Residual Venous Obstruction, alone and in Combination with D-Dimer, as a Risk Factor for Recurrence after Anticoagulation Withdrawal following a First Idiopathic Deep Vein Thrombosis in the Prolong Study

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Abstract *Objective:* This study aims to assess the predictive value of residual venous obstruction (RVO) for recurrent venous thrombo-embolism (VTE) in a study using D-dimer to predict outcome.
Design: This is a multicentre randomised open-label study.
Methods: Patients with a first episode of idiopathic VTE were enrolled on the day of anticoagulation discontinuation when RVO was determined by compression ultrasonography in those with proximal deep vein thrombosis (DVT) of the lower limbs. D-dimer was measured after 1 month. Patients with normal D-dimer did not resume anticoagulation while patients with

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abnormal D-dimer were randomised to resume anticoagulation or not. The primary outcome measure was recurrent VTE over an 18-month follow-up.

Results: A total of 490 DVT patients were analysed (after excluding 19 for different reasons and 118 for isolated pulmonary embolism (PE)). Recurrent DVT occurred in 19% (19/99) of patients with abnormal D-dimer who did not resume anticoagulation and 10% (31/310) in subjects with normal D-dimer (adjusted hazard ratio: 2.1; p = 0.02). Recurrences were similar in subjects either with (11%, 17/151) or without RVO (13%, 32/246). Recurrent DVT rates were also similar for normal D-dimer, with or without RVO, and for abnormal D-dimer, with or without RVO.

Conclusions: Elevated D-dimer at 1 month after anticoagulation withdrawal is a risk factor for recurrence, while RVO at the time of anticoagulation withdrawal is not.

The optimal duration of treatment with vitamin K antagonists (VKAs) after a first episode of unprovoked venous thromboembolism (VTE) is still uncertain.[1–3] The latest edition of the American College of Chest Physicians' guidelines recommends that patients with unprovoked VTE receive at least 3 months of anticoagulation. Later, patients should be evaluated for the risk-benefit ratio of long-term therapy.[4] Long-term treatment is recommended in those in whom risk factors for bleeding are absent and for whom good anticoagulant monitoring is achievable. This recommendation attaches a relatively high value to the prevention of recurrent VTE and a lower value to the burden of long-term therapy. However, the risk of recurrence gradually decreases in the first 6–12 months after the initial episode.[5] As a result, the benefits of extending anticoagulation should be balanced against the risk of bleeding.[1–4,6,7]

Several factors such as D-dimer, thrombophilia and residual venous obstruction (RVO) have been evaluated for their predictive value for recurrence of VTE. In previous reports,[8–10] post-anticoagulation D-dimer levels were shown to have a high negative predictive value for recurrent VTE. So far only one randomised 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.[11] The PROLONG study showed that, in patients treated with VKAs for at least 3 months for a first episode of idiopathic VTE, an abnormal D-dimer at 1 month after anticoagulation suspension was associated with a statistically significant higher risk for recurrence when compared with normal D-dimer and prolonging anticoagulation significantly reduced the risk of recurrent VTE in patients with abnormal D-dimer.[11]

Two prospective studies in single centres have shown that markers of hypercoagulability, such as D-dimer and prothrombin fragment F_{1+2}, but not RVO, are risk factors for recurrent VTE after anticoagulation suspension.[12,13] However, more recently, the AESOPUS[14] and DACUS[15] randomised studies indicated that the duration of anticoagulation could be guided by ultrasound findings as patients with recanalised veins had a lower risk of recurrence when compared with subjects with RVO. It is unknown whether RVO, alone and in combination with D-dimer, could also be a predictor of cardiovascular events and occult cancer in subjects with a first episode of idiopathic proximal deep vein thrombosis (DVT).

