Role of D-dimer in guiding duration of anticoagulant therapy in the management of first unprovoked proximal lower limb deep venous thrombosis

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Background
The optimal duration of anticoagulant therapy in management of patients with first episode of unprovoked deep venous thrombosis is uncertain. D-dimer test may play a role in the assessment of duration of anticoagulant therapy to decrease the rate of recurrence.
Aim
To evaluate if D dimer test can be used as predictor to guide the duration of anticoagulation in patients with first unprovoked proximal lower limb deep venous thrombosis.
Patients and Methods
One hundred patients with a first unprovoked proximal deep-vein thrombosis who completed 3 months of Vitamin K Antagonists (VKAs) and had elevated d dimer test 1 month after discontinuation of anticoagulation were randomly assigned either to resume (group A) or to discontinue treatment (group B). The patients were followed up for 1 year for recurrent venous thromboembolism and treatment complications.
Results
The mean age of the patients was 49.96±7.88 and 51.78±7.98 years for group A and B respectively. Male to female ratio was nearly similar in both groups 3:2 . The base line D-dimer level was 3.05±0.84 and 3.15±1.00 for group A and B respectively with no statistical significant difference. The mean duration of follow up was 10.6 months for both groups. The recurrence rate was higher in group B (7 cases) compared to group A (1 case) (*P* value 0.027) and this difference was statistically significant. No major bleeding or pulmonary embolism have been noticed in any patients during follow up.
Conclusion
Elevated D dimer test 1 month after discontinuation of 3 months anticoagulation, in the absence of recent thrombosis, could be an indicator for resumption of anticoagulant therapy for another 3 months.

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Introduction

Venous thromboembolism (VTE) has an annual incidence of one to two cases per 1000 persons in the general population and is the third most common cause of vascular death after myocardial infarction and stroke [1–3].

The risk of a recurrent venous thromboembolic event after oral anticoagulant therapy varies greatly from 1 to 27% during the first year [4–6].

The risk of recurrence increases in the first 6–12 months after the initial episode and gradually decreases thereafter [7]. The American College of Chest Physicians recommended that patients with unprovoked deep venous thrombosis (DVT) should receive at least 3 months of anticoagulant therapy and then should be evaluated for the risk–benefit ratio of long-term anticoagulant therapy [8].

The decision whether to stop or to continue anticoagulation after 3 months is important because stopping anticoagulant therapy may carry risk for morbidity and mortality owing to recurrent DVT and pulmonary embolism, whereas continuing anticoagulation exposes patients to higher risk of bleeding, inconvenience, and higher costs. So, identifying patients at low risk for recurrent DVT who may benefit little from prolonged anticoagulation will probably help clinicians decide whether to stop or to continue anticoagulant therapy [9].

Measurements of D-dimer levels 1 month after stopping 3 months of anticoagulant therapy have

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been shown to predict recurrence in patients with a first episode of unprovoked DVT [10,11].

Patients and methods

A prospective, randomized, controlled study was done between December 2017 and December 2018 at Menoufia University Hospital on 100 adults patients above 18 years old with first proximal unprovoked lower limb DVT, which was objectively confirmed by compression ultrasonography, and who completed 3 months of uninterrupted Vitamin K Antagonists (VKA) therapy with target international normalized ratio two to three and had elevated D-dimer level measured 1 month after discontinuation of anticoagulant therapy. Written informed consent was obtained from all patients to be included in this study. This study was accepted and approved by an ethical committee. Patients with serious liver disease; renal insufficiency (plasma creatinine >2 mg/dl); any other conditions that could influence the result of D-dimer, such as infection, tumor, recent surgery, trauma or burns, disseminated intravascular coagulopathy (DIC), liver or renal disease, and inflammatory bowel disease; other indications for anticoagulation [e.g. atrial fibrillation (AF)] or contraindications for such treatment; patients with DVT in pregnancy or puerperium; patients who had recent fracture or plaster casting of a leg within 3 months; immobilized patients with confinement to bed for 3 or more consecutive days; patients with surgery with general anesthesia lasting at least 30 min; patients with cancer; patients with antiphospholipid antibody syndrome; patients with or antithrombin deficiency (absent of risk factor transient or persistent) were excluded from the study.

Patients with elevated D-dimer level were included (100 patients) and randomly divided into group A (50 patients), which resumed anticoagulant therapy with VKAs for another 3 months, and group B (50 patients), which discontinued anticoagulant therapy.

D-dimer testing was performed by a quantitative assay with reagent kits 'STA LIATEST D-DI' with estimated cutoff level of 0.5 μg/ml.

