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REVIEW ARTICLES

Richard P. Cambria, MD, Section Editor
From the Society for Vascular Surgery

A meta-analysis of anticoagulation for calf deep venous thrombosis

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Objective: **This meta-analysis was initiated to assess the efficacy and safety of anticoagulation therapy for adult patients with isolated calf vein deep venous thrombosis (DVT).**
Methods: **We searched MEDLINE (1950-October 2010), the Cochrane Library (1993-October 2010), trial registries, meeting abstracts, and selected references, using no limits. Included studies compared the results of anticoagulation (vitamin K antagonist or therapeutic heparin) for a minimum of 30 days vs the results of no anticoagulation in adults with calf vein DVT proved by ultrasound imaging or venograph who were monitored for at least 30 days. Two independent reviewers extracted data using a piloted standardized form. Methodologic quality was assessed using the Cochrane Risk of Bias tool for randomized controlled trials (RCTs) and the Newcastle-Ottawa Quality Assessment Scale for cohort and case-control studies. Discrepancies were resolved by consensus or by a third reviewer. Authors were contacted for additional information if necessary. Outcomes were pooled using Peto fixed-effects models.**
Results: **Of 2328 studies identified, two RCTs and six cohorts (126 patients treated with anticoagulation and 328 controls) met selection criteria. The methodologic quality of most studies was poor. Pulmonary embolism (PE; odds ratio, 0.12; 95% confidence interval, 0.02-0.77; $P = .03$) and thrombus propagation (odds ratio, 0.29; 95% confidence interval, 0.14-0.62; $P = .04$) were significantly less frequent in those who received anticoagulation. Significant heterogeneity existed in studies reporting mortality rates, but these demonstrated a trend toward fewer deaths with anticoagulation. When limited to randomized trials, the protective effect of anticoagulation for PE was no longer statistically significant, but the benefit for preventing thrombus progression persisted. Adverse events such as bleeding were sparsely reported but favored controls ($P = .65$).**
Conclusions: **Our review suggests that anticoagulation therapy for calf vein DVT may decrease the incidence of PE and thrombus propagation. However, due to poor methodologic quality and few events among included studies for PE, this finding is not robust. Thrombus propagation appears reduced with anticoagulation treatment. A rigorous RCT will assist in treatment decisions for calf vein DVT. (J Vasc Surg 2012;56:228-37.)**

Extensive evidence supports anticoagulation for patients with proximal deep venous thrombosis (DVT) to reduce death from pulmonary embolus (PE).[1] No similar consensus exists for thrombosis of the deep veins of the calf (cDVT).[2] Proponents of anticoagulation for cDVT cite the only randomized trial of anticoagulation for cDVT by Lagerstedt et al.[3] This study demonstrated a 3.5% nonfatal PE rate and 17% proximal thrombus extension rate in patients who did not receive anticoagulation. Others eschew anticoagulation for cDVT, citing a low venous thrombotic event rate during surveillance of cDVTs.[2]

To date, published observational studies of cDVT are inconsistent in their reporting of the risks associated with untreated cDVT: rates of PE and proximal extension range from 0% to 31%[4-6] and 0% to 20%, respectively.[5-8] Many of these studies report uncontrolled, single-center analyses of few patients. Risks associated with anticoagulation therapy in these series are infrequently examined. Therefore, we performed a systematic review and meta-analysis of anticoagulation vs no anticoagulation for cDVT to inform evidence-based guidelines.

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METHODS

Protocol and study eligibility criteria. Methodology outlined in the Cochrane Database of Systematic Reviews[9] was used to identify appropriate studies. In addition, Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[10] and Meta-analysis Of Observational Studies in Epidemiology (MOOSE)[11] guidelines were followed for reporting. A copy of our search protocol is included in Appendix A, B, and C (online only). The following inclusion criteria were specified:

1. The study design must include a control group, which could be historic;
2. The intervention group must receive therapeutically dosed oral, intravenous, or subcutaneous anticoagulation with a vitamin K antagonist, fractionated or unfractionated heparin, or fondaparinux for a minimum duration of 1 month;
3. Controls could not receive therapeutic anticoagulation, although prophylactic dosed anticoagulation, antiplatelet therapy, and serial compression devices were allowed;
4. The subjects were aged ≥17 years, with cDVT proven by venography or ultrasound imaging;
5. Patients with histories of clotting disorders or contraindications to therapy were excluded; and
6. The minimum duration of patient follow-up had to be 30 days.

We were unable to limit the study design to randomized controlled trials (RCTs) because there were too few such studies. Historic controls were included to capture as many subjects as possible for our review. A minimum of 30 days of follow-up was used because many studies use this measure for reporting, although the recommended duration of therapy at the time of our review was 6 weeks.

Outcome measures. Our primary outcome was development of any PE, diagnosed by axial computed tomography, conventional arteriogram, ventilation/perfusion (V/Q) scan, or clinical criteria at 30 days (sudden unexplained death with antecedent leg swelling).

Secondary outcomes were divided into benefits and harms. Benefits included detection of (1) duplex or venogram evidence of proximal extension of thrombosis to the popliteal vein, (2) postthrombotic syndrome (PTS), and (3) reduced mortality. PTS was defined as pain, swelling, or chronic venous insufficiency after acute treatment of the DVT (>30 days). Harms included any bleeding requiring cessation or reversal of anticoagulation.

Search methods. We searched two electronic databases, MEDLINE (1950 to October 2010) and the Cochrane Library (1993 to October 2010). We used exploded Medical Subject Headings (MeSH) terms and key words to generate sets for the following themes: calf, deep venous thrombosis, and anticoagulation therapy. We used the Boolean term "*and*" to find their intersection. No limits or restrictions, including language, were used.