The aim of the present study was to assess the predictive value of RVO and D-dimer, alone and in combination, for recurrent VTE, cardiovascular events and cancer after anticoagulation withdrawal for a first episode of DVT of the lower limbs in subjects enrolled in the randomised multicentre PROLONG study.
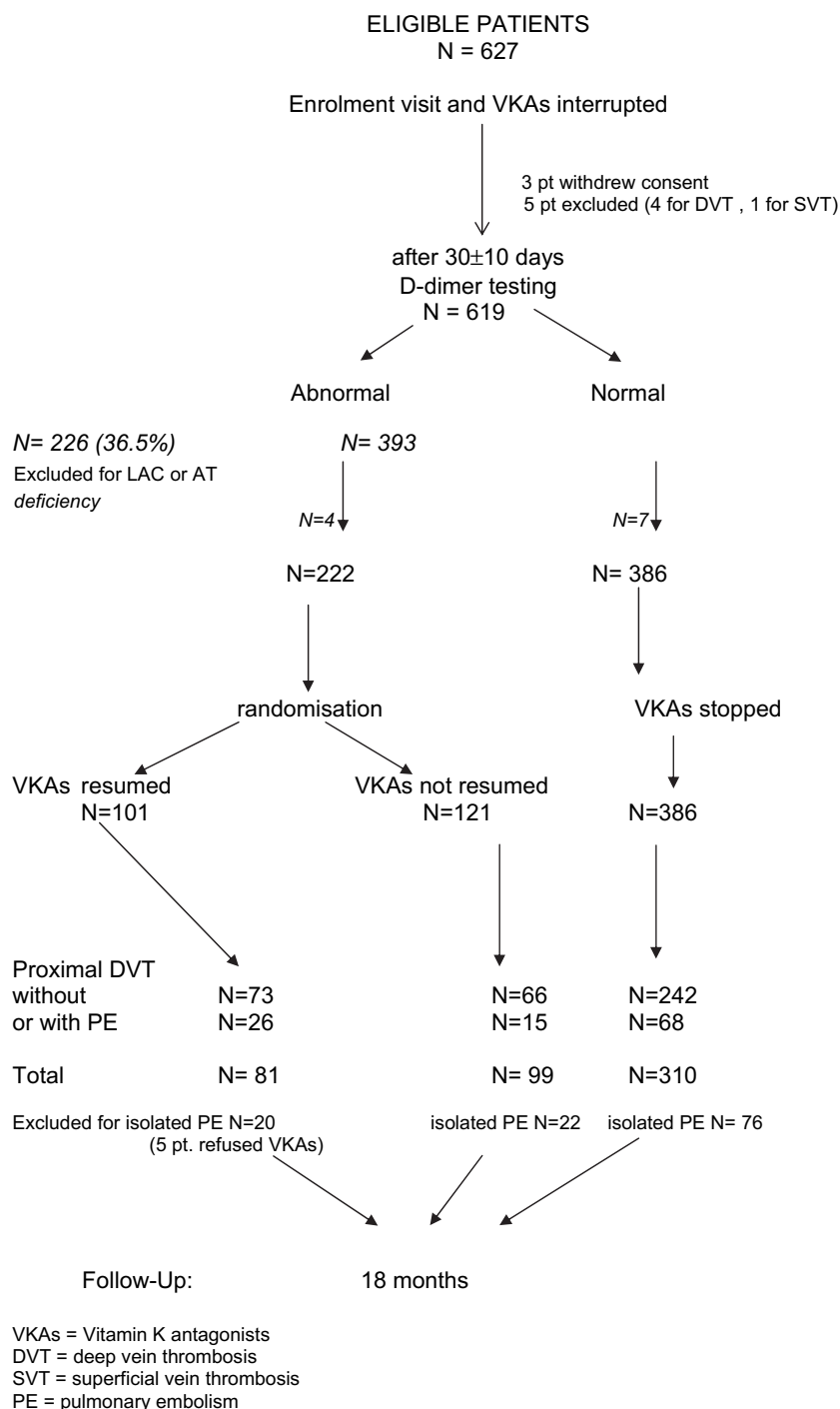
Methods

Study patients

As reported previously,[11] the PROLONG study was a multicentre randomised open-label clinical trial in patients aged 18–85 years with a first episode of objectively documented symptomatic idiopathic VTE, either proximal lower extremity DVT and/or pulmonary embolism (PE). In this *post hoc* analysis, results are reported only in the subgroup of patients with proximal DVT with or without PE. Patients were eligible after receiving at least 3 months of VKA therapy (either warfarin (Coumadin, Bristol Myers Squibb) or acenocoumarol (Sintrom®, Novartis Pharma)) with a target International normalised ratio (INR) of 2.5 (range 2.0–3.0).

Idiopathic or unprovoked VTE was defined as an episode not associated with pregnancy or puerperium, recent (i.e., within 3 months) fracture or plaster casting of a leg, immobilisation with confinement to bed for 3 or more consecutive days, surgery under general anaesthesia lasting ≥30 min, active malignancy, antiphospholipid antibody syndrome or antithrombin deficiency. Exclusion criteria were serious liver disease, renal insufficiency (plasma creatinine >2 mg dl^{-1}), other indications for anticoagulation or contraindications for such treatment, limited life expectancy or geographical inaccessibility. The institutional Ethics Committees of all participating clinical centres approved the study. Written informed consent was obtained by all enrolled patients.

