Residual vein thrombosis for assessing duration of anticoagulation after unprovoked deep vein thrombosis of the lower limbs: The extended DACUS study

Sergio Siragusa,[1]* Alessandra Malato,[1] Giorgia Saccullo,[1] Alfonso Iorio,[2] Mauro Di Ianni,[3] Clementina Caracciolo,[1] Lucio Lo Coco,[1] Simona Raso,[1] Marco Santoro,[1] Francesco Paolo Guarneri,[1] Antonino Tuttolomondo,[4] Antonio Pinto,[4] Iliana Pepe,[5] Alessandra Casuccio,[6] Vincenzo Abbadessa,[1] Giuseppe Licata,[4] Giovan Battista Rini,[5] Guglielmo Mariani,[2] and Gaetana Di Fede[7]

The safest duration of anticoagulation after idiopathic deep vein thrombosis (DVT) is unknown. We conducted a prospective study to assess the optimal duration of vitamin K antagonist (VKA) therapy considering the risk of recurrence of thrombosis according to residual vein thrombosis (RVT). Patients with a first unprovoked DVT were evaluated for the presence of RVT after 3 months of VKA administration; those without RVT suspended VKA, while those with RVT continued oral anticoagulation for up to 2 years. Recurrent thrombosis and/or bleeding events were recorded during treatment (RVT group) and 1 year after VKA withdrawal (both groups). Among 409 patients evaluated for unprovoked DVT, 33.2% (136 of 409 patients) did not have RVT and VKA was stopped. The remaining 273 (66.8%) patients with RVT received anticoagulants for an additional 21 months; during this period of treatment, recurrent venous thromboembolism and major bleeding occurred in 4.7% and 1.1% of patients, respectively. After VKA suspension, the rates of recurrent thrombotic events were 1.4% and 10.4% in the no-RVT and RVT groups, respectively (relative risk = 7.4; 95% confidence interval = 4.9–9.9). These results indicate that in patients without RVT, a short period of treatment with a VKA is sufficient; in those with persistent RVT, treatment extended to 2 years substantially reduces, but does not eliminate, the risk of recurrent thrombosis. Am. J. Hematol. 86:914–917, 2011.   © 2011 Wiley-Liss, Inc.

Introduction

Long-term anticoagulant treatment is highly effective in preventing recurrent venous thromboembolism (VTE) in patients with idiopathic deep vein thrombosis (DVT) of the lower limbs [1–3] but is associated with an increased risk for major bleeding that may offset the benefits of anticoagulation [4]. Since the risk of recurrent VTE is believed to gradually diminish over time, many patients with idiopathic DVT may not require prolonged treatment with a vitamin K antagonist (VKA) [5,6]. According to recent guidelines, patients with unprovoked DVT should be treated for at least 3 months and should then be evaluated for the risks and benefits of long-term therapy [1]; however, identification of these patients is not always straightforward.

In recent years, several markers for the assessment of the individual risk for recurrent thrombosis have been proposed. Among these, D-dimer (D-d) assay and residual vein thrombosis (RVT), detected by compression ultrasonography (C-US), have shown to be the most suitable methods for assessing the optimal duration of VKA administration. In fact, a number of studies have shown that negative results with these parameters after 3–6 months of therapy can identify a group of patients at low-risk for recurrent thrombosis in whom VKA treatment can be stopped [7–10]. However, these previous investigations have some limitations; first, in some trials, 30% of the patient population had provoked DVT [8,9]. In addition, no clear indications were given for how long patients with persistent RVT or positive D-dimer should be treated, since a significant risk for recurrent VTE persists even after 1 year of anticoagulation [7–9]. In fact, none of these studies has offered clear results regarding assessment of the optimal duration of VKA treatment, even after the analysis of pooled data [11,12].

To overcome some of these shortcomings, the current investigation enrolled patients with a first episode of unprovoked DVT and managed patients based on ultrasonography-detected RVT findings after 3 months of oral anticoagulant therapy.

© 2011 Wiley-Liss, Inc.

