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Normalization rates of compression ultrasonography in patients with a first episode of deep vein thrombosis of the lower limbs: association with DVT recurrence and new thrombosis

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Background and Objectives. Delayed thrombus regression after a first episode of deep vein thrombosis (DVT) of the inferior limbs has been implicated in the development of the post-thrombotic syndrome. Whether normalization of vein segments involved in the index DVT has prognostic significance with respect to the probability of DVT recurrence or new thrombosis is currently unknown. In this study, we prospectively monitored thrombus regression in consecutive patients with symptomatic and asymptomatic DVT. Factors affecting normalization rates and the relationship between previous normalization and DVT recurrence or new thrombosis were explored.

Design and Methods. One hundred and seventy-nine patients with a first episode of symptomatic DVT of the lower limbs (38 with cancer) and 104 patients with DVT occurring after hip replacement surgery were serially monitored by real time B-mode compression ultrasonography (C-US) over a period of 12 months (months 1, 3, 6 and 12). C-US normalization of popliteal and femoral venous segments was arbitrarily assigned to be residual thrombus occupying, at maximum compressibility, less than 40% of the vein area in the absence of compression.

Results. In patients with no DVT recurrence or new thrombosis, C-US normalization was observed at 12 months in 100% of 99 patients with post-operative DVT, in 59% of 134 cancer-free symptomatic DVT outpatients and in 23.3% of 30 symptomatic DVT outpatients with cancer ($p = 0.0001$). Independent negative effects on the probability of C-US normalization were observed for younger age ($p < 0.05$), for the outpatient presentation of the index DVT ($p \leq 0.017$), for DVT involving the entire femoro-popliteal axis ($p \leq 0.05$), and for the presence of cancer ($p \leq 0.05$). DVT recurrence or new thrombosis was observed in 5 patients with post-operative DVT (4.8%), in 7 cancer-free patients with symptomatic DVT (5.0%) and in 8 patients with cancer (21.1%). Only 4 of these patients had shown normalization of their index DVT prior to the event. The presence of cancer was the only significant predictor of DVT recurrence and/or new thrombosis occurring within 3 months from the index DVT (OR = 4.90, $p = 0.002$). The absence of previous C-US normalization was the only predictor of recurrence or new thrombosis occurring after 3 and 6 months from the index DVT (OR ≥ 5.26, $p \leq 0.027$).

Interpretation and Conclusions. Absence of C-US normalization after a first episode of DVT appears to be a factor favoring recurrence or new thrombosis and may be relevant to the optimal duration of oral anticoagulant treatment.

Key words: acute deep vein thrombosis, compression ultrasonography, DVT resolution, DVT recurrence.

A number of studies evaluated thrombus regression by compression ultrasonography (C-US) in patients with symptomatic deep vein thrombosis (DVT) of the lower limb. Normalization rates at 6 months after a first episode of DVT ranged from 24% to 44% of normalized patients[1,2] to 70%-78% of normalized venous segments,[3,4] Corresponding figures at 1 year or later ranged from 36% to 96% of normalized patients[2,5-11] and from 81% to 84% of normalized venous segments.[12,13] Thrombus burden,[1,4-6,8,12-14] age,[5] immobilization,[15] previous occurrence of recurrent episodes,[5,6] occlusiveness of the initial clot,[6] and duration of symptoms prior to treatment[6] were found to be unfavorable factors for normalization. No information is presently available on normalization rates of patients with asymptomatic post-operative DVT.