We conducted a manual review of references from articles that were included in the study. To find unpublished studies, we reviewed abstracts from the following scientific meetings: Society for Vascular Surgery Annual Meeting (2007 to 2010), American Venous Forum Annual Meeting (2004 to 2010), and the American College of Chest Physicians (2008 to 2010). We also searched the ClinicalTrials.gov Web site (http://ClinicalTrials.gov; 2000 to October 2010).

Study selection. One of two reviewers independently screened titles and abstracts of the identified 2328 articles from our initial search in a nonblinded fashion. Any potentially relevant articles with incomplete information by title and abstract were screened in full text by an individual reviewer for potential eligibility. All articles meeting inclusion criteria by title and abstract were reviewed in full text by two reviewers in an independent, nonblinded fashion for final eligibility. Each reviewer classified the articles as meets inclusion criteria or not based on the full text. Discrepancies were resolved by discussion among all reviewers. All studies classified as meeting inclusion criteria were then used for data extraction. Articles were screened for overlapping population to eliminate duplicate reporting of outcomes.

Data collection. Two independent reviewers extracted data from included studies using a piloted standardized data abstraction form in an unblinded fashion. Discrepancies between reviewers were resolved by consensus or by a third reviewer if a consensus could not be reached. Attempts were made to contact authors of studies with pertinent missing data. We recorded basic patient demographics, study type, intervention type, length of follow-up, methods of DVT and PE detection, and outcomes determined a priori on our data collection form.

Assessment of methodologic quality. The quality of each individual cohort study was assessed using the Newcastle-Ottawa Quality Assessment Scale (NOS) for cohort studies[12] or the Cochrane Risk of Bias tool for RCTs.[9] For observational studies, two independent reviewers scored each article on the domains of case selection, comparability, and outcome. The maximum score possible was 9, with 4 points for selection, 2 points for comparability, and 3 points for outcome. RCTs were assessed using the Cochrane Risk of Bias tool, which contains six domains related to randomization, blinding, outcomes, reporting, and other potential sources of bias.[9] Each of the six aspects of methodology was graded as yes, no, or unclear. Discrepancies between reviewers were resolved by consensus or by a third reviewer if a consensus could not be reached.

Analysis. All outcomes of interest were dichotomous variables. RevMan 5 software (Cochrane Information Management System) was used to pool individual study results in a weighted fashion and to compute a summary estimate with 95% confidence intervals (CIs) for each major outcome. This was done using the Peto fixed-effect model, which is useful when effects are small or no events are present in one or both arms of a study and the groups are roughly equal in size.[9] These data were then included in the pooled odds ratio (OR) calculation for the overall summary effect. If the absolute numbers necessary for these calcula-

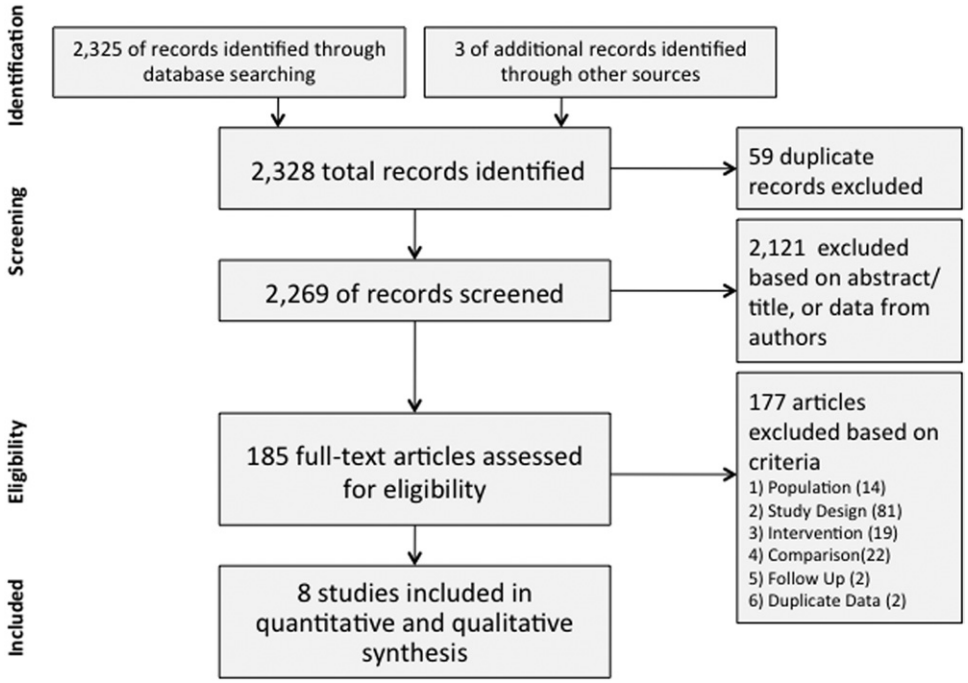

Fig 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of information through the phases of the systematic review of patients with isolated calf vein deep venous thrombosis (DVT). Articles excluded in full text based on failure to fulfill the inclusion criteria: (1) patients >17 years of age with venographic or duplex ultrasound-proven peroneal or tibial DVT; (2) comparative study of anticoagulation treatment vs no anticoagulation treatment for isolated calf DVT; (3) intervention group received therapeutically dosed heparin, warfarin, low-molecular-weight heparin, or fondaparinux for at least 30 days; (4) control group did not receive any therapeutic anticoagulation; (5) minimum follow-up was 30 days; and (6) article contained duplicate data as another series already included.

tions were not available, the study was excluded from that portion of the analysis. No data were estimated.

Assessment of heterogeneity. Heterogeneity was assessed for each summarized outcome using the DerSimonian-Laird method, where $P < .1$ indicated significant heterogeneity. Additionally, I^2 index values >0.5 were considered to represent significant heterogeneity. If significant heterogeneity was identified, the analysis was repeated, excluding individual studies in a sequential fashion in an effort to identify outliers. Each summary estimate was analyzed in two fashions: first, using all studies; second, using only those studies that passed the test of heterogeneity. If we were unable to obtain homogeneity after exclusion of individual studies, the pooled summary effect was reported despite heterogeneity.

