

REVIEW ARTICLES

Richard P. Cambria, MD, Section Editor
From the American Venous Forum

The controversy of managing calf vein thrombosis

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Background: Controversy persists as to whether all calf vein thrombi should be treated with anticoagulation or observed with duplex surveillance. We performed a systematic review of the literature to assess whether data could support either approach, followed by examination of its natural history by stratifying results according to early clot propagation, pulmonary emboli (PE), recurrence, and postthrombotic syndrome (PTS).

Methods: A total of 1513 articles were reviewed that were published from January 1975 to August 2010 using computerized database searches of PubMed, Cochrane Controlled Trials Register, and extensive cross-references. English-language studies specifically examining calf deep vein thrombosis (C-DVT) defined as axial and/or muscular veins of the calf, not involving the popliteal vein, were included. Papers were independently reviewed by two investigators (E.M., F.L.) and quality graded based on nine methodologic standards reporting on four outcome parameters.

Results: Of the 1513 citations reviewed, 31 relevant papers meeting predefined criteria were found: six randomized controlled trials (RCT) and 25 observational cohort studies or case series. There was a single RCT directly comparing anticoagulation with no anticoagulation with compression and duplex surveillance, and they found no difference in propagation, PE, or bleeding in a low-risk population. Based on two studies of moderately strong methodology, C-DVT propagation was reduced with anticoagulation. When treatment was unassigned, moderately strong evidence suggested that about 15% propagate to the popliteal vein or higher. However, based on nonrandomized data but with moderate to high quality (level A and B studies), propagation to popliteal or higher was 8% in those with no anticoagulation treated with surveillance only. Propagation involving adjacent calf veins but remaining in the calf occurred in up to one-half of all those who propagate. Major bleeding was an intended endpoint in three RCTs and was reported as 0% to 6%, with a trend toward lower bleeding risk in more recent studies. PE during surveillance in studies with unassigned treatment was strikingly lower than the historical reports of PE recorded at presentation, emphasizing the distinction that must be made between the two entities. Recurrence in C-DVT is lower than thigh DVT, and data suggest that in low-risk groups with transient risk factors, 6 weeks of anticoagulation may be sufficient, as opposed to 12 weeks. Studies of PTS reported that patients with C-DVT had fewer symptoms than their thigh DVT counterparts. Approximately one out of 10 showed symptoms of CEAP Class 4 to 6; however, C5 or C6 with healed or active ulceration were not commonly encountered.

Conclusions: No study of strong methodology could be found to resolve the controversy of optimal treatment of C-DVT. Given the risks of propagation, PE, and recurrence, the option of doing nothing should be considered unacceptable. In the absence of strong evidence to support anticoagulation over imaging surveillance with selective anticoagulation, either method of managing calf DVT must remain as current acceptable standards. (J Vasc Surg 2012;55:550-61.)

While anticoagulation remains the mainstay treatment of proximal limb deep venous thrombosis, treatment of calf deep vein thrombosis (C-DVT) that does not involve the

popliteal vein remains controversial. On the one hand, the significance of C-DVT is clinically important because it can potentially propagate, result in pulmonary emboli (PE) and/or death, recur, and/or lead to postthrombotic syndrome (PTS). On the other hand, anticoagulation for all is challenged by the potentially undesirable effects of major bleeding, including death, burden of treatment, and increased utilization of costly resources. This is in stark contrast to anticoagulation for proximal thigh DVT, which is not disputed and universally accepted as standard of care.

Guidelines for treatment of C-DVT are lacking and do not address the current practice of C-DVT management. In an electronic poll of attendees taken at the 2009 American Venous Forum and the 2009 American College of Phlebology, there were approximately equal numbers of votes for and against anticoagulation for C-DVT. In 2008, the American College of Chest Physicians (ACCP)¹ published their recommendation specifically for first unprovoked C-DVT, and assigned it a Grade 2B with suggestion that

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duration of anticoagulation be limited to 3 months as opposed to indefinite therapy. Although treatment of C-DVT was implied, there were no direct recommendations addressing C-DVT, particularly those with transient or reversible risk factors.

Because of this controversy, we undertook this review to identify pertinent evidence in either supporting or not supporting anticoagulation for C-DVT and examine four features of C-DVT – clot propagation, PE, recurrence, and PTS – which may provide further evidence of the natural history of calf vein thrombi and a foundation for future evidence-based research.

METHODS

Studies selected for review were required to fulfill the following inclusion criteria. For many of these questions, randomized controlled trials (RCTs) did not provide sufficient data and were not the appropriate design to address the clinical question raised. As a result, observational studies with or without internal or historic controls and case series with explicit details of one or more of the four parameters studied were included in this analysis. The literature was examined by searching using keywords: “calf vein thrombosis,” “calf DVT,” “isolated calf DVT,” “distal DVT,” and “lower limb DVT.” The search was limited to English language papers published between January 1975 and August 2010 using computerized database searches of PubMed, Cochrane Controlled Trials Register, and extensive cross-references.

Inclusion criteria

1. Calf vein thrombi are defined by involvement of the axial veins (peroneal, posterior tibial, and/or anterior tibial veins) and/or muscular calf veins (soleal or gastrocnemius veins), not involving the popliteal or higher veins.
2. Diagnosis must include imaging studies of the entire leg, including the calf.
3. To examine the natural history of C-DVT, the specific aim(s) of each study should include one or more of the following: propagation of C-DVT, PE during surveillance, DVT recurrence, and/or PTS.