Patients and Methods

Patients with a first episode of unprovoked proximal DVT were eligible for the study; informed consent for participation was given at the index DVT episode. Unprovoked DVT was defined as a thrombotic episode in apparently healthy individuals without evident risk factors, such as surgery, trauma, immobilization, or acute medical illness in the previous 4 weeks. Patients with active cancer, limited life expectancy, antiphospholipid antibody syndrome, known thrombophilic states (deficiencies of antithrombin, protein C and S, homozygosity for the FV Leiden or F II G20210A mutations or combined heterozygosity for the same), severe liver disease, renal failure and, finally, those who lived too far from the recruiting center were excluded from the study. This extended duration of anticoagulation based on compression ultrasonography (DACUS) study was approved by the Institutional Review Boards of participating centers (Palermo, Perugia, L'Aquila). All patients provided written informed consent obtained in accordance with the Declaration of Helsinki.

Study design. This multicenter prospective study was conducted in patients with a first episode of symptomatic proximal DVT (index DVT) detected by compression ultrasonography (C-US). Participants underwent clinical examination to assess baseline conditions and exclude contraindi-

cations. All patients received oral anticoagulants for 3 months [warfarin (Coumadin®, Bristol-Myers Squibb) or acenocoumarol (Sintrom®, Novartis Pharma)]; at this time, patients underwent C-US assessment for detection of RVT. C-US of the affected leg was performed, and images were obtained in transverse sections only. Lumen compressibility was evaluated by gentle pressure of the probe; 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. The examination was performed with the patient in the supine position with the leg externally rotated and slightly flexed at the knee. Measurements were taken at the common femoral vein, 1 cm below the inguinal ligament and at popliteal vein, at the most prominent crease in the midpopliteal fossa. RVT was calculated as follows: RVT = vein diameter during compression (diameter b) $\times$ 100/vein diameter before compression (diameter a) (Fig. 1). RVT was arbitrarily scored as "absent" when $\leq$40% of vein diameter. Patients were considered to have RVT when a persistent thrombus was present in at least one of the two vein segments examined. C-US of the affected leg was performed, and images were obtained in transverse sections only. The result of this assessment demonstrated fairly good correlation (κ = 0.7403, 95% confidence interval (CI) = 0.70–0.86) [8].

Patients without RVT (no-RVT) suspended VKA therapy at 3 months after diagnosis. Those with RVT (RVT group) continued VKA (International Normalized Ratio (INR) = 2.0–3.0) for an additional 21 months; all patients were evaluated at 1 year after discontinuation of VKA (Fig. 2).
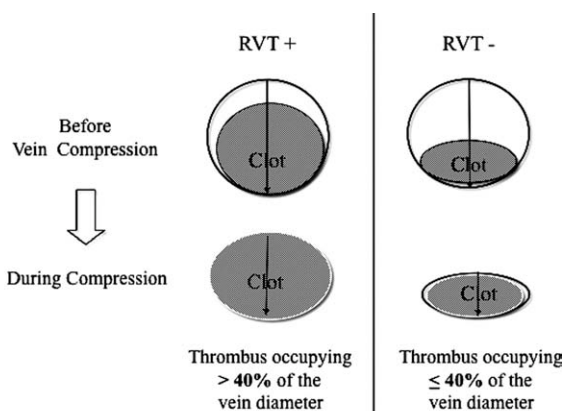
Figure 1. Evaluation of residual vein thrombosis. RVT calculation = vein diameter during compression (diameter b) $\times$ 100/vein diameter before compression (diameter a). RVT, residual vein thrombosis.

