Early outcome after isolated calf vein thrombosis

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Purpose: **The clinical significance of isolated calf vein thrombosis (CVT), particularly with respect to development of the postthrombotic syndrome, remains controversial. The purpose of this study was to define the early natural history of CVT in relation to persistent lower extremity symptoms, propagation, recanalization, and the development of valvular incompetence.**
Methods: **Over a 116-month period, 499 patients with acute deep venous thrombosis (DVT) were referred to our research laboratory, of whom 58 (12%) had thrombosis confined to the calf veins of at least one extremity. The lower extremities of 268 patients (29 with isolated CVT) were followed-up clinically and with duplex ultrasonography at intervals of 1 day, 7 days, 1 month, every 3 months for the first year, and yearly thereafter.**
Results: **Seventy percent of extremities with CVT were symptomatic at presentation. Although the prevalence of clinical signs and symptoms decreased to 29% by 1 month, 23% of patients had persistent pain, edema, or both at 12 months. In contrast, 9% of uninvolved extremities contralateral to a CVT and 54% of extremities with proximal DVT remained symptomatic at 1 year ($p = 0.004$). Recanalization proceeded rapidly such that the mean thrombus load was reduced by 50% at 1 month and to zero at 1 year. The prevalence of valvular incompetence progressively increased such that reflux was present in 24% of extremities at 1 year. Although its investigation was not a primary goal of this study, pulmonary embolism was diagnosed at presentation and during follow-up in 11% and 3% of patients, respectively.**
Conclusions: **The natural history of CVT is complicated by persistent symptoms and the development of valvular incompetence in approximately one-quarter of patients. This potential for persistent lower extremity symptoms should be considered in evaluating the clinical relevance of isolated calf vein DVT. (J Vasc Surg 1997;26:749-56.)**

In defining the natural history of acute deep venous thrombosis (DVT), a distinction is often made between involvement of the proximal and distal (calf) veins. This differentiation arises from perceived differences in the incidence of the two primary complications of DVT, pulmonary embolism (PE) and the postthrombotic syndrome. The risk of these complications after a proximal thrombosis has been well defined over the past several years.[1,2] Correspondingly, multiple clinical trials have assisted in defining the optimal management of proximal DVT, particularly with respect to minimizing thrombus propagation and PE.[3-5]

Isolated calf vein thrombosis (CVT) is thought to be associated with a substantially lower risk of PE,[6,7] although the significance of this risk remains controversial.[8-11] The relationship between CVT and the postthrombotic syndrome is even more poorly defined and is often not considered in discussing the clinical significance of CVT. Although such thrombi may undergo rapid spontaneous lysis,[12] their distal anatomic location poses a theoretical risk for the ultimate development of postthrombotic syndrome.[1] Given these limitations, it is not surprising that the optimal management of isolated calf vein thrombosis, including the need for anticoagulation, remains controversial.

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The purpose of this study was to define the early natural history of isolated CVT in a series of patients who were followed-up with serial clinical and duplex ultrasound evaluations.

METHODS

All patients who had an acute lower extremity DVT documented by duplex ultrasonography at the University of Washington Medical Center have been asked to participate in a longitudinal study of the natural history of acute DVT. Patients who consent to participate are requested to return for clinical and duplex ultrasound examinations of the lower extremities at intervals of 1 and 7 days; 1, 3, 6, 9, and 12 months; and yearly thereafter. At each visit, patients are questioned about lower extremity symptoms; their limbs are evaluated for edema, hyperpigmentation, and ulceration; and a detailed ultrasound examination of all deep venous segments from the inferior vena cava to the tibial veins is performed. Ultrasound evaluation includes an assessment of the paired posterior tibial and peroneal veins as well as the sural veins. Isolated thrombosis of the anterior tibial veins is uncommon,[13] and these segments were not routinely imaged. The results of all studies are communicated to the patients' primary physician, who makes all treatment decisions. Only patients who have pulmonary symptoms underwent further diagnostic studies for PE, and this was at the discretion of their primary physician. The study protocol has been approved by the Human Subjects Committee at the University of Washington.

