Risk of Deep Vein Thrombosis Following a Single Negative Whole-Leg Compression Ultrasound

A Systematic Review and Meta-analysis

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Context In patients with suspected lower extremity deep vein thrombosis (DVT), compression ultrasound (CUS) is typically the initial test to confirm or exclude DVT. Patients with an initial negative CUS result often require repeat CUS after 5 to 7 days. Whole-leg CUS may exclude proximal and distal DVT in a single evaluation.

Objective To determine the risk of venous thromboembolism after withholding anticoagulation in patients with suspected lower extremity DVT following a single negative whole-leg CUS result.

Data Sources MEDLINE, EMBASE, CINAHL, LILACS, Cochrane, and Health Technology Assessments databases were searched for articles published from January 1970 through November 2009. Supplemental searches were performed of Internet resources, reference lists, and by contacting content experts.

Study Selection Included studies were randomized controlled trials and prospective cohort studies of patients with suspected DVT and a negative whole-leg CUS result who did not receive anticoagulant therapy, and were followed up at least 90 days for venous thromboembolism events.

Data Extraction Two authors independently reviewed and extracted data regarding a single positive or negative whole-leg CUS result, occurrence of venous thromboembolism during follow-up, and study quality.

Results Seven studies were included totaling 4731 patients with negative whole-leg CUS examinations who did not receive anticoagulation. Of these, up to 647 patients (13.7%) had active cancer and up to 725 patients (15.3%) recently underwent a major surgery. Most participants were identified from an ambulatory setting. Venous thromboembolism or suspected venous thromboembolism–related death occurred in 34 patients (0.7%), including 11 patients with distal DVT (32.4%); 7 patients with proximal DVT (20.6%); 7 patients with nonfatal pulmonary emboli (20.6%); and 9 patients (26.5%) who died, possibly related to venous thromboembolism. Using a random-effects model with inverse variance weighting, the combined venous thromboembolism event rate at 3 months was 0.57% (95% confidence interval, 0.25%-0.89%).

Conclusion Withholding anticoagulation following a single negative whole-leg CUS result was associated with a low risk of venous thromboembolism during 3-month follow-up.

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CONTRAST VENOGRAPHY IS THE diagnostic criterion standard for patients with suspected lower extremity deep vein thrombosis (DVT).[1] Compression ultrasound (CUS) has largely replaced venography to diagnose proximal DVT.[2] Compression ultrasound reliably confirms and excludes DVT of the proximal veins (above the knee) but its accuracy for distal vein DVT (below the knee) has been questioned.[2,3] This has led to diagnostic algorithms that use serial CUS to detect distal DVT that has propagated proximally.[4-6]

Up to 25% of distal DVTs may propagate into proximal veins, increasing the risk of pulmonary embolism and the postthrombotic syndrome.[7] Consequently, practice guidelines recommend serial CUS of the proximal veins 5 to 7 days after an initial negative result to safely exclude clinically suspected DVT.[3,8] Because only 1% to 2% of repeat CUS tests detect thrombus propagation, many repeat studies are conducted to detect a small number of DVTs.[4] Furthermore, some patients do not return for repeat CUS.[4] Recently developed algorithms incorporating pre-

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test probability assessment with sensitive D-dimer can reduce the number of imaging studies performed. For patients with low pretest probability, a negative CUS or a negative D-dimer excludes DVT.[5,6] However, patients with moderate to high pretest probability or a positive D-dimer require repeat CUS after 5 to 7 days to assess for propagation of undetected distal DVT.[5,6]

Whole-leg CUS, which captures images from the iliac to calf veins, may improve initial detection of distal DVT and obviate repeat CUS. Several studies have assessed whole-leg CUS in patients with suspected DVT.[9-16] However, concerns exist regarding the technical feasibility and safety of using a single whole-leg CUS to exclude DVT following an initially negative result.

A systematic review and meta-analysis was performed to assess the risk of venous thromboembolism in patients with suspected lower extremity DVT following a single negative whole-leg CUS result for whom anticoagulation is withheld. Our aim was to address the safety of withholding anticoagulation after a negative whole-leg CUS by providing estimates of the incidence of symptomatic venous thromboembolism during the 3 months after a single negative result. Secondarily, the safety of this approach in patients with intermediate to high pretest probability for DVT was assessed, in whom clinicians may be reluctant to exclude DVT after a single negative whole-leg CUS result.