Study procedures

Study procedures were previously described.[11] Briefly, at the end of the intended anticoagulation period, subjects were assessed for eligibility. Patients also underwent compression ultrasonography (CUS) of the proximal deep veins in both legs to measure the diameter of any residual thrombus in the common femoral, superficial femoral and popliteal veins according to the method of Prandoni et al.[16] In an effort to

ELIGIBLE PATIENTS
N = 627

Enrolment visit and VKAs interrupted

3 pt withdrew consent
5 pt excluded (4 for DVT , 1 for SVT)

after 30±10 days
D-dimer testing
N = 619

Abnormal   Normal

N= 226 (36.5%)   *N= 393*
Excluded for LAC or AT
deficiency
                              N=4   *N=7*
                         N=222   N= 386

                      randomisation   VKAs stopped

VKAs resumed   VKAs not resumed
N=101   N=121   N=386

Proximal DVT
without   N=73   N=66   N=242
or with PE   N=26   N=15   N=68

Total   N= 81   N= 99   N=310

Excluded for isolated PE N=20   isolated PE N=22   isolated PE N= 76
       (5 pt. refused VKAs)

Follow-Up: 18 months

VKAs = Vitamin K antagonists
DVT = deep vein thrombosis
SVT = superficial vein thrombosis
PE = pulmonary embolism

Figure 1   Prolong study flow-chart.

standardise the measurement of RVO across 30 centres, a video of a practical session showing the measurement of RVO was sent to all the participating centres.

Anticoagulation was stopped on the same day and the next visit was scheduled after 30 ± 10 days. Patients with recurrent events between discontinuation of VKA therapy and the follow-up visit were excluded from further analysis.

At the 30-day visit, venous blood samples were taken for D-dimer and thrombophilia tests. D-dimer was assessed using the Clearview Simplify D-dimer assay (Inverness Medical Professional Diagnostics, Bedford, UK and Louisville, CO, USA; kindly provided by the Instrumentation Laboratory company, Milan, Italy). This is a qualitative, fast, whole blood method, previously shown to perform well in VTE diagnosis.[17] Patients with a normal D-dimer test

Table 1 Base-line characteristics of the 490 patients with proximal DVT with or without PE.

	Normal-Dd (n = 310)[a]	All patients with abnormal-Dd (n = 180)	pc	Abnormal-Dd No VKA (n = 99)[b]	Abnormal-Dd + VKA (n = 81)	p[c]	RVO absent (n = 300)[a]	RVO present (n = 178)[b]	p[c]
Female sex n (%)	129 (41.6)	91 (50.5)	0.07	54 (54.5)	37 (45.6)	0.30	140 (46.6)	75 (42.1)	0.75
Age									
Mean±(95%CI) yr	46.9 (4.2)	70.7 (1.25)	<0.001[d]	67.8 (0.89)	79.6 (0.86)	0.26[d]	62.7 (2.8)	63.2 (2.2)	0.75[d]
≥65 yr n (%)	133 (42)	132 (73)	<0.0001	71 (72)	61 (75)	0.7	157 (52)	101 (57)	0.70
Type of venous thromboembolism n (%)									
Proximal DVT (no PE)	242 (78)	139 (77)	0.91	73 (81)	66 (81)	0.29	223 (74)	150 (84)	0.015
DVT + symptomatic PE	68 (22)	41 (13)	0.91	26 (20)	15 (19)	0.29	77 (26)	28 (16)	<0.001
Residual venous obstruction (%)	111 (37)	67 (38)	0.82	40 (42)	27 (33)	0.4	Abnormal-DD 110 (37)	Abnormal-DD 67 (38)	0.90
Congenital thrombophilic alteration/s n (%)	Examined 291	Examined 174		Examined 97	Examined 77		Examined 281	Examined 173	
	60 (21)	42 (24)	0.35	19 (20)	23 (30)	0.20	64 (23)	35 (20)	0.74
Duration of previous anticoagulant treatment n (%)									
≤6 months — n (%)	65 (21)	29 (16)	0.2	13 (13)	16 (20)	0.31	59 (20)	33 (19)	0.85
7–12 months — n (%)	149 (48)	106 (59)	0.02	61 (67)	45(56)	0.50	151 (50)	99 (56)	0.30
>12 months — n (%)	96 (31)	45 (25)	0.19	25 (25)	20 (25)	0.93	90 (30)	46 (26)	0.38
Time elapsed between enrolment and assignment to the groups									
Mean ± SD days	31 SD 9.6	33 SD 7.0	0.15[d]	33 SD 6.4	33 SD 7.6	0.81[d]	32 SD 8.3	31 SD 6.4	0.85[d]
Total duration of follow-up yr	566	314		162	152		535	331	
Follow-up Mean (95% CI) yr	1.8 (0.1)	1.8 (0.1)		1.6 (0.2)	1.9 (0.2)		1.8 (0.1)	1.9 (0.1)	

