Clinical relevance of distal deep vein thrombosis

Righini, Marc Philip; Paris, Samuel; Le Gal, Grégoire; Laroche, Jean-Pierre; Perrier, Arnaud; Bounameaux, Henri

Review Article

Clinical relevance of distal deep vein thrombosis

Review of literature data

Marc Righini[1], Samuel Paris[1], Grégoire Le Gal[4], Jean-Pierre Laroche[3], Arnaud Perrier[2], Henri Bounameaux[1]

[1]Division of Angiology and Hemostasis, [2]Division of Internal General Medicine, Geneva University Hospital, Geneva, Switzerland
[3]Department of Vascular Medicine, University Hospital, Montpellier, France
[4]Department of Internal Medicine and Chest Diseases and EA 3878, Brest University Hospital, France

Summary

The standard diagnostic approach of suspected deep vein thrombosis (DVT) is serial lower limb compression ultrasound (CUS) of proximal veins. Although it only assesses the proximal veins, withholding anticoagulant treatment in patients with a negative CUS on day one and after one week has been proven to be safe. However, in many centres, distal DVT is systematically screened for and treated by anticoagulants. The objectives of the review were 1) to evaluate the rate of extension of distal DVTs to proximal veins 2) to compare the safety of proximal limited CUS versus single complete CUS. We performed a MEDLINE search covering the period from January 1983 to January 2005 by using the key-words "calf vein thrombosis", "distal thrombosis" and "compression ultrasonography". English, German and French language original studies were retrieved. Moreover, references of retrieved articles were screened in order to detect missed pertinent articles. We pooled data of management studies where proximal or complete (i.e. proximal and distal) CUS were used, respectively. Studies evaluating CUS limited to the proximal veins showed a good safety profile with a pooled estimate of the 3-month thromboembolic rate of 0.6% (95% CI: 0.4–0.9%) in patients in whom anticoagulation was withheld. Studies using proximal and distal CUS showed a similar pooled estimate of the 3-month thromboembolic rate (0.4%, 95% CI: 0.1–0.6%) but distal DVT accounted for as many as 50% of all diagnosed DVTs in those series. Therefore, searching for distal DVT potentially doubles the number of patients given anticoagulant therapy and entails a risk of over-treatment. Data suggesting that anticoagulation is indicated for distal DVT are limited, and realizing distal CUS entails a risk of over-treatment. There is an urgent need for randomised trials assessing the usefulness of anticoagulant treatment in distal DVT.

Keywords

Calf thrombosis, distal deep vein thrombosis, compression ultrasonography, proximal deep vein thrombosis

Thromb Haemost 2006; 95: 56–64

Introduction

During the last two decades, diagnosis of deep venous thrombosis (DVT) has made considerable progress. Invasive procedures such as phlebography have been replaced by non-invasive diagnostic tests, in particular lower limb venous compression ultrasonography (CUS). By definition, proximal DVT involves the popliteal and/or more proximal veins. Distal DVT involves infrapopliteal veins: i.e. posterior tibial veins, peroneal veins, anterior tibial veins, and muscular calf veins (soleal or gemellar veins). The sensitivity and specificity of CUS for proximal DVT are high (97% and 98%, respectively) (1) and the necessity for treating proximal DVT by anticoagulants is based on robust evidence (2). On the other hand, the sensitivity and specificity of CUS for distal and possibly non-occlusive DVT are certainly lower (1, 3) and a meta-analysis by Kearon et al. reported sensitivity of 50% to 75% and specificity of 90% to 95% (1). Moreover, due to considerable uncertainty on the natural history of distal DVT, in particular the rate of extension to proximal veins, the need for anticoagulant treatment is debated. Therefore, contrarily to proximal DVT, the diagnostic and the therapeutic approach of distal DVT remain controversial.

We first reviewed the available data on the natural history of distal DVT, in particular the rate of extension to proximal veins.

Correspondence to:
Marc Righini, MD
Division of Angiology and Hemostasis
Geneva University Hospital
24, rue Micheli-du-Crest
1211 Geneva 14, Switzerland
Tel. +41.22.372.92.94, Fax: +41.22.372.92.99
E-mail: Marc.Righini@hcuge.ch

Received August 29, 2005
Accepted after resubmission November 17, 2005

Financial support:
The study was supported by a grant (3200B0–105991/1) from the Swiss National Research Foundation

Prepublished online December 12, 2005 DOI: 10.1160/TH05–08–0588

To better evaluate the necessity of searching for and treating distal DVTs, we then reviewed, pooled and compared 1) the data of outcome studies using CUS limited to the proximal veins and 2) the data of outcome studies using proximal and distal veins CUS in patients with clinically suspected DVT.

Methods

Study identification

We attempted to identify all published data encompassing: 1) prospective studies assessing the rate of extension of distal DVT to proximal veins (group 1), 2) prospective trials using CUS limited to the proximal veins where patients were left untreated if proximal CUS was normal (group 2, reported in Table 3), and 3) prospective trials using proximal and distal veins CUS where patients were left untreated if proximal and distal CUS were normal (group 3, reported in Table 4). Studies matching our research criteria and assessing the rate of extension of distal DVTs to proximal veins (group 1) were separated in two Tables according to the administration (Table 2) or not (Table 1) of anticoagulant treatment. Studies were identified by a MEDLINE (PubMed) search covering the period from January 1983 to January 2005 by using the key-words *calf vein thrombosis, distal thrombosis* and *compression ultrasonography.* We reviewed the titles of all retrieved studies, and irrelevant ones were excluded. Articles in English, German and French languages were accepted. We augmented our searches by manually reviewing the reference lists of all original articles and all review articles. This was done by two of the authors (MR, GLG). Case reports and abstracts were excluded.