Study outcomes and follow-up. Study outcomes were recurrent proximal VTE (rVTE) and major bleeding detected during VKA therapy, and rVTE detected during one-year of follow-up after VKA suspension (post-RVT detection period (Fig. 2). Therefore, the post-RVT detection period lasted 12 months in the no-RVT group and 33 months (21 while on VKA and 12 of follow-up) in the RVT group. Comparison among groups for rate of rVTE and death was analyzed considering only the one-year follow-up after VKA suspension. Patients were instructed to contact the clinical center and were trained to recognize symptoms suggestive of VTE or bleeding. In cases of recurrence, the results of C-US were compared with those of the previous examination; ultrasonography was performed by investigators unaware of RVT status at study entry. Diagnosis of recurrent proximal DVT was based on C-US findings only; recurrent events were confirmed if a previously fully compressible segment (contralateral or ipsilateral) was no longer compressible or if an increase of 4 mm or more in the diameter of the residual thrombus during compression was detected [13]; in unclear cases, repetition of the test (after 5–7 days) or contrast venography was performed. In patients with suspected pulmonary embolism, diagnosis of rVTE was based on objective algorithms, accordingly to the protocol of the center [14]. Major bleeding was defined as a decrease in hemoglobin of 2.0 g/dL or more, intracranial or retroperitoneal bleeding, or bleeding needing surgical intervention or blood transfusion. Minor bleedings comprised all other bleeding events. To avoid potential bias in the evaluation of suspected rVTE-standardized diagnostic algorithms were used [13,14]. All events were evaluated by the adjudication panel that was unaware of patients' treatment, center, and RVT status.

Statistics and ethics. Baseline differences between groups were assessed by the χ^2 test (Yates' correction) for categorical variables and ANOVA test or Kruskal–Wallis test for parametric and nonparametric analyses, as appropriate. Relative risks (RRs) and 95% CIs were also evaluated. Data were analyzed using Epi Info software (version 6.0, Centers for Disease Control and Prevention, Atlanta, GA) and SPSS Software (version 14.0, SPSS, Chicago, IL). All P values were two-sided, and P values less than 0.05 were considered statistically significant.

Results

Patients and treatment groups

Of the 670 patients with unprovoked DVT diagnosed over a period of 8 years (until October 2007), 166 patients were excluded because they were enrolled in the DACUS study, 15 did not agree to participate, 58 had exclusion criteria, and 22 experienced recurrent events in the period between index DVT and the 3-month C-US. Thus, a total of 409 patients were included in the study. Baseline characteristics are reported in Table I. Mean patient age was lower in the no-RVT group; the presence of nonextensive DVT (involve-
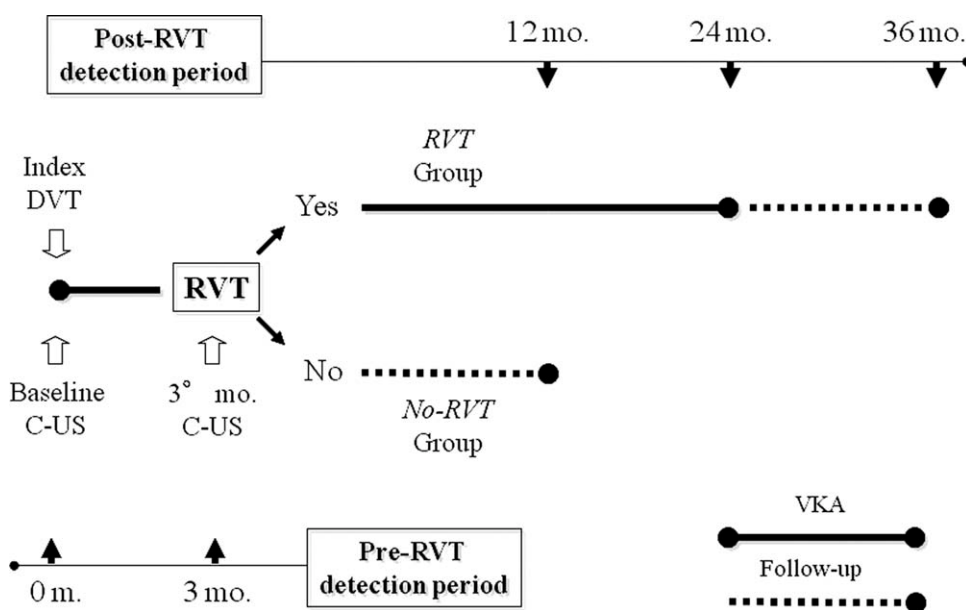

Figure 2. Study design. RVT Group indicates patients with RVT who continued VKA for 24 months after the index DVT; No-RVT Group indicates patients without RVT who stopped VKA after 3 months from the index DVT. DVT, deep vein thrombosis; RVT, residual vein thrombosis; C-US, compression ultra-sonography; VKA, vitamin K antagonist.