Exclusion criteria

1. Since the purpose to this review was to report the outcome of treatment and the natural history of calf vein thrombi, studies reporting only the prevalence of C-DVT or PE were not included in the analysis but may be cited in the discussion.
2. Studies with the arbitrary sample size of 20 or less were excluded.
3. Any study reporting early outcome with 40% or more subjects lost to follow-up from the original study group were excluded.

Grading of methodology

Studies that qualified for review were graded based on methodology, utilizing a modified rating system published by Philbrick and Becker.² Since most of the studies were not designed to study the natural history of C-DVT, if compliance with the standards were not achieved, this did not infer that the study quality was poor or inadequate. The standards (see Appendix) were used to rate the overall quality of the study and provide an estimate for the strength of evidence that can be assigned to each of four outcomes measured.

Grading strength of evidence

Papers were graded based on whether they met any or all of nine standards. Papers were rated “strong” or assigned a grade “A” in methodology if eight or more standards were met, moderately strong or grade “B” if they met a total of six to seven standards, and all others were rated as weak or grade “C.”

RESULTS

One thousand, five hundred thirteen citations were reviewed (Fig 1), and, after exclusion based on previously stated criteria, 31 were included for analysis.

Studies not included in analysis. Several studies did not meet the inclusion criteria because C-DVT cases included popliteal DVT and separate analysis was not made,^{3,4} C-DVT was not distinguished from popliteal DVT,⁵ “distal DVT” was not defined,^{6,7} sample size was less than 20,⁸⁻¹¹ complete imaging studies of the entire leg, including calf were lacking,¹²⁻¹⁴ results were not analyzed separately from proximal DVT,^{15,16} details of the C-DVT group were not specified,¹⁷ reports described prevalence or incidence of disease, without surveillance data,^{5,18-21} and 40% or more of the initial study group were excluded from analysis because of lack of follow-up in the process of measuring early outcome.²²

Randomized controlled trials. Six RCTs (Table I) were identified with five of the six designed to study drug doses, routes, and duration of therapy of C-DVT.

Rate of propagation. There were only two studies of high quality^{27,28} (Grade A) examining the rate of DVT propagation (Table II). In an RCT by Schwarz et al,²⁸ the rate of propagation was not significantly different between those who received therapeutic Nadroparin for 10 days compared with compression therapy alone (3.7% vs 3.8%; $P = NS$). In the low risk group of 107 patients, only 4.67% had active cancer, and 20% to 47% had a transient risk factor such as trauma or surgery. When calculated for only progression of thrombi to the popliteal vein or higher, both groups had the same rate of 1.9%. They concluded their data did not show superiority of short-term anticoagulation over compression for muscular calf vein thrombi (MCVT) in a low-risk population. Ferrara and colleagues²⁷ examined the optimal duration of anticoagulation in one versus two or more vein involvement. They found that clot propagation was equivalent in C-DVT limited to

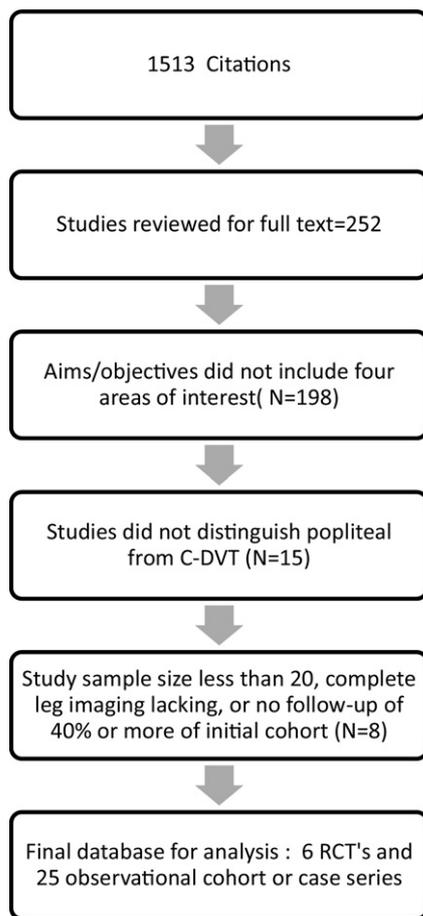


Fig 1. Summary of literature search and derivation of studies for analysis.

one vein, whether treated for 6 or 12 weeks; however, the rate of propagation was significantly worse if two or more calf vein thrombi were treated for 6 weeks versus 12 weeks (35.5% vs 9.7%; $P = .001$), advocating the longer treatment for two or more veins.

Of the remaining 16 studies, 11 were rated “moderately strong” in methodology and reported the risk of propagation to the popliteal vein or higher in 2.9% to 17.9%. Any propagation, including thrombus extension within the calf that involved adjacent calf veins and clot ascending up into the popliteal vein, was reported by Lohr et al³⁰ of 32%, with a second report³² of 28%. When analyzed for propagation only to the popliteal or above, the number reduced to one-half the initial estimate and is reported at 14.7% and 10.9%, respectively.^{30,32} Similarly, Labropoulos³⁸ found propagation to adjacent uninvolved calf veins and popliteal veins in 27%, but only 13% propagated to the popliteal.

In two studies of no anticoagulation, the risk of propagation to the popliteal level was 3% to 4.6%.^{39,42} MacDonald et al³⁹ found any propagation in 16.3%, with only 3% propagation to the popliteal or higher in MCVT. Based on the low

rate of serious propagation, they concluded that MCVT can be observed with serial duplex surveillance.

In Fig 2 and Table III, analysis of cases receiving no anticoagulation provided some insight into the possible natural history of C-DVT. The pooled data from Grade A and B studies without anticoagulation showed that with ascent up the limb, the rate of propagation above the calf diminished. However, the data must be interpreted with caution as there may have been selection bias with only one study being an RCT.