A slow rate of normalization has been related to the occurrence of late sequelae of DVT, such as reflux and post-phlebitic syndrome,[6,7,9,10,12] but knowledge of normalization rates in symptomatic and asymptomatic DVT patients might have clinical relevance also with respect to the prediction of recurrent events. The optimal duration of anticoagulation aimed at preventing recurrence of DVT is still a matter of debate. The early suggestion that

a 3-month course of oral anticoagulation may provide a reasonable balance between reducing recurrence and avoiding undesired excess bleeding complications[16,17] has been challenged by data showing a lower recurrence rate with a six-month course of oral anticoagulation.[18] However, even oral anticoagulant treatment lasting one year was recently judged unsatisfactory in preventing recurrence in patients with idiopathic DVT.[19] Whether normalization of vein segments involved in the index DVT has prognostic significance with respect to the probability of DVT recurrence or new thrombosis is currently unknown. If this were the case, C-US normalization may represent an important factor in the individual tailoring of oral anticoagulant treatment for patients with a first episode of deep vein thrombosis of the lower limbs. Although in some of the aforementioned studies recurrent DVT occurred in 8% to 31% of the patients,[8,9] no association was reported between normalization rates and likelihood of DVT recurrence.

In this study, we prospectively monitored C-US normalization rates in consecutive patients with symptomatic and asymptomatic DVT. Factors affecting C-US normalization rates and the relationship between previous C-US normalization and DVT recurrence or new thrombosis were explored.

Design and Methods

Patients

Two categories of patients with a first episode of DVT were considered for inclusion in the study: a) consecutive symptomatic outpatients with C-US-detected DVT of the lower limbs referred by general practitioners, and b) consecutive patients with DVT of the lower limbs detected by C-US and confirmed by venography after hip replacement surgery. Symptomatic patients were submitted to real time B-mode C-US on the day of referral. Postoperative patients were monitored by serial C-US on days 5 and 9 after hip surgery;[20] C-US findings were confirmed by ascending venography on postoperative day 10.

After diagnosis, patients were treated with unfractionated or low-molecular-weight heparin for 5 to 7 days. Oral anticoagulants were administered within 3 days of heparin treatment which was discontinued when INR values were greater than 2.0 on 2 consecutive days.

Patients were invited to undergo serial C-US examinations 1, 3, 6, and, if normalization of C-US findings (see below) had not occurred, 12 and 24 months after the index DVT. They were advised to wear graduated compression stockings and to contact our Institutions in the event of symptoms of recurrent or new DVT.

Real time B-mode compression ultrasonography

Trained examiners performed C-US as previously described.[21] Images were obtained in transverse planes only, after accurate search for the minimal vein diameter, using a portable Aloka DS 500, with a 7.5 MHz linear array transducer. Lumen compressibility was evaluated on the common femoral and popliteal venous segments by gentle pressure of the probe. The major and the minor diameters of the venous segments were measured and recorded before and after compression. Before analyzing the data, C-US findings were arbitrarily scored as normalized when residual thrombus occupied, at maximum compressibility, less than 40% of the vein area calculated in the absence of compression.

Recurrent events

In patients with a clinical suspicion of DVT recurrence, the following diagnostic criteria were applied. If complete C-US normalization had previously occurred, a new non-compressibility of the same venous segment(s) originally involved by thrombosis was considered diagnostic. In the absence of previous C-US normalization, DVT recurrence was diagnosed if a previously non-occlusive thrombus had changed to an occlusive thrombus, provided the vein area before compression had increased by more than 50%.[22] DVT recurrence was also diagnosed if a previously fully compressible venous segment – ipsilateral with respect to the original DVT – had become non-compressible at follow-up. In the absence of symptoms, a variation in the area occupied by residual thrombus was not considered diagnostic of DVT recurrence. In postoperative DVT patients, recurrence of DVT as detected by C-US according to aforementioned criteria was always confirmed at venography.

New thromboses were diagnosed by C-US if they occurred in the contralateral leg, originally free of DVT.