Dd denotes D-dimer; VKA = vitamin K antagonist treatment; DVT = deep vein thrombosis; PE = pulmonary embolism.
[a] In 9 subjects CUS was not available.
[b] In 3 subjects CUS was not available.
[c] P value refers to chi-squared test unless specified.
[d] t-test.

Table 2A Main outcomes by treatment assignment (intention-to-treat analysis).

Outcomes	Normal-Dd	Abnormal-Dd No VKA	Abnormal-Dd + VKA
	n. 310	n. 99	n. 81
n/n Total (%)	31/310 (10)	19/99 (19)	4/81 (4.9)
n/100 Person-Yr (%)	31/566 (5.5)	19/162 (12)	4/152 (2.6)
Type of recurrent VTE[a]			
DVT	28	16	1
DVT + PE	3	3	0
Isolated PE	0	0	1
Major bleeding episode	0	0	2

VKA denotes vitamin K antagonist treatment; Dd = D-dimer; VTE = venous thromboembolism; DVT = deep vein thrombosis; PE = pulmonary embolism.
[a] 27 DVTs occurred in the contralateral and 23 in the ipsilateral leg; 1 event was DVT of the upper limb.

did not resume VKAs, whereas those with an abnormal D-dimer result were randomly assigned to either resume or not resume VKAs (INR range 2.0–3.0) during the subsequent follow-up period of up to 18 months. A different randomisation sequence for each study site, using blocks of 10, was computer-generated and encapsulated in a randomisation computer program.

Thrombophilia testing was performed as previously reported.[11] Patients diagnosed with antiphospholipid syndrome or antithrombin deficiency resumed anticoagulation and were excluded from further analysis.

Follow-up and study outcomes

Study enrolment started in September 2002 and ended on 31 January 2005. After enrolment, patients were seen at each clinical centre at 3- to 6-month intervals. The primary outcome was the composite of confirmed recurrent VTE and major bleeding events. Patients were instructed to refer to the clinical centre immediately if they developed symptoms suggestive of VTE or bleeding.

In cases of suspected recurrent DVT, the results of CUS were compared with those of the last available previous examination. A recurrent DVT 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.[18] When thrombus diameter changed between 1.1 mm and 3.9 mm, or in cases of high/moderate clinical probability and normal CUS, the examination was repeated 5–7 days later. In patients with suspected PE, the diagnosis of recurrence was based on objective algorithms[11] using clinical probability, ventilation–perfusion lung scanning or helical computed tomography, compression ultrasonography and/or D-dimer, if indicated.

Bleeding events were defined as major if retroperitoneal or intracranial, or associated with a decrease in the haemoglobin of ≥ 2.0 g dl^{-1}, or if they required transfusion of ≥ 2 units of blood, or if surgery or invasive procedures were necessary to stop bleeding.[6]

During follow-up, cardiovascular events such as acute coronary syndromes, stroke, transient ischaemic attacks and peripheral acute thrombosis were recorded. Events were diagnosed on the basis of hospital discharge letters,

according to the international and national guideline diagnostic criteria.[19,20] Death was considered of cardiovascular origin in the absence of other known causes (e.g., cancer). Newly diagnosed cancers were also recorded with information taken from hospital discharge letters or oncological evaluation. All suspected outcome events, deaths, hospital discharge letters and clinical investigation results were evaluated by a central adjudication committee whose members were unaware of the name of the subject, the enrolling centre, the results of D-dimer, presence or absence of RVO, thrombophilia and the assigned group.

Statistical analysis

Base-line differences between groups were assessed by the chi-square test (Yates' correction) for categorical variables and t-test or Mann–Whitney U test for continuous variables, as appropriate. Data were analysed on an intention-to-treat basis. Patients who developed important clinical conditions different from the study outcomes (such as ischaemic heart disease, cancer, stroke and superficial vein thrombosis) and changed their assigned treatment were regularly followed up and included in the analysis.

