ORIGINAL ARTICLE

The prediction role of D-dimer in recurrence of venous thromboembolism 1-year after anticoagulation discontinuing following idiopathic deep vein thrombosis

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Background: After discontinuing oral anticoagulant therapy (OAT), the recurrence of venous thromboembolism (VTE) is greatest in the 1st year and gradually diminishes. D-dimer assay was proposed to be effective in selecting patients with idiopathic DVT. The aim of this study was to determine the rate of VTE recurrence after discontinuing OAT according to the results of D-dimer. **Materials and Methods:** This prospective study was conducted in patients with a first episode of symptomatic proximal deep vein thrombosis (DVT) who had received OAT for at least 3 months. Patients were re-evaluated at 1st, 6th and 12th months of their follow-up. At the first (T0) and 30-day (T1) visits, venous blood samples were taken for D-dimer test. At each follow-up visit, we examined patients for clinical symptoms or signs of recurrent VTE, bleeding, postthrombotic manifestations, adherence to treatment, and concomitant analgesic or antiinflammatory therapy. The endpoint outcomes were VTE recurrence and complete of this survey follow-ups. **Results:** A total of 68 eligible patients was enrolled. Four patients (two patients need to use long-term oral anticoagulation, and two patients lost their first follow-up) were excluded. At T0, D-dimer and compression ultrasonongraphy (CUS) was normal in 28 patients (44%). Moreover, 36 patients had abnormal D-dimer but normal CUS. A follow-up of 12 months was available in 44 patients. During the follow-up, three recurrent events were recorded. All Recurrent events were ipsilateral DVT. Among these index cases, all had an abnormal D-dimer at either T0 and/or T1. The recurrence rate was higher in males than in females (8.6% vs. 2.2%, $P = 0.04$) with an abnormal D-dimer at T0 and/or T1 with a multivariate hazard ratio of 2.1 (95% confidence intervals [CI]: 1.2-5.2; $P = 0.02$). Patients older than 65 years had a higher rate of events than younger and hazard ratio was about 3.8 (95% CI: 2.1-4.2; $P = 0.02$). Patients with recurrences had higher mean D-dimer at both T0 and T1 when compared with those without recurrences, but the difference was significant only for D-dimer at T1 ($P = 0.03$). During the follow-up, two patients died (3%). **Conclusion:** Within 12 months follow-up, the risk of recurrence with an abnormal D-dimer, either during or at 1-month after discontinuing OAT, was 4.6% which is much lower to the annual risk of recurrence in most studies with idiopathic and provoked VTE. D-dimer has an acceptable prognostic value in detecting recurrence of idiopathic VTE before discontinuing the anticoagulant therapy.

Key words: D-dimer, deep vein thrombosis, recurrent venous thromboembolism, residual vein obstruction

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INTRODUCTION

Approximately, 900,000 people are diagnosed with venous thromboembolism (VTE) annually with 5% Americans experiencing a deep vein thrombosis (DVT) during their lifetime.[1] Immediate mortality associated with DVT has been estimated at 5%, but cumulative mortality in the first 6 months after a thromboembolic event is 5-10% increasing to 20% by 2 years, mainly because of malignancy.[2]

Under-anticoagulation with a Vitamin K antagonist (VKA), increases the risk of thrombotic events, and over-anticoagulation increases the risk of serious bleeding. The narrow therapeutic range of VKAs is further complicated by numerous drug, diet, and metabolic interactions.[2]

In patients with unprovoked VTE, long-term anticoagulant treatment is highly effective in preventing recurrent VTE, the risk of a recurrent event in the 1st year following discontinuation of anticoagulation varies from 5% to 15%, and such duration of therapy is controversial, but the optimal duration of this therapy remains uncertain. After oral anticoagulant therapy (OAT) withdrawal, the recurrence of risk is greatest in the 1st year and gradually diminishes while the increased bleeding risk may offset the benefits of prolonged OAT.[3,4] After the first 3 months, the American College of Chest Physicians recommends an individual evaluation

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for the risk-benefit ratio of long-term therapy in patients with unprovoked VTE for their relevant risk of recurrence.[5] Hence, the benefits of extending anticoagulation should be balanced against the risk of bleeding.[6]

New parameters have, however, been proposed to optimize OAT duration; among them, D-dimer assay and measurement of residual thrombosis on ultrasonography, so-called residual vein obstruction (RVO) were proposed to be effective in selecting patients with idiopathic DVT who may benefit from a prolonged anticoagulation.[3,4]