Statistical analysis

A statistical software program (Systat 7.0) was used for all calculations. Continuous variables were compared by Kruskal Wallis analysis of variance and Mann-Whitney's U test. Proportions, with 95% confidence intervals, were compared by the χ^2 statistics. Odds ratios and 95% confidence intervals are reported. Unadjusted cumulative probabilities of C-US normalization obtained by actuarial life table analysis were calculated separately for different groups of patients in relation to DVT pre-

sentation (post-operative or not), presence of cancer, topographical distribution of DVT and later occurrence of DVT recurrence and/or new thrombosis. For patients with C-US normalization who had not undergone the previous C-US examination but were still not normalized at a preceding examination, normalization was considered to have occurred at the intermediate time. Relative risks of C-US normalization at 1, 3, 6 and 12 months contributed independently by selected variables were evaluated by logistic regression analysis. Relative risks of DVT recurrence or new thrombosis at 1, 3, and 6 months contributed independently by selected variables were also evaluated by logistic regression analysis.

Results

Baseline characteristics of DVT patients

One hundred and four patients were included in the post-operative DVT group. They were all recruited in Pavia, and 12 patients (11.5%) had signs and/or symptoms suggestive of venous obstruction at diagnosis. Fifty-eight of the 179 outpatients with symptomatic DVT were recruited in Pavia, and 38 (21.2%) had active cancer at the time of DVT. The demographic characteristics of patients and the topography of DVT are shown in Table 1.

Post-operative patients were older than symptomatic outpatients (p <0.0001) Women were more represented than men in all but cancer patients (p <0.01). The right and the left leg were affected by DVT to a similar extent, but femoro-popliteal DVT was more common in symptomatic outpatients than in post-operative patients (p < 0.0001).

All post-operative patients received oral anticoagulation for 3 months. Fifty-two percent of cancer-free outpatients with symptomatic DVT were anticoagulated for 3 months, 24% received oral anticoagulants for 4 to 8 months and 24% for ≥ 9 months. Twenty-nine percent of cancer patients received oral anticoagulants for 3 months, 32% for 4 to 8 months, and 39% for ≥ 9 months.

C-US normalization at follow-up

Of the 283 patients, 27 (9.5%), 32 (11.3%), 28 (9.9%) and 41 (14.5%) did not undergo C-US examination at month 1, 3, 6 and 12, respectively. Cumulative normalization rates during the one-year follow up, after exclusion of 20 patients with DVT recurrence or new thrombosis, are reported in Table 2. One year after their first DVT all post-operative patients had C-US normalization compared to 59% (95% C.I.: 47.9-68.8) of cancer-free symptomatic patients (p< 0.0001) and 23.3% (7.1-45.3) of symptomatic patients with cancer (p<0.01). Because at any time considered, cumulative normalization rates were not significantly different when considering the entire series of patients or only patients attending C-US examination (Table 2), these estimates are unlikely to be biased by the loss of patients at follow-up.

Cumulative probabilities of C-US normalization according to DVT presentation, presence of cancer and extension of thrombosis are reported in Figure 1. The mean C-US normalization time was 3.4 months in post-operative DVT patients, 7.1 months in cancer-free symptomatic outpatients and 10.3 months in symptomatic DVT outpatients with cancer (p<0.0001, Figure 1, left panel). The mean C-US normalization time was not significantly different in patients with isolated popliteal or femoral DVT (4.1 vs. 3.1 months), but it was longer in patients with femoro-popliteal DVT (8.4 months, p<0.0001, Figure 1, right panel). Variables independently affecting C-US normalization were analyzed at 1,

Table 1. Demographic characteristics of patients and topography of DVT.

	n.	*Age (yrs, mean ± SD and range*	*Gender (F/M)*	*Leg affected by DVT n, (%)*			*Venous segments affected by DVT n, (%)*		
				Right	*Left*	*Both*	*Femoral*	*Popliteal*	*Femoro-popliteal*
Post-operative patients	104	71.9 ± 6.3 (45-82)	80/24	43 (41.4)	58 ((55.8)	3 (2.9)	18 (17.3)	57 (54.8)	29 (27.9)
Cancer-free symptomatic outpatients	141	60.5 ± 17.2 (12-92)	86/55	58 (41.1)	78 (55.3)	5 (3.6)	14 (9.9)	50 (35.3)	77 (54.6)
Symptomatic outpatients with cancer	38	62.1 ± 14.2 (10-84)	20/18	17 (44.7)	19 (50.0)	2 (5.3)	5 (13.1)	6 (15.8)	27 (71.1)
All patients	283	64.9 ± 14.7 (10-92)	186/97	118 (41.7)	155 (54.8)	10 (3.5)	37 (13.1)	113 (39.9)	133 (47.0)