Moderately strong evidence suggests that anticoagulation reduces propagation as indicated by one observational cohort study by Schwarz et al,³⁷ of MVCT. They found that 25% propagated into any vein, which was defined as unaffected axial calf veins or popliteal veins in the cohort with observation, compression stockings, and duplex surveillance (confirmed by direct correspondence with primary author), whereas the group receiving low-molecular-weight heparin for 10 days showed no propagation. Despite the nonrandomized design and possibility of bias, results suggest that clot propagation in the calf, including adjacent veins without extension into the popliteal, can be reduced with a short course of anticoagulation.

While these studies suggest benefits of anticoagulation, risks of bleeding pose an undesirable effect that must be considered in weighing the benefits against risks. Three of the six randomized studies measured bleeding as an outcome (Table I), ranging from 0% to 6%.^{24,26,28} Lagerstedt²⁵ described two cases of major bleeds, including one each of retroperitoneal hematoma, and calf hematoma with compartment syndrome; however, bleeding was not one of their endpoints.

PE during surveillance. There were 13 studies that reported PE during surveillance (Table IV) and of these, three of the 11 were graded “moderately strong to strong” as they provided predetermined repeat lung ventilation/perfusion (V/Q) scans, which allowed identification of both asymptomatic and symptomatic emboli. Hull,²³ Bentley,²⁴ and Partsch⁴³ found that in patients treated with anticoagulation, PE during surveillance was 0% to 6.2%. The largest report of 238 patients by Partsch⁴³ demonstrated 3.4% new PE in those with V/Q scan surveillance at day 1 and day 10, the majority of which were asymptomatic, and only a few developed mild symptoms. The limitation, however, was the study’s short follow-up of 10 days. In three studies with cohorts that did not receive anticoagulation with follow-up of 3 months or more,^{28,37,42} the incidence of symptomatic PE was 0% to 1.5%. There was one death from a pulmonary embolus during surveillance reported by O’Shaughnessy,³⁴ in which case the DVT propagated first to the popliteal vein; however, no details were given with respect to whether the patient was receiving anticoagulation or undergoing surveillance.

Recurrence. There were no strong studies reporting recurrence between anticoagulation and surveillance. The study that comes closest is the RCT by Lagerstedt,²⁵ in which the entire group was treated with anticoagulation for 5 days, then randomized to warfarin or no warfarin for at

Table I. Randomized controlled trials of C-DVT

<i>Author</i>	<i>Type of study</i>	<i>Aim</i>	<i>Endpoint</i>	<i>Findings/comments:</i>	<i>% Major bleeding</i>
Hull (1979) ²³	RCT	Compared warfarin with low-dose heparin subcutaneous for 6 weeks; all preceded by heparin IV for 14 days.	Recurrence	Subgroup analysis of C-DVT patients showed no difference between either therapy.	NR
Bentley (1980) ²⁴	RCT	Compared heparin IV vs subcutaneous for 7 days, measuring safety and efficacy	Proximal extension, PE during surveillance, bleeding	Subcutaneous heparin resulted in lower propagation rates than IV heparin. No difference found with PE rates.	6/100 (6%)
Lagerstedt (1985) ²⁵	RCT	All received heparin IV for 5 days, then compared warfarin vs no warfarin	Recurrence	Recurrences within 90 days was lower in group receiving warfarin for at least 3 months, as opposed to no warfarin.	2/51 (4%)
Pinede DOTAVK study (2001) ²⁶	RCT	Compared oral anticoagulation 6 vs 12 weeks for subgroup C-DVT; all received initial subcutaneous or IV heparin	Recurrence, bleeding	Subgroup analysis of C-DVT patients showed 6-weeks treatment was sufficient and no difference in recurrence from 12 weeks. C-DVT lower risk for recurrence than proximal DVT.	4/197 (2%)
Ferrara (2006) ²⁷	RCT	Compared 6-week with 12-week anticoagulation in single vs two C-DVT	Proximal extension	C-DVT involving single vein, 6-week treatment was sufficient. Twelve-week treatment was better for C-DVT involving two or more veins, in postsurgical, "low-risk" group.	0
Schwarz (2010) ²⁸	RCT	LMWH ×10 days vs compression treatment plus surveillance	Proximal extension, PE bleeding, recanalization	In low-risk population, did not show superiority of LMWH over compression therapy in calf muscle DVT.	0

C-DVT, Calf deep vein thrombosis; DVT, deep vein thrombosis; IV, intravenous; LMWH, low-molecular-weight heparin; NR, not reported; PE, pulmonary emboli; RCT, randomized controlled trial.

least 3 months. The recurrence was 29% in 90 days, all of which occurred in the cohort not receiving warfarin for 3 months as compared with no recurrence in the group receiving warfarin ($P < .01$). In Table V, the difference in outcome of C-DVT and proximal DVT were reported and the study by Hull²³ was rated strong in methodology in which low-dose heparin treatment of C-DVT was associated with a low recurrence as opposed to a higher recurrence with proximal DVT (0% vs 47%; $P < .001$). In the Duree Optimale du Traitement Antivitamines K (DOTAVK) trial consisting of 197 calf DVT patients, Pinede and colleagues²⁶ found overall recurrence was lower for C-DVT than proximal DVT or PE (2.6% vs 8.4%, respectively), and their results supported a shorter duration of anticoagulation of 6 weeks as opposed to 12 weeks of anticoagulation for C-DVT. In addition, they were one of the few studies to report a higher risk of recurrence with cancer, idiopathic DVT, and permanent risk factors.