Duplex venous examination at the time of D-dimer test was done to exclude new episode of DVT. Both groups were followed up regularly every month for a period of 8–12 months for recurrence. Duplex ultrasound was done for clinically suspected DVT and symptomatic patients. Recurrent deep vein thrombosis was diagnosed if a previously fully compressible segment (contralateral or ipsilateral) was no longer compressible or if an increase of at least 4 mm in the diameter of the residual thrombus during compression was detected [11]. When the diameter of the thrombus changed by 1.1–3.9 mm, or in cases of high or moderate clinical probability and normal findings on proximal compression ultrasonography, the examination was repeated 5–7 days later [12].

Results

A total of 576 patients with proximal lower limb DVT were referred to Menoufia University Hospitals from December 2017 to December 2018. Of these 576 patients, 223 (38.7%) had first unprovoked proximal lower limb DVT. Of these 223 patients, only 100 (44.8%) had been included in our study after fulfilling the inclusion and exclusion criteria (Fig. 1).

The mean age of the patients in our study was 49.96 ±7.88 and 51.78±7.98 years for groups A and B, respectively, with no statistically significant difference (P=0.25) (Table 1). Male to female ratio was nearly similar in both groups at 3 : 2 (Table 2). Hypertension and diabetes mellitus were present in 38 and 40% of patients, respectively, in group A compared with 44 and 36%, respectively, in group B. Thirteen (26%) patients were smokers in group A versus 18 (36%) patients in group B (Table 3). There was no statistically significant difference between both groups regarding associated comorbidities or smoking.

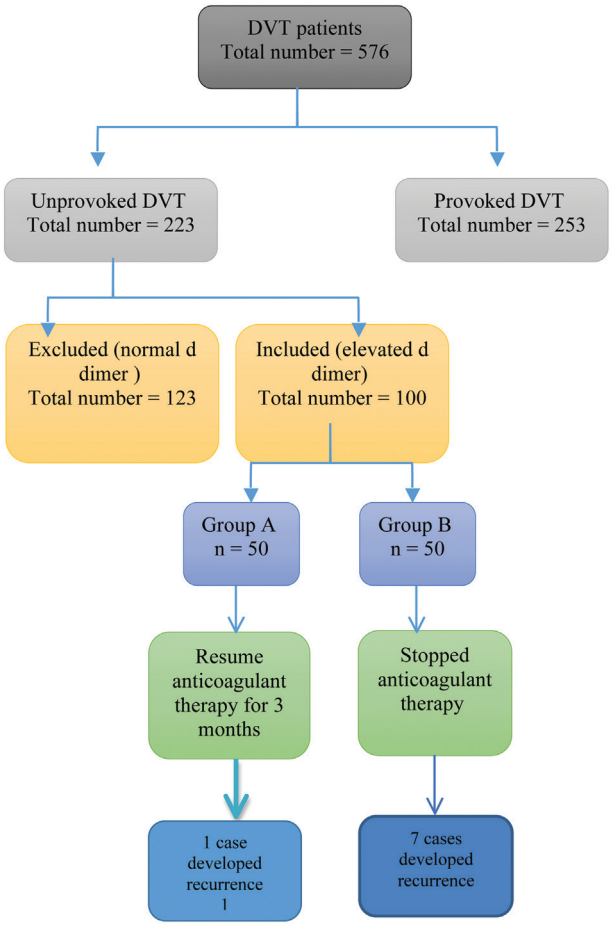
The mean duration of follow-up was 10.6±1.58 months for both groups (range, 8–12 months). The baseline D-dimer level was 3.05±0.84 and 3.15±1.00 for groups A and B, respectively, with no statistically significant difference (Table 4).

During the follow-up, seven patients developed recurrent DVT in group B compared with one patient in group A, and this difference was statistically significant (P=0.027).

The patient in group A who experienced recurrent DVT was a 55-year-old male, diabetic but not hypertensive, with baseline D-dimer level of 4.2 μg/ml, however at recurrence was 1.2 μg/ml. Duplex ultrasound revealed recurrent popliteal DVT (Tables 5 and 6).

Seven patients developed recurrent DVT in group B; five were males and two were females, with mean age 53.43±7.67 year ranged from 41 to 64 years. Of them, two had hypertension, two had diabetes mellitus, two had both hypertension and diabetes, and one was a

Figure 1



Inclusion and exclusion criteria of patients selection.

Table 1 Age distribution between the study groups

Age	Group A		Group B
Range	35–64		37–64
Mean±SD	49.96±7.88		51.78±7.98
t test		1.317	
P value		0.254	

Table 2 Sex distribution between the study groups

Sex	Group A (*N*=50) [*n* (%)]	Group B (*N*=50) [*n* (%)]	χ^2	*P* value
Male	30 (60)	31 (62)	0.042	0.838
Female	20 (40)	19 (38)		

Table 3 Associated comorbidities in the study groups

	Group A (*N*=50) [*n* (%)]	Group B (*N*=50) [*n* (%)]	χ^2	*P* value
Hypertension	19 (38)	22 (56)	0.372	0.542
Diabetes	20 (40)	18 (36)	0.170	0.680
Smoker	13 (26)	18 (36)	1.169	0.280

smoker. Four patients developed recurrent femoropopliteal DVT, whereas three patients developed recurrent popliteal DVT (Table 6).