Table 2B Main outcomes according to the absence or presence of RVO.

Outcomes	RVO absent[a]	RVO present[a]
	N = 246 (no VKA)[b]	N = 151 (no VKA)[c]
n/n total (%)	32/246 (13)	17/151 (11.2)
n/100 person-Yr (%)	32/535 (6.0)	17/331 (5.1)
Type of recurrent VTE		
DVT	28	15
DVT + PE	4	2
Isolated PE	0	0

VKA denotes vitamin K antagonist treatment; RVO = residual venous obstruction; VTE = venous thromboembolism; DVT = deep vein thrombosis; PE = pulmonary embolism.
[a] CUS was not available in 12 subjects (of whom 1 had a recurrent event).
[b] 1 Recurrence was observed in the group of subjects without RVO (n.55) who resumed VKA (1.8%).
[c] 1 Recurrence and 2 bleeding events were observed in the group of subjects with RVO (n.27) who resumed VKA (11.1%).

Table 3A Hazard ratios for main outcomes.

	Hazard ratios (95% CI)			
	Unadjusted	P value	Adjusted	P value
Abnormal-Dd no VKA vs. Normal Dd	2.05 (1.16—6.64)	0.014	2.07[a] (1.12—3.81)	0.02
Abnormal-Dd + VKAs vs. Normal Dd	2.1 (0.7—5.6)	N.S.	2.23[b] (0.75—6.6)	N.S.
Abnormal-Dd no VKA vs. Abnormal-Dd + VKA	4.2 (1.42—12.3)	0.009	3.76[c] (1.26—11.2)	0.018
RVO present vs. RVO absent	0.81 (0.45—1.46)	N.S.	0.74[d] (0.41—1.34)	N.S.

VKA denotes vitamin K antagonist treatment; Dd = D-dimer; CI = confidence intervals.

[a] Adjusted for sex ($p = 0.038$), age (N.S.), duration of anticoagulation before enrolment (N.S.), presence or absence of congenital thrombophilia (N.S.), presence or absence of RVO (N.S.).
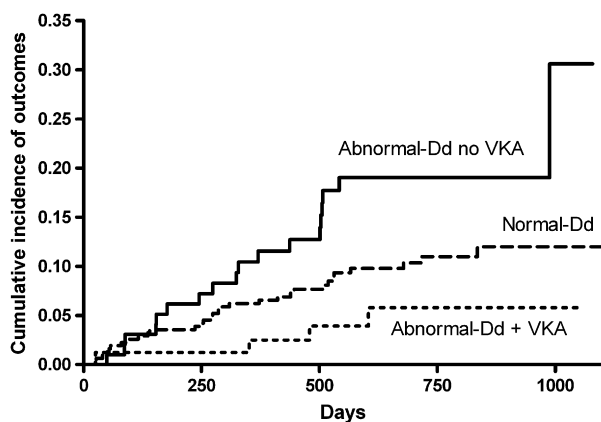
[b] Adjusted for sex ($p = 0.1$), age (N.S.), duration of anticoagulation before enrolment ($p = 0.09$), presence or absence of congenital thrombophilia (N.S.), presence or absence of RVO (N.S.).

[c] Adjusted for sex (N.S.), age (N.S.), duration of anticoagulation before enrolment (N.S.), presence or absence of congenital thrombophilia (N.S.), presence or absence of RVO (N.S.).

[d] Adjusted for sex ($p = 0.038$), age (N.S.), duration of anticoagulation before enrolment (N.S.), presence or absence of congenital thrombophilia (N.S.), D-dimer ($p = 0.02$).