Assessment of reporting biases. Publication bias was assessed by funnel plots, when possible, for each major outcome. These were created by plotting the effect size from each study against its respective sample size. Funnel plots were then visually inspected for symmetry.

Subgroup analyses. Because monitoring and ensuring therapeutic levels of anticoagulation may be variable based on the type of anticoagulation used and the provider, we performed a subgroup analysis examining the relationship between PE and treatment of distal venous thrombosis with anticoagulation that was documented to be within therapeutic range for ≥80% of the patients' treatment course. For the purposes of our study, therapeutic anticoagulation was defined as an international normalized ratio of 2 to 3 or partial thromboplastin time >1.5, the upper limit of normal; if not defined, a value of 90 to 140 was considered therapeutic.

Sensitivity analyses. Several sensitivity analyses were performed. First, we limited the results to RCTs only. Then, we limited the results for each element of the NOS to evaluate the effect of various methodologic parameters on our results. We then performed an additional sensitivity analysis to examine the effect of duration of anticoagulation therapy (≤6 vs >6 weeks) on our primary outcomes.

RESULTS

Description of studies. We identified 2325 potential studies from the Cochrane Library and MEDLINE searches. Two additional studies that met inclusion criteria were identified in ClinicalTrials.gov; however, neither study was included in the analysis because they are both currently recruiting subjects. By reviewing meeting abstracts and relevant references, we identified three additional studies for potential inclusion. After duplicate studies were removed, we excluded 2121 articles by title and abstract screening. The remaining

Table I. A, Characteristics of included studies

Author	*Year*	*Study design*	*Population*	*No.*	*Age (years)*	*Male sex (%)*
Lagerstedt[3]	1985	RCT	Medical inpatients	51	62.8	56.9
Pellegrini[4]	1993	Prospective (nested)	Post-op patients in RCT to evaluate prophylactic warfarin vs SCDs for DVT	25	63.7	ND
Nielson[13]	1994	RCT	Inpatients admitted for DVT	16	55	64.4
Dorr[14]	2007	Retrospective	Post-op patients	45	64.9	43
Masuda[15]	1997	Retrospective and prospective	Outpatients seen in clinic	46	64	43
Solis[16]	1992	Retrospective	Orthopedic surgery patients in study to evaluate prophylaxis for DVT	42	70	35.7
Lohr[17]	1995	Prospective	NS; inpatients and outpatients	193	56.8	42
Sachdev[18]	2006	Retrospective	Rehab patients in study to evaluate prophylaxis for DVT	87	64.7	50

DVT, Deep venous thrombosis; *ND,* no data; *NS,* not specified; *RCT,* randomized controlled trial; *SCD,* sequential compression device.

Table I. B, Characteristics of included studies

Author	*Year*	*Intervention*	*Duration (months)*	*Comparison*	*Detection method*		*Follow-up duration*
					PE	*DVT*	
Lagerstedt[3]	1985	IV heparin for 5 days plus warfarin	3	IV heparin for 5 days and compression hose	V/Q scan	Venogram	>6 weeks
Pellegrini[4]	1993	Warfarin	1.5	SCDs	V/Q scan, clinical diagnosis	Venogram	>6 weeks
Nielson[13]	1994	IV heparin plus phenprocoumon	3	Phenylbutazone for 9 days	V/Q scan	Venogram	>6 weeks
Dorr[14]	2007	LMWH or warfarin	3-6	Aspirin, dipyridamole, clopidogrel	V/Q scan	Ultrasound	>6 weeks
Masuda[15]	1997	IV heparin for 5 days plus warfarin	3	Not specified	V/Q scan	Ultrasound	>6 weeks
Solis[16]	1992	Warfarin; IV heparin; or LMWH at therapeutic dose	ND	Prophylactic dextran, heparin, or warfarin	NS	Venogram, ultrasound	<6 weeks
Lohr[17]	1995	IV heparin	1	SCDs, ASA, dipyridamole, prophylactic warfarin	V/Q scan	Ultrasound	<6 weeks
Sachdev[18]	2006	Warfarin; IV heparin; or LMWH	ND	Prophylactic heparin	NS	Ultrasound	<6 weeks

ASA, Acetylsalicylic acid; *DVT,* deep venous thrombosis; *IV,* intravenous; *LMWH,* low-molecular-weight-heparin; *ND,* no data; *NS,* not specified; *PE,* pulmonary embolism; *SCD,* sequential compression device; *V/Q,* ventilation/perfusion.

185 articles were reviewed in full text. Eight studies met full inclusion criteria (Fig 1).

Included studies. Eight studies, consisting of 505 patients, were included in our review: two were RCTs, three were retrospective cohort studies, two were prospective cohort studies, and one was a combined retrospective and prospective cohort study. All studies occurred between 1985 and 2007 and consisted primarily of medical and surgical inpatients. One study was performed in an ambulatory setting and one study had a mixture of hospitalized and ambulatory patients. Study size ranged from 16 to 193, with a mean patient age of 55 to 70 years. Intervention patients were treated with vitamin K antagonist alone (one study), unfractionated heparin alone (one study), or combinations of vitamin k antagonists plus heparin (six studies). Follow-up ranged from 1 to 12 months (Table I).