TABLE I. Baseline Patient Characteristics

	RVT group (n = 273)	No-RVT group (n = 136)	P value[*]
Female sex (%)	132 (48.3)	62 (45.5)	0.683
Age, mean + SD (years)	57.8 ± 13.9	54.5 ± 14.6	0.054[**]
One segment DVT, n (%)[a]	78 (28.5)	42 (30.8)	0.065
Prevalence of prothrombin mutation[b]	19/181 (10.4%)	9/89 (10.1%)	n.s.
Prevalence of factor V Leiden[b]	68/194 (35%)	29/91 (31.8%)	n.s.

[*] P value refers to χ^2 test unless specified.
[**] ANOVA test.
[a] This means involvement of popliteal or common femoral vein only.
[b] In patients tested at the moment of diagnosis or during follow-up.
RVT, residual vein thrombosis.

ment of one venous segment only) was detected in about 30% in both groups.

Assessment of RVT after 3 months of VKA showed the absence of residual vein thrombi in 136 (33.2%) patients (no-RVT group) and the presence of residual thrombi in the remaining 273 patients (66.8%; RVT-group).

Outcomes

Because of the study design, outcomes occurring during VKA therapy after RVT detection were analyzed in the RVT group only. rVTE occurred in 13 of 273 patients (4.7%), while major bleeding was seen in three of 273 cases (1.1%; Table II).

Considering the one-year follow-up period after suspension of anticoagulants, analysis of outcomes was performed in both groups. rVTE and the number per 100 persons/year are reported in Table II. The analysis was performed after excluding, in the RVT group, the patients who developed rVTE during VKA therapy (n = 13) and those lost to follow-up (n = 2); in total, 258 patients in the RVT group were analyzed. Recurrences occurred in more than 10% of patients in the RVT group compared with less than 2% in the no-RVT group, with a RR of rVTE of 7.4 (95% CI = 4.9–9.9), between patients treated for an additional 21 months (RVT group) versus the no-RVT group. Among patients with RVT, more than 20% had recurrent DVT in the contralateral leg, whereas concomitant DVT and PE occurred in 25% of cases. In the no-RVT group, all the two events occurred in the same leg of the index DVT without suspicion of pulmonary embolism (Table II).

We also analyzed differences in the rate of recurrent events considering sex and age. Older age and male sex conferred a higher risk for rVTE in the RVT and no-RVT groups; especially in patients with RVT, the presence of age ≥65 years was associated with a RR of 1.69 (95% CI = 1.23–4.61) in comparison with younger patients. Regarding sex, there was a nonsignificant trend for male patients to have a higher risk of developing rVTE (RR = 1.32, 95% CI = 0.02–2.62) when compared with females (Table III).

Seventeen deaths occurred during follow-up (14 in the RVT and three in the no-RVT group): two deaths were due to acute myocardial infarction, three deaths were due to cerebral ischaemia (one in the no-RVT group), and the other 12 deaths were due to cancer (two in the no-RVT group) diagnosed during follow-up. No deaths due to thrombotic recurrences or bleeding were recorded. Two patients in the RVT group were lost to follow-up.