METHODS

The Meta-analysis of Observational Studies in Epidemiology (MOOSE) checklist was used for our meta-analysis.[17] The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) checklist for reporting systematic reviews and meta-analyses became available near completion of this article. Our work was executed prior to knowledge of the PRISMA checklist, but it appears to be in compliance.[18]

Randomized controlled trials (RCTs) and prospective studies evaluating whole-leg CUS as a diagnostic tool for suspected symptomatic DVT were sought. There is no universally accepted term referring to an ultrasound of the entire lower extremity venous system. Previous authors have referred to this as "whole-leg ultrasonography,"[13,16] "complete lower-limb ultrasound,"[12] "complete venous ultrasound,"[9] "comprehensive duplex ultrasonography,"[11] and "complete CUS."[10,15] We will use "whole-leg CUS" because of its descriptive nature and simplicity.

The MEDLINE, EMBASE, CINAHL, LILACS, Cochrane, and Health Technology Assessments databases were searched for articles published from January 1970 through November 2009 using multiple keywords and standardized terminology, which appears in the eTable available at http://www.jama.com. Internet-based searches also were conducted of Google, Google Scholar, clinicaltrials.gov, meeting abstracts, and conference proceedings. Reference lists of studies meeting inclusion criteria were manually reviewed. Content experts were contacted to discover additional potential studies not identified by the database searches.

Two investigators (S.M.S. and S.C.W.) independently reviewed all identified publications for inclusion using predetermined criteria. Disagreements were resolved by an independent adjudicator. There were no exclusions due to non-English language. Any study published in a language other than English was translated prior to consideration for inclusion.

Studies were included if they satisfied the following criteria: (1) RCTs or prospective cohort studies of symptomatic patients with suspected lower limb DVT evaluated with a single whole-leg CUS; (2) patients were monitored throughout a prespecified follow-up period of at least 90 days during which anticoagulant therapy was withheld after a negative whole-leg CUS; and (3) there was objective confirmation of venous thromboembolism that occurred during the follow-up period. Selection of the 3-month follow-up period was based on prior research.[4]

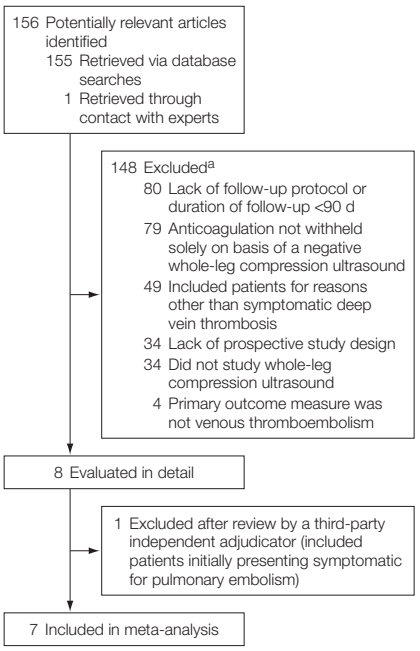
Retrospective studies were excluded. Prospective studies that included asymptomatic patients, did not withhold anticoagulant therapy, or used only limited (above the knee) CUS evaluation of the lower limbs were excluded. Finally, for studies with multiple publications, interim analyses were excluded if the final analysis was published.

Two investigators blinded to study title, journal, and author independently assessed all studies meeting our inclusion criteria. The Newcastle-Ottawa Quality Assessment Scale for Cohort Studies[19] was used as a framework for quality assessment, including the RCT by Bernardi et al[13] because only 1 cohort from the clinical trial was analyzed. Studies were assessed for representativeness of cohorts, comparability of cohorts, outcome assessment method, duration of follow-up, and adequacy of follow-up. The study design, method of enrollment, diagnostic criteria for presence of DVT, and funding source also were noted.

From each included study, data were extracted in duplicate and in an unblinded manner due to the small number of studies. Extracted data included baseline patient characteristics, number of patients screened, enrolled, initially positive for DVT, initially negative for DVT, selected to complete follow-up, lost to follow-up; number of venous thromboembolism events during follow-up period and possible venous thromboembolism–related deaths; and pretest probability assessment when available. Primary data were requested from study authors when core data required for our analyses were not reported. For all studies, only the cohort with a negative whole-leg CUS result was analyzed.