Pulmonary embolus. Five homogeneous studies, including 209 patients, reported rates of PE for both the anticoagulation and control arms ($P = .87$, $I^2 = 0\%$). The summary effect demonstrated significantly lower rates of PE in patients treated with anticoagulation than in controls (OR, 0.12; 95% CI, 0.02-0.77; Fig 2). The diagnosis of PE was made by V/Q scan in four studies. In the remaining study, combinations of V/Q scans, pulmonary angiography, and clinical presentation were used to make the diagnosis of PE. Two PEs were made by clinical diagnosis. These two patients experienced sudden, unexplained death caused by a cardiopulmonary event that was preceded by progressive leg swelling with documented DVTs.[4]

Proximal thrombus progression. Six studies with 419 patients reported results of proximal thrombus progression and were homogeneous ($P = .15$, $I^2 = 38\%$). The

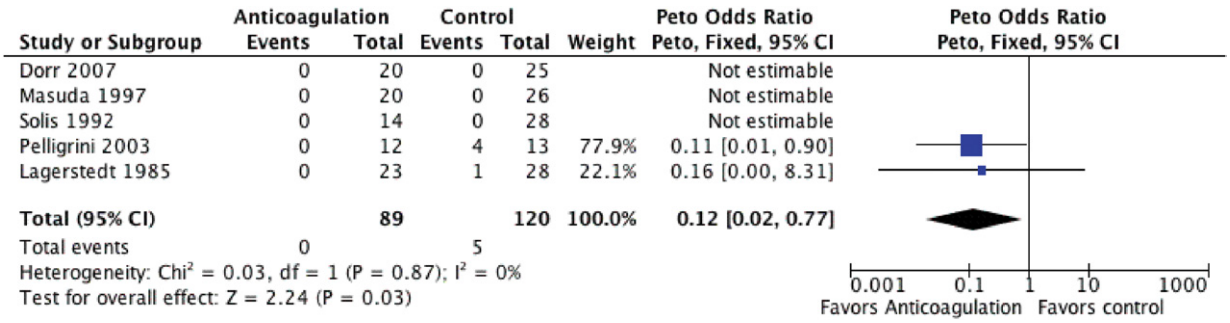

Fig 2. Rates of pulmonary embolus (PE) among treated and control patients with isolated calf vein deep venous thrombosis (DVT). *CI,* Confidence interval.

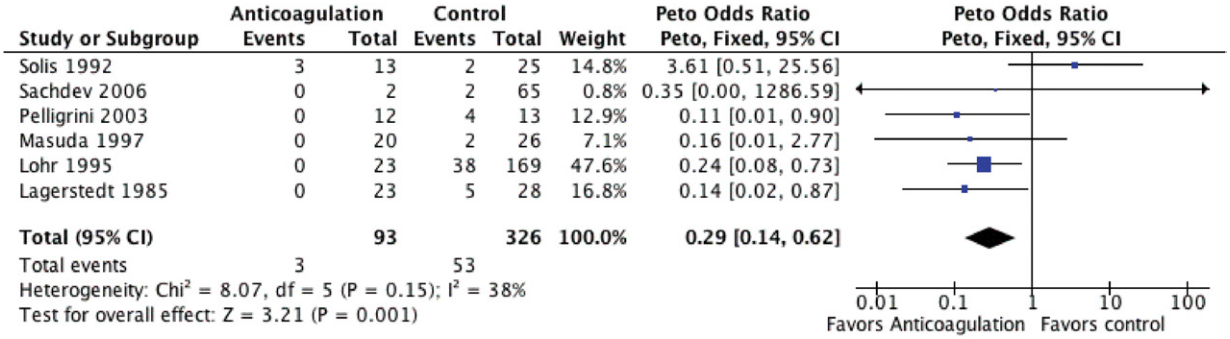

Fig 3. Rates of thrombus propagation to the popliteal vein among treated and control patients with isolated calf vein deep venous thrombosis (DVT). *CI,* Confidence interval.

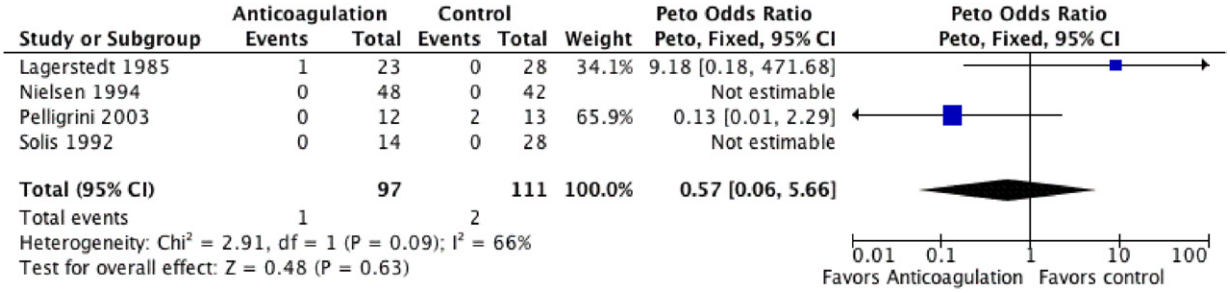

Fig 4. Mortality rates among treated and control patients with isolated calf vein deep venous thrombosis (DVT). *CI,* Confidence interval.

diagnosis of thrombus progression was made by duplex imaging alone (three studies), venography alone (two studies), and a combination of duplex and venography (one study). As with PE, the summary effect showed a significant reduction in thrombus propagation among patients treated with anticoagulation compared with those not receiving anticoagulation (OR, 0.29; 95% CI, 0.14-0.62; Fig 3).

Postthrombotic syndrome. One study[3] reported data pertaining to PTS. Eight control patients had DVT recurrence and had higher pain scores than treated patients. Of patients without recurrence, 56% reported no pain at 14 days of follow-up, and 93% reported no pain by 90 days. The remaining seven studies did not present PTS data.