Discussion

Optimal duration of VKA treatment in patients with a first episode of idiopathic DVT is still a matter of debate, and current recommendations are often difficult to implement [6,15]. Assessment of individual risk of recurrent thrombosis is important as it simplifies management strategies in patients with VTE, which is especially relevant if tailored to specific groups of patients with different risks of recurrence [16]. Recently, new parameters for the assessment of the individual risk for recur-

TABLE II. Study Outcomes

Outcomes	RVT group (n = 273)	No-RVT group (n = 136)	P value[*]
During VKA therapy after RVT detection[a]			
Recurrences, n [(%), 95% Confidence Intervals]	13 [(4.7), 1.5–7.9]	–	–
Major bleeding, n [(%), 95% Confidence Intervals]	3 [(1.1), −0.1–2.3]	–	–
1 year after VKA discontinuation[b]	n = 258[c]	n = 136	
Recurrences, n [(%), 95% Confidence Intervals]	27 [(10.4), 6.7–14.1]	2 [(1.4), −0.5−3.3]	0.0026
Recurrences, no. per 100 person-years	10.4	1.4	0.022[d]
Types of rVTE (%)			
DVT only	16 (59.2)	2 (1.4)	
DVT + PE	7 (25.9)	0	
Isolated PE	4 (14.8)	0	
Controlateral DVT n (%)	6 (22.2)	0	
Death, n (%)	14 (5.4)	3 (2.2)	0.038

[*] P value refers to χ^2 test unless specified.
[a] Accordingly to study design, considered for RVT group only.
[b] Excluding 13 patients having recurrent DVT during treatment in RVT group.
[c] Two patients were lost to follow-up.
[d] χ^2 test for the comparison of two proportions, expressed as percentage.
RVT, residual vein thrombosis; VKA, vitamin-K antagonist.

TABLE III. Recurrent Venous Thromboembolism in Subgroups After VKA Discontinuation

	RVT group (n = 258)		No-RVT group (n = 136)	
Subgroups	No. of events/total (%)	No. per 100 person-years	No. of events/total (%)	No. per 100 person-years
Sex				
Male	15/131 (11.4)	11.4	2/72 (2.7)	2.7
Female	12/127 (9.4)	8.6	0/64 (0.0)	0.0
Age				
<65 years	11/139 (7.9)	7.9	0/78 (0.0)	0.0
≥65 years	16/119 (13.4)	13.4	2/58 (3.4)	3.4

RVT, residual vein thrombosis; VKA, vitamin-K antagonist.

rent thrombosis have been proposed, that is, RVT assessment and the D-dimer assay. Both are characterized by advantages and disadvantages; the D-dimer assay is easy to perform, but not all kits have been validated for this purpose and there is no comparison between the different methods and assays [17]. Moreover, D-dimer testing can yield false positive results in a number of clinical situations (cancer, chronic diseases, advanced age, inflammatory status, infections, etc.). RVT assessment is an easy method, does not seem to be influenced by the aforementioned conditions, but requires some expertise and is, to a certain extent, a subjective technique. A very important issue is the fact that these tools can identify patients carrying a low risk for recurrent VTE; these patients, in fact, may safely benefit from a short course (3 months) of VKA treatment [7–9]. Concerning RVT specifically, the absence of a residual clot is associated with a negligible risk for recurrent VTE; this may allow a short course of VKA in about one-third of the entire DVT patient population.

However, the correlation between RVT and the risk of recurrent DVT (after VKA suspension) is still unclear. Le Gal et al. carried out a multicenter, multinational prospective cohort study in tertiary care centers. Patients with a first unprovoked major VTE were enrolled over a 4-year period and completed a mean follow-up of 18-months. All 452 patients with DVT had baseline C-US at inclusion to assess RVT before stopping VKA at 5–7 months. All episodes of suspected recurrent VTE were independently adjudicated with reference to baseline imaging after VKA suspension. It was found that 45 of 231 patients with abnormal CUS (19.5%) had recurrent VTE during follow-up,

compared with 32 of 220 patients with normal CUS (14.6%). The association between abnormal CUS at inclusion and risk of recurrent VTE yielded a hazard ratio that was not significant (1.4, 95% CI = 0.9–2.1) [18]. These data were not confirmed by a recent systematic review showing that residual thrombosis positively correlated with recurrent VTE, although large heterogeneities were present, due to differences in study population, timing, and differences in methods of measuring residual thrombosis [12].