PTS. Studies of PTS (Table VI) included a longitudinal study by Meissner³³ who reported 23% with symptoms limited to pain and swelling; however, no hyperpigmentation or ulceration were found at 1 year. Compared with

controls, McLafferty⁵¹ found that at 3.4 years, few showed signs of significant venous symptoms. With follow-up extended to 5 years, Asbeutah⁵³ reported 11% with CEAP Class 4 to 6 findings. In a unique study of asymptomatic C-DVT, Rosfors and colleagues⁵⁴ reported a low incidence of PTS symptoms of 4% at 5 years, and a mild degree of PTS by Villalta scoring. Overall venous ulceration was not commonly encountered in follow-up.

DISCUSSION

The studies presented in this review confirm the lack of scientific evidence substantiating either anticoagulation or observation with surveillance testing as optimal treatment for C-DVT. Although three national societies or international consensus groups (ACCP, Australian Society of Thrombosis and Haemostasis, and the British DVT consensus group) have recommended anticoagulation for C-DVT, observation and compression therapy with duplex surveillance remains a commonly practiced approach. In fact, the single RCT published to date

Table II. Calf vein thrombosis propagation

Author (year)	No. patients (limbs)	Surveillance methods	Treatment	% Any propagation ^b	% Propagation popliteal or higher	Rating
Bentley (1980) ²⁴	100	Venography	Heparin subcutaneous + warfarin × 6 weeks Heparin intravenous + warfarin × 6 weeks	—	0 2%	C ^c
Lagerstedt (1985) ²⁵	51	99TC plasmin supplemented by venography	Heparin + no warfarin Heparin + warfarin	—	17.9% 0	B
Kakkar and Lawrence (1985) ²⁹	98	Venogram	Heparin + coumadin 3 months	—	10%	B
Lohr (1991) ³⁰	75	DUS	Mixed ^a	32%	14.7%	C
Solis (1992) ³¹	42 (50)	DUS in 32	Anticoagulation No anticoagulation	—	23% 8%	C
Lohr (1995) ³²	192	DUS	Anticoagulation No anticoagulation	13% 22.4%	10.9% ^d	B
Meissner (1997) ³³	29 (37)	DUS	Mixed ^a	—	16%	B
O'Shaughnessy (1997) ³⁴	50	DUS	Mixed ^a	—	15%	B
Masuda (1998) ³⁵	49	DUS	Anticoagulation No anticoagulation	—	0 7.7%	B
Kazmers (1999) ³⁶	71	DUS	Mixed ^a	—	15.5%	C
Schwarz (2001) ³⁷	84	Venous compress ultrasound	LMWH × 10 days Observation, stockings	0 25%		B
Labropoulos (2002) ³⁸	48 (52)	DUS	Anticoagulation No anticoagulation	10.5% 17.2%	13% ^d	B
MacDonald (2003) ³⁹	135	DUS	No anticoagulation	16.3%	3%	B
Ferrara (2006) ²⁷	192	DUS	Anticoagulation: single calf vein, 6 and 12 weeks Anticoagulation: two calf veins, 6 and 12 weeks	—	8.8% 22.6%	A
Wang, CJ(2007) ⁴⁰	160	Venogram 5-7 days, then 3 months	Mixed, prophylactic dosing ^a	1.2%	—	C
Parisi TICT (2009) ⁴¹	171	DUS	Anticoagulation; LMWH full dose × 7 days, + LMWH 1/2 dose × 3 weeks	—	2.9%	B
Palareti(2010) ⁴²	65	DUS	No anticoagulation		4.6%	B
Schwarz (2010) ²⁸	107	DUS	Randomized: Anticoagulation LMWH × 10 days No anticoagulation: compression treatment plus surveillance	3.7% 3.8%	1.9% 1.9%	A

DUS, Duplex ultrasound; LMWH, low-molecular-weight heparin.

^aMixed: outcomes not reported by treatment.

^bAny propagation defined as propagation in the same vein, adjacent uninvolved calf vein, or popliteal vein and higher.

^cShort follow-up of 7 days.

^dNumber represents both the Anticoagulation and No Anticoagulation groups.

comparing the two approaches by Schwarz et al²⁸ revealed no statistically significant difference between 10 days of low molecular weight heparin and compression therapy for 3 months.

The current review suggests the overall propagation rate to the popliteal or femoral vein is approximately 15% in reports with unassigned treatment; however, it may be as low as 2% in low-risk groups with transient risk factors and calf muscle vein thrombi.²⁷ In a pooled analysis of nonran-

domized studies of level A and B quality, the estimated rate of propagation to the popliteal or higher in those treated by surveillance only and no anticoagulation is 8% (Fig 2). This discrepancy between propagation rates underscores the need for controlled studies specifically analyzing the effects of surveillance or treatment. Unlike the report by Philbrick and Becker,² who reported no fatal PE, we found one single report of a fatal PE while under study,³³ but no mention was made as to whether this occurred under observation or