The event rate of confirmed venous thromboembolism and venous thromboembolism–attributable deaths during the follow-up period was estimated and the corresponding 95% confidence interval (CI) from each study was calculated using the exact binomial method. The incidence rates on a percentage scale from the 7 studies were pooled using inverse variance

Figure 1. Selection of Studies for Meta-analysis



The search was conducted with the MEDLINE, EMBASE, CINAHL, LILACS, Cochrane, and Health Technology Assessments databases to identify studies up to November 1, 2009.
[a]Articles may have been excluded for more than 1 reason.

weighting and the random-effects model to calculate an overall venous thromboembolism event rate and the 95% CI. Individual and pooled venous thromboembolism event rates on a percentage scale at 3 months with corresponding 95% CIs were graphed as a forest plot. Data from the 6 prospective cohort studies were pooled with that from the RCT[13] because only the whole-leg CUS group from the RCT was relevant to our analysis. Patient-level data from all included studies were requested from the original investigators, but was only provided for 2 studies.[11,15] Because different pretest probability assessment tools were used in the original analyses, the revised Wells score[6] was recalculated for both data sets to regroup patients based on pretest probability. Individual venous thromboembolism incidence rates were calculated for each probability subgroup using the exact binomial method. Overall subgroup venous thromboembolism incidence rates were estimated by the probit regression model, which was adjusted for clustering effects, and meta-analysis with the random-effects model. To compare the event rate differences between risk groups (moderate vs low and high vs low), odds ratios with corresponding 95% CIs and *P* values were estimated using the logistic regression model adjusted for clustering effects defined by each study. Between-study heterogeneity was tested using the Cochrane χ^2 test (*Q* test). The significance and amount of statistical heterogeneity were reported as *P* value and I^2.[20] Publication bias was assessed using a funnel plot and the Egger test of statistical significance.[21] Statistical analysis was performed using Stata software version 10.2 (StataCorp, College Station, Texas).

RESULTS

A total of 156 studies were identified for review (FIGURE 1). There were 132 studies identified from MEDLINE, 2 from EMBASE, 1 from the Cochrane Library, 13 from LILACS, and 7 from review of the nondatabase resources. Contact with a content expert revealed another potentially eligible study, which was reviewed following acceptance for publication. This study was determined by both investigators to meet all inclusion criteria and therefore was included for analysis.[16] After screening titles and abstracts and based on predefined inclusion and exclusion criteria, 148 studies were excluded. The 8 remaining studies were obtained for more thorough review. Disagreement over including 1 study[14] was resolved by an independent adjudicator. Exclusion of this study was based on inclusion of patients with suspected pulmonary embolism (without mention of suspected DVT) into the negative whole-leg CUS cohort. Manual review of reference lists of included studies revealed no additional studies for consideration. In total, 7 studies were included in this meta-analysis[9-13,15,16] consisting of 6 prospective cohort studies[9-12,15,16] and 1 RCT.[13]

TABLE 1 outlines the quality assessment of each study. Prospective enrollment of consecutive patients occurred in all studies. In the 2 studies by Sevestre et al,[15,16] follow-up was limited to randomly selected patients from a larger study population. Methods for objective confirmation of suspected venous thromboembolism during the clinical follow-up period were defined by each trial (eg, repeat CUS or venography for suspected DVT and CT pulmonary angiogram, V-Q scan, or conventional pulmonary angiogram for suspected pulmonary embolism). All studies ascertained outcomes through in-person or telephone follow-up interviews and medical record review. All studies included at least 90 days of follow-up.[9-12,15,16] Three studies reported 100% follow-up rates.[10-12] Bernardi et al[13] and Elias et al[9] each reported 5 patients were lost to follow-up; 0.6% and 1.2%, respectively. Sevestre et al[15,16] reported 5 ambulatory patients (0.4%) and 9 inpatients (1.8%) were lost to follow-up.