D-dimer levels were shown to have a high negative predictive value (NPV) for recurrent VTE. So far only one randomized trial, the prolong study, has been performed to establish the role of D-dimer for assessing the risk of recurrence after a first episode of VTE.[6] On the other hand, RVO might impair venous flow, leading to stasis and activation of the coagulation cascade, or be a surrogate marker for a hypercoagulable state. Whereas some previously published studies have shown an association between RVO and recurrent VTE, others have not. It is unknown D-dimer could be a predictor of cardiovascular events and occult cancer in subjects with a first episode of idiopathic proximal deep vein thrombosis (DVT).[3,6-8]

The purpose of the current study was to determine the rate of VTE recurrence and predictive values of D-dimer test after OAT withdrawal according to the results of D-dimer in patients with idiopathic DVT.

MATERIALS AND METHODS

Study design

This single center prospective study was conducted in patients with a first episode of symptomatic proximal DVT, detected by compression ultrasonography (CUS), and who received OAT for at least 3 months.

Those who agreed to participate in the study underwent an examination to assess baseline clinical conditions and to exclude contraindications. Study enrolment started on September 2011 and ended on June 30, 2012 at Alzahra Hospital in Isfahan. Follow-up was extended from October 30, 2011, to August 21, 2013. After enrolment, patients were re-evaluated at 1st, 6th and 12th months of their follow-up [Figure 1].

Study patients

Patients with a first episode of documented idiopathic proximal DVT were eligible for the study if they had completed at least 3 months of OAT with reaching target international normalized ratio between 2.0 and 3.0.

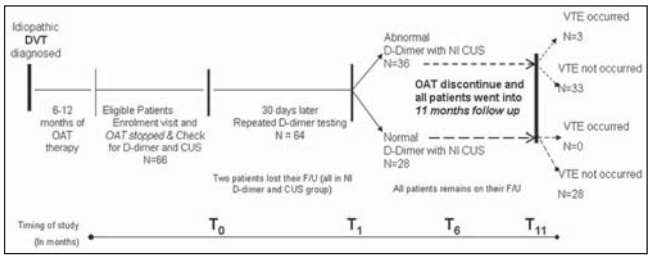

Figure 1: Schematic diagram of patients selection and follow-ups in this study hazard ratio for D-dimer at T0 hazard ratio for D-dimer at T1

Idiopathic DVT[6] was defined as a thrombosis episode in apparently healthy individuals with the absence of pregnancy or puerperium, recent fracture or plaster casting of a leg, immobilization with confinement to bed for 3 consecutive days, active malignancy, known thrombophilic states, using precipitating drugs and surgery with general anesthesia lasting >30 min during the last 3 months.

Patients with secondarily DVT such as severe liver or renal insufficiency (glomerular filtration rate <30), antiphospholipid antibody syndrome, other known thrombophilic states (such as deficiencies of antithrombin and protein C and S, homozygous for FV Leidenm or prothrombin gene (20210G_A) mutations, coexistence definite indications for cardiac or cerebral for using anticoagulation, limited life expectancy, or those who lived too far from the research center did not include.

The duration of anticoagulation based on CUS and D-dimer study was approved by our university research committee (University Research Project Number 391015). All enrolled patients provided written informed consent.

On the day of VKA discontinuation, CUS of the lower limbs was performed by investigators unaware of the laboratory findings of D-dimer. Hence, lumen compressibility was assessed by pressure of the probe; RVT diameter was taken by measuring the distance between the anterior and posterior walls of the vein, on freeze frame of B-mode images, during compression with the ultrasound probe. RVT was arbitrarily scored as "absent" when the figure was 40% or less of the vein diameter.

All patients with present RVT at the beginning of this study were excluded D-dimer was assessed using the VIDAS® D_Dimer exclusion II™ (DEX2) qualitative, whole blood method assay (BIOMÉRIEX, Marcy, France; cut-off: 500 ng/ml) by technicians unaware of the clinical characteristics of the patients. Anticoagulation was stopped on the same day, and the next visit was scheduled after 30-day. Patients with recurrent events before the 30-day visit were excluded from further analysis.

At the 30-day visit, venous blood samples were taken for D-dimer repeated test. All enrolled patients (with and without RVT) were stopped OAT.