Study eligibility

The crucial issue was to retrieve studies where the extension to proximal veins was assessed by accepted diagnostic means. Proximal ultrasonography has shown to have excellent diagnostic accuracy at the proximal level. Therefore, to analyze the rate of extension to the proximal veins of distal DVT, we included only studies in which diagnosis of proximal extension was made by phlebography or ultrasonography. Only prospective studies were considered. As the number of studies assessing the rate of extension of distal DVTs is limited, we accepted studies including in- or outpatients and studies including post-surgical patients.

Concerning trials about the safety of CUS limited to the proximal veins (group 2) or of proximal and distal CUS (group 3) in patients with clinically suspected DVT, we selected publications only if 1) the diagnosis of DVT was based on objective tests; 2) the studies were prospective; 3) included consecutive patients; 4) patients were left untreated if ultrasound examination was normal and 5) had a formal follow-up of at least three months. At least two authors evaluated each study for inclusion. Any disagreements were resolved by discussion. Authors were not blinded to journal, authors, or institution.

Study selection

On preliminary review of the titles and abstracts of citations found by our search algorithm, we identified 100 potentially pertinent studies. We then reviewed the full text of each of those 100 articles, and excluded a further 72 publications: 21 because the major aim of the study was the diagnostic accuracy or the usefulness of ultrasound in the diagnosis of DVT or in diagnostic strategies for pulmonary embolism (4–24), 6 because they reported data on the diagnostic value of phlebography (25, 26), plethysmography (27, 28), and of magnetic resonance (29, 30) in suspected DVT; 12 because they were general review articles (1, 3, 31–40), 10 because they reported the association of distal DVT and pulmonary embolism but did not specify the rate of extension to proximal veins (7, 41–49), 6 because they were retrospective (8, 50–54), 1 because it compared complete CUS with proximal CUS associated with clinically-guided and not systematic distal CUS (55), 3 because they studied the patterns and distribution of isolated calf DVT (56–58), 2 because the extension of distal DVT to adjacent distal veins or to proximal veins was not specified (59, 60), 5 because they analyzed relations between distal DVT and the post-thrombotic syndrome (61–65), 1 because it was a prospective study assessing the safety of a single complete CUS, but the proportion of proximal and distal DVTs was not specified (66), 1 because it studied the role of systematic detection of distal DVT in orthopedic patients (67), 1 because it reported (68) the same data as a previously published work (69), 3 because they used incomplete proximal and/or incomplete distal examination (70–72). This left us with 28 studies that met our selection criteria: 19 prospective studies including 1355 patients where the proximal extension of distal DVT could be analysed (Tables 1 and 2); 6 prospective outcome studies including 5876 patients (Table 3) and assessing the safety of CUS limited to proximal veins in suspected DVT (73–78); 3 prospective outcome studies (Table 4) including 2714 patients and assessing the safety of complete CUS in suspected DVT (79–81). The first 19 studies were divided in two Tables: Table 1 displays studies including patients with distal DVTs left untreated and Table 2 displays studies where patients with distal DVTs were treated with various anticoagulant regimens.

Data analysis

It is important to point out that these studies of the group 1, displayed in the Tables 1 and 2, were highly heterogeneous as they included patients in very different clinical settings and as variable proportions of patients were given anticoagulant treatment. Therefore, a pooled estimate of the rate of extension in treated and not treated patients could not be calculated.

For groups 2 and 3, differences between studies for the estimation of the three-month thromboembolic risk were assessed by a chi-2 test. The results of the homogenous studies were pooled into an overall estimate of the three-month thromboembolic risk, with its 95% confidence interval, using averaged, inverse variance-weighted estimates from each study (Tables 3 and 4).

Results

Prevalence of distal DVT

In studies including inpatients, 80% of DVTs are proximal and distal DVT accounts for only 20% of all DVTs (3, 58, 82). However, some studies with outpatients report a proportion of distal DVT as high as 60 to 70%, underlining the potential relevance of the problem in clinical practice (83, 84).

Table 1: Reported rate of distal DVT extension to proximal veins in surgical and medical patients without anticoagulant treatment.

Source, year	Study type	No. of patients included/ Patients with distal DVT and complete follow-up	Proportion of MVT/ all distal DVTs (%)	Clinical context of included patients	Initial diagnosis	Type of treatment, number of patients assigned to treatment ( )	Type of follow-up (FU)	Diagnosis of extension	Proximal Propagation n/n,(%)
Kakkar et al.(98), 1969	Prospective	132/39	No data	Asymptomatic post-surgical patients	^{125}I FUT confirmation by phlebography	None (39)	Daily clinical FU. symptom-driven ^{125}I FUT follow-up	Phlebography	9/39, (23%)
Doouss et al.(99), 1976	Prospective	379/124	No data	Asymptomatic post- surgical patients	^{125}I FUT, CUS confirmation by phlebography	None (124)	Daily clinical FU. symptom-driven ^{125}I FUT follow-up	CUS Phlebography	7/124, (6%)
Hull et al.(100), 1981	Prospective	322/11	No data	Symptomatic medical patients	^{125}I FUT, IPG confirmation by phlebography	None (11)	Sytematic ^{125}I FUT, IPG and phlebography	Phlebography	0/11 (0%)
Moser et al.(101), 1981	Prospective	68/21	No data	Symptomatic medical patients or at risk (trauma, surgery)	^{125}I FUT, IPG confirmation by phlebography	None (21)	Systematic daily ^{125}I FUT and IPG. Systematic phlebography at days 5–7	Phlebography	0/21, (0%)
Solis et al.(69), 1992	Prospective	42/38	No data	Asymptomatic, post orthopedic surgery	CUS Phlebography	None (25)	Systematic post-operative CUS and phlebography	CUS, Phlebography	2/25, (8%)
Lohr et al.(102), 1995	Prospective	288/192	No data	Symptomatic surgical and medical patients	CUS	None (169)	Systematic CUS at 3-day intervals	CUS	21/169, (12%)
Oishi et al.(103), 1994	Prospective	273/41	No data	Asymptomatic post surgical patient	CUS	None (41)	Systematic CUS at day 4 after total hip or knee arthroplasty	CUS	7/41, (17%)
Lagerstedt et al.(92), 1985	Prospective	51/51	No data	Symptomatic medical patients	^{125}I FUT confirmation by phlebography	5 days IV. heparin (28) then no anticoagulation	Symptom-driven clinical and ^{125}I FUT follow-up	Phlebography if clinical symptoms or positive ^{125}I FUT	8/28, (29%)
Schwarz et al.(104), 2001	Prospective	84/84	100%	Symptomatic surgical and medical patients	CUS	Class II stockings alone (32)	Sytematic CUS at days 3;5–7;10–12; 4 w.,3 m.	CUS	0/32, (0%)
Wang et al.(105), 2003	Prospective	55/37	No data	Symptomatic and asymptomatic post-surgical patients	Phlebography	Asymptomatic patients: no treatment (24)	Systematic clinical FU. and phlebography 3–4 years after total knee arthroplasty	Phlebography	0/37, (0%). No details about phlebographic results in function of presence or abence of symptoms
MacDonald et al.(96), 2003	Prospective	135/120	100%	Symptomatic surgical and medical patients	CUS	None (120)	Systematic CUS at days 5;9;14;30;30.	CUS	4/120, (3%)
Total (n/n), (%, 95% CI)	-	-	-	-	-	-	-	-	58/610, (10%, 7-12%)