Duplex examinations were performed in 15 degrees reverse Trendelenburg (feet down) position using an Ultramark 8 or 9 scanner (Advanced Technology Laboratories, Bothell, Wash.). A 5 MHz pulsed Doppler was used for evaluation of the proximal venous segments, and a 10 MHz transducer was used for the tibial veins. Beginning in 1990, a 5 MHz linear array color transducer was used to facilitate visualization of the tibial veins. Examinations included an evaluation of flow characteristics and compressibility as well as an assessment of reflux in response to Valsalva's and compression maneuvers. All venous segments were classified as completely occluded, partially occluded, or patent. An incompressible segment without flow by either pulsed or color flow Doppler was considered completely occluded, whereas an incompressible segment with flow present was considered partially occluded. As spontaneous flow may be normally absent in the calf veins, a completely compressible vein that demonstrated flow with or without distal augmentation was defined as patent.

Thrombi isolated to the posterior tibial, peroneal, or sural veins were defined as CVTs; those involving venous segments from the vena cava to the popliteal vein were considered proximal thromboses. A tibial thrombosis score was calculated for each extremity with CVT on the basis of a modification of the SVS/ISCVS reporting standards in venous disease.[14] For each calf vein, including the sural veins, the thrombus load was scored as 2 if completely occluded, 1 if partially occluded, and 0 if patent. An extremity without thrombosis of any calf vein would therefore be given a score of 0, whereas a limb with complete occlusion of both pairs of posterior tibial and peroneal veins would receive a score of 8. The rate of recanalization was then quantified by the decrease in tibial thrombosis score over time, whereas propagation was defined as extension of thrombus to more proximal segments in the same limb.

Because the number of patients with isolated CVT was small and because not all patients attended each scheduled visit, follow-up intervals were grouped as the initial visit, 1 to 14 days (2 weeks), 15 to 45 days (1 month), 46 to 135 days (3 months), 136 to 270 days (6 months), 271 to 547 days (1 year), 548 to 912 days (2 years), and greater than 912 days (3 years).

Because most variables were not normally distributed, all results are reported as the median and interquartile range (IQR, 25th to 75th percentile). In evaluating thrombotic risk factors and PE, patients with unilateral or bilateral isolated CVT were compared with those who had a proximal DVT with or without CVT in the contralateral limb. Analysis of postthrombotic manifestations was performed on the basis of involved extremities after excluding limbs that had a history of DVT, hyperpigmentation, or ulceration. All extremities with CVT and at least one follow-up visit were included in the evaluation of propagation, recanalization, and the development of valvular incompetence. Comparisons among categorical variables were made using Pearson's χ^2 or Fisher's exact test, whereas continuous variables were compared using the Mann-Whitney U test. In comparing the prevalence of symptoms among uninvolved limbs contralateral to a CVT, extremities with CVT, and limbs with proximal DVT, the test for departure from a linear trend of proportions assumed equal increases across the three groups.[15] Statistical significance for all comparisons was defined as a p value of 0.05 or less.

RESULTS

Presenting features of CVT. Over the 116-month interval from December 1986 to July 1996, 499 patients with acute DVTs in 576 extremities were referred as candidates for the natural history study and have information regarding risk factors and presenting symptoms available. Among these, 58 patients (12%) had an acute DVT confined to one or more calf veins in 62 extremities (11%). These 62 extremities included 11 limbs (18%) with a proximal DVT in the contralateral extremity and eight limbs (13%) with a previous history of DVT or evidence of chronic venous disease (hyperpigmentation or ulceration) in that limb.

Among the 47 patients who had CVT and no contralateral proximal disease, thrombosis was unilateral on the right side in 21 (45%) patients, unilateral on the left side in 22 (47%), and bilateral in four (8%). Thrombosis in these 51 extremities involved the posterior tibial veins in 32 (63%) limbs, the peroneal veins in 17 (33%), and the sural veins in six (12%). Twenty-seven patients (57%) were men, and the median age was 48 years (IQR, 36 to 67 years). The gender and age distribution were not statistically different from the 452 patients who had a proximal thrombosis (54% men; median age, 55 years; IQR, 39 to 68 years). Bilateral DVT was more common among patients with proximal thrombosis (16% vs 9%), but this difference was not statistically significant ($p = 0.17$). The prevalence of thrombotic risk factors is shown in Table I. Concurrent malignancy was significantly less common among CVT patients ($p = 0.03$), whereas the prevalence of other risk factors was not significantly different between the two groups. Patients with isolated CVT had a median of one risk factor (IQR, 0 to 2) in comparison with two risk factors (IQR, 1 to 2) among those who had proximal thrombosis ($p = 0.04$; Fig. 1).