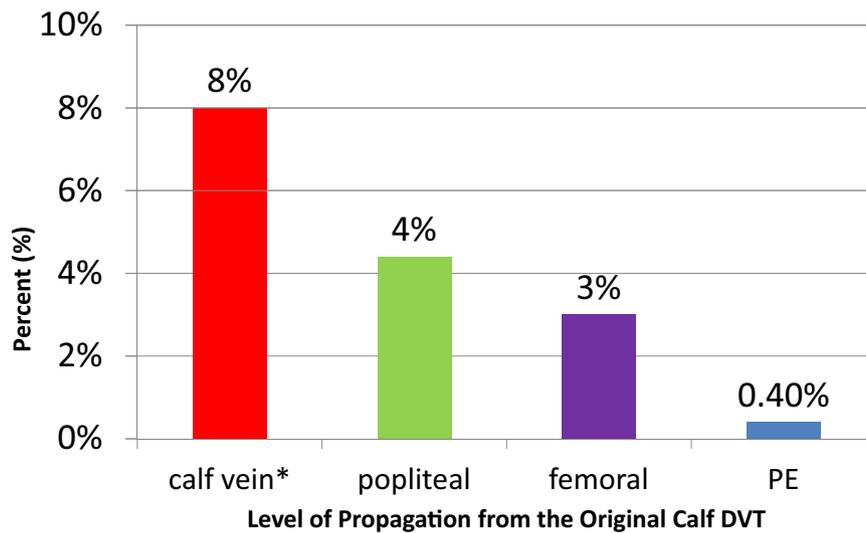


Fig 2. Level of propagation with no anticoagulation. DVT, Deep vein thrombosis; PE, pulmonary embolism. *Calf DVT propagated within the axial calf veins or muscular veins.

Table III. Data for level of propagation with no anticoagulation, in grade A and B studies within 3 months follow-up

Author	Calf	Popliteal	Femoral	Pulmonary emboli	Total cases
Palareti ⁴²	1		3 ^a	1	65
MacDonald ³⁹	18	4			135
Schwarz ²⁸	1	1			53
Lohr ³²	17	11	10		169
Masuda ³⁵		1	1		26
Labropoulos ³⁸		4 ^b		1	29
Total					477

^aPalareti: three cases of “proximal deep vein thrombosis.”

^bLabropoulos: four cases of “popliteal or higher.”

anticoagulation. Aside from this single event, the findings from this review revealed few major adverse events early on with observation, compression therapy, and duplex surveillance and would support this as an option.

What role does anticoagulation have in reducing the propagation rate? Two strong to moderately strong studies reported that anticoagulation reduced propagation rate. Lagerstedt²⁵ studied the effects of treating 51 cases of C-DVT with 5 days of intravenous heparin and randomized them to receive warfarin for 3 months or no warfarin. They found a statistically significant number of patients with warfarin resulted in reduction in recurrence, proximal extension, and PE when compared with no warfarin. However, the diagnosis of DVT and follow-up studies relied on the 99 m Technesium plasmin test, which currently is not used in practice. Schwart et al³⁷ found, in a nonrandomized observational cohort study of 84 patients, that those not receiving anticoagulation developed a statistically significant higher rate of progression from muscle calf vein

thrombosis to deep or axial calf vein thrombi and popliteal DVT. Contrary to their initial report, the same authors published their RCT²⁸ nine years later comparing low molecular weight heparin for 10 days with compression and found no statistical significance in propagation, PE, bleeding, and death.

The outcome of this review would support anticoagulation if a higher value was placed on preventing clot propagation and recurrence and a lower value was placed on the burden of treatment, cost for intervention, and if the risk of major bleeding was deemed acceptable. Notably, the report of major bleeding from the six RCTs ranged from 0% to 6%, with bleeding risk decreasing over time. This is not surprising since improved methods of anticoagulation with LMWH heparins and other alternatives to unfractionated heparin have evolved favorably. In the RCT by Schwarz,²⁸ the risk of bleeding was the same in the anticoagulation and nonanticoagulation groups, although the study may have been under-powered to detect differences in major bleeding, given the limited sample size of 107.

In many ways, C-DVT differs from proximal DVT and explains differences in approaches. C-DVT propagates less often than proximal DVT,⁴¹ has a lower PE risk,¹⁸ is more likely asymptomatic,^{54,55} and does not appear to lead to PTS as often.^{33,52} Further, recurrence rates are reported to be lower with C-DVT as opposed to proximal DVT when treated with anticoagulation.^{17,26}

For those who choose a selective approach to anticoagulation, identifying the high-risk patient is critical. Three studies^{36,37,39} found that malignancy was associated with increased risk of propagation and advocate anticoagulation for this high-risk group. MacDonald³⁹ reported that malignancy was associated with propagation, whereas transient risk factors such as recent surgery and trauma were not; prior venous disease, cardiac disease, and hypercoagu-

Table IV. Pulmonary emboli during surveillance

Author	No. of patients (limbs)	Surveillance method	Type of treatment	Results: % pulmonary emboli	Rating of methodology
Hull (1979) ²³	32	V/Q scan at 2 and 6 weeks	Anticoagulation	0	A
Bentley (1980) ²⁴	32	V/Q scans at 1 and 7 days	Anticoagulation	6.2%	A
Solis (1992) ³¹	42 (50)	Clinical ^b	Mixed ^a	0	C
O'Shaughnessy (1997) ³⁴	50	Clinical ^b	Mixed ^a	2%	C
Meissner (1997) ³³	29 (37)	Clinical ^b	Mixed ^a	3%	C
Masuda (1998) ³⁵	49	Clinical ^b	Mixed ^a	0	C
Partsch (2001) ⁴³	238	V/Q scans at 1 and 10 days	Anticoagulation	3.4%	B
Schwartz (2001) ³⁷	84	Clinical ^b	Anticoagulation	0	C
			No anticoagulation	0	
Labropoulos (2002) ³⁸	48 (52)	Clinical ^b	Mixed ^a	2%	C
Wang, CJ(2003) ⁴⁴	48	Clinical ^b	Mixed ^a	0	C
Gillet (2007) ⁴⁵	128	Clinical ^b	Anticoagulation	4.7% ^c	C
Palareti (2010) ⁴²	65	Clinical ^b	No anticoagulation	1.5%	C
Schwarz (2010) ²⁸	107	Clinical ^b	Anticoagulation	0	B
			No anticoagulation	0	

^aMixed: outcomes not reported by treatment.