Baseline patient characteristics are outlined in TABLE 2. A total of 11 851 patients were screened and 10 090 patients (85.1%) were enrolled (TABLE 3). At presentation, objectively confirmed DVT was present in 2349 patients (23.3%). These patients were excluded from further analysis. There were 7626 patients (75.6%) with a negative whole-leg CUS result in whom anticoagulation was withheld. Patients were excluded from analysis if anticoagulant therapy was initiated during the follow-up period for unrelated indications (eg, atrial fibrillation) or empirical reasons by the treating physician (eg, superficial thrombophlebitis).

Of the 7626 patients with an initial negative whole-leg CUS result, 4731 patients were selected for analysis based on the individual study protocols and were included in the meta-analysis. The majority of patients not analyzed (n=2623) came from the 2 studies that performed follow-up on a random portion of the original study population.[15,16] Objectively confirmed venous thromboembolism and venous thromboembolism–attributable death occurred in 34

of 4731 patients (0.7%) during follow-up. Of these 34 events, 11 patients had distal DVT (32.4%); 7 had proximal DVT (20.6%); 7 had nonfatal pulmonary embolism (20.6%); and 9 patients (26.5%) died, which may have been related to venous thromboembolism. Using the exact binomial method, calculated individual rates of venous thromboembolism were as low as 0.24% (95% CI, 0.01%-1.34%)[12] and as high as 1.95% (95% CI, 0.94%-3.56%)[16] at 3-month follow-up. The pooled incidence rate was 0.57% (95% CI, 0.25%-0.89%; FIGURE 2).

Individual patient data were requested from all study authors and successfully obtained from 2 of the 7 included studies.[11,15] A total of 1618 patients from these 2 studies were grouped and analyzed based on their pretest probability. Wells scores[6] determined pretest probability as low risk in 1071 patients (66.2%), moderate risk in 467 patients (28.9%), and high risk in 80 patients (4.9%). Nine venous thromboembolism events occurred across the pretest probability subgroups; 3 with low risk, 4 with intermediate risk, and 2 with high risk. The pooled venous thromboembolism incidence rate from meta-analysis was 0.29% (95% CI, 0%-0.70%) for the low probability group, 0.82% (95% CI, 0%-1.83%) for the moderate probability group, and 2.49% (95% CI, 0%-7.11%) for the high probability group (TABLE 4). The probit regression model yielded a similar venous thromboembolism incidence rate of 0.28% (95% CI, 0.16%-0.49%) for the low probability group, 0.86% (95% CI, 0.17%-3.26%) for the moderate probability group, and 2.50% (95% CI, 0.87%-6.13%) for the high probability group. Moderate and high probability venous thromboembolism incidence rates compared with the low probability incidence rate yielded an odds ratio of 3.80 (95% CI, 1.10-8.61; $P=.03$) and 9.13 (95% CI, 4.64-17.96; $P<.001$), respectively.

Table 1. Study Quality Assessment

	Sevestre et al 2010[16]	Sevestre et al 2009[15]	Bernardi et al,[13] 2008	Subramaniam et al,[12] 2005	Stevens et al,[11] 2004	Elias et al,[9] 2003	Schellong et al,[10] 2003
Study design and enrollment	Multicenter cohort of randomly selected nonconsecutive patients	Multicenter cohort of randomly selected nonconsecutive patients	Randomized multicenter trial of consecutive patients	Single-center cohort of consecutive patients	Single-center cohort of consecutive patients	Multicenter cohort of consecutive patients	Single-center cohort of consecutive patients
Study cohort	Inpatients with suspected LE DVT and negative initial whole-leg CUS	Ambulatory patients with suspected LE DVT and negative initial whole-leg CUS	Ambulatory patients with first episode of suspected symptomatic LE DVT and negative initial whole-leg CUS	Ambulatory patients with suspected LE DVT and negative initial whole-leg CUS	Ambulatory and inpatients with first episode of suspected symptomatic LE DVT and negative initial whole-leg CUS	Ambulatory patients with first episode of suspected symptomatic LE DVT and negative initial whole-leg CUS	Ambulatory patients and inpatients with suspected LE DVT and negative initial whole-leg CUS
Diagnostic criteria for DVT on whole-leg CUS	Noncompressibility[a] plus lack of augmentation for muscular calf veins	Noncompressibility[a] plus lack of augmentation for muscular calf veins	Noncompressibility plus lack of augmentation for muscular calf veins	Noncompressibility	Noncompressibility	Noncompressibility plus intraluminal thrombus	Noncompressibility[a]
Follow-up period	3 mo	3 mo	≥3 mo	≥3 mo	≥3 mo	3 mo	90 d
Follow-up methods	Telephone interview, medical record review, vital status	Telephone interview, medical record review, vital status	Clinic follow-up with interview and physical examination, follow-up CUS, telephone interview	Telephone interview with patient or clinician, medical record review	Telephone interview with patient, medical record review	Telephone interview with patient or clinician on days 15, 30, and 90	Telephone interview, mailer, or home visit, medical record review
Outcome assessment	High probability V-Q scan, chest CT angiogram, pulmonary angiogram, whole-leg CUS	High probability V-Q scan, chest CT angiogram, pulmonary angiogram, whole-leg CUS	CUS or contrast venography, high-probability V-Q scan, chest CT angiogram, pulmonary angiogram	Whole-leg CUS on symptomatic side, chest CT angiogram (if negative then CUS)	CUS, V-Q scan, pulmonary angiogram, or chest CT angiogram plus CUS	CUS plus contrast venography, V-Q scan or pulmonary angiogram	Whole-leg CUS, contrast venography, V-Q scan, pulmonary angiogram
Lost to follow-up, No. (%)	9 (1.8)	5 (0.4)	5 (0.6)	0	0	5 (1.2)	0
Funding source	Grants from French Ministry of Health and Sanofi-Aventis	Grants from French Ministry of Health and Sanofi-Aventis	Società Italiana per lo Studio dell'Emostasi e della Trombosi; AGEN Biomedical Ltd provided the D-dimer testing kits	NR	Deseret Foundation	NR	NR