A detailed assessment of pulmonary symptoms was not available for all patients. However, in those with such data, PE was diagnosed at presentation in five of 47 patients with CVT (11%) in comparison with 64 of 419 patients with proximal DVT (15%; $p = 0.46$). Among patients with CVT, this diagnosis was suspected clinically in one patient and was established by a high-probability ventilation/perfusion (V/Q) lung scan in four patients.

Early clinical outcome. Among the 499 potential candidates for inclusion in the natural history study, 268 were enrolled and had at least one follow-up visit. This included 29 patients with an isolated CVT (two bilateral) and 239 patients with a proximal DVT (six with contralateral CVT). The median follow-up was 163 days (IQR, 25 to 407 days) for patients with isolated CVT versus 240 days (IQR, 28 to 1066 days) among those with a proximal DVT ($p = 0.26$). Initial treatment with anticoagulants, thrombolytic agents, or a vena caval filter was undertaken in 229 patients with a proximal DVT (96%), in comparison with 21 patients with CVT (72%; $p < 0.001$; Table II). Among patients with isolated CVT, one patient (3%) had a PE documented by V/Q scan 33 days after presentation. This patient was receiving anticoagulation medication at the time of the PE and had no evidence of proximal propagation by duplex ultrasonography. In contrast, 14 of 239 patients (6%) with proximal DVT had a new diagnosis of PE during the course of follow-up.

In evaluating postthrombotic manifestations, 50 extremities with CVT were available for analysis after excluding patients who had evidence of previous venous disease within either extremity. At the time of presentation, symptoms including edema (n = 21) and pain (n = 30) were present in 35 of these 50 extremities (70%). Among patients enrolled in follow-up, the prevalence of symptoms progressively decreased over time such that nine of 27 limbs (33%) were symptomatic at 2 weeks and three of 13 (23%) at 1 year. In contrast, only three of 35 uninvolved extremities (9%) contralateral to a CVT were symptomatic at presentation, with persistent symptoms in 9% of those followed-up for 1 year. Among limbs that had a proximal thrombosis, symptoms were present in 290 of 368 (79%) at presentation, decreasing to 51 of 95 (54%) after 1 year of follow-up (Fig. 2). The prevalence of symptoms in limbs with CVT, normal limbs contralateral to a CVT, and extremities with proximal thrombosis was significantly different at 1 year ($p = 0.004$). These data are consistent with a linear trend in rates of symptoms across the three

Table I. Risk factors

Risk factor	*Percent with risk factor**		
	Proximal DVT	*CVT*	*p*
Malignancy	35.3% (416)	19.1% (47)	0.03
Bedrest	35.2% (418)	23.4% (47)	0.11
Recent surgery	32% (416)	36.2% (47)	0.56
Previous venous disease	27.2% (452)	17% (47)	0.13
Recent trauma	13.5% (378)	13.3% (45)	0.98
Remote trauma	13.3% (375)	8.9% (45)	0.40
Family history	9.1% (407)	6.4% (47)	0.79
Recent travel	4.8% (415)	2.1% (47)	0.71
Congestive heart failure	4.1% (411)	2.1% (47)	1.0
Pregnancy	1.9% (417)	2.1% (47)	1.0
Oral contraceptives	1% (417)	0% (47)	1.0

*Total number of patients assessed for individual risk factor.