Kaplan—Meier survival curves were plotted to estimate the cumulative incidence of the primary outcome of symptomatic recurrent VTE combined with major bleeding. Hazard ratios and their 95% confidence intervals were calculated using the Cox proportional hazards model. Initially an unadjusted hazard ratio was calculated. Then, a multivariate model was constructed, including age, sex, duration of anticoagulation before enrolment, presence or absence of RVO and presence/absence of factor V Leiden and/or prothrombin gene mutation. The data were analysed using the Prism statistical software package (Version 3.0, GraphPad Software Incorporated, San Diego, CA, USA) and the SPSS statistical package (Version 11.0, SPSS Inc., Chicago, IL, USA).
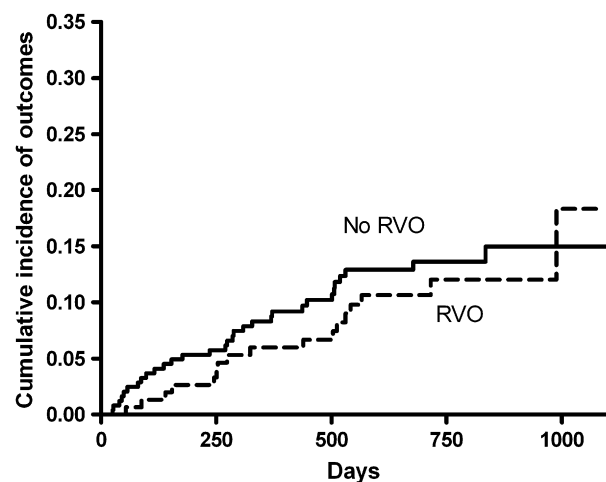
Results

Patients and treatment groups

Patients were enrolled at 30 centres of the Italian Federation of Anticoagulation Clinics. Fig. 1 shows the study flow-chart.

Among 627 patients, eight were excluded before 1 month. Of the remaining 619 patients, 226 had an abnormal D-dimer and four were excluded because of the presence of lupus anticoagulant. The remaining 222 patients were randomised to either resume or stop VKAs. For this analysis, 42 patients with isolated PE were excluded and among the remaining 180 patients with proximal DVT with or without PE, 81 patients resumed while 99 did not resume VKAs. Among 326 patients with a normal D-dimer, 76 had an isolated PE and were excluded from the analysis. This left 310 patients with proximal DVT with or without PE. Patient base-line characteristics are reported in Table 1. In general, 45% were female and 54% were aged 65 or older with a mean of 63 years. The mean duration of VKAs was 12 months (95% confidence interval (CI): 11—13). Abnormal D-dimer results were significantly more frequent in older patients. The presence of RVO was not affected by the duration of treatment, and its frequency was similar in subjects with either a normal or abnormal D-dimer. RVO was more frequently present in

Figure 2 Cumulative incidence of main outcomes according to D-dimer (Dd denotes D-dimer and VKA vitamin K antagonist treatment).

Figure 3 Cumulative incidence of main outcomes according to residual venous obstruction (RVO).

Table 3B Rate of recurrent VTE according to the combination of D-dimer and RVO.

	Recurrent VTE &		Hazard ratios (95% CI)			
	n/n total (%)	(95% CI)	Unadjusted	P value	Adjusted[a]	P value
Normal-Dd RVO absent	21/190 (11)	7—16	1	—	1	—
Normal-Dd RVO present	9/111 (8.1)	4—15	0.70 (0.32—1.54)	N.S.	0.68 (0.31—1.49)	N.S.
Abnormal-Dd RVO absent	11/56 (19.6)	10—32	2.01 (0.97—4.19)	N.S.	1.92 (0.90—4.12)	N.S.
Abnormal-Dd RVO present	8/40 (20)	9—36	1.76 (0.78—3.98)	N.S.	1.58 (0.68—3.69)	N.S.

[a] Adjusted for sex (N.S.), age (N.S.), duration of anticoagulation before enrolment (N.S.), presence or absence of congenital thrombophilia (N.S.).

patients with a previous proximal DVT without PE than in patients with proximal DVT with PE.

Total follow-up was 881 patient years with a mean of 1.8 years (range: 1—40 months). A total of 364 patients (68%) were followed for a minimum of 18 months. One patient with normal D-dimer (0.2%) was lost to follow-up.

During follow-up, 15 patients changed their assigned treatment because of the onset of various clinical conditions (11 for superficial vein thrombosis, three for atrial fibrillation and one for kidney infarction) and their subsequent follow-up was included in the analysis, according to the originally assigned treatment group.

Recurrent venous thromboembolism

Fifty-two recurrences were recorded (23 ipsilateral and 27 contralateral, one case of upper limb DVT and one case of isolated EP). RVO was present in only 22% (5/23) of patients with recurrent ipsilateral DVT.

As shown in Table 2(A), primary outcome recurrence rates were significantly higher in patients with an abnormal D-dimer randomised not to resume anticoagulation than in those who resumed VKAs or in those with a normal D-dimer, with associated hazard ratios which were statistically significant (Table 3(A)). No difference was observed between subjects with normal D-dimer and those with an abnormal D-dimer, who resumed VKAs.