Table 4 D-dimer levels after 1 month of discontinued 3 months of anticoagulant therapy

D-dimer	Group A		Group B
Range	1.6–4.9		1.4–4.8
Mean±SD	3.05±0.84		3.15±1.00
t test		0.329	
P value		0.568	

Table 5 Recurrence of venous thrombosis in the study groups

	Group A (*N*=50) [*n* (%)]	Group B (*N*=50) [*n* (%)]	χ^2	*P* value
Recurrence	1 (2)	7 (14)	4.891	0.027*

**P* value is statistically significant.

Discussion

The optimal duration of anticoagulant therapy for patients with a first episode of unprovoked VTE is uncertain [13]. Buller *et al.* [3] recommend at least 6 months of anticoagulation owing to higher rates of recurrence with shorter durations of treatment, whereas the American College of Chest Physicians recommended at least 3

Table 6 Demographic data of recurrent cases

	Group A	Group B
Age (years)	55	53.43±7.67 (41–64)
Sex		
Male	1	5
Female	–	2
Mean baseline D-dimer	4.2 μg/ml	3.9±0.48
Mean D-dimer at recurrence	1.2 μg/ml	1.01±0.23
Level of recurrence		
Femoropopliteal	–	4
Popliteal	1	3

months of anticoagulant therapy and then the patients should be evaluated for the risk–benefit ratio of long-term anticoagulant therapy [8].

Agnelli *et al*. [14] claimed that the duration of anticoagulation seems to have little effect on the rate of disease recurrence in patients with unprovoked VTE and longer treatment only delays recurrence until after anticoagulation is stopped.

Palareti *et al*. [15] measured D-dimer test after anticoagulation is stopped. A negative (or low) D-dimer level may identify patients at low risk for recurrent VTE, in whom anticoagulation therapy may be stopped. Similarly, a positive (or increased) D-dimer level may identify patients at relatively high risk for recurrent DVT.

There was a clear benefit of extended treatment with vitamin K antagonists in patients with elevated D-dimer levels 1 month after discontinuation of 3 months anticoagulant therapy in the form of decreasing the rate of recurrence of DVT. These results confirm that the D-dimer level is related to the risk of recurrence after a first episode of VTE and may be useful in guiding the duration of anticoagulation by helping to select patients who may benefit from extended anticoagulant therapy in spite of its adverse effects.

Palareti *et al*. [16] did a prolonged study to determine the duration of anticoagulant on patients with first unprovoked VTE using D-dimer test, where the rate of recurrent DVT in patients who stopped anticoagulant was 15% and patients who resumed anticoagulant was 2.9%, which is closer to our results, being 14% and 2% in groups B and A, respectively.

During the follow-up duration for both groups, no major bleeding or pulmonary embolism was noticed in any patients, whereas one patient developed major bleeding in a study done by Palareti *et al*. [16] in the group that resumed anticoagulation. Moreover, no deaths from recurrent VTE or from bleeding occurred in both groups in our study, whereas Palareti *et al*. [16] recorded three deaths during their follow-up but for causes other than VTE.

Some studies have assessed other predictors of recurrent disease in patients with unprovoked VTE, such as the presence of residual disease on venous ultrasonography may increase the risk for recurrent disease [17], whereas other studies do not show this effect [18], but we did not evaluate the effect of this factor on recurrence rate in our study.

Our study has some limitations. First, the timing of D-dimer testing after anticoagulation was stopped varied greatly between studies, and this might have influenced the rate of false-positive and false-negative results if D-dimer levels were low because they were measured too soon after anticoagulation was stopped [19]. This study and the study by Palareti *et al*. [16] measured D-dimer level 1 month after stopping anticoagulant therapy, but Palareti *et al*. [16] used qualitative test, whereas we used a quantitative test.

Second, the cutoff level of D-dimer that best predicts recurrent VTE is not known, especially in patient subgroups, such as elderly persons, in whom baseline D-dimer levels are increased. We used an estimated cutoff level of 0.5 μg/ml in our study whereas other studies used a cutoff of 250 μg/l to determine rates of VTE recurrence in patients with D-dimer results above and below this level [9].

Finally, all the studies did not use the same assays of D-dimer. Without a worldwide standard for D-dimer testing, comparison of data obtained with different studies is difficult.

We recommend the use of D-dimer as single test to determine whether to stop or to continue anticoagulation in patients with a first unprovoked VTE. D-dimer test could be a part of a clinical prediction rule that incorporates both clinical and laboratory features to better guide the proper duration of anticoagulation.