Other studies have evaluated whether detection of RVT may establish the optimal duration of VKA therapy. Prandoni et al. used residual thrombus assessed over time to drive anticoagulant therapy [9]. Patients were randomly assigned to fixed-duration anticoagulation (no further anticoagulation for secondary thrombosis and an extra 3 months for unprovoked thrombosis) or flexible-duration, ultrasonography-guided anticoagulation (no further anticoagulation in patients with recanalized veins and continued anticoagulation in all other patients for up to 9 months for secondary DVT and up to 21 months for unprovoked thrombosis). It was found that 46 (17.2%) of 268 patients allocated to fixed-duration anticoagulation and 32 (11.9%) of 270 patients allocated to flexible-duration anticoagulation developed recurrent VTE [adjusted hazard ratio (HR) = 0.64, 95% CI = 0.39–0.99]. Considering patients with unprovoked DVT, the adjusted HR was 0.61 (CI = 0.36–1.02).

In the DACUS study, we showed that among patients (n = 180) with RVT after 3 months of VKA, recurrent events occurred in 27.2% of those who discontinued (25 of 92 patients; 15.2% person-years) and 19.3% of those who continued VKA (17 of 88 patients; 10.1% person-years) for an additional 9 months. Of the 78 (30.2%) patients without RVT, only one (1.3%; 0.63% person-years) experienced recurrence. The adjusted HR of patients with RVT versus those without was 24.9 (95% CI = 3.4–183.6; P = 0.002) [8]. Considering all unprovoked DVT patients without RVT (28 from the DACUS study and 136 in the current study), the risk of rVTE after VKA suspensions is as low as 1.2% (two of 164 patients, 95% CI = 0.15–2.63). The situation is quite different in high-risk patients identified by the presence of a residual vein clot after 3 months of VKA treatment (RVT-group). In this population, in fact, the continuation of VKA up to 1 year (9 months after RVT detection) only delayed the incidence of recurrent events [8].

Considering the above, RVT-based management of patients with unprovoked DVT still requires further study. Toward this end, we investigated 409 patients with unprovoked DVT, managed entirely accordingly to RVT detection after 3 months of VKA. Detection of RVT at this time may be considered somewhat premature, although our approach reflects previous findings [8,12,19]. In this view, early RVT detection may be an appropriate marker for assessing the minimal length of VKA in low risk patients. In our study, we stopped VKA after 3 months in patients without RVT, while those with RVT received longer treatment schedules (additional 21 months after RVT detection); all patients underwent a 1-year follow-up visit after VKA discontinuation. This approach reflects our current clinical practice and is also in accordance with the 8th ACCP guidelines that suggest periodic revaluation of the risk-benefit ratio of long-term therapy. Results of the present investigation clearly confirm that in patients without RVT, the risk of recurrent thrombosis remains low even after 1 year of follow-up; in patients with RVT, recurrent events still occur in up to 10% of cases even if patients were treated for almost 2 years. In this group of patients, no significant differences were found compared with those observed in the DACUS study where RVT patients were treated for an additional 9 months instead of 21 months in present investigation [8]. It is clear that the results of these two trials are difficult to compare because the DACUS study also included patients with provoked DVT; however, these results may suggest that there is an advantage of indefinite anticoagulation in high-risk patients. On the other hand, in patients with RVT anticoagulation with VKA is unsatisfactory, because it cannot completely eliminate the "predisposition" to relapse, as suggested by the rate of recurrences observed during anticoagulant therapy (4.7%). As we did not further evaluate RVT during follow-up, it cannot be excluded that some of these patients may reduce their RVT burden over time and, thus, carry a different risk for relapsing [9]. Obviously, such considerations need to be evaluated prospectively.

In conclusion, this study indicates that in patients with idiopathic DVT, the absence of RVT is associated with a low risk for recurrence and safely permits discontinuation of VKA after 3 months.