Mortality. Four of the included studies reported absolute mortality rates for the anticoagulation and control arms. The combined summary effect from these studies demonstrated no difference in mortality rates between patients who were and were not anticoagulated (OR, 0.57; 95% CI, 0.06-5.66; Fig 4). However, these studies were heterogeneous ($P = .09$, $I^2 = 66\%$). Quantitative interpretation revealed that mortality rates overall were low in the included studies and did not favor the intervention or the control arm.

Bleeding requiring cessation or reversal of therapy. Four studies reported results for adverse bleeding effects of anticoagulation. The data from these studies were hetero-

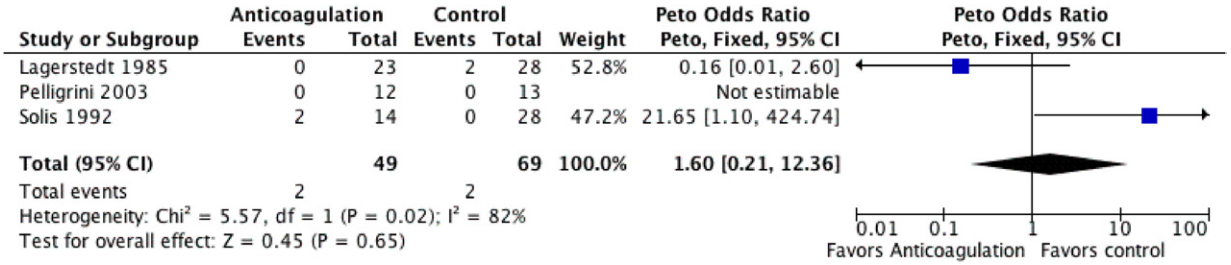

Fig 5. Bleeding rates among treated and control patients with isolated calf vein deep venous thrombosis (DVT). *CI,* Confidence interval.

geneous ($P = .02$, I^2 82%). The summary effect of these combined studies demonstrated no statistical difference in bleeding events in the anticoagulation and control arms (OR, 1.60; 95% CI, 0.21-12.36; Fig 5).

Subgroup analysis: documented vs unspecified therapeutic anticoagulation. Two studies reported data confirming that most patients who received anticoagulation were within the therapeutic range during the study period.[3,13] The remaining studies did not provide data to document adequacy of anticoagulation.[4,14-18] One of the two studies that provided documentation to support therapeutic anticoagulation also reported absolute rates of PE. There was no difference in the rate of PE between this study and the remaining studies that did not document therapeutic anticoagulation, with ORs for PE of 0.16 (95% CI, 0.00-8.31) vs 0.12 (95% CI, 0.02-0.77). Both studies documenting therapeutic anticoagulation reported rates of thrombus progression. There was no difference between the pooled rate of thrombus progression between this subgroup and the subgroup of studies that did not report efficacy of anticoagulation, with ORs for thrombus progression of 0.14 (95% CI, 0.02-0.87) vs 0.34 (95% CI, 0.15-0.77). Mortality results were unchanged based on subgroup analysis. In studies reporting therapeutic anticoagulation, there appeared to be an increase in bleeding events compared with those not reporting anticoagulation, with an OR of 21.7 (95% CI, 1.1-424.7) vs 0.16 (95% CI, 0.01-2.6).

Sensitivity analyses. From the results of an RCT that demonstrated 6 weeks of anticoagulation was sufficient for the treatment of calf vein DVT,[19] we dichotomized included studies into those that treated patients for >6 weeks or <6 weeks. Sensitivity analysis performed by treatment length showed no change in the pooled effect for PE, thrombus propagation, or death. The pooled summary effect for bleeding changed to favor anticoagulation treatment but was not significant (OR, 0.16; 95% CI, 0.01-2.6, $P = .2$).

Sensitivity analysis was also performed by methodologic quality. When only randomized trials were selected, reduction in thrombus propagation with anticoagulation remained statistically significant. Prevention of PE was favored by anticoagulation but was not statistically significant (OR, 0.16; 95% CI, 0.0-8.31). Sensitivity analysis was performed by each component of the NOS. Our finding of thrombus propagation was robust and only affected by analysis by adequacy of follow-up, and PE was sensitive to methods of assessment.

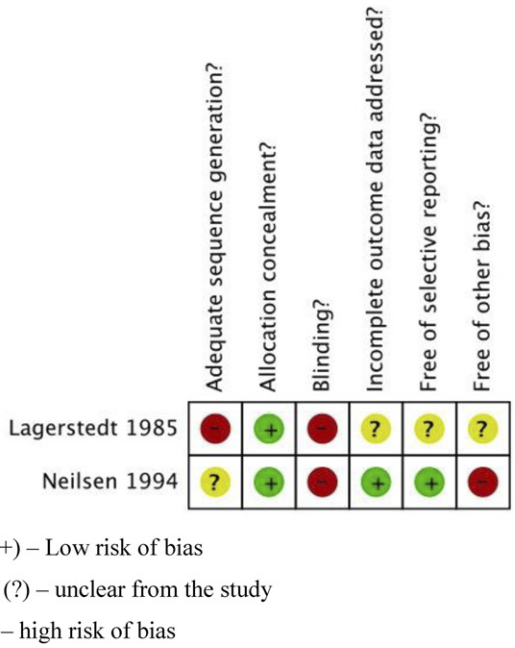

Fig 6. Cochrane Risk of Bias tool for randomized controlled trials. *Green* (+), Low risk of bias; *yellow* (?), unclear from the study; *red* (−), high risk of bias.

Methodologic quality of included studies. Overall, included studies had poor to moderate methodologic quality. The two RCTs were not blinded, and the randomization had inadequate sequence generation (Fig 6). The six remaining observational studies had a mean NOS score of 5 (range, 4-7). Demonstration that the outcome of interest was not present at baseline and adequacy of follow-up were the most frequent missing items (Table II).