Natural history of distal DVT

In a consecutive series of 189 outpatients with a first episode of venographically diagnosed symptomatic DVT, 99% of patients with proximal DVT also had associated calf vein thrombosis, and there was a continuous involvement between the proximal and distal veins in > 90%, suggesting that most thrombi originated in the calf (58). The natural history of deep vein thrombosis seems to be in the vast majority of cases the development of a thrombus in the distal veins of the calf that extend proximally, the so-called ascending thrombosis. The embolic potential of proximal vein thrombosis is unanimously recognized. On the other hand, although data are scarce, distal clots appear to have a much lower embolic potential (41). Therefore, the rate of proximal extension of distal DVT is a crucial issue as it largely determines the potential clinical relevance of distal DVT. Table 1 displays available studies in which the rate of propagation to proximal veins was reported in patients left untreated. Table 2 displays studies in which the rate of propagation was reported in patients receiving various anticoagulant regimens. The global rate of extension was highly variable (0 to 44%) and the variations in study design and target population were too large to allow a pooled estimate or a comparison between the proportion of patients who extended their distal DVT to proximal veins in treated and untreated patients. Therefore, data displayed at the bottom of Tables 3 and 4 simply reflect the number of distal DVTs having extended to proximal veins/ all followed-up distal DVTs.

In a previous review of the literature analysing both studies where patients were anticoagulated-or not-, Philbrick et al. reported that extension to the proximal veins varied between 0% and 29% (33). It is difficult to establish the definitive rate of extension of distal DVT based on those studies which are unlikely to be repeated. Indirect data from studies using serial proximal

Table 2: Reported rate of distal DVT extension to proximal veins in surgical and medical patients with various anticoagulant treatment. One study included some patients given streptokinase (106).

Source, year	Study type	No. of patients included/ Patients with distal DVT and complete follow-up	Proportion of MVT/all distal DVTs (%)	Clinical context of included patients	Initial diagnosis	Type of treatment, number of patients assigned to treatment ( )	Type of follow-up	Diagnosis of extension	Proximal Propagation n/n, (%)
Hull et al.(107), 1979	Prospective	68/32	No data	Symptomatic and screening of high-risk patients	^{125}I FUT, IPG confirmation by phlebography	14 days IV. Heparin then 6 wk warfarin (16) or sc.heparin (16)	Systematic 3 and 6 weeks, clinical, IPG and ^{125}I FUT follow-up	Phlebography	0/32, (0%)
Bentley et al.(108), 1980	Prospective	100/100	0% (only posterior tibial DVTs)	Symptomatic and asymptomatic medical and post-surgical patient	Phlebography	7 days sc. Heparine (50) or IV. Heparin (50)	Systematic phlebography at day 7	Phlebography	1/100 (1%)
Lagerstedt et al.(92), 1985	Prospective	51/51	No data	Symptomatic medical patients	^{125}I FUT confirmation by phlebography	5 days IV. heparin then 3 mo warfarin (23)	Symptom-driven clinical and ^{125}I FUT follow-up	Phlebography if clinical symptoms or positive ^{125}I FUT	0/23, (0%)
Schulman et al.(106), 1986	Prospective	36/36	No data	Symptomatic medical and post-surgical patients	Phlebography	IV.heparin then 5–6 m. warfarin (19) Heparin and streptokinase then 5–6 m.warfarin (17)	Systematic one week phlebography	Phlebography	0/36, (0%)
Krupski et al.(109), 1990	Prospective	24/9	No data	Symptomatic medical patients	CUS	IV. heparin then warfarin (unknown duration)	Systematic CUS (repeated 3 times)	CUS	4/9, (44%)
Lohr et al.(110), 1991	Prospective	75/75	No data	Medical symptomatic or post-surgical asymptomatic patients	CUS	Not specified	Systematic CUS at 3 to 4-day intervals	CUS	11/75, (15%)
Solis et al.(69), 1992	Prospective	42/38	No data	Asymptomatic, post orthopedic surgery	CUS Phlebography	IV. heparin and warfarin (13)	Systematic post-operative CUS and phlebography	CUS, Phlebography	3/13, (23%)
Lohr et al.(102), 1995	Prospective	288/192	No data	Symptomatic surgical and medical patients	CUS	IV. heparin (23) (unknown duration)	Systematic CUS at 3-day intervals	CUS	0/23, (0%)
Meissner et al.(85), 1997	Prospective	58/29	12%	Data missing	CUS	Various {Anticoagulation (21), VCI filter (2), unknown or no treatment (8)}	Systematic CUS at D1;D7;M1;M3;M6; M9;M12; then yearly	CUS	4/29, (14%)
Astermark et al.(111), 1998	Prospective	143/119	19%	Symptomatic medical patients	Phlebography	IV. heparin or LMWH, then warfarin (119)	Systematic phlebography 24 months after index event	Phlebography	4/119 (3%) at 3 m 11/119 (9%) at 2 y.
Pinede et al.(95), 2001	Prospective	736/197	No data	Symptomatic surgical and medical patients	CUS	IV. or sc.heparin then fluindione 6 vs 12 weeks	Symptom-driven CUS	CUS	4/197, (2%)
Schwarz et al.(104), 2001	Prospective	84/84	100%	Symptomatic surgical and medical patients	CUS	10 days LMWH (52)	Sytematic CUS at days 3; 5–7; 10–12; 4 W.; 3 M.	CUS	0/52, (0%)
Wang et al.(105), 2003	Prospective	55/37	No data	Symptomatic and asymptomatic post-surgical patients	Phlebography	Symptomatic: IV. heparin 3–5 days then asa. 325 mg td. or LMWH 3–7 days (24)	Systematic clinical FU. and phlebography 3–4 years after total knee arthroplasty	Phlebography	0/37, (0%). No details about phlebographic results in function of presence or absence of symptoms
Total (n/n), (%, 95% CI)	-	-	-	-	-	-	-	-	31/745 (4%, 3–6%)