Table 2. Cumulative rates of C-US normalization in patients with post-operative DVT and in outpatients with symptomatic DVT divided according to the presence or absence of cancer, after exclusion of patients with DVT recurrence and/or new thrombosis. Normalization rates are calculated with respect to all patients or to patients actually examined at follow-up as the denominator term.

		Month 1	*Month 3*	*Month 6*	*Month 12*
Post-operative patients	All patients (n, cumulative %, 95% C.I.)	30/99 30.3 (19.5-42.2)	71/99 71.7 (59.1-81.6)	92/99 92.9 (83.5-97.5)	99/99 100 (94.6-100)
	Patients attending follow-up (n, cumulative %, 95% C.I.)	30/95 31.6 (20.3-43.8)	71/97 73.2 (60.5-82.9)	92/97 94.8 (85.9-98.5)	99/99 100 (94.6-100)
Cancer-free symptomatic outpatients	All patients (n, cumulative %, 95% C.I.)	19/134 14.2 (7.6-22.6)	48/134 35.8 (25.8-46.2)	71/134 53.0 (42.0-63.2)	79/134 59.0 (47.9-68.8)
	Patients attending follow-up (n, cumulative %, 95% C.I.)	19/121 15.7 (8.4-24.9)	48/125 38.4 (27.8-49.2)	71/131 54.2 (43.1-64.4)	79/123 64.2 (52.7-74.0)
Symptomatic outpatients with cancer	All patients (n, cumulative %, 95% C.I.)	1/30 3.3 (0.0-19.8)	3/30 10.0 (0.8-29.4)	6/30 20.0 (5.2-41.6)	7/30 23.3 (7.1-45.3)
	Patients attending follow-up (n, cumulative %, 95% C.I.)	1/28 3.6 (0.0-21.1)	3/29 10.3 (0.9-30.3)	6/29 20.7 (5.4-42.8)	7/23 30.4 (9.5-56.1)

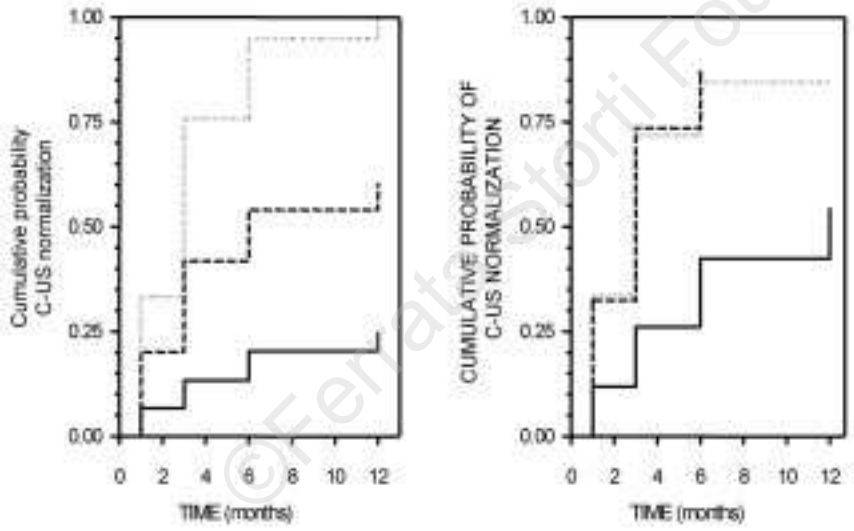

Figure 1. Unadjusted cumulative probabilities of C–US normalization in different groups of patients with deep vein thrombosis during the one-year follow-up. Left panel: post-operative patients (dotted line); cancer-free symptomatic patients (dashed line); symptomatic outpatients with cancer (solid line). Right panel: patients with isolated popliteal DVT (dotted line); patients with isolated femoral DVT (dashed line); patients with femoropopliteal DVT (solid line).