Assessment for publication bias. Thrombus progression was the only outcome with enough studies to create a funnel plot for evaluation of publication bias. On visual inspection, it appears that a bias is present for studies observing a treatment effect (Fig 7).

Table II. Newcastle-Ottawa Quality Assessment Scale for Observational Studies

	Selection					*Outcome*			
Study	*Representativeness of the exposed cohort*	*Selection of the nonexposed cohort*	*Ascertainment of exposure*	*Absence of outcome at baseline*	*Comparability*	*Assessment of outcome*	*Length of follow-up*	*Adequacy of follow-up*	*Total score*
Dorr[14] 2007	★	–	★	–	–	★	★	–	4
Lohr[17] 1995	★	★	★	–	–	★	★	–	5
Masuda[15] 1997	★	★	★	–	★	★	★	–	4
Pellegrini[4] 2003	★	★	★	–	–	★	★	★	6
Sachdev[18] 2006	★	★	★	★	–	–	–	–	5
Soils[16] 1992	★	★	★	–	★★	★	–	★	7

Selection: (1) *Representativeness of the exposed cohort*: ★if truly or somewhat representative of the average patient with deep venous thrombosis; (2) *Selection of the nonexposed cohort*: ★if drawn from the same community as the exposed cohort; (3) *Ascertainment of exposure*: ★if secure record or structural interview; (4) *Absence of outcome at baseline*: ★if demonstration that outcome of interest was not present at start of study.
Comparability: *Comparability of cohorts on the basis of the study design or analysis*: ★if study controls for comorbidities; additional ★if study controls for any additional risk factors (such as age or thrombophilia).
Outcome: (1) *Assessment of outcomes*: ★if independent blind assessment or record linkage; (2) *Length of follow-up*: ★if follow-up long enough for outcomes to occur; (3) *Adequacy of follow-up of cohorts*: ★if all subjects completed follow-up or subjects lost to follow-up unlikely to introduce bias (small number lost to follow-up).

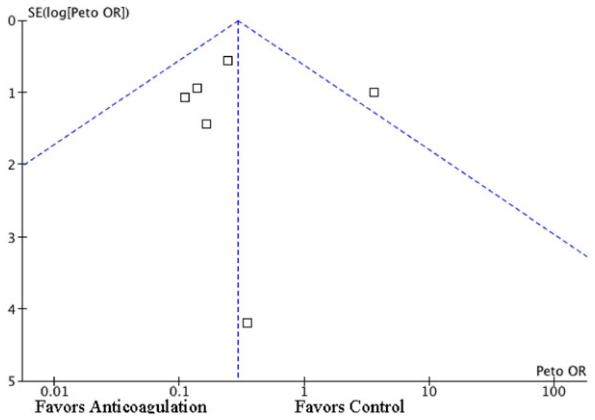

Fig 7. Funnel plot of studies reporting clot propagation. *OR,* Odds ratio.

DISCUSSION

Clinicians struggle to balance the morbidity and mortality from thromboembolic complications after isolated cDVT with the risks of anticoagulation. The current study attempts a systematic appraisal of the available literature concerning comparative anticoagulation treatment for cDVT. Our findings suggest that treatment of cDVT with anticoagulation may result in a significant reduction in occurrence of PE and proximal thrombus propagation. However, although the outcomes of bleeding and mortality weakly favored the controls in our analysis, the data available are not robust enough to make any inference regarding the potential harms of anticoagulation. Subgroup and sensitivity analysis did not have any effect on our findings.

The treatment of cDVT has been extensively debated in prior reviews without reaching clear consensus.[2,20-23] This debate stems from the lack of empiric knowledge about the true risk and natural history of cDVT. Proponents of anticoagulation for cDVT argue that the incidence of PE from cDVT alone warrants treatment.[3,24] However, opponents suggest that this rate is low, and that even surrogate points, such as propagation of thrombus, do not meet clinically important cutoffs for treatment.[2,21] Unlike the current study, prior reviews[20,22] did not search the literature in a systematic fashion, thus introducing potential selection, reporting, and publication bias, as suggested by the Cochrane Collaboration for Systematic Reviews.[9] Further, prior reviews did not adhere to proposed standards for reviews of observational studies,[11] including assessment of the methodologic quality.

This study has incorporated all such efforts to derive the most objective assessment of treatment efficacy. However, despite our systematic efforts to compile the current literature and generate a pooled effect, many included studies failed to analyze and report the full spectrum of potential treatment benefits and harms, making an objective assessment difficult. Overall, our findings are similar to those of prior reviews in PE rates and thrombus propagation.[20,22] In general, patients treated with anticoagulation have few if any thromboembolic events, whereas patients who remain untreated experience a variable but low rate of events.

Although our meta-analysis found a significant reduction in the rate of PE treated with anticoagulation for isolated cDVT, we believe it is important to place the results of our meta-analysis in context. Few of the studies included in our analysis were designed to address our research question directly. Many were investigating the relationships between anticoagulation therapy and the treatment of any DVT (including proximal),[14] PE,[13] or duplex surveillance.[16,18] Therefore, we extracted data pertinent to our review from these larger populations, resulting in a small number of included patients (n = 200) and a very low event rate overall (n = 5). In addition, although our sensitivity and subgroup analysis was limited, it revealed that PE was highly determined by the included studies in the pooled

estimate. For these reasons, we believe the data pertaining to PE are not robust and should be used cautiously when informing clinical decision making.

Alternatively, we believe that the quality of the evidence to support anticoagulation for reduction of thrombus propagation is adequate. This is due to higher event rates and a larger number of patients present in the pooled estimate. In addition, this finding was more robust under sensitivity analysis. Prevention of thrombus propagation is important because more proximal thrombus carries increased thromboembolic risk and a potentially higher risk of PTS.