References

1. Kearon C, Kahn SR, Agnelli G, et al. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133:454S–545S
2. Heit JA, Mohr DN, Silverstein MD, et al. Predictors of recurrence after deep vein thrombosis and pulmonary embolism. A population-based cohort study. Arch Intern Med 2000;160:761–768.
3. Kearon C, Gent M, Hirsh J, et al. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. N Engl J Med 1999;340:901–907.
4. Palareti G, Leali N, Coccheri S, et al. Bleeding complications of oral anticoagulant treatment: An inception-cohort, prospective collaborative study (ISCOAT). Italian Study on Complications of Oral Anticoagulant Therapy. Lancet 1996;348:423–428.
5. Kearon C, Ginsberg JS, Kovacs MJ, et al. Comparison of low-intensity warfarin therapy with conventional-intensity warfarin therapy for long-term prevention of recurrent venous thromboembolism. N Engl J Med 2003;349:631–639.
6. Schulman S, Rhedin AS, Lindmarker P, et al. A comparison of six weeks with six months of oral anticoagulant therapy after a first episode of venous thromboembolism. N Engl J Med 1995;332:1661–1665.
7. Palareti G, Cosmi B, Legnani C, et al. D-dimer testing to determine the duration of anticoagulation therapy. N Engl J Med 2006;355:1780–1789.
8. Siragusa S, Malato A, Anastasio R, et al. Residual vein thrombosis to establish duration of anticoagulation after a first episode of deep vein thrombosis: The Duration of Anticoagulation based on Compression UltraSonography (DACUS) study. Blood 2008;112:511–515.
9. Prandoni P, Prins MH, Lensing AW, et al. Residual thrombosis on ultrasonography to guide the duration of anticoagulation in patients with deep venous thrombosis: A randomized trial. Ann Intern Med 2009;50:577–585.
10. Cosmi B, Legnani C, Tosetto A, et al. Usefulness of repeated D-dimer testing after stopping anticoagulation for a first episode of unprovoked venous thromboembolism: The PROLONG II prospective study. Blood 2010;115:481–488.
11. Carrier M, Rodger M, Wells PS, et al. Residual vein obstruction to predict the risk of recurrent venous thromboembolism in patients with deep vein thrombosis: A systematic review and meta-analysis. J Thromb Haemost 2011;9:1119–1125.
12. Tan M, Mos IC, Klok FA, Huisman MV. Residual venous thrombosis as predictive factor for recurrent venous thromboembolim in patients with proximal deep vein thrombosis: A sytematic review. Br J Hematol 2011 Mar 6; doi: 10.1111/j.1365-2141.2011.08578.x. [Epub ahead of print].
13. Prandoni P, Lensing AW, Bernardi E, et al. The diagnostic value of compression ultrasonography in patients with suspected recurrent deep vein thrombosis. Thromb Haemost 2002;88:402–406.
14. Fedullo PF, Tapson VF. The evaluation of suspected pulmonary embolism. N Engl J Med 2003;349:1247–1256.
15. Siragusa S, Caramazza D, Malato A. How should we determine length of anticoagulation after proximal deep vein thrombosis of the lower limbs? Br J Haematol 2009;144:832–837.
16. Eichinger S, Heinze G, Jandeck LM, Kyrle PA. Risk assessment of recurrence in patients with unprovoked deep vein thrombosis or pulmonary embolism: The Vienna prediction model. Circulation 2010;121:1630–1636.
17. Verhovsek M, Douketis JD, Yi Q, et al. Systematic review: D-dimer to predict recurrent disease after stopping anticoagulant therapy for unprovoked venous thromboembolism. Ann Intern Med 2008;149:481–490.
18. Le Gal G, Carrier M, Kovacs MJ, et al. Residual vein obstruction as a predictor for recurrent thromboembolic events after a first unprovoked episode: Data from the REVERSE cohort study. J Thromb Haemost 2011;9:1126–1132.
19. Piovella F, Crippa L, Barone M, et al. Normalization rates of compression ultrasonography in patients with a first episode of deep vein thrombosis of the lower limbs: Association with recurrence and new thrombosis. Haematologica 2002;87:515–522.