CUS, which show a low rate of proximal DVTs (1 to 5.7%) detected by the repeated CUS (73, 74, 76–78) in patients left untreated, while at least 20% of DVTs are distal in phlebographic series (58), may add useful information in this context and are discussed later in this review.

The relationship between distal thrombosis and the post-thrombotic syndrome is far from established. Some studies reported the development of venous reflux in the affected distal or in the adjacent distal veins, with persisting symptoms in the leg (51, 85). However, these studies included limited number of patients and a very limited follow-up. Conversely, other studies suggested that only popliteal vein involvement was correlated with the risk of developing a post-thrombotic syndrome (86, 87). The question of whether the limited reflux in a calf vein may lead to severe post-thrombotic syndrome (i.e. ulceration) will require further studies.

Table 3: **Performances and safety of proximal compression ultrasonography for diagnosing DVT in outcome management studies. Calf DVTs were not searched for in these studies.**

Source, year	Patients (n)	Prevalence of DVT (%)	Proportion of proximal DVTs detected by the 2nd CUS % (95%CI)	Timing of follow-up CUS	Three-month thrombo-embolic risk, % (95% CI)*
Birdwell et al.(78), 1998	405	16	2 (0.8–4.2)	5–7 days	0.6 (0.1–2.1)
Cogo et al.(74), 1998	1702	24	0.9 (0.3–1.2)	7 days	0.7 (0.3–1.2)
Bernardi et al.(73), 1998	946	28	5.7 (1.9–12.8)	7 days	0.4 (0–0.9)
Wells et al.(76), 1997	593	16	1.8 (0.3–5.2)	7 days	0.6 (0.1–1.8)
Perrier et al.(75), 1999	474	24	N.A.*	Not done	2.6 (0.2–4.9)
Kraaijenhagen et al.(77), 2002	1756	22	3 (1.9–5.2)	7 days	0.6 (0.1–1.8)
Pooled estimate	**5876**	**23**	**N.A.**	**-**	**0.6 (0.4–0.9)**

During 3-month follow-up in patients left untreated after normal proximal compression ultrasonography. Abbreviations: DVT: deep vein thrombosis; CUS: compression ultrasonography; N.A.: not applicable. N.A: In the study by Perrier et al, only one CUS limited to proximal veins was realized.

Proximal serial CUS in outcome studies

The limited performances of distal venous examination reported in most studies explain why many centres use only proximal CUS, i.e. limited to the popliteal, and supra-popliteal veins. Since such protocols do not search for distal DVT that could potentially extend to the proximal veins with a significant risk of pulmonary embolism, the standard diagnostic approach consists in performing two CUS limited to the proximal veins at day 1 and 7, the so-called "serial proximal ultrasonography ". Patients with a proximal DVT on the initial ultrasonographic examination are treated with anticoagulants. When the initial examination is negative, patients are not anticoagulated, and a second proximal CUS is repeated one week later to detect the potential extension of distal DVT. Patients with a second normal CUS are considered as definitely not having a proximal DVT and are not treated.

Many prospective, well designed, outcome studies have shown the safety of serial proximal CUS (Table 3). Six studies used only proximal veins CUS (73–78). Five of these studies used the classical repeated CUS and one used a single proximal CUS associated with D-dimer dosage and pre-test clinical probability (75). In this study, the diagnostic strategy was based on assessment of clinical probability, D-dimer dosage, and a single proximal CUS. Patients with low or moderate clinical probability, positive D-dimer and a normal proximal CUS were left untreated and followed for 3 months. Patients with a high clinical probability and a normal CUS underwent phlebography. As the second CUS depicts 1% to 5.7% of proximal DVT (see Table 3), it is possible that not realizing the second CUS results in the slightly higher 3– month thromboembolic risk reported in this study, but confidence interval for that risk widely overlaps with that of the other similar studies

The pooled estimate of the 3-month thromboembolic risk of these studies using only proximal veins CUS was 0.6 (95% CI: 0.4–0.9%). There was no significant difference in the estimation of the 3-month thromboembolic risk between these six studies (p=0.16). If one considers each study individually, the 3-month thromboembolic risk in patients with a negative proximal CUS is low: in management studies, it is lower than 1% in series using serial CUS (CUS repeated after 1 week in patients with an initially negative CUS) (73, 74, 76–78) and 2.6% (95% CI: 0.2–4.9%) in the single study that used a single proximal CUS (75) (Table 3). This compares favourably with the 3-month thromboembolic risk in patients with clinically suspected DVT who had a negative venogram, which was found to be 1.9% (95% CI 0.4–5.4%) (25). Even if serial proximal CUS is very safe, its main limitation is the need for a second ultrasound exam, which is costly and has a very low yield as it reveals a proximal DVT in only around 1% to 5.7% of patients (74, 77). Therefore, some authors proposed to use diagnostic strategies based on evaluation of clinical probability, D-dimer measurement and a single CUS limited to the proximal veins. Perrier et al. have shown that strategy to be safe with an acceptable 3-month thromboembolic risk (2.6%, 95% CI: 0.2–4.9%) and cost-effective (75, 88).