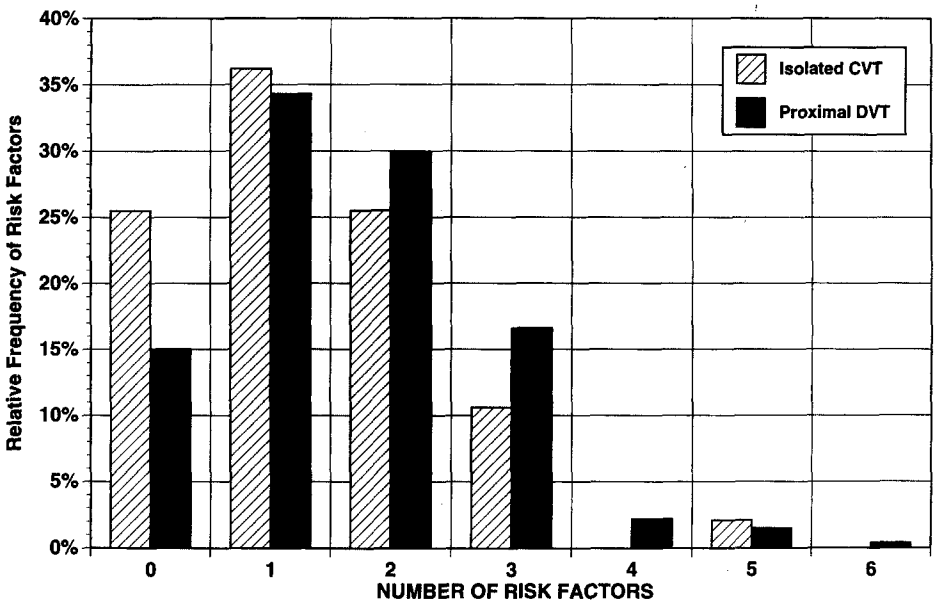


Fig. 1. Number of thrombotic risk factors among patients with isolated CVT in comparison with patients with a proximal DVT. Median number of risk factors was significantly greater ($p = 0.04$) among patients with a proximal DVT.

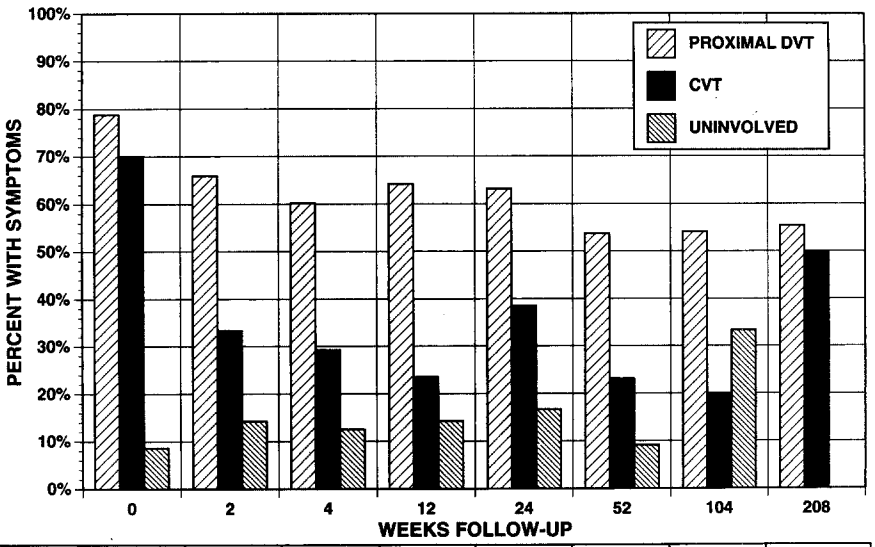
Table II. Initial DVT treatment

Treatment	*Proximal DVT (%) (n = 239)*	*CVT (%) (n = 29)*
Anticoagulation	212 (88.7)	21 (72.4)
Vena caval filter	28 (11.7)	2 (6.9)
Thrombolytic therapy	2 (0.8)	0 (0)
Unknown	1 (0.4)	2 (6.9)
No treatment	9 (3.8)	6 (20.7)

groups: uninvolved contralateral limbs (9%), isolated calf thrombosis limbs (23%), and proximal DVT limbs (54%; $p > 0.5$ for rejecting hypothesis of linear trend). The number of extremities with isolated CVT followed-up beyond 1 year was too small for meaningful comparison. Persistent symptoms in CVT limbs were limited to pain and swelling, with no hyperpigmentation or ulceration developing during follow-up. Although no ulceration was observed among patients with proximal DVT at 1 year, hyperpigmentation had developed in three patients (3%).