As shown in Table 2(B), the rate of recurrent VTE was similar in subjects with or without RVO who did not resume anticoagulation with associated non-significant hazard ratios (Table 3(A)). Figs. 2 and 3 show the cumulative incidence of primary outcomes according to D-dimer and RVO, respectively.

When D-dimer and RVO were considered in combination (excluding patients who resumed VKAs from the analysis) as shown in Table 3(B) and Fig. 4, the rate of recurrence was similar in the two subgroups with normal D-dimer, without or with RVO, and in the two subgroups with abnormal D-dimer, without or with RVO. However, due to the small size of samples in these subgroups, the differences were not statistically significant.

Cardiovascular events, deaths and newly diagnosed cancers

During follow-up 14 cardiovascular events (2.8%; 1.6% patient years), eight deaths (1.6%; 0.9% patient years) and 18 newly diagnosed cancers (3.7%; 1.4% patient years) were recorded. Although the rate of these events was higher in subjects with abnormal D-dimer than in subjects with normal D-dimer, the difference was not significant (data not shown). No effect of RVO, alone or in combination with D-dimer, was observed on these events (data not shown).
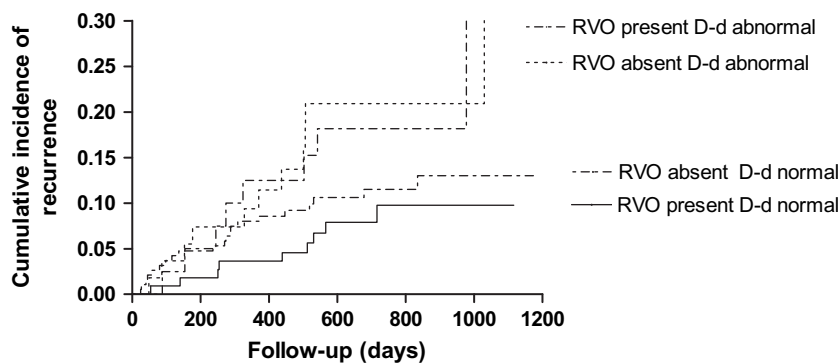
Figure 4 Cumulative incidence of main outcomes according to the combination of residual venous obstruction (RVO) and D-dimer (D-d).

Discussion

In a prospective single-centre study,[12] we showed that measuring RVO at the time of VKA withdrawal following a first episode of idiopathic DVT of the lower limbs was not predictive of VTE recurrence. Similarly, another single-centre study reported that both D-dimer and prothrombin fragment F_{1+2}, alone and in combination, at 1 month after VKA withdrawal were associated with a significant risk of recurrence after a first episode of VTE, while RVO, when measured at the time of VKA discontinuation, was not predictive of recurrences.[13] In the randomised PROLONG study,[11] we have shown that an abnormal D-dimer at 1 month after anticoagulation withdrawal for a first episode of VTE is associated with a significant risk of recurrence and patients benefit from resuming VKAs.

In this *post hoc* analysis of the PROLONG study, we evaluated the role of RVO measured at a single time point in combination with D-dimer in subjects with a first episode of DVT of the lower limbs enrolled in 30 different centres. We did not observe a significant effect of RVO at the time of VKA withdrawal on subsequent recurrences and we confirmed that an abnormal D-dimer measured 1 month after VKA withdrawal is associated with a significantly higher risk of recurrence than normal D-dimer in patients with proximal DVT of the lower limbs. We also confirmed that D-dimer is not associated with RVO and in the presence of abnormal D-dimer, RVO does not contribute to the risk of recurrence. The rate of recurrence was similar in subjects with abnormal D-dimer, either with or without RVO.

These results are in contrast to those of the AESOPUS[14] and DACUS[15] studies. These discrepancies could be explained by several factors, such as different study design and patient populations and differences in methods and timing of RVO determination and data analysis.

The AESOPUS[14] study randomised patients with both provoked and unprovoked DVT after 3 months of anticoagulation to a fixed duration of anticoagulation (no further anticoagulation for secondary DVT and an extra 3 month for idiopathic DVT) or to a flexible duration of ultrasound-guided anticoagulation (no further anticoagulation in patients with recanalised veins, continuation of anticoagulation in all other patients up to a maximum of 9 months for secondary DVT and 21 months for idiopathic DVT). RVO was measured according to the method of Prandoni et al.[16] Recurrences were higher in patients allocated to the fixed anticoagulant duration than in patients randomised to the flexible duration, for an adjusted hazard ratio of 0.62 (95% CI, 0.39–0.97).