Abbreviations: CT, computed tomography; CUS, compression ultrasound; DVT, deep vein thrombosis; LE, lower extremity; NR, not reported; V-Q, ventilation perfusion.
[a]Doppler ultrasound was used if ileocaval DVT was suspected and the common femoral vein was compressible.

Table 2. Baseline Characteristics of Patients With Negative Whole-Leg Compression Ultrasound[a]

	Sevestre et al						
	2010[16]	2009[15]	Bernardi et al[13]	Subramaniam et al[12]	Stevens et al[11]	Elias et al[9]	Schellong et al[10]
Age, mean (SD), y	67 (52-78)[b]	60 (47-74)[b]	62.5 (16.2)[c]	55.8 (20.3)	56.1 (17.3)	53 (NR)	58 (16)
Female sex	320 (61.2)	877 (69.9)	623 (59.2)[c]	281 (68.0)	258 (68.8)	278 (67.8)	831 (65.7)
Prior VTE	34 (6.5)	134 (10.7)	NA	36 (8.7)	NA	NA	146 (12)
Family history of VTE	NR	NR	NR	NR	70 (18.7)	NR	NR
Active cancer	81 (15.5)	60 (4.8)	315 (29.9)[c]	18 (4.4)	18 (4.8)	NR	155 (12)
Paralysis, paresis, or plaster immobilization	30 (5.7)	38 (3.0)	288 (27.4)[c]	NR	7 (1.9)	NA	117 (9)
Bedridden ≥3 d	106 (20.3)	22 (1.7)	147 (14.0)[c]	NR	44 (11.7)	NA	NR
Recent major surgery (≤4 wk)	119 (22.7)	53 (4.2)	126 (11.9)[c]	NR	77 (20.5)	NR	350 (28)
Long-distance travel (≥8 h)	NR	NR	11 (1.0)[c]	NR	NR	NR	NR
Pregnancy or postpartum	NR	22 (1.7)	11 (1.0)[c]	NR	7 (1.9)	NA	17 (1)
Reported leg pain	NR	NR	NR	NR	307 (81.9)	238 (58)	NR
Localized tenderness	41 (7.8)	187 (14.9)	NR	NR	181 (48.3)	NR	NR
Entire leg swelling	62 (11.8)	58 (4.6)	NR	NR	133 (35.5)	NR	NR
Calf swelling ≥3 cm	202 (38.6)	644 (51.4)	NR	NR	51 (13.6)	NR	NR
Pitting edema	99 (18.9)	250 (19.9)	NR	NR	70 (18.7)	88 (21.5)[d]	NR
Collateral superficial veins	4 (0.8)	3 (0.2)	NR	NR	1 (0.3)	NR	NR
Alternate diagnosis ≥likely as DVT	292 (55.8)	831 (66.3)	NR	NR	NR	NR	NR
Probability model for DVT							
Low risk	NR	NR	NR	NR	157 (42.0)	NR	500 (30.4)
Moderate risk	NA	NA	NR	NR	180 (48.0)	NR	928 (56.4)
High risk	111 (21.2)[e]	182 (14.5)[e]	NR	NR	38 (10.1)	NR	217 (13.2)