3, 6 and 12 months from the index DVT (Table 3). At 1 month, extension and presentation of the index DVT were the only variables independently affecting C-US normalization (p <0.05). At subsequent examinations, the probability of C-US normalization was higher in older patients, in post-operative DVT patients, in patients with only one venous segment involved by thrombosis, and in cancer-free patients (Table 3).

DVT recurrence and new thrombosis

During the 12 month follow-up, 27 patients complained of symptoms of DVT recurrence or new thrombosis. Symptoms suggestive of pulmonary embolism were not reported by any patient. Based on the diagnostic criteria selected, DVT recurrence or new thrombosis – occurring in 5 cases within 6 months from the index DVT - were detected in 20 patients (12 women and 8 men, mean age 60.3 ±

Table 3. Predictors of C-US normalization at 1, 3 , 6 and 12 months after the index DVT in patients presenting no recurrence or new thrombosis at follow-up (logistic regression analysis).

	Month 1		*Month 3*		*Month 6*		*Month 12*	
	OR (95% C.I.)*	*p*	*OR (95% C.I.)*	*p*	*OR (95% C.I.)*	*p*	*OR (95% C.I.)*	*p*
Age°	–	ns	0.98 (0.95-0.99)	0.036	0.97 (0.94-0.99)	0.004	0.97 (0.95-0.99)	0.035
One venous segment vs. more venous segments	2.39 (1.17-4.86)	0.017	5.44 (2.99-9.91)	0.0001	6.22 (3.11-12.45)	0.0001	4.21 (1.96-9.04)	0.0001
Post-operative vs. symptomatic DVT outpatients	2.12 (1.01-4.49)	0.049	4.49 (2.26-8.92)	0.0001	21.0 (7.33-60.0)	0.0001	–	0.0001
No cancer vs. cancer	–	ns	4.44 (1.20-16.45)	0.026	3.64 (1.26-10.49)	0.017	3.71 (1.41-9.98)	0.008

**Odds ratio and 95% confidence interval. °Per year of age. Gender, DVT location (right or left leg), and center of patient recruitment had no significant effect on normalization rates.*

19.6 years). Recurrence of DVT was established in 15 patients (5.3%, 2.5-9.3), while 5 patients had a new DVT in a different site (1.8%, 0.4-4.6). Recurrent DVT was observed in 5 patients with post-operative DVT (4.8%, 1.0-12.1) and 10 outpatients with symptomatic DVT (5.6%, 2.1-10.9). DVT recurrence or new thrombosis was significantly more frequent in cancer patients (OR = 5.11, 1.7-17.1, $p = 0.004$) than in the remaining patients. The time frame (median and range) for DVT recurrence or new thrombosis was similar in the different groups of patients; however, new thromboses, only observed in symptomatic outpatients, occurred earlier than DVT recurrences (3 months, 2-9 vs. 9 months, 2-9, $p = 0.007$). Four of 5 new thromboses versus 3 of 15 recurrences ($p = 0.015$) occurred while patients were on oral anticoagulant treatment.

Recurrent or new DVT occurred in the absence of normalization of the index DVT in 16 of 20 patients (80%, 48.4-95.1). C-US normalization prior to DVT recurrence or new thrombosis was observed at 1 month in one patient and at 3 months in 3 patients (2 cancer patients). All recurrences observed in patients with post-operative index DVT (n = 5) occurred in the absence of previous C-US normalization. Probabilities of DVT recurrence and/or new thrombosis were 4.46 (0.61-44.8), 3.46 (1.05-12.6) and 8.08 (2.44-29.6) times higher in patients without C-US normalization at 1, 3 and 6 months after their index DVT than in patients with C-US normalization at the corresponding times.