Early venous outcome. Recanalization, propagation, and the development of valvular incompetence were evaluated in the 37 limbs with CVT and at least one follow-up visit. The median follow-up among these extremities was 111 days (IQR, 26 to 391 days). Recanalization proceeded rapidly from an initial median tibial thrombosis score of 4 such that the median score was reduced by 50% at 1 month and to 0 at 1 year (Fig. 3). Propagation to a more proximal level in the same extremity occurred in six limbs (16%), four (13%) of those with isolated CVT in comparison with two extremities (29%) with CVT contralateral to a proximal thrombosis ($p = 0.32$). Among these six extremities, two had propagation limited to the popliteal vein; two to the popliteal and superficial femoral vein; one to the common femoral and profunda veins; and one to the external iliac vein. Propagation occurred a median of 29 days (range, 4 to 34 days) after presentation, at which time one patient was being anticoagulated with heparin and two with warfarin.

In analyzing the development of reflux in these 37 extremities, each involved vein was considered separately and presumed to behave independently of thrombus in other calf veins. A total of 52 initially thrombosed, individual calf veins were therefore available for analysis. Reflux was not observed in any involved vein until the twelfth week, after which the prevalence of reflux progressively increased to 24% at 1 year (Fig. 4). In contrast, among 104 uninvolved peroneal and posterior tibial vein segments in 26 contralateral limbs, reflux was present in one segment at the time of presentation and was not noted to develop in any other segments during follow-up. The prevalence of reflux among involved (five of 21) and contralateral uninvolved (0 of 48) calf vein segments was significantly different ($p = 0.002$) at 1 year.



# LIMBS	0	2	4	12	24	52	104	208
PROXIMAL DVT	368	179	128	123	111	95	61	56
CVT	50	27	24	17	13	13	5	2
UNINVOLVED	35	21	16	14	12	11	3	1

Fig. 2. Prevalence of symptoms (edema, pain, hyperpigmentation, or ulceration) during follow-up among extremities with proximal DVT, CVT, and in uninvolved limbs contralateral to a CVT. Differences among the three groups are statistically significant at 12 months (p = 0.004). Table shows total number of extremities within each group evaluated at each follow-up interval.

DISCUSSION

The most important issues in defining the clinical relevance, and thus appropriate treatment, of acute DVT are the rates of PE and development of the postthrombotic syndrome. Recurrent thrombotic events are associated with an increased risk of both PE and valvular incompetence[2,16] and are also an important consideration. Although our understanding remains incomplete, the relationship between proximal DVT, PE, and recurrent thrombosis has been extensively investigated and optimal treatment established. Early therapeutic anticoagulation with heparin followed by oral warfarin is critical in preventing recurrent venous thromboembolism in this setting.[3,4] The natural history of proximal DVT with respect to the postthrombotic syndrome has also been well described. Manifestations of pain, hyperpigmentation, and ulceration develop during long-term follow-up in 29% to 79% of patients.[1,2,17] Because rates of recanalization, recurrent thrombotic events, and persistent proximal obstruction are major determinants of postthrombotic sequelae,[2,16,18] long-term outcome may also be influenced by early treatment and should be considered in defining therapy.

In contrast, the natural history of CVT remains poorly defined and controversial. At least some of the confusion may arise from the fact that thrombi detected in screening asymptomatic high-risk patients may behave differently than symptomatic thrombi. Asymptomatic thrombi are often smaller, more often confined to the tibial veins, and more frequently nonocclusive than symptomatic thrombi.[6,19] Detection of these small thrombi by duplex ultrasonography is also more difficult.[13] The natural history of these thrombi may differ from symptomatic CVT, which is substantially less common than proximal venous thrombosis among symptomatic patients.[20,21]

Furthermore, discussions regarding the clinical significance of CVT have often been limited to the risk of PE, the investigation of which has yielded conflicting results. It does appear that the incidence of clinically significant PE with isolated CVT is less than with proximal DVT and that most emboli that occur in this setting are small.[8] However, whether this rate is trivial remains in dispute. For example, the incidence of symptomatic PE among patients with asymptomatic CVT discovered in routine screening of postoperative patients has been reported to be as