Study outcomes and follow-up

Patients were followed for about 12 months after OAT discontinuation. Study outcomes were recurrent VTE. Patients were trained to contact the clinical center if symptoms developed suggestive of VTE or bleeding. In cases of recurrence, results of CUS were compared with those of the previous examination. Diagnosis of recurrent DVT was made if a previously fully compressible segment (contralateral or ipsilateral) became no longer compressible or if an increase of 40% or more in the diameter of the residual thrombus during compression was detected. In patients with suspected pulmonary embolism, diagnosis of VTE recurrence was based on results of D-dimer assay, pulmonary computed tomography angiography or pulmonary ventilation/perfusion scanning. Although in the case of low clinical pretest probability, D-dimer was measured and if normal, patients were not investigated further. In case of suspected recurrence in the contralateral leg of the index event, patients with negative CUS and normal D-dimer (cut-off: 500 ng/ml) were not investigated further. In the case of negative CUS and abnormal D-dimer, a repeated CUS was scheduled after 5-7 days. If the repeated CUS was negative, patients were not investigated further. In the case of a suspected DVT recurrence in the same leg of the index event, CUS results were compared with the results of the last available previous CUS. If the CUS was nondiagnostic and D-dimer normal, a repeated CUS was scheduled after 5-7 days.

We scheduled a follow-up visit at 1, 6 and 12 months after stopping of VKA for all patients. At each follow-up visit, we examined patients and inquired about health status, clinical symptoms or signs of recurrent VTE, bleeding, postthrombotic manifestations, adherence to treatment, and concomitant analgesic or antiinflammatory therapy. D-dimer was assessed only at the first and the end of 1st month of patients follow-up.

Patients received a card with the telephone numbers of the thrombosis centers and were instructed to return to the study center if clinical manifestations suggestive of recurrent venous thrombosis in either leg (edema, redness, tenderness, pain, or swelling), or pulmonary embolism (dyspnea, chest pain, or tachycardia) occurred. If this was the case, we invited patients to the Alzahra Hospital (research center) for further diagnostic procedures. At first, all patients were requested to wear 40 mmHg elastic stockings for >2 years. In the case of suspected recurrent event, D-dimer was sampled only for diagnostic purposes.

Statistical analysis

We used the Chi-square test to compare the rate of persistent residual venous thrombosis at the last ultrasonography assessment and also abnormal D-dimer at 0, 1 month between the two groups. Differences between groups were assessed by the Fisher's exact test, Chi-square test (Yates' correction) or *t*-test when appropriate. Approximately, 95% confidence intervals (95% CI) were calculated based on the binomial distribution. Hazard ratio was calculated to assess the risk for recurrent VTE for patients with abnormal D-dimer versus those with normal D-dimer at both T0 and T1 versus those without. Kaplan — Meier estimates and 95% CI were calculated to assess the risk for recurrent VTE for patients with abnormal D-dimer versus those with normal D-dimer at both T0 and T1.

A two-sided $P \leq 0.05$ was considered as statistically significant. The SPSS software package (13.0 release, Chicago, IL, USA) was used for data processing.

RESULTS

Patients

A total of 68 eligible patients were enrolled since March 2011 at medical clinics of Alzahra Hospital. Figure 1 shows the study flow chart of the 68 patients included in the study. After excluding four patients (two patients need to use long-term oral anticoagulation, and another two patients were excluded for lost to their first follow-up). Therefore, 64 patients were enrolled at the end of 1st month. D-dimer and CUS at first was normal in 28 patients (44%) while the remaining 36 patients had abnormal D-dimer but normal CUS (both groups did not consuming their anticoagulant). The baseline characteristics of the two groups of patients are reported in Table1. Patients with normal D-dimer results were more likely to be younger ($P < 0.03$) [Table 1].

Follow-up

A follow-up of 12 months was available in 44 patients (68%). We have no reports of D-dimer at T1 in two patients but these patients were returned to our study in the next follow-up. In the extended follow-up, no patients were lost.