Abbreviations: DVT, deep vein thrombosis; NA, not applicable; NR, not reported; VTE, venous thromboembolism.
[a] Values are expressed as number (percentage) unless otherwise indicated.
[b] Reported as median age (25th and 75th percentiles).
[c] Represents combined whole-leg compression ultrasound cohorts (initial positive and negative whole-leg compression ultrasound results).
[d] Combination of swollen leg or edema.
[e] Indicates simplified clinical model published by Wells et al.[5]

Table 3. Data of Included Studies

	Sevestre et al							
	2010[16]	2009[15]	Bernardi et al[13]	Subramaniam et al[12]	Stevens et al[11]	Elias et al[9]	Schellong et al[10]	Total
No. of patients								
Screened	1926	3871	2465	542	523	878	1646	11 851
Enrolled	1926	3871	1053	526	445	623	1646	10 090
Initial whole-leg CUS, No. (%)								
Positive for DVT	395 (20.5)	1023 (26.4)	278 (26.4)	113 (21.5)	61 (13.7)	204 (32.7)	275 (16.7)	2349 (23.3)
Proximal	155 (39.2)	454 (44.4)	213 (77.6)	49 (43.4)	42 (68.9)	92 (45.1)	121 (33.1)	1126 (47.9)
Distal	240 (60.8)	569 (55.6)	65 (23.4)	64 (56.6)	19 (31.1)	112 (54.9)	154 (42.1)	1223 (52.1)
Negative for DVT	1531 (79.5)	2848 (73.6)	775 (73.6)	413 (78.5)	384 (86.3)	410 (65.8)	1265 (76.9)	7626 (75.6)
No. analyzed								
Yes[a]	513	1243	763	413	375	401	1023	4731
No[b]	1018	1605	12	0	9	9	242	2895
Lost to follow-up, No. (%)	9 (1.8)	5 (0.4)	5 (0.6)	0	0	5 (1.2)	0	24 (0.5)
No. of VTE events (weighted %)	10 (1.9)	6 (0.5)	9 (1.2)	1 (0.2)	3 (0.8)	2 (0.5)	3 (0.3)	34 (0.6)
During follow-up, No.								
Proximal DVT	0	2	4	0	1	0	0	7
Distal DVT	2	1	2	0	2	2	2	11
Nonfatal pulmonary emboli, No.	1	2	3	1	0	0	0	7
VTE-related death, No.	7	1	0	0	0	0	1[c]	9

Abbreviations: CUS, compression ultrasound; DVT, deep vein thrombosis; VTE, venous thromboembolism.
[a] Defined as patients selected to complete the follow-up protocols specified by each study and included for analysis.
[b] Defined as patients not selected to complete individual follow-up protocols (not randomized to follow-up, excluded due to protocol violation, death unrelated to VTE, lost to follow-up).
[c] Determined to be fatal pulmonary embolism.

To address statistical heterogeneity, a random-effects model was used instead of a fixed-effects model, which incorporated the between-study variation into the analysis. The between-study heterogeneity was not significant with respect to venous thromboembolism incidence rates at 3-month follow-up (I^2=34.2%; P=.17). The funnel plot and the Egger test of statistical significance showed evidence of publication bias (P=.05; eFigure is available at http://www.jama.com).