Table 4: Performances and safety of a single proximal and distal compression ultrasonography for diagnosing DVT in outcome management studies.

Source, year	Patients (n)	Prevalence of DVT %, (n)			Three-month thromboembolic risk, % (95% CI) *
		All n, (%)	Proximal n, (%)	Distal n, (%)	Single proximal and distal CUS
Elias et al. (79), 2003	623	204, (33)	112, (55)	92, (45)	0.5 (0.1–1.8)
Schellong et al. (80), 2003	1646	275, (17)	121, (44)	154, (56)	0.3 (0.1–0.8)
Stevens et al. (81), 2004	445	61, (14)	42, (69)	19, (31)	0.8 (0.2–2.3)
Pooled estimate	**2714**	**540, (20)**	**275, (51)**	**265, (49)**	**0.4 (0.1–0.6)**

*During 3-month follow-up of patients left untreated after a normal complete (proximal and distal) compression ultrasonography. Abbreviations: N.A.: not applicable; DVT: deep vein thrombosis

Proximal and distal CUS in suspected DVT

Three prospective outcome studies using a single complete (i.e. proximal and distal) CUS matched our search strategy (79–81). Patients were treated if CUS showed a proximal or distal DVT and were left untreated if proximal and distal veins were normal. As shown in Table 4, they show that extending the ultrasonographic examination to distal vein is very safe. Indeed, the pooled estimate of the 3-month thromboembolic risk is of 0.4 (95% CI: 0.1–0.6%) and there is no significant difference in this

estimation between these 3 studies (p=0.53). However, these studies point to some important problems. First, such an approach may be quite costly and time-consuming as complete CUS is proposed to all patients with suspected DVT. Noteworthy, in patients with clinically suspected DVT, a normal Enzyme Linked Immuno-adsorbent Assay (ELISA) D-dimer test allows to withhold anticoagulation without further testing in about one third of outpatients at a much lesser expense (88) and with a similar safety. Second, the pooled estimate of the 3-month thromboembolic risk of these studies is similar to that computed for studies using only proximal CUS (Table 3). Therefore, detecting calf DVT may be deleterious: it does not reduce the 3-month thromboembolic risk and it entails a significant risk of false positive findings and subsequent unnecessary anticoagulant treatment in patients who could be left untreated (as shown by the low 3-month thromboembolic risk with a normal proximal compression ultrasonography). A pooled analysis of these studies (Table 4) shows that of a total of 2714 included patients, 265/540 (49%) of diagnosed DVTs were distal.

One additional recent paper, that was not included in our systematic review because it was published after our search period, confirmed the safety (three month thromboembolic risk : 0.24%; 95% CI:0.01 %-1.3%) of a single CUS in 542 consecutive patients with suspected DVT (89).

Selective Distal CUS

The option of performing a distal CUS only in patients presenting with localized calf pain has been analyzed in one prospective study. Gottlieb et al. randomised more than 500 patients with suspected DVT to undergo routine complete CUS of the lower limb veins, or proximal CUS associated with a selective exam of the calf only if localised symptoms were present (55). The rate of isolated calf DVT detected was very low and similar in the two groups (1.3% and 1.5% respectively). The 3-month thromboembolic risk was below 1% with no differences between the groups. Therefore, even in this comparison study, there was no obvious advantage to perform routine extensive CUS of distal deep veins.

Discussion

Should we treat distal DVT? Indeed, if treating distal DVT does not improve the outcome, a systematic search for distal clots is useless. Unfortunately, there is no universal consensus on the necessity of searching for and treating distal DVTs and medical care varies dramatically from one centre to another.

In spite of the reassuring data obtained from the outcome studies using proximal CUS, recent consensus conferences, including that of the American College of Chest Physicians (90) (ACCP) and the Australasian Society of Thrombosis and Haemostasis (91) still recommend to treat distal DVT with anticoagulants for a period of three months.

Why these recommendations? The only randomized study about the usefulness of anticoagulation in distal DVT was published by Lagerstedt et al. (92). It included only 51 patients with symptomatic distal DVT diagnosed by phlebography. Recurrence rate at 3 months was 28% in patients not anticoagulated (8/28) compared with 0% in anticoagulated patients. However, extension of DVT was not evaluated by systematic phlebography at 3 months but by physical examination and serial isotopic tests, later abandoned because of insufficient performances. In the non-treated group, 8 patients had a proximal extension of their DVT and one experienced PE. However, 50% of these patients had previous thromboembolic events, and were therefore at high risk of recurrence. Therefore, it seems unreasonable to recommend to systematically search for and to treat distal DVT on the basis of this single study and the 1A grade of recommendation delivered by the ACCP consensus conference (90) for this indication seems not to be supported by the available evidence. Moreover, the results of our pooled analysis of the three-month thromboembolic risk in studies using CUS limited to proximal veins (Table 3) and in studies using proximal and distal veins (Table 4) are similar and questions the interest of searching for and treating distal veins.