The DACUS[15] study was also a randomised trial in which patients with a first episode of DVT both provoked and unprovoked, treated with VKAs for 3 months, were managed according to RVO findings. Those with RVO were randomised to either stop or continue anticoagulants for 9 additional months, whereas in those without RVO VKAs were stopped. Recurrent events occurred in 27% of those who discontinued and 19% of those who continued VKAs. Of the 78 (30%) patients without RVO, only one (1%) had a recurrence. The adjusted hazard ratio of patients with RVO vs. those without was 25 (95% CI, 3.4–183; P = 0.002).

In contrast to the AESOPUS[14] and DACUS[15] studies, only patients with unprovoked DVT were enrolled in our study. As no standardised and universally accepted method of RVO measurement is available, the reproducibility of this measurement could be a relevant issue across studies due to the lack of widely accepted criteria for the definition of vein recanalisation. While in the AESOPUS and PROLONG studies the method of Prandoni et al.[16] was adopted, in the DACUS study RVO was measured with CUS of the common femoral and popliteal veins and defined as a residual thrombus occupying more than 40% of the vein area calculated in the absence of compression. The DACUS study was conducted in only three centres and reproducibility was assessed only in one centre with adequate inter-observer and intra-observer variation (kappa = 0.74; 95% CI, 0.70–0.86). The AESOPUS study was conducted in nine centres without any formal assessment of RVO reproducibility and only a consensus meeting was held before the beginning of the study to agree on standard procedures. In the PROLONG study,[11] a formal intra- and inter-observer variation assessment was not conducted, due to the large number of centres, which in itself may better reflect the clinical practice of a wide variety of clinicians.

Finally, neither the AESOPUS nor the DACUS studies evaluated RVO in combination with D-dimer, as we did in the PROLONG study. So far, our study is the only randomised study evaluating both parameters, albeit with patients randomised according to D-dimer and not RVO. An abnormal D-dimer and also the presence of RVO after VKA withdrawal could be predictors of an increased risk of cardiovascular events and of occult cancer[21] but no effect of the presence of RVO was observed possibly due to the small number of events and the small sample size, which was not calculated for this secondary outcome. After anticoagulation withdrawal, some patients were started on anti-platelet agents but it was not possible to accurately retrieve these data during follow-up.

The results of this study should be evaluated with some caution. First, the trial was unblinded, and bias could not be completely ruled out, in spite of a blinded central adjudication committee and the conduction of a *post hoc* analysis. However, event rates in the treated and untreated patients (both with abnormal and normal D-dimer) are in the range of those reported in the literature. Second, while RVO was measured on the day of VKA discontinuation, D-dimer was tested after 30 ± 10 days. Although RVO, when present on the day of VKA withdrawal, could be absent after 30 ± 10 days, it was absent at the subsequent CUS evaluation (i.e., at 3 months after VKA withdrawal), only in 21/178 (12%) of the patients with RVO on the day of VKA withdrawal. This seems to indicate that RVO is quite stable and thus, if present at the time of VKA withdrawal, its absence is unlikely after 30 ± 10 days. Our patients had undergone different VKA periods when RVO and D-dimer were determined; however, the duration of VKA treatment did not seem to influence either D-dimer or RVO at the time of VKA withdrawal.

Although RVO could bias the diagnosis of ipsilateral recurrent DVT, recurrences were ipsilateral in only 23 cases and RVO was present in five (22%) of subjects with recurrent ipsilateral DVT, suggesting a lack of association of RVO with ipsilateral recurrence. Investigators evaluating suspected

recurrences were aware of the characteristics of the index event but unaware of thrombophilia and D-dimer results.

In conclusion, the PROLONG study confirms that D-dimer at 1 month after VKA withdrawal is an independent risk factor for recurrent VTE after a single episode of idiopathic proximal DVT of the lower limbs and that a single measurement of RVO at the time of VKA withdrawal neither predicts late recurrences nor does it increase the risk of recurrences in the presence of an abnormal D-dimer.

Conflict of interest

Drs. Palareti, Cosmi, Legnani, Pengo, Testa and Tripodi report having been paid lecture fees by the Instrumentation Laboratory company.

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Appendix

Study sites and investigators[i] (all the participating centres are affiliated in the Italian Federation of Anticoagulation Clinics — FCSA; numbers in parentheses are the numbers of patients who underwent randomisation):

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Adjudication Committee: A. Ghirarduzzi (Reggio Emilia), C. Pattacini (Parma), V. Pengo (Padua).

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