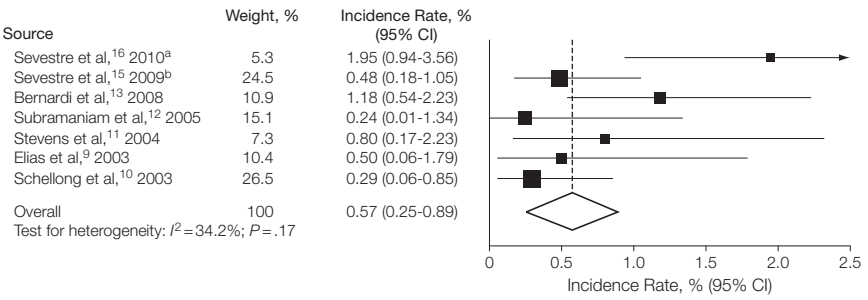
COMMENT

We aimed to assess whether a single whole-leg CUS would exclude suspected proximal and distal DVT by providing reliable and precise estimates of symptomatic venous thromboembolism after a negative whole-leg CUS result among patients not treated with anticoagulation. Our findings are based on a pooled analysis of more than 4700 patients with a negative whole-leg CUS result who were followed up without anticoagulation for symptoms of venous thromboembolism over 3 months. Overall, the risk for symptomatic venous thromboembolism was low, with a pooled venous thromboembolism event rate of 0.57%. To our knowledge, these results represent the first reported pooled risk assessment of venous thromboembolism following a negative lower extremity whole-leg CUS result.

We performed a comprehensive search of available literature and identified several high-quality prospective studies of patients with suspected lower extremity DVT from both ambulatory and inpatient settings for whom anticoagulant therapy was withheld after a negative whole-leg CUS. Patients were followed up for symptoms of venous thromboembolism for at least 90 days, permitting a thorough assessment for DVT missed on initial whole-leg CUS. Objective confirmation of venous thromboembolism was required for all patients returning with suspected venous thromboembolism. Our findings are supported by the absence of significant heterogeneity for venous thromboembolism event rates across the individual studies included in our analysis. Finally, the 9 suspected venous thromboembolism–related deaths (0.19% of all patients) may be overreported because none were objectively attributed to venous thromboembolism due to the absence of necropsies. All occurred in either acutely ill hospitalized patients or patients with advanced cancer.

The clinical utility of identifying distal DVT by whole-leg CUS warrants discussion. Because many distal thrombi appear to resolve without use of anticoagulant therapy, it may be argued that detection and treatment of distal DVT is unnecessary because it may place patients at undue risk for anticoagulant-related complications.[22-25] Despite this debate, clinical practice guidelines recommend 3 months of anticoagulation for distal DVT.[22,26] Isolated distal DVT represented 52.1% of all DVTs diagnosed on initial whole-leg CUS in our analyses. Identifying and treating such thrombi in symptomatic patients may alleviate symptoms and reduce the risk for the postthrombotic syndrome[27] and likely prevents thrombus extension in up to 25% of isolated calf thrombi, which would otherwise propagate into the proximal deep veins.[7] However, these putative therapeutic benefits must be weighed against the harms of anticoagulant therapy (ie, an

Figure 2. Individual and Pooled Venous Thromboembolism Incidence Rates



The size of the point estimates indicates the relative weight of each trial in the meta-analysis as determined by random-effects analysis. CI indicates confidence interval.
[a]Indicates inpatient cohort.
[b]Indicates ambulatory cohort.

Table 4. Individual and Pooled Venous Thromboembolism (VTE) Incidence Rates for Pretest Probability Cohorts

	Stevens et al[11]			Sevestre et al[15]			
	No. of Patients (n = 375)	No. of VTE Events (n = 3)	Incidence Rate, % (95% CI)	No. of Patients (n = 1243)	No. of VTE Events (n = 6)	Incidence Rate, % (95% CI)	Pooled VTE Incidence Rate, % (95% CI)[a]
Pretest probability assessment[b]							
Low risk	157	0	0 (0-2.32)	914	3	0.33 (0.07-0.96)	0.29 (0-0.70)
Moderate risk	180	2	1.11 (0.14-3.96)	287	2	0.70 (0.08-2.49)	0.82 (0-1.83)
High risk	38	1	2.63 (0.07-13.81)	42	1	2.38 (0.06-12.57)	2.49 (0-7.11)

Abbreviation: CI, confidence interval.
[a]Calculated using the exact binomial method and random-effects model.
[b]Determined using the modified Wells[6] score.

estimated 1.1% annual risk for major bleeding).[28]

Other concerns about adopting whole-leg CUS relate to its interobserver reliability, time needed to complete each examination, regional availability, additional training for ultrasonographers, and cost. Two prospective studies evaluating interobserver agreement found reproducibility equal to or better than venography.[29,30] Bilateral whole-leg CUS requires only 10 to 15 minutes to perform, whereas venography requires 30 to 90 minutes to complete.[10] Although whole-leg CUS may not be widely available, its successful implementation has been shown in a wide range of clinical settings. To our knowledge, a cost-effectiveness analysis of whole-leg CUS has not been conducted in the United States, and further study is needed to directly address this issue.