Age, gender, extension of DVT, presence of cancer, and previous C-US normalization were analyzed as predictors of DVT recurrence and/or new thrombosis 1, 3 and 6 months after the index DVT. At one month after the index DVT, the presence of cancer was the only variable predicting recurrence and/or new thrombosis (OR = 4.90; 1.76-14.3, $p = 0.002$). The absence of previous C-US normalization was the only significant predictor of recurrence and/or new thrombosis occurring 3 (OR = 5.66; 1.22-26.14, $p = 0.027$) and 6 months (OR = 5.26; 1.58-17.54, $p = 0.007$) after the index DVT. Cancer-free patients with no C-US normalization at 3 or 6 months after the index DVT had 11.55 (1.45-91.8, $p = 0.02$) and 11.29 (2.37-53.6, $p = 0.002$) greater probabilities of suffering recurrence and/or new thrombosis than cancer–free patients with C-US normalization.

Discussion

In this inception-cohort study, C-US normalization rates over a period of one year were evaluated in a large number of patients with a first episode of symptomatic or post-operative acute DVT. The characteristics of patients, topography of DVT, and prevalence of cancer at the time of enrollment in the study were similar to those reported in previous studies of acute DVT of the lower limbs.[8,9,23-25] Thrombophilia defects were not systematically investigated, but the mean age of symptomatic outpatients at their first event does not suggest a selection bias.

The criteria selected for definition of C-US normalization of previously occluded venous segments were chosen arbitrarily. A 60% reduction of the apparent thrombus size perpendicular to the vein axis was considered significant to permit unimpeded blood flow in the originally occluded vein, but in more than 75% of the cases no residual

thrombus was observed at the time of C-US normalization. C-US normalization rates were evaluated in patients who did not suffer DVT recurrence or new thrombosis within the first year of follow-up. The extension of thrombosis, the outpatient status and cancer all negatively influenced normalization rates. The mean C-US normalization time of patients with femoro-popliteal DVT was two times longer than that of patients with isolated femoral or popliteal DVT. Normalization rates were higher in patients with post-operative DVT than in outpatients with symptomatic DVT. The mean C-US normalization time was two times longer in cancer-free symptomatic outpatients than in post-operative patients and it was even longer in DVT outpatients with cancer. Thus, 6 months after the acute DVT, C-US normalization was observed in 93% of post-operative patients vs. 53% of cancer-free outpatients and in only 20% of outpatients with cancer. These results obtained in a large series of patients are in line with those reported in small series by other authors who showed greater complete C-US normalization in patients with isolated femoral or popliteal DVT than in those with femoro-popliteal DVT,[1,5,6,8,9,12-14] Because the outpatient status and thrombus extension independently influenced C-US normalization, the higher normalization rate of post-operative patients cannot be only attributed to a lower prevalence of femoro-popliteal DVT observed in these patients relative to in symptomatic DVT outpatients. Only 12 of the 104 post-operative patients – as opposed to 100% of symptomatic outpatients – presented with totally occlusive thrombi, in the absence of a clinical suspicion of DVT by the attending physician. It is likely that occlusive thrombi may undergo normalization at a much lower rate than non-occlusive thrombi, as suggested by animal experiments.[26] An additional explanation stems from the earlier anticoagulant treatment received by these patients because of post-operative serial C-US screening, possibly influencing thrombus extension, organization and resolution.[6,27] Irrespective of factors responsible for earlier normalization, these data are a strong indication that C-US may be a reliable tool in the diagnosis of DVT recurrence in orthopedic patients with post-operative DVT.