Outcomes

Recurrent venous thromboembolism

During follow-up, three recurrent events were recorded (4.6% of patients - 95% CI: 3-7%) [Table 2]. Recurrent events were ipsilateral in all cases. Among these patients, all had an abnormal D-dimer at either T0 and/or T1. The recurrence rate was higher in males than in females (8.6% vs. 2.2%) with an abnormal D-dimer at T0 and/or T1 with a multivariate hazard ratio of 2.1 (95% 1.2-7; $P = 0.04$). However, the rate of recurrence did not differ in relation to VKA duration among the patients who had been treated

Table 1: The baseline characteristics of the two groups of patient

Variables	D-dimer at T0 (first)				D-dimer at T1 (after 1-month)			
	Normal	Abnormal	Total	*P* value	Normal	Abnormal	Total	*P* value
Number	28	36	64		26	36	62[a]	
Male	12 (54)	20 (55)	32 (50)	0.5	14 (53)	18 (50)	28 (51)	0.4
Age, median (year)	42	57	50	0.03	44	55	50	0.2
Age over 65 years (%)	5 (18)	10 (30)	15 (22)	0.03	8 (30)	14 (39)	22 (35)	0.2
VKA duration (month)	8.3±0.6	7.7±0.4	8.1±0.3	0.2	8.7	8.4	8.5	0.3
Recurrence rate	0 (0)	3 (8.3)	3 (5.5)	0.04	0 (0)	3 (8.8)	3 (5.8)	0.2
Follow-up (months)	10.8±0.7	9.9±0.5	10.2±0.4	0.3	10.8±0.8	9.8±0.5	10.2±0.4	0.4

[a]In 2 subjects results for D-dimer at T1 was not available; VKA = Vitamin K antagonist; SD = Standard deviation; The results are presented as number (%) or mean ± SD where appropriate

Table 2: rate of primary outcomes by treatment assignment according to D-dimer at zero time

Outcomes	Normal-Dd0	Abnormal-Dd0	Total	*P* value
Death/total (%)	0/28 (0)	2/36 (5.5)	2/64 (3.1)	0.03
VTE related		1/36 (~2.7)		0.04
Ischemic heart disease related		1/36 (~2.7)		0.04
Recurrence	0/28	3/36) 8.3)	3/64 (4.6)	0.02

VTE = Venous thromboembolism

for ≤5 or >5 months, respectively (hazard ratio 1.4: 95% CI: 0.8-4.8; $P = 0.06$). Patients older than 65 years had a higher rate of events than younger patients (2/12: 16%; 95% CI: 4-24% vs. 1/52: 2%; 95% CI: 0.05-3%) and hazard ratio was about 3.8; (95% CI: 1.95-8.4 $P = 0.04$).

Table 2 shows the rate of primary outcomes by treatment assignment. Event rates were significantly higher in patients with an abnormal D-dimer did not resume anticoagulation drugs than those with a normal D-dimer.

D-dimer at T0 and T1

Patients with recurrences had higher mean D-dimer at both T0 and T1 time when compared with those without recurrences, but the difference was significant only for D-dimer at T1 (mean ± standard error; 593 ± 81 vs. 343 ± 35 ng/ml at T0, $P = 0.04$; 638 ± 57 ng/ml vs. 435 ± 35 ng/ml at T1, $P < 0.01$).

The characteristics of patients according to D-dimer at T0 and T1 time, classified as normal or abnormal (cut-off 500 ng/ml) are shown in Table 1. All patients who had an abnormal D-dimer at T0 had also an abnormal D-dimer at T1. The rate of abnormal D-dimer increased significantly at T1 when compared to T0 ($P < 0.01$). The characteristics of subjects with an abnormal or normal D-dimer either at T0 or T1 were similar except for a significant older age among subjects with abnormal D-dimer at both time points and a higher rate of males with a normal than with an abnormal D-dimer at T1.

The cumulative incidence of recurrence for D-dimer both at T0 and T1 are shown in Figure 2.

Deaths

During follow-up, two patients died (3%). The cause of death was attributed to VTE in only one subject and to ischemic heart disease in another. All these patients had abnormal D-dimer at zero time [Table 2].

When death or VTE was used as the end point of study, sensitivity of D-dimer was maintained at 100%. The VIDAS test at time of drug withdrawal had a Specificity of 67%, giving a negative likelihood ratio of 1.41. Table 3 shows the D-dimer test characteristics at two different times in this study.

The sensitivity and NPV of D-dimer at T0 and T1 was similar. Specificity was 67.3% at T0 and 79% at T1. PPV of the test was 14.3% at T0 and 23% at T1.

DISCUSSION

In this single center study, we have evaluated a population of patients with idiopathic DVT presenting to a general hospital thrombosis center.

In our cohort of DVT patients, the annual risk of recurrence with an abnormal D-dimer, either during or at 1-month after VKA withdrawal, was 4.6% which is much lower to the annual risk of recurrence in most studies with idiopathic and provoked VTE.[5] Prandoni[7] reported that the cumulative incidence of recurrent VTE was 11% and Young *et al*.[2] in 2006 showed that recurrence rate was only 4%.[2-7] According to patient selection, our results were contributed to idiopathic DVT results as shown in Young study.