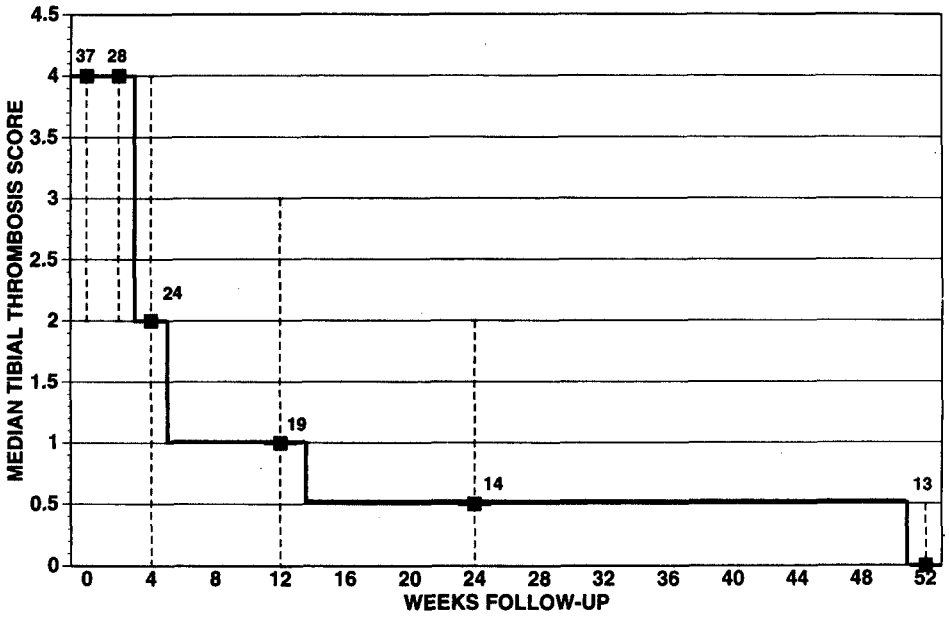


Fig. 3. Median thrombosis score versus follow-up interval among extremities with CVT. *Error bars* denote the IQR (25th to 75th percentile). Numbers represent the number of patients evaluated at each follow-up interval.

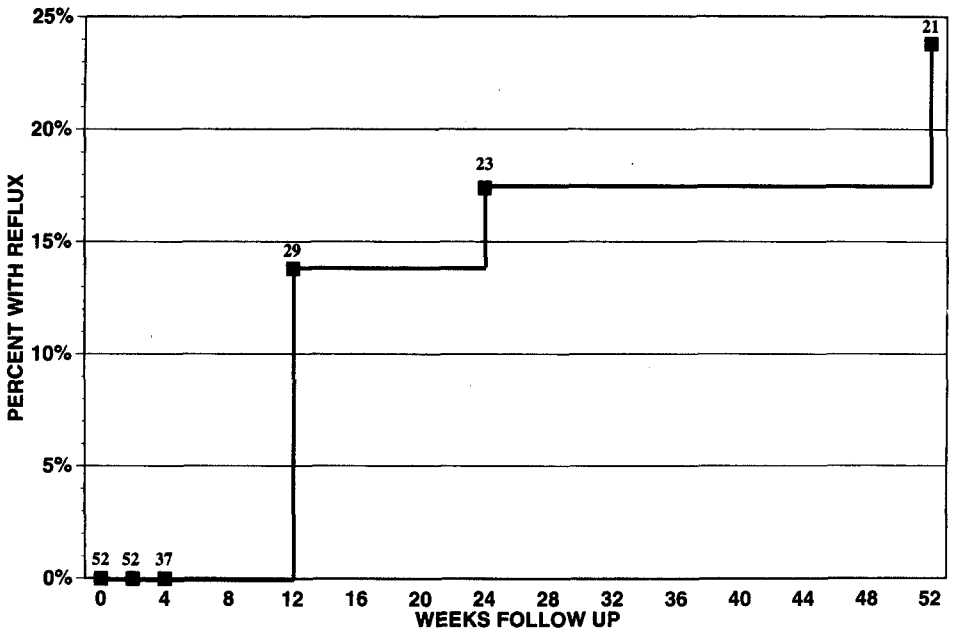


Fig. 4. Prevalence of reflux with respect to follow-up interval among veins with isolated tibial thrombosis. Numbers represent the number of calf vein segments (posterior tibial, peroneal, sural) evaluated at each follow-up interval.