^bClinical identification of symptomatic pulmonary emboli, with diagnosis confirmed by V/Q scanning, pulmonary angiography, and/or computed tomography angiogram of the chest when clinically suspected.

^c15.5% of series included popliteal vein deep vein thrombosis.

lable states were also not associated. In a large series reported by Lohr and colleagues³² of 192 patients predominantly consisting of patients with transient risk factors such as surgery, trauma, and estrogen use, predictors of propagation could not be identified; however, the group was comprised of <10% malignancy, and idiopathic DVT was not analyzed. In the DOTAVK trial of 197 C-DVT cases, Pinede²⁶ found a higher rate of recurrence with cancer, idiopathic DVT, and permanent risk factors.

Unprovoked or idiopathic DVT may be a significant risk factor for C-DVT propagation. In the Treatment of Isolated Calf Thrombosis (TICT) trial, Parisi et al⁴¹ found clot extension occurred despite anticoagulation in 2.9%, and the association between complication of DVT and unprovoked C-DVT was significant ($P < .005$). Idiopathic C-DVT was not analyzed in most studies in this review, but is a known important risk factor for recurrence in proximal and distal DVT,^{17,58} and future studies should account for this variable.

Bilateral leg C-DVT may be a marker of worse prognosis and is associated with increased recurrence,⁴⁶ increased mortality,⁴⁷ and increased association with malignancy.⁴⁷ Galanaud⁴⁸ found an increased association of bilateral C-DVT and mortality than those with unilateral C-DVT (17.4% vs 3.0%; $P = .008$) and an association of bilateral leg DVT with active cancer.

Multiple calf vein involvement and initial clot burden may be associated with increased propagation.^{27,45} In an RCT by Ferrara,²⁷ propagation and recurrence was significantly higher in two calf vein thrombi as opposed to a single vein clot. Gillet and colleagues⁴⁵ reported increased risk for propagation and risk of PE with increased initial calf vein diameters >8 mm, and, according to a report by

Ohgi,¹⁹ thrombus distending the vein to a diameter >7 mm was associated with a greater chance for thromboembolic complications. Thrombophilias, especially hereditary, and those with positive family history are known risks for DVT complications.⁵⁶ Due to small numbers and limited reports examining thrombophilia in C-DVT cases, its relationship with calf vein thrombi complications could not be determined by this review. However, other interesting aspects of recurrence under investigation include d-dimer levels⁵⁷ and residual thrombosis on ultrasonography,⁵⁸ both of which may prove to be important predictors of recurrence and guide duration of anticoagulation.

Should those with C-DVT and low risk be offered a shorter duration of anticoagulation? Two RCTs^{26,27} suggest that 6 weeks is adequate length of anticoagulation and found that extending treatment to 12 weeks did not prove advantageous. Ferrara²⁷ reports that for single C-DVT, 6 weeks of anticoagulation would suffice, and only if two or more calf veins were involved would 12 weeks be needed. In the DOVTAK trial, Pinede et al²⁶ likewise reported their findings where extending anticoagulation to 12 weeks did not confer an advantage over a 6-week regimen. Although not included in this analysis, the Duration of Anticoagulation (DURAC) trial¹⁷ found, in a subgroup analysis of first-time distal DVT patients with 2-year follow up, that there was no benefit in extending duration of anticoagulation to 6 months as opposed to 6 weeks, supporting a shorter duration of treatment. These findings are in contrast to the report by Kearon and colleagues¹⁵ who found in a mixed group of proximal and distal DVT, those with transient risk factors showed higher recurrences when treatment was reduced to 1 month as opposed to 3

Table V. Recurrence

Author	No. of patients (Limbs)	Duration of follow-up	Surveillance testing	Predetermined repeat studies	Treatment	% Recurrence	Rating of methodology
Hull (1979) ²³	32	6 weeks	Impedance plethysmography, 125 I-fibrinogen, and venography	At 3 and 6 weeks	Heparin intravenous then warfarin 6 weeks Heparin subcutaneous × 6 weeks	0 0	A
Lagerstedt (1985) ²⁵	51	1 year	99Tc plasmin and venography	Day 5, 14, and 30 and 90 days	Heparin intravenous plus warfarin Heparin intravenous plus no warfarin	4.3% 32%	B
O'Shaughnessy (1997) ³⁴	50	Up to 1 year	DUS	At 1 week, 1 month, 6 months, and 1 year.	Mixed ^a	14%	B
Astermark (1998) ⁴⁶	126	2 years	Venography	None	Heparin + VKA 6 weeks	8.7%	C
Pinede (2001) ²⁶	197	12 months	Clinical	None	Heparin + VKA 12 weeks Heparin + VKA 6 weeks	3.4% 2%	B
Wang (2003) ⁴⁴	48	3-4 years	Venography in 33	None	Not reported	0	C
Senturier (registry) (2005) ⁴⁷	895	2 years	Clinical		Mixed ^a	7.7% unilateral DVT 13.3% bilateral DVT	C
					Mixed ^a	13.3% bilateral DVT	
Gillet (2007) ⁴⁵	128	26.7 months	DUS	At 1, 3, and 9 months.	Anticoagulation	18.8%	B
Parisi TICT (2009) ⁴¹	171	3 months	DUS	At 1 day and 4 weeks	LMWH 7days, then half dose 3 weeks	2.9%	B
Galanaud, ^b OPTIMEV (2010) ⁴⁸	725	3 months	Clinical	None	Anticoagulation, 92.5-94.4%	Muscular C-DVT: 1.5% Axial C-DVT: 1.4%	C

C-DVT, Calf deep vein thrombosis; DUS, duplex ultrasound; DVT, deep vein thrombosis; LMWH, low-molecular-weight heparin; VKA, vitamin K agonist.