Our results also demonstrated that in subjects with idiopathic DVT, an abnormal D-dimer, either at the end of treatment or at 1-month after VKA withdrawal, is associated with a higher risk of recurrence than a normal D-dimer.

In 2010, PROLOG study, confirmed that an abnormal D-dimer measured 1-month after VKA withdrawal is associated with a significantly higher risk of recurrence than normal D-diner in patients with proximal DVT of

Table 3: Calculating sensitivity and specificity and likelihood ratio for quantitative D-dimer test with cut point of about 500 ng/ml in predicting DVT recurrence

D-Dimer characteristics	Sensitivity %	Specificity %	Positive predictive value %	Negative predictive value %	Positive Likelihood ratio	Negative likelihood ratio
D-dimer at T0	100	67.3	14.3	100	1.51	1.41
D-dimer at T1	100	79	23	100	1.28	1.25

DVT = Deep venous thrombosis

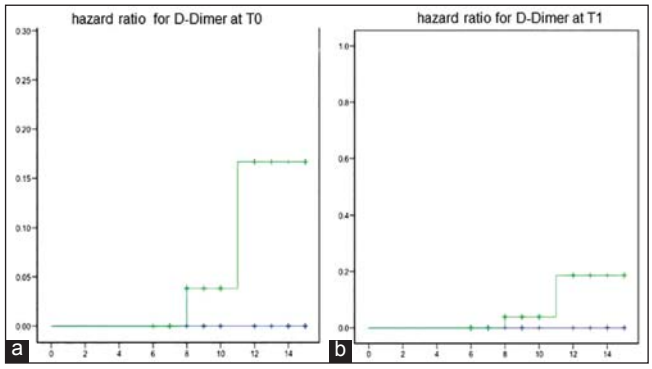

Figure 2: Hazard ratio for D-dimer at (a) T0 and (b) T1 for DVT patients

the lower limbs.[9] Besides, Bruinstroop *et al*., in 2009, showed that elevated D-dimer level measured 1-month after discontinuation of OAT identify patients with idiopathic VTE at a significantly higher risk of recurrent VTE.[10]

Results of the extended follow-up of the PROLNG study confirmed the benefit of prolonging VKAS in patients with an abnormal D-dimmer at 1-month after anticoagulation withdrawal. These results strengthen the finding that D-dimmer is associated with the individual risk of recurrence after a first episode of unprovoked VTE. The optimal course of therapy in patients with normal D-dimmer remains unclear also with the extended follow-up.

Contrary, Baglin *et al*., evaluated patients with nonsurgical provoked VTE over a median follow-up of 36 months. Results showed that post anticoagulation D-dimmer was not predictive of recurrent evens over the follow-up.[11]

The NPV of D-dimmer in our study was 100% which was near to results of verhovesk at all, (NPV of D-dimmer was 92%) and in the study by Bruinstroop *et al*. and Palareti *et al*. were 93%.[10,12,13]

The AESPUS and DACUS studies was conducted in patients with both provoked and unprovoked DVT, but only patients with unprovoked DVT were enrolled in our study.[3,14] Neither the AESPUS nor the DACUS studies evaluated RVO in combination with D dimmer, but PROLONG study do it. PROLONG study is the only randomized study evaluating both parameters.[9,15]

In our study, no effect of the presence of RVO was observed possibly due to the small number of events and the small sample size.

The study also demonstrates that patients with a confirmed diagnosis of DVT have significant cumulative mortality with rates of 3% at the end of 1st year, which was similar to Young results, with 4%, 12% and 27% at 1, 2, and 5 years, respectively.[2]

CONCLUSION

This study confirms that D-dimmer at the time of withdrawal and 1-month after VKA discontinuation is an independent risk factor for recurrent VTE after a single episode of idiopathic proximal DVT of the lower limbs and very useful for the clinicians in selecting patients at high risk of recurrent VTE.

Study limitations

This study has some limitations. The sample size was not calculated to assess the relative risk of cardiovascular events, death and cancer. Future studies should focus on determining optimal D-dimer cut-off level and optimize multi risk factor model and duration of extended therapy in patients with elevated D-dimmer levels.

AUTHORS' CONTRIBUTIONS

All authors have contributed in designing and conducting the study. All authors have assisted in preparation of the first draft of the manuscript or revising it critically for important intellectual content. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

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