Another potential limitation of searching distal DVT is the limited reported performance of CUS at the infra-popliteal level. Admittedly, the gold standard for diagnosing DVT remains phlebography. However, it is no more widely used in the everyday clinical practice and has some limitations for the diagnosis of distal DVT (26, 93, 94). The reported diagnostic performances of CUS for distal DVT are highly variable, with sensitivities ranging from 0% to 92.5% compared with phlebography (5–7). Even if those variations may be explained in part by the inclusion of asymptomatic patients in whom even proximal ultrasonography has limited diagnostic performance, such variations suggest that the diagnostic performances of ultrasonography in distal DVT are poorer than for proximal clots. A meta-analysis by Kearon et al. suggested a sensitivity of 50–75% and an acceptable specificity (90 to 95%) (31). Some papers, however, report much higher diagnostic performances. In a study, where results of complete CUS were compared to phlebography, Bressolette et al. reported values of 100% for both sensitivity and specificity in 12 patients (83). Even if better results may be obtained in some centres, with the best ultrasound equipment and in the hands of highly skilled ultrasonographers, they can probably not be translated in everyday clinical practice. Indeed, contrarily to proximal compression ultrasonography, examination of the distal veins is quite difficult. For example, Simons et al. found that only 55% of patients could benefit from a well conducted examination (10). In a meta-analysis (7), the overall rate of indeterminate distal CUS was 54.6% (i.e. distal CUS tests which could not be reliably interpreted), with a wide variation in the reported frequency of indeterminate examinations (9.3–82.7%).

Opting for a 3-month anticoagulant treatment in the presence of a distal DVT raises several problems in clinical practice. First, series based on serial ultrasonography indicate that only a small fraction of distal DVT extend proximally. Indeed, the rate of proximal DVTs detected by the repeated ultrasound varies from 0.9% to 5.7% (Table 2), while at least 20% of DVT are distal in most phlebographic series (58). Second, the randomised DOTAVK study showed a similar safety of an anticoagulant treatment of 6 or 12 weeks for distal DVT, suggesting that a shorter period of anticoagulation (6 weeks) would be safe (95). Third, muscle vein thromboses (i.e. gemellar and solear thrombosis) are probably less dangerous than thrombosis of the deep distal veins (i.e. peroneal and tibial posterior veins). Mc Donald et al.(96) showed in a prospective study where muscular throm-

boses were not treated but followed by ultrasonograpy that only 3% of muscular thrombosis extended in the popliteal vein. Extension occurred only until the 15th day. This suggests that the vast majority of muscular vein thromboses need no anticoagulation or a shorter period of anticoagulation. Fourth, in studies using proximal and distal CUS, half of detected thrombosis were distal (Table 4) and a risk of over-treatment should not be neglected. This point deserves further comment. It is troublesome that in centres where distal veins are systematically assessed, one of two thrombosis is a distal DVT. As shown in the Tables 3 and 4, the reported prevalence of DVT is globally similar in centres using proximal or complete CUS. It is possible that populations screened are different and that physicians working in centres using complete CUS have a lower index of suspicion for DVT. One can wonder if adopting a complete examination in centres with experience of CUS limited to proximal veins would really double the prevalence of the disease and the proportion of treated patients. Obviously, there is no definitive answer. However, using distal CUS may potentially unnecessarily increase the number of patients given anticoagulant therapy, a treatment associated with a major hemorrhagic risk evaluated to 0.6 to 1.2% and a risk of fatal bleeding of 0.1 to 0.4% for a 3-month period (97).

In conclusion, even if well-conducted management studies have shown the safety of a diagnostic strategy limited to proximal (i.e. without visualisation of distal DVT) ultrasonography in patients with suspected DVT, many clinicians still search for and treat isolated distal DVT. However, this attitude is not supported by hard data. In fact, distal CUS has probably limited diagnostic performances and its systematic use may increase the prevalence of diagnosed DVT. This may result in over-treatment of a substantial proportion of patients, who might have fared well without anticoagulant therapy, as suggested by studies in which distal DVT where not searched for.

Admittedly, complete leg ultrasonography may be useful in everyday clinical practice because it can help diagnose other conditions, as calf haematoma, partial muscle rupture, and popliteal cyst. However, its advantage in diagnosing venous thromboembolism appears to be at least debatable. As distal DVT is a frequent encountered problem, and no universal consensus about the care of this pathology is accepted, there is an urgent need for randomised trials assessing the usefulness of anticoagulant treatment in symptomatic distal DVT.

Abbreviations

MVT: muscular vein thrombosis (i.e. gemellar or soleal veins thrombosis). IV :intravenous. ^{125}I FUT: ^{125}I-labelled fibrinogen uptake test. LMWH: Low molecular weight heparin. CUS : compression ultrasonography. IPG : impedance plethysmography. DVT: deep vein thrombosis; N.A.: not applicable. FU: follow-up.

References

1. Kearon C, Ginsberg JS, Hirsh J. The role of venous ultrasonography in the diagnosis of suspected deep venous thrombosis and pulmonary embolism. Ann Intern Med 1998; 129: 1044–9.

2. Brandjes DP, Heijboer H, Buller HR et al. Acenocoumarol and heparin compared with acenocoumarol alone in the initial treatment of proximal-vein thrombosis. N Engl J Med 1992; 327: 1485–9.

3. Anand SS, Wells PS, Hunt D et al. Does this patient have deep vein thrombosis? JAMA 1998; 279: 1094–9.

4. Atri M, Herba MJ, Reinhold C et al. Accuracy of sonography in the evaluation of calf deep vein thrombosis in both postoperative surveillance and symptomatic patients. AJR Am J Roentgenol 1996; 166: 1361–7.

5. Cronan JJ, Dorfman GS, Scola FH et al. Deep venous thrombosis: US assessment using vein compression. Radiology 1987; 162: 191–4.

6. Yucel EK, Fisher JS, Egglin TK et al. Isolated calf venous thrombosis: diagnosis with compression US. Radiology 1991; 179: 443–6.

7. Gottlieb RH, Widjaja J, Tian L et al. Calf sonography for detecting deep venous thrombosis in symptomatic patients: experience and review of the literature. J Clin Ultrasound 1999; 27: 415–20.