^aMixed: outcomes not reported by treatment.

^bFor previous publication by same authors, see Galanaud (2009)⁴⁹; OPTIMEV trial period 2004-2006.

months and recommended against shortening the duration of anticoagulation.

Clot lysis in C-DVT appears to be lysed in one-half of patients by the 3rd month, and by the 6th month, all have lysed. This is according to duplex surveillance studies.^{28,35,39,45,52} Whether this finding influences duration of anticoagulation remains to be further examined.

PE during surveillance of C-DVT with serial pulmonary V/Q scans of both asymptomatic and symptomatic PE up to 10 days after initial diagnosis is 3.4%,⁴³ and the majority appear asymptomatic. From a methodologic standpoint, PE at presentation must be distinguished from PE during surveillance. In contrast to the low incidence of PE during surveillance, reports of PE at presentation^{33,34,36,43,46} are higher and range from 5% to 56%, with the largest series by Partsch,⁴³ who reported 35.1% with PE at presentation. In a registry of 895 distal DVT, Senturier et al⁴⁷ reported PE at presentation in 29% with single-leg distal DVT, and 45% in bilateral C-DVT. These strikingly large numbers of PE identified in the presence of C-DVT may be the result of dislodgement of a more proximal clot

leaving residual thrombus in the calf. Browse and Thomas⁵⁹ showed that in one out of three cases of PE, the leg venograms were negative for DVT, and concluded that the thrombi in the legs may have left the leg entirely. Barter et al⁶⁰ reported a case of a patient with multiple PE and correlated the finding with disappearance of a below-knee thrombus, providing evidence that embolization can result in the absence of clot in the limb. Multiple studies^{23,61-63} suggest that most fatal PE occur as a result of prior proximal extension and lack of treatment, as opposed to clot arising directly from the calf veins. Because there is no way of determining whether a more proximal clot had detached from the leg above the C-DVT, it is difficult to estimate the true risk of PE based on the initial presentation.

Adding to the confusion of the association of C-DVT and PE is the fact that many PE at presentation are asymptomatic. In a study designed to examine the prevalence of PE in those with C-DVT, Kistner and Moreno-Cabral¹⁸ found PE at presentation in 33%, of which 45% were silent. In the majority of these emboli, the defects by V/Q were

Table VI. Postthrombotic syndrome

Author	No. of patients/limbs	Length of follow-up	Diagnostic test for PTS	% Abnormal test for PTS	Clinical findings	Rating
Lawrence and Kakkar (1980) ⁵⁰	58	2 years	Foot volumetry	Normal 45%, mild-moderate 41%, severe 14%	Not reported	C
Kakkar and Lawrence (1985) ²⁹	(98)	2 years	Foot volumetry	Normal 40%, mild-moderate 41%, severe 19%	Asymptomatic or minimal symptoms 78%, moderate 16%, severe 5%.	C
Meissner (1998) ³³	72 (including 35 controls)	1 year	DUS	Reflux in 24% C-DVT in calf veins, 0 in controls, $P = .002$	Symptomatic in C-DVT limbs 23%, in controls 9% at 1 year	B
McLafferty (1998) ⁵¹	71 (including 34 controls)	3.4 years	DUS	Reflux in 26% C-DVT limbs ^a , 6% controls, $P \leq .05$	CEAP Class 1-6 in 38%, all "Mild except one patient."	B
Masuda (1998) ³⁵	49 (including 26 controls)	3 years	DUS	Reflux 39%: 9% in original C-DVT vein, 30% in vein not involved with DVT, no difference from controls.	CEAP Class 0 in 74%, Class 2 in 8.7%, Class 3-4 in 17.4%, Class 5-6 in 0.	C
Saarinen (2002) ⁵²	62	6-10 years	None	None	Asymptomatic 37%, moderate 58%, severe 5%	C
Asbeutah (2004) ⁵³	76 (including 48 controls)	5 years	DUS	Reflux in 36% C-DVT ^a , 52% in controls primarily superficial veins 64%.	CEAP Class 0 in 46%, Class 1-3 in 43%, Class 4-6 in 11%	B
Rosfors (2010) ^{54b}	46	5 years	DUS and plethysmography	Reflux 50% in distal veins; deep vein reflux more common in two or more calf veins than single, $P < .05$	Villalta score 7% score ≥ 5 (indicative of PTS), all classified as mild.	B

C-DVT, Calf deep vein thrombosis; DUS, duplex ultrasound; DVT, deep vein thrombosis; PTS, postthrombotic syndrome.

^aLevel of reflux not specified.

^bAll asymptomatic C-DVT.

small. Although most would likely choose to anticoagulate a patient found to have an asymptomatic PE at presentation, its clinical significance remains controversial, and routine pulmonary scans in all asymptomatic patients is probably not economically feasible.