Interestingly, more than half of the studies included in this review failed to specify the rates of clinically significant bleeding associated with treatment.[14,15,17,18] This omission is mirrored in other reviews[2,20,23] and limited our ability to derive a reliable pooled estimate for the effect of anticoagulation on this outcome. Treatment with a vitamin K antagonist or heparin may result in major bleeding in 3% to 5% of patients per year.[25] Although the risk of short-term therapy may be less, initiation of anticoagulation represents a tangible bleeding risk that must be considered in future trials of anticoagulation therapy for cDVT.

Lastly, only one study reported sequelae of PTS from prior cDVT despite our attempts to capture this outcome. Prior reports suggest that 23% to 33% of patients with cDVT may develop PTS.[26-28] This is a severe limitation to prior comparative studies concerning the treatment of cDVT with anticoagulation therapy that requires further investigation.

Our study has several limitations. First, as noted, qualitative and quantitative assessment of included studies both revealed that the overall methodologic quality of these studies was low. Within RCTs, issues surrounding adequate sequence generation, blinding, and selective reporting make conclusions drawn less robust. Among the included observational studies, major drawbacks in methodology revolved around verifying that the outcomes were not present at the beginning of the study and inadequate follow-up for outcome identification. We are most concerned by the latter, because a lack of appropriate follow-up may underestimate true event rates. Many of the studies performed follow-up venography or ultrasound imaging in only 75% patients, allowing for potential bias in the incidence of thrombus propagation.[13,16,18] Despite the methodologic flaws of individual included studies, our review is strengthened because our results were consistent in outcomes across trials.

Second, we did not have standardized criteria for control status of subjects, and the management of controls varied between studies. Included control therapies ranged from antiplatelet agents to sequential compression devices, prophylactic heparin, or a combination of these. However, we believe that this only strengthens our findings, assuming that these agents are expected to minimize event rates in the control arm.

Despite using protocols derived from Cochrane Handbook for Systematic Reviews,[9] our search and analysis had several limitations. First, our search involved two major electronic databases, but access to other databases, such as EMBASE, was not available. However, searches of both EMBASE and MEDLINE have been found to contain similar overlapping content and return similar numbers of relevant references.

In addition, although 10 studies are desirable for a meta-analysis, our systematic search was only able to identify eight studies that directly compared treated and control patients. Although there are additional studies that have investigated treatment of cDVT, they did not fully meet our inclusion criteria intended to minimize bias.

Lastly, although a useful statistic, we did not include a calculation of number needed to treat in our review. Calculations performed using the relatively weak data extracted from these studies may be a misrepresentation of the truth. This may give the impression that the data reflect a level of precision that is yet present in the current literature.

Although anticoagulation appears to successfully reduce proximal thrombus propagation in patients with isolated cDVT, the effects of this therapy on the risk of PE are less unclear. Further, it is unknown whether the harms associated with anticoagulation therapy outweigh the potential benefits. Properly designed prospective randomized studies are necessary that compare anticoagulation treatment vs control with assessment of PE, clot propagation, bleeding events, death, and follow-up long enough to adequately assess PTS.

Presently, the Contention Alone vs Anticoagulation for Symptomatic Calf Vein Thrombosis Diagnosed by Ultrasonography (CACTUS) trial (registered at http://clinicaltrials.gov, identifiers NCT00421538 and NCT00539058) is currently active in Europe to attempt to answer this clinical question. The protocol for the CACTUS trial compares 6 weeks of low-molecular-weight heparin, nadroparin, and compression stockings vs placebo and compression stockings on proximal propagation of cDVTs. PE is listed as a secondary outcome of this study.

CONCLUSIONS

Our review suggests that anticoagulation therapy for cDVT significantly reduces proximal thrombi propagation. On the basis of existing data, we cannot comment on the effects of anticoagulation for clinically important outcomes such as PE, death, and bleeding. Clinicians should incorporate a patient's known risk factors for venous thromboembolic events and bleeding risk when determining whether to treat patients with cDVT. A rigorous, randomized controlled study is needed to assist clinicians by guiding treatment decisions for isolated cDVT.

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AUTHOR CONTRIBUTIONS

Conception and design: RD, JW, AP, AZ, DW
Analysis and interpretation: RD, JW, AP, AZ, BS, DW
Data collection: RD, JW, AP, AZ
Writing the article: RD, JW, AP, AZ, DW
Critical revision of the article: RD, JW, AP, AZ, BS, DW

Final approval of the article: RD, JW, AP, AZ, BS, DW
Statistical analysis: RD, JW
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Overall responsibility: RD

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DISCUSSION

Dr Joseph Ricotta (*Atlanta, Ga*). How long were these patients anticoagulated for? Was there variability between the studies in terms of the duration of anticoagulation therapy?

Dr Randall R. De Martino. There was some variation. We required a minimum of 30 days because most of these were postoperative patients and that is what reporting goes to, although I think treatment should last for at least 6 weeks. We did a sensitivity analysis of outcomes by studies reporting 6 weeks of anticoagulation treatment or less. There was no change in the effect on clot propagation or PE.

Dr Ricotta. The longer the duration?

Dr De Martino. Correct.

Dr James Debord (*Peoria, Ill*). Do you think your analysis and results can be extrapolated to isolated gastrocnemius and soleus plexus clots in the absence of the named tibial vessel clots?

Dr De Martino. We did not look specifically at gastrocnemius or soleal clots in this study. We were focused on tibial and peroneal thrombi. I think that they may follow a similar pattern, although we can't make any conclusions based on this study. Other studies that have addressed that question and maybe a compilation of those studies can help identify if they are similar in characteristics. But I don't know that the clinical history of them is as well defined as is tibial and peroneal.

Dr Firas Mussa (*New York, NY*). Your last bullet suggests future studies. Can you elaborate on design of those studies?