Conclusion

Elevated D-dimer test 1 month after discontinuation of 3 months anticoagulation, in the absence of recent thrombosis, could be an indicator for resumption of anticoagulant therapy for another 3 months to decrease the incidence of recurrent DVT.

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Conflicts of interest
There are no conflicts of interest.

References

1 Goldhaber SZ, Bounameaux H. Pulmonary embolism and deep vein thrombosis. Lancet 2012; 379:1835–1846.

2 Baglin T, Luddington R, Brown K, *et al.* Incidence of recurrent venous thromboembolismin relation to clinical and thrombophilia risk factors: prospective cohort study. Lancet 2003; 362:523–526.

3 Buller HR, Agnelli G, Hull RD, *et al.* Antithrombotic therapy for venous thromboembolic disease: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004; 126:401S–428S.

4 Agnelli G, Prandoni P, Santamaria MG, *et al.* Three months versus one year of oral anticoagulant therapy for idiopathic deep venous thrombosis. Warfarin Optimal Duration Italian Trial Investigators. N Engl J Med 2001; 345:165–169.

5 Prandoni P, Noventa F, Ghirarduzzi A, *et al.* The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1, 626 patients. Haematologica 2007; 92:199–205.

6 Ridker PM, Goldhaber SZ, Danielson E, *et al.* Long-term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism. N Engl J Med 2003; 348:1425–1434.

7 Kearon C, Kahn SR, Agnelli G, Goldhaber S, Raskob GE, Comerota AJ. Antithrombotic therapy for venous thromboembolic disease. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th ed). Chest 2008; 133 (6 suppl):454S–545S.

8 Heit JA, Mohr DN, Silverstein MD, Petterson TM, Ofallon WM, Melton LJ. Predictors of recurrence after deep vein thrombosis and pulmonary embolism: a population-based cohort study. Arch Intern Med 2000; 160:761–768.

9 Eichinger S, Minar E, Bialonczyk C, Hirschl M, Quehenberger P, Schneider B, *et al.* D-dimer levels and risk of recurrent venous thromboembolism. JAMA 2003; 290:1071–1074.

10 Douketis J, Tosetto A, Marcucci M, Baglin T, Cushman M, Eichinger S, *et al.* Patient-level meta-analysis: effect of measurement timing, threshold, and patient age on ability of D-dimer testing to assess recurrence risk after unprovoked venous thromboembolism. Ann Intern Med 2010; 153:523–531.

11 Kearon C, Akl EA. Duration of anticoagulant therapy for deep vein thrombosis and pulmonary embolism. Blood 2014; 123:1794–1801.

12 Prandoni P, Cogo A, Bernardi E, *et al.* A simple ultrasound approach for detection of recurrent proximal-vein thrombosis. Circulation 1993; 88:1730–1735.

13 Snow V, Qaseem A, Barry P, Hornbake ER, Rodnick JE, Tobolic T, *et al.* The Joint American College of Physicians/American Academy of Family Physicians Panel on Deep Venous Thrombosis/Pulmonary Embolism.Management of venous thromboembolism: a clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians. Ann Intern Med 2007; 146:204–210.

14 Agnelli G, Prandoni P, Becattini C, Silingardi M, Taliani MR, Miccio M, *et al.* Warfarin Optimal Duration Italian Trial Investigators.Extended oral anticoagulant therapy after a first episode of pulmonary embolism. Ann Intern Med 2003; 139:19–25.

15 Palareti G, Legnani C, Cosmi B, Valdre? L, Lunghi B, Bernardi F, *et al.* Predictive value of D-dimer test for recurrent venous thromboembolism after anticoagulation withdrawal in subjects with a previous idiopathic event and in carriers of congenital thrombophilia. Circulation 2003; 108:313–318.

16 Palareti G, Cosmi B, Legnani C, Tosetto A, Brusi C, Iorio A, *et al.* PROLONG Investigators.D-Dimer testing to determine the duration of anticoagulation therapy. N Engl J Med 2006; 355:1780–1789.

17 Young L, Ockelford PA, Milne D, McKelvie S, Rolfe-Vyson V, West T, *et al.* Post treatment residual thrombus is associated with an increased risk of DVT recurrence, mortality and a trend towards increased vascular death. J Thromb Haemost 2005; 3 (Suppl 1):365.

18 Rodger MA, Kovacs MJ, Zeng W. Residual venous thrombosis after 5-7 months of oral anticoagulant (OAC) therapy as a predictor of subsequent recurrent venous thromboembolism. J Thromb Haemost 2007; 5 (Suppl 2):508.

19 Aguilar C, del Villar V. Diagnostic performance of D-dimer is lower in elderly outpatients with suspected deep venous thrombosis [Letter]. Br J Haematol 2005; 130: 803–804.