low as 0% to 2%.[9,11] Such observations support the conclusion of Philbrick and Becker[7] that, based on reports in the literature, PE rarely occurs in the absence of proximal propagation. In contrast, Lohr et al.[22] observed pulmonary emboli at presentation in 5% of patients and concluded that CVT was not a benign disorder. Similarly, studies that used routine lung scanning have documented pulmonary emboli

in 33% of patients with CVT, 44% of which were estimated to involve greater than 20% of the lung volume.[8]

The relationship between CVT and development of the postthrombotic syndrome is even less clear. Based on a 20% rate of proximal propagation, Hirsh and Lensing[6] calculated that postthrombotic manifestations would develop 4% of patients with CVT, whereas Philbrick and Becker[7] concluded that the evidence is too limited to show a relationship between CVT and chronic venous disease. A lower incidence of postthrombotic sequelae might be expected with CVT because these thrombi tend to recanalize more rapidly than proximal thromboses[18] and are not associated with persistent proximal obstruction. However, recurrent thrombotic events, reported in approximately 20% of untreated CVT patients,[12,23] may also contribute to the development of valvular incompetence.[16] Despite initial anticoagulation in 72% of patients in this study, the 16% incidence of proximal propagation is remarkably similar to that reported in untreated patients. Although these rates are lower than the 30% incidence reported[16] among patients with proximal DVT, likely reflecting the fewer number of risk factors and lower prevalence of malignancy in CVT patients, they may be a cause for concern. These concerns tend to be validated by studies that report late symptoms (4 to 7 years) in 22% to 47% of patients after CVT.[17,24] A similar prevalence of abnormal clinical or hemodynamic findings has been reported in uninvolved limbs, although few of these extremities have been noninvasively followed-up to exclude recurrent thrombotic events.

Although this study only provides information regarding the early outcome after isolated CVT, it does suggest that the long-term prognosis is not entirely benign. As previously suggested,[25] tibial vein recanalization begins early after the acute event and is essentially complete in the majority of patients by 1 year. Similarly, the prevalence of symptoms rapidly decreases within 2 weeks of presentation. However, approximately one quarter of involved limbs will remain symptomatic after 1 year. The proportion of symptomatic limbs is less than after a proximal DVT, but is substantially higher than in the contralateral uninvolved extremity. This is in distinct contrast to reports that 93% of initially symptomatic patients are asymptomatic within 3 months[23] and is consistent with the prevalence of late symptoms reported by others.[17,24,26] The finding that symptoms were limited to edema and pain is not surprising given the short follow-up interval. Whether these patients would progress to the development of hyperpigmentation and ulceration is unknown, but the 24% prevalence of reflux at 1 year may make such late manifestations possible. Reports of late ambulatory venous pressure elevations among patients followed-up after isolated CVT suggest that such reflux does have hemodynamic significance.[17,24,27]

In addition, although this study was designed to follow the natural history of DVT with respect to chronic lower extremity manifestations, it confirms reports that PE may be associated with calf vein thromboses. Six patients either originally had or developed symptomatic PE during follow-up, with this diagnosis confirmed by V/Q lung scanning in five patients. Although embolization of a proximal extension before presentation cannot be excluded, this finding validates earlier suggestions that pulmonary symptoms in the patient with CVT warrant thorough evaluation.[28]

With respect to the clinical management of patients with isolated tibial thrombosis, this study does not specifically address the need for anticoagulation. However, among 35 patients followed-up for CVT in one extremity, six had a contralateral proximal DVT, four patients had a previous history of venous disease, four patients had a PE, one had a PE during follow-up, and four had proximal propagation. Thus 19 of 35 patients (54%) followed-up for a CVT in one extremity had established indications for anticoagulation therapy either at presentation or during follow-up. The impact of anticoagulation medication in minimizing development of the postthrombotic syndrome is unknown but certainly has the potential to decrease the impact of thrombus propagation and recurrent thrombosis as contributing factors. Furthermore, this study does suggest that isolated CVT should not be regarded as a clinically insignificant event. Although less than after a proximal DVT, the number of patients that remain symptomatic and the incidence of valvular incompetence after 1 year of follow-up is not trivial. Whether this will be associated with the development of lipodermatosclerosis and ulceration is not known, but it at least argues for consideration of late lower extremity symptoms in evaluating the importance and treatment of CVT.

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