Dr De Martino. I think there is still clinical equipoise as to whether or not we can treat or not treat these patients. Based on

the data and the studies that are available, I think that there is still a debate about this. I think clinical randomized trials will need to assess the benefits and the harms of treatment, including bleeding, mortality rates, and post-thrombotic syndrome. I am aware of one ongoing clinical study in Europe, but I am unaware of the current enrollment status. I was told yesterday in discussion, the University of Washington has applied for a grant to perform a randomized trial for this, and we hope that that will be funded and shed light on this topic.

Dr Cynthia Shortell (*Durham, NC*). It is no surprise that anticoagulation prevents thrombotic complications of calf vein clot. The question has always been, when is the risk of anticoagulation worth the benefit? And in calf vein thrombosis, that issue gets down to what the risks of those patients are. One would intuit that high-risk patients with calf clots, such as neurosurgical patients or immobile patients, would be at higher risk, but that's unknown at this point. Did any of the studies that you included contain that information? And if so, do you think you could use it to help us identify those patients with calf clot that would really benefit from anticoagulation?

Dr De Martino. I think we agree that there are patients who are at higher risk. Several of these studies did try to identify specific risk factors that would identify those patients with thrombi that are going to propagate or cause PE. The most consistent risk factor identified was inpatient status. Many other patient-level variables that they were able to analyze were not predictive in their analyses. We didn't include that type of review in the present study, but that is what I have been able to extract from the data that is available to date.

Dr Mark Meissner (*Seattle, Wash*). I was somewhat surprised that although bleeding was heterogeneous, pulmonary embolism and thrombus propagation was remarkably homogeneous. I think this is surprising, because perhaps even more so than with proximal vein thrombosis, calf vein thrombosis is often perceived to be a heterogeneous disease with the risk of complications based on the underlying risk factors for thrombosis. Your analysis seems to imply that all calf vein thrombi should be treated as equal, which may not be correct. Can you explain the homogeneity of your findings?

Dr De Martino: In regards to PE and clot propagation, I think our pooled summary was homogeneous because of our strict entry criteria. There are other studies reported on calf DVT that were excluded because they didn't meet this criteria. I think that helped in creating a homogeneous estimate.

The majority of studies did report on PE and clot propagation. Very few studies reported bleeding and mortality complications, so the data that we were able to extract were sparse and spread across eight studies, where only two to three may have contributed to the data, and I think that that affected our ability to make a homogeneous summary effect.

I think that while we were able to make a homogeneous study effect, we acknowledge that the strength of our findings comes from the quality of the studies that they were derived from. And so a robust clinical trial will really answer this question in the best light possible.

Dr Peter Gloviczki (*Rochester, Minn*). Did you notice a difference in symptomatic and asymptomatic calf vein thrombosis, or were all these patients symptomatic?

Dr De Martino. We didn't perform a formal subgroup analysis of studies that were symptomatic or asymptomatic. Approximately half of the studies identified their patients as symptomatic, two of those four being the randomized controlled trials. But we are unable to make a comment about whether the symptomatic status does make a difference.

Dr Gloviczki. And was the diagnosis of PE made using similar techniques in these studies?

Dr De Martino. The diagnosis of PE was similar in all but one study, which used a combination of V/Q scan and clinical diagnosis based on patients with a sudden death that was preceded by rapid leg swelling. And so it was felt that that was a clinical diagnosis of PE and we did include that.

Dr Roger Shinnerl (*Evansville, Ind*). I was wondering if you could please tell me if I am wrong, but I was left with the distinct impression, after looking at your data briefly, that all of the positive results were out of one study, the Pellegrini study. And that disturbs me. Does that not make that study an outlier? And even if not, should we really be endorsing that finding with the results of a pooled analysis?

Dr De Martino. That one study was a nested case-control study within a randomized trial. While they did identify a lot of outcomes, I do not think that their methods were any different than the other randomized trial that would make me think that they should be excluded or be an outlier. I think the fact that our summary of facts remained homogeneous despite their inclusion attests that it was appropriate to include them within our analysis.

Appendix A (online only). MEDLINE search protocol (1950-2010), last searched Oct 19, 2010

Search	*Term(s)*
#1	Venous thrombosis
#2	DVT
#3	Thrombosis
#4	#1 or #2 or #3
#5	Leg
#6	Calf
#7	Tibial
#8	Crural
#9	Below knee vein
#10	#5 or #6 or #7 or #8 or #9
#11	#4 and #10
#12	Calf vein thrombosis
#13	Tibial vein thrombosis
#14	Crural vein thrombosis
#15	Below knee vein thrombosis
#16	#11 or #12 or #13 or #14 or #15
#17	Anticoagulation
#18	Coumadin
#19	Warfarin
#20	Heparin
#21	Low-molecular-weight heparin
#22	Enoxaparin
#23	Fondaparinux
#24	Dalteparin
#25	Tinzaparin
#26	Anticoagulants
#27	#17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26
#28	#16 and #27

Appendix B (online only). Cochrane search protocol, last searched Oct 19, 2010

Search	*Term(s)*
#1	(Deep vein thrombosis) *or* (DVT) or (venous thrombosis) or (thrombosis)
#2	Calf *or* below knee *or* infrageniculate
#3	Anticoagulation *or* warfarin *or* Coumadin *or* heparin
#4	(#1 and #2 and #3)

Appendix C (online only). ClinicalTrials.gov search protocol, last searched Oct 18, 2010

Search terms: anticoagulation ***and*** deep venous thrombosis | venous thrombosis
or DVT
or thrombosis
or "calf vein thrombosis"
or "tibial vein thrombosis"
or "crural vein thrombosis"
or "below knee vein thrombosis" | anticoagulation
or Coumadin
or warfarin
or heparin
or "low molecular weight heparin"
or enoxaparin
or fondaparinux
or Dalteparin
or tinzaparin
or anticoagulants