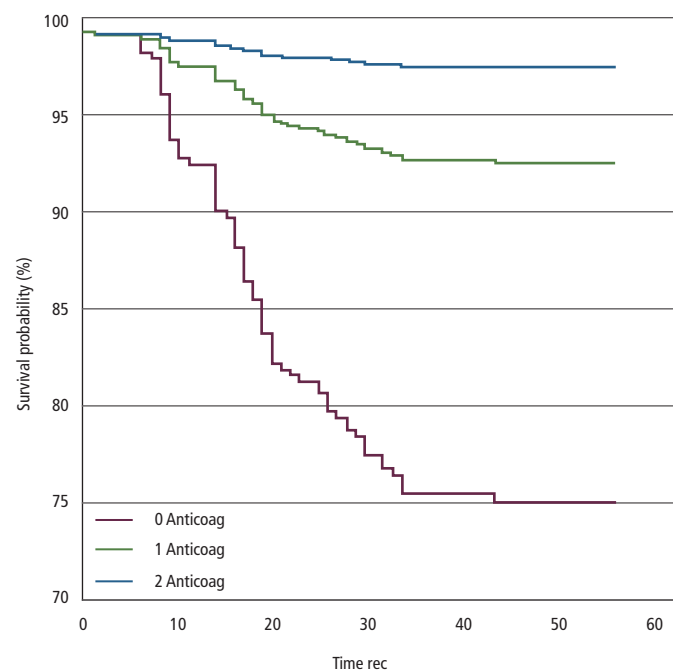
All studies looking at residual thrombosis as a risk factor for recurrent events showed that, regardless of the criteria used for assessing RVT, persistence of this parameter correlates with an increased risk of re-thrombosis.[9,10] This method can be easily and widely applied as its reproducibility is high. The result of inter- and intra-observer variation assessment among operators has been proved to be adequate: κ 0.7403, 95% CI 0.70–0.86.

At least 20% of the recurrent thromboses occurred in the contralateral leg, a finding that supports the hypothesis that RVT can indicate the

Figure 2: Kaplan-Meier of Recurrent Thrombosis in the Randomised Study

VTE = venous thromboembolism.
• Group A1 indicates patients with RVT randomised to continue OAT for an additional nine months (one year in total);
• Group A2 indicates patients with RVT randomised to stop OAT; and
• Group B indicates patients without RVT who stop OAT after three months.

Figure 3: Kaplan-Meier of Recurrent Thrombosis in the Prospective Extended Study

VTE = venous thromboembolism.
• 0 = patients with RVT who continued OAT for 12 months after the index DVT;
• 1 = patients with RVT who continued OAT for at least 18 months after the index DVT; and
• 2 = patients without RVT who stopped OAT after three months from the index DVT.

presence of an underlying pro-thrombotic state triggering a sustained hyper-coagulability. A prolonged OAT only delayed recurrences,[15] further supporting the hypothesis.

New investigations are under way that will demonstrate that RVT may be used as a tool for establishing the optimal duration of OAT. It is now clear that the absence of individual markers for recurrence (RVT and D-dimer)

Table 1: Baseline Patient Characteristics

	Group A1 (n=88)	Group A2 (n=92)	Group B (n=78)	p-value*
Female sex (%)	43 (46.7)	42 (47.7)	37 (47.4)	0.991
Age, mean + SD (years)	57.1±14.1	61.1±11.5	55.3±14.9	0.017**
Type of DVT, n (%):				
Idiopathic	66 (75.0)	72 (78.3)	28 (35.9)	0.0005
Provoked	22 (25.0)	20 (21.7)	50 (64.1)	0.0005
Total duration of follow-up (years)#	184.2	191.0	157.9	
Mean follow-up (years)#	2.1 (±0.71)	2.1 (±0.68)	2.0 (±0.71)	

*P value refers to chi-squared test unless specified; **ANOVA test; #Time from randomisation (three months after the index deep vein thrombosis [DVT]).
• Group A1 indicates patients with RVT who continued OAT for 12 months (in total).
• Group A2 indicates patients with RVT randomised to stop OAT after three months.
• Group B indicates patients without RVT who stopped OAT after three months.

Table 2: Study Outcomes

Outcomes	Group A1 (n=88)	Group A2 (n=92)	Group B (n=78)	p-value
Recurrences, n/total	17/88	25/92	1/78	0.213 (A1 versus A2)
(%)	(19.3)	(27.2)	(1.3)	0.0005 (A1 versus B)
				0.0005 (A2 versus B
Recurrences, n/100 person-year	17/168.9	25/163.9	1/157.6	0.421 (A1 versus A2)*
(%)	(10.1)	(15.2)	(0.63)	0.021 (A1 versus B)*
				0.001 (A2 versus B)*
Type of recurrent VTE				
DVT	17	25	1	
DVT + PE	0	0	0	
Isolated PE	0	1§	0	
Contralateral	4	5	0	
Major bleeding, n/total	2/88	1/92	0/78	0.534
(%)	(2.3)	(1.1)	(0)	(A1 versus A2)**
Major bleeding n/100 person-year	2/183.6	1/190.3	0/157.9	0.685
(%)	(1.1)	(0.53)	(0)	(A1 versus A2)*

* Chi-square test for the comparison of two proportions, expressed as a percentage; §PE was associated with an isolated distal DVT in the contralateral leg; **p-value refers to chi-squared test unless specified.

allows the withdrawal of OAT after a short period of time, even in patients in whom a clear cause for thrombosis has not been demonstrated (so-called idiopathic DVT). This advantage is not negligible since up to 30% of patients with idiopathic DVT may benefit from this approach. In patients with RVT, the recurrence rate is high and relapses occur soon after OAT suspension (see *Figure 2*). This evidence correlates with that of a previous study,[15] suggesting that RVT-positive patients are probably in need of indefinite anticoagulation.

RVT assessment has a practical advantage over D-dimer as it seems not to be influenced by transient factors (surgery, inflammation, cancer,

pregnancy, etc.) activating coagulation. This usually produces a positive D-dimer result even in the absence of a clinically detectable thrombus.

To conclude, results from our studies, as well as those of others, indicate that the absence of RVT identifies patients at a low risk of recurrent thrombotic events.

Anticoagulation therapy may be safely stopped after a short period. The advantages of such an approach are evident, especially when taking into account that these patients have a consistent reduction of major bleeding. ■

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