8. Cornuz J, Pearson SD, Polak JF. Deep venous thrombosis: complete lower extremity venous US evaluation in patients without known risk factors--outcome study. Radiology 1999; 211: 637–41.

9. Fraser JD, Anderson DR. Deep venous thrombosis: recent advances and optimal investigation with US. Radiology 1999; 211: 9–24.

10. Simons GR, Skibo LK, Polak JF et al. Utility of leg ultrasonography in suspected symptomatic isolated calf deep venous thrombosis. Am J Med 1995; 99: 43–7.

11. Bosson JL, Riachi M, Pichot O et al. Diameters of acute proximal and distal deep venous thrombosis of the lower limbs. Int Angiol 1998; 17: 260–7.

12. Elias A, Cadene A, Elias M et al. Extended lower limb venous ultrasound for the diagnosis of proximal and distal vein thrombosis in asymptomatic patients after total hip replacement. Eur J Vasc Endovasc Surg 2004; 27: 438–44.

13. Bounameaux H, Righini M, Perrier A. Diagnosing deep vein thrombosis: the case for compression ultrasonography limited to the proximal veins. J Thromb Haemost 2004; 2: 2260–1.

14. Dupuy DE. 1999 plenary session: Friday imaging symposium : venous US of lower-extremity deep venous thrombosis: when is US insufficient? Radiographics 2000; 20: 1195–200.

15. Garcia ND, Morasch MD, Ebaugh JL et al. Is bilateral ultrasound scanning of the legs necessary for patients with unilateral symptoms of deep vein thrombosis? J Vasc Surg 2001; 34: 792–7.

16. Elias A, Colombier D, Victor G et al. Diagnostic performance of complete lower limb venous ultrasound in patients with clinically suspected acute pulmonary embolism. Thromb Haemost 2004; 91: 187–95.

17. Mac Gillavry MR, Sanson BJ, Buller HR et al. Compression ultrasonography of the leg veins in patients with clinically suspected pulmonary embolism: is a more extensive assessment of compressibility useful? Thromb Haemost 2000; 84: 973–6.

18. Eskandari MK, Sugimoto H, Richardson T et al. Is color-flow duplex a good diagnostic test for detection of isolated calf vein thrombosis in high-risk patients? Angiology 2000; 51: 705–10.

19. Schwarz T, Schmidt B, Schellong SM. Interobserver agreement of complete compression ultrasound for clinically suspected deep vein thrombosis. Clin Appl Thromb Hemost 2002; 8: 45–9.

20. Bucek RA, Kos T, Schober E et al. Ultrasound with Levovist in the diagnosis of suspected calf vein thrombosis. Ultrasound Med Biol 2001; 27: 455–60.

21. Forbes K, Stevenson AJ. The use of power Doppler ultrasound in the diagnosis of isolated deep venous thrombosis of the calf. Clin Radiol 1998; 53: 752–4.

22. Krunes U, Teubner K, Knipp H et al. Thrombosis of the muscular calf veins--reference to a syndrome which receives little attention. Vasa 1998; 27: 172–5.

23. O'Shaughnessy AM, Fitzgerald DE. The value of duplex ultrasound in the follow-up of acute calf vein thrombosis. Int Angiol 1997; 16: 142–6.

24. Robertson PL, Goergen SK, Waugh JR et al. Colour-assisted compression ultrasound in the diagnosis of calf deep venous thrombosis. Med J Aust 1995; 163: 515–8.

25. Hull R, Hirsh J, Sackett DL et al. Clinical validity of a negative venogram in patients with clinically suspected venous thrombosis. Circulation 1981; 64: 622–5.

26. Bounameaux H, Prins TR, Schmitt HE et al. Venography of the lower limbs. Pitfalls of the diagnostic standard. The ETTT Trial Investigators. Invest Radiol 1992; 27: 1009–11.

27. Hull RD, Hirsh J, Carter CJ et al. Diagnostic efficacy of impedance plethysmography for clinically suspected deep-vein thrombosis. A randomized trial. Ann Intern Med 1985; 102: 21–8.

28. Huisman MV, Buller HR, ten Cate JW et al. Serial impedance plethysmography for suspected deep venous thrombosis in outpatients. The Amsterdam General Practitioner Study. N Engl J Med 1986; 314: 823–8.

29. Sica GT, Pugach ME, Koniaris LS et al. Isolated calf vein thrombosis: comparison of MR venography and conventional venography after initial sonography in symptomatic patients. Acad Radiol 2001; 8: 856–63.

30. Fraser DG, Moody AR, Morgan PS et al. Diagnosis of lower-limb deep venous thrombosis: a prospective blinded study of magnetic resonance direct thrombus imaging. Ann Intern Med 2002; 136: 89–98.