Our review has limitations. First, variability in whole-leg CUS techniques may limit the validity and generalizability of our findings. The CUS techniques varied slightly across studies. All studies used vein incompressibility to diagnose DVT. Elias et al[9] added direct visualization of the endoluminal thrombus. Bernardi et al[13] and Sevestre et al[15,16] added absence of flow with augmentation (manual squeezing of the calf) for DVT confirmation in muscular calf veins. Second, clinical pretest probability with a standardized clinical prediction rule was not assessed by most studies. The study by Elias et al[9] excluded patients who would have been classified as high risk by the Wells score[6] for suspected DVT. Rates of venous thromboembolism in the 3 months following a single negative whole-leg CUS result increased with increasing pretest probability of disease. However, sample sizes for patients with intermediate or high pretest probability of venous thromboembolism were small and the 95% CIs around these estimates were broad. Further study is needed to establish rates of venous thromboembolism when anticoagulation is withheld after a single negative whole-leg CUS result in patients with intermediate or high pretest probability for venous thromboembolism.

Third, the generalizability of our findings is limited by the populations enrolled in the analyzed studies. Few pregnant or postpartum patients (at most, n=57) and relatively few patients with cancer (at most, n=647) were enrolled. Thus, generalizability of our findings to these populations is limited. Fourth, outcomes beyond 3 months were not assessed. However, the 3-month period of follow-up has been commonly used in studies of DVT diagnosis. A missed diagnosis of DVT during initial evaluation is likely to result in symptomatic progression during that period.[4] Longer periods of follow-up may be more likely to detect de novo venous thromboembolism events. Fifth, verification bias is a potential limitation of the studies in our analysis because only individuals with symptoms were assessed for venous thromboembolism during the 90-day follow-up period; although this outcome measure has been commonly used for studies of serial proximal CUS as well.[4]

We assessed for publication bias using a funnel plot and the Egger test of statistical significance. The small number of studies analyzed may have limited our power to detect such bias. When restricting the analysis of publication bias to mixed or outpatient cohorts, no evidence of publication bias was observed.

Results from the inpatient cohort study by Sevestre et al[16] demonstrated a higher rate of incident venous thromboembolism compared with other included studies. Inpatients are at increased risk for venous thromboembolism and mortality for several reasons including transient risk factors (eg, immobilization, surgery, trauma), malignancy, and acute illness.[31-33] Because most of the participants in our meta-analysis were identified from an ambulatory setting, our overall results may not be generalizable to inpatients undergoing evaluation for DVT.

The included studies used strategies to mitigate bias. Selection bias was minimized in all studies through either consecutive enrollment or a randomization scheme. All studies used active outcome ascertainment. Each study used prespecified definitions for outcome measures as a means to limit the effect of interobserver variability. Incorporation bias was possible because all studies used whole-leg CUS to evaluate symptomatic patients during follow-up. However, previous studies have verified that repeated ultrasonography is a highly sensitive technique for detecting DVT missed on initial ultrasonography.[4,34]

Our results demonstrate that whole-leg CUS has a low failure rate to exclude DVT in symptomatic patients who were primarily identified from an ambulatory setting. The efficiency and convenience of whole-leg CUS as a single study is superior to that of repeated CUS evaluations. The rate of venous thromboembolism events within 90 days following a negative whole-leg CUS result increases with increasing pretest probability. However, relatively few patients with intermediate or high pretest probability for venous thromboembolism were included in our analyses and the 95% CIs around our estimates are broad. Further investigations should focus on these patient groups. Additional studies are needed that prospectively combine whole-leg CUS with D-dimer testing and formal pretest probability assessment.

In summary, withholding anticoagulation following a single negative whole-leg CUS result was associated with a low risk for venous thromboembolism during 3-month follow-up in patients with suspected DVT. Using a single negative whole-leg CUS result as the sole diagnostic modality in patients with high pretest probability of DVT requires further study.

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