Recurrence in C-DVT is lower than DVT of the thigh.^{23,26} Recurrence may be reduced by anticoagulation²⁵ with treatment up to 12 weeks, particularly in those with two or more calf vein thrombi,²⁷ or risk factors such as malignancy, permanent risk factors, or idiopathic causes.²⁶

The studies of PTS showed that patients with C-DVT fared better over time with fewer symptoms of PTS than those with proximal DVT.^{33,52} At 1 year, based on a longitudinal study by Meissner,³³ 23% of C-DVT were symptomatic with pain and swelling. At 3 to 4 years, McLafferty⁵¹ reported few with significant venous symptoms, and at 5 years, one out of 10 showed CEAP Class 4 to 6 findings according to Asbeutah and colleagues.⁵³ Both McLafferty⁵¹ and Asbeutah⁵³ reported approximately one-third with reflux of the affected limb and unexpectedly high incidence of reflux in unaffected venous segments⁵⁰ and unaffected limbs,⁵² which suggests underlying valvular dys-

function may have preceded the DVT, possibly predisposing them to clotting, or the DVT may be the result of a systemic valvular problem. Of note is that venous ulceration was not commonly reported by 5-year follow-up studies.^{53,54} If patients are asymptomatic, their prognosis at 5 years may be even better than their symptomatic counterparts with only 4% mild PTS findings.

How do clot propagation, PE, recurrence, and PTS interrelate? Based on this review, propagation of C-DVT with no anticoagulation did not appear to lead to a large number of PE despite a propagation rate of 2% to 15% to the popliteal or higher, which is likely the result of close duplex surveillance, prompt recognition of propagation, and appropriate anticoagulation. What is concerning is that not all PE were preceded by propagation, demonstrating how duplex surveillance and selective monitoring may not be protective in all cases. Such a risk for PE during surveillance would need to be considered when determining best management. Although this review did not show it, recurrence may contribute to development of valvular reflux⁶⁴ and possibly greater risk for PTS.

This review has major limitations inherent in any systematic review. Unfortunately, a meta-analysis was not possible because of lack of sufficient well-designed comparative trials aimed at addressing the question posed. Further, studies could have been missed that were not included in our search under our keywords or those not written in English, validity of the grading system has not been previously tested, sample sizes were small even in the RCTs, and bias can never be totally eliminated. We found significantly more studies reporting results of anticoagulation than observation, which may lead to sampling error, and may not represent actual clinical practice.

The current body of literature does not appear to support a universal recommendation for treating C-DVT. Based on the grading system by Guyatt et al,⁶⁵ there is Grade IIB evidence for managing with either anticoagulation for an undetermined duration or observation with elastic support and surveillance imaging studies. A third option of no specific therapy other than support stockings and ignoring the calf is inappropriate given the established reality of clot propagation, clot recurrence, and small but not insignificant risk of PE. In considering the first two options, well-designed and adequately powered studies are necessary to prove which alternative is better for any given clinical setting, and also which would be preferred given patient risk factors for ongoing complications of venous thromboembolism. Guidelines based on the current evidence must allow for these two choices.

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AUTHOR CONTRIBUTIONS

Conception and design: EM, FL
Analysis and interpretation: EM, RK, CM, FL, OG, QH
Data collection: EM, FL
Writing the article: EM, RK
Critical revision of the article: EM, RK, CM, OG
Final approval of the article: EM, RK, CM, FL, OG
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APPENDIX

Standard 1: Comparative trials

Comparative studies examining outcomes of different management strategies would provide the most meaningful data with the strongest evidence derived from randomized studies containing controls. Studies that had no controls, either internal or historic, would not have satisfied this standard.

Standard 2: Unbiased recruitment of patients and patient assembly

Papers were graded as to whether the recruitment was unbiased or consecutive. This standard would be met if the

study was consecutive or if a detailed report of exclusions was described. To better understand the natural history of C-DVT, the study group at inception should be identified early in the disease process or at a uniform point in the disease process.

Standard 3: Adequate description of the group, demographics, risk factors

Numerous risk factors and demographics could influence outcome of DVT propagation; therefore, characteristics of each group should be specified, including demographics (age, gender) and risk factors for DVT such as cancer, recent surgery, or previous DVT, history of thrombophilia, provoked or reversible risk factors, or unprovoked idiopathic circumstances.

Standard 4: Adequate surveillance with objective testing

To satisfy this standard, determination of clot propagation required repeat venous leg studies and PE during surveillance-required repeat, predetermined pulmonary studies such as V/Q studies or computed tomography (CT) angiograms of the chest for both asymptomatic and symptomatic patients.

Standard 5: Adequate testing for DVT and pulmonary emboli

To identify C-DVT limited to the calf veins not involving the popliteal vein, objective testing by either duplex ultrasound scanning, compression ultrasound, contrast venography, or radionuclide leg studies validated by venography was required.

For reporting PE at presentation and PE during surveillance, diagnosis must be confirmed by V/Q scanning

with perfusion and ventilation examinations, or CT angiogram of the chest. Clinical diagnosis of PE would not be considered meeting this standard.

For postthrombotic syndrome, objective testing for anatomic or physiological abnormalities such as reflux and/or obstruction was needed to determine presence of PTS.

Standard 6: Treatment and dose of anticoagulation

Details of the type of anticoagulant and dosing should be specified in studies examining cases with anticoagulation.

Standard 7: Adequate follow-up

For propagation of DVT, a minimum of 2 weeks' follow-up with surveillance imaging was required to meet the standard. For PE during surveillance and recurrence, a minimum for duration of follow-up was not set because the length of follow-up even if short was felt to be of value. For rating postthrombotic syndrome, the length of follow-up was critical, and therefore a minimum follow-up of 1 year was required to satisfy this standard.

Standard 8: Identifying PE at presentation

In order to accurately assess the incidence of PE during management of C-DVT, those presenting with PE must be identified early at the time of entry into the study and must be distinguished from PE during surveillance.

Standard 9: Bleeding

To more fully assess the risk of anticoagulation in treatment, we required that details of bleeding be reported in those studies where anticoagulation was used.