Venography was used in all post-operative patients to establish the presence of DVT recurrence. For patients with a symptomatic index DVT, and in line with the criteria recommended by Prandoni *et al.*,[22] only a greater than 50% increase in the vein area, fully uncompressible, was taken as evidence of DVT recurrence in a vein segment not normalized at a previous C-US examination. The one-year incidence of DVT recurrence and/or new thrombosis was 4.8% in post-operative patients, 5.0% in cancer-free symptomatic patients and 21.1% in cancer patients. Whereas the estimates obtained for post-operative and cancer patients in this study are substantially similar to those reported in the literature,[16,25] the estimate for the incidence of recurrent DVT in cancer-free symptomatic outpatients is lower than expected.[16-18] It should, however, be remarked that over 18% of symptomatic outpatients received oral anticoagulant treatment for the entire duration of follow-up. Three cancer-free patients and 4 patients with cancer had events while on treatment, with these events representing 80% of all new thromboses vs. only 30% of all DVT recurrences occurring in symptomatic outpatients. Our study shows, for the first time, the strict association between non-normalization of C-US findings and an increased risk of DVT recurrence or new thrombosis. Crude odds ratios for recurrent events 6 months after the index DVT were 8-fold higher in patients not showing C-US normalization than in the remaining patients. When accounting for events occurring within 3 months from the index DVT, the presence of cancer was a highly significant predictor of DVT recurrence or new thrombosis. However, for events occurring 3 months after the index DVT, thrombus persistence was the only independent predictor of DVT recurrence or new thrombosis. Because cancer was also a major risk factor for thrombus persistence, the relationship between C-US normalization and recurrence of events was also analyzed in cancer-free patients. In this group, patients without C-US normalization had a greater than 10-fold higher risk of recurrent events than did patients with C-US normalization. These data are suggestive of a strong, direct or indirect association between thrombus persistence and DVT recurrence.

Studies analyzing the optimal duration of oral anticoagulation in patients with a first episode of DVT did not evaluate, for practical reasons, persistence of thrombus as a risk factor for recurrent events. Recent reviews[28,29] recommend that patients with post-operative venous thromboembolism should receive anticoagulant treatment for at least 3 months, patients with idiopathic DVT for at least 6 months and patients with persistent risk factors (metastatic cancer, certain hypercoagulable states) for longer periods of time. Our data suggest that in post-operative patients C-US examinations carried out at 3 months may support prolonged

anticoagulation for the subgroup of patients who have not shown thrombus resolution. Similarly, cancer-free outpatients with symptomatic DVT may benefit from C-US examinations at 6 and 12 months for optimal judgement about the individual duration of oral anticoagulant treatment. Patients with cancer and with certain hypercoagulable states are probably candidates for life-long anticoagulation[28,29] irrespective of C-US normalization, as also suggested by the occurrence of new thromboses in our series.

In conclusion, our findings show a strong association between failure of DVT resolution at C-US and risk of future recurrent events. Occurrence of C-US normalization should be taken into account in future trials evaluating the optimal duration of anticoagulant treatment in patients with a first episode of DVT.[30]

Contributions and Acknowledgments

FP and ADA designed the study, were responsible for data management and prepared the manuscript. LG collaborated in data management and was responsible for statistical evaluation. LC, MB, SVD, SS and CB were responsible for data collection and patient care and collaborated in the preparation of the manuscript.

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Disclosures

Conflict of interest: none.

Redundant publications: no overlapping with previous papers.

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Peer Review Outcomes

Manuscript processing

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What is already known on this topic

Delayed thrombus regression after a first episode of deep vein thrombosis (DVT) of the inferior limbs has been implicated in the development of the post-thrombotic syndrome.

What this study adds

This study investigates whether several factors could have prognostic significance with respect DVT recurrence or new thrombosis.

Potential implications for clinical practice

Absence of compression ultrasonography normalization after a first deep vein thrombotic episode appears a factor favouring recurrence. Moreover, this observation may help to indicate the optimal duration of oral anticoagulant treatment.

Vicente Vicente, Deputy Editor