31. Kearon C, Julian JA, Newman TE et al. Noninvasive diagnosis of deep venous thrombosis. McMaster Diagnostic Imaging Practice Guidelines Initiative. Ann Intern Med 1998; 128: 663–77.
32. Kearon C. Natural history of venous thromboembolism. Circulation 2003; 107: I22–30.
33. Philbrick JT, Becker DM. Calf deep venous thrombosis. A wolf in sheep's clothing? Arch Intern Med 1988; 148: 2131–8.
34. Schellong SM. Complete compression ultrasound for the diagnosis of venous thromboembolism. Curr Opin Pulm Med 2004; 10: 350–5.
35. Michiels JJ, Freyburger G, van der Graaf F et al. Strategies for the safe and effective exclusion and diagnosis of deep vein thrombosis by the sequential use of clinical score, D-dimer testing, and compression ultrasonography. Semin Thromb Hemost 2000; 26: 657–67.
36. Comerota AJ. Myths, mystique, and misconceptions of venous disease. J Vasc Surg 2001; 34: 765–73.
37. Kassai B, Boissel JP, Cucherat M et al. A systematic review of the accuracy of ultrasound in the diagnosis of deep venous thrombosis in asymptomatic patients. Thromb Haemost 2004; 91: 655–66.
38. Badgett DK, Comerota MC, Khan MN et al. Duplex venous imaging: role for a comprehensive lower extremity examination. Ann Vasc Surg 2000; 14: 73–6.
39. Giannoukas AD, Labropoulos N, Burke P et al. Calf deep venous thrombosis: a review of the literature. Eur J Vasc Endovasc Surg 1995; 10: 398–404.
40. Deitcher SR, Caprini JA. Calf deep venous thrombosis should be treated with anticoagulation. Med Clin North Am 2003; 87: 1157–64.
41. Monreal M, Ruiz J, Olazabal A et al. Deep venous thrombosis and the risk of pulmonary embolism. A systematic study. Chest 1992; 102: 677–81.
42. Passman MA, Moneta GL, Taylor LM, Jr. et al. Pulmonary embolism is associated with the combination of isolated calf vein thrombosis and respiratory symptoms. J Vasc Surg 1997; 25: 39–45.
43. Gottlieb RH, Widjaja J, Mehra S et al. Clinically important pulmonary emboli: does calf vein US alter outcomes? Radiology 1999; 211: 25–9.
44. Browse NL, Thomas ML. Source of non-lethal pulmonary emboli. Lancet 1974; 1: 258–9.
45. Kistner RL, Ball JJ, Nordyke RA et al. Incidence of pulmonary embolism in the course of thrombophlebitis of the lower extremities. Am J Surg 1972; 124: 169–76.
46. Giachino A. Relationship between deep-vein thrombosis in the calf and fatal pulmonary embolism. Can J Surg 1988; 31: 129–30.
47. Moreno-Cabral R, Kistner RL, Nordyke RA. Importance of calf vein thrombophlebitis. Surgery 1976; 80: 735–42.
48. Ohgi S, Tachibana M, Ikebuchi M et al. Pulmonary embolism in patients with isolated soleal vein thrombosis. Angiology 1998; 49: 759–64.
49. Guias B, Simoni G, Oger E et al. Calf muscle venous thrombosis and pulmonary embolism. J Mal Vasc 1999; 24: 132–4.
50. Kazmers A, Groehn H, Meeker C. Acute calf vein thrombosis: outcomes and implications. Am Surg 1999; 65: 1124–7; discussion 1127–8.
51. Masuda EM, Kessler DM, Kistner RL et al. The natural history of calf vein thrombosis: lysis of thrombi and development of reflux. J Vasc Surg 1998; 28: 67–73; discussion 73–4.
52. Gottlieb RH, Widjaja J. Clinical outcomes of untreated symptomatic patients with negative findings on sonography of the thigh for deep vein thrombosis: our experience and a review of the literature. AJR Am J Roentgenol 1999; 172: 1601–4.
53. Pezzullo JA, Perkins AB, Cronan JJ. Symptomatic deep vein thrombosis: diagnosis with limited compression US. Radiology 1996; 198: 67–70.
54. Wolf B, Nichols DM, Duncan JL. Safety of a single duplex scan to exclude deep venous thrombosis. Br J Surg 2000; 87: 1525–8.
55. Gottlieb RH, Voci SL, Syed L et al. Randomized prospective study comparing routine versus selective use of sonography of the complete calf in patients with suspected deep venous thrombosis. AJR Am J Roentgenol 2003; 180: 241–5.
56. Labropoulos N, Webb KM, Kang SS et al. Patterns and distribution of isolated calf deep vein thrombosis. J Vasc Surg 1999; 30: 787–91.
57. Mattos MA, Melendres G, Sumner DS et al. Prevalence and distribution of calf vein thrombosis in patients with symptomatic deep venous thrombosis: a color-flow duplex study. J Vasc Surg 1996; 24: 738–44.
58. Cogo A, Lensing AW, Prandoni P et al. Distribution of thrombosis in patients with symptomatic deep vein thrombosis. Implications for simplifying the diagnostic process with compression ultrasound. Arch Intern Med 1993; 153: 2777–80.
59. Meissner MH, Caps MT, Bergelin RO et al. Propagation, rethrombosis and new thrombus formation after acute deep venous thrombosis. J Vasc Surg 1995; 22: 558–67.
60. Menzoian JO, Sequeira JC, Doyle JE et al. Therapeutic and clinical course of deep vein thrombosis. Am J Surg 1983; 146: 581–5.
61. Saarinen JP, Domonyi K, Zeitlin R et al. Postthrombotic syndrome after isolated calf deep venous thrombosis: the role of popliteal reflux. J Vasc Surg 2002; 36: 959–64.
62. Labropoulos N, Kang SS, Mansour MA et al. Early thrombus remodelling of isolated calf deep vein thrombosis. Eur J Vasc Endovasc Surg 2002; 23: 344–8.
63. McLafferty RB, Moneta GL, Passman MA et al. Late clinical and hemodynamic sequelae of isolated calf vein thrombosis. J Vasc Surg 1998; 27: 50–6; discussion 56–7.
64. Haenen JH, Janssen MC, Wollersheim H et al. The development of postthrombotic syndrome in relationship to venous reflux and calf muscle pump dysfunction at 2 years after the onset of deep venous thrombosis. J Vasc Surg 2002; 35: 1184–9.
65. Labropoulos N, Giannoukas AD, Nicolaides AN et al. The role of venous reflux and calf muscle pump function in nonthrombotic chronic venous insufficiency. Correlation with severity of signs and symptoms. Arch Surg 1996; 131: 403–6.
66. Noren A, Ottosson E, Rosfors S. Is it safe to withhold anticoagulation based on a single negative color duplex examination in patients with suspected deep venous thrombosis? A prospective 3-month follow-up study. Angiology 2002; 53: 521–7.
67. Schmidt B, Michler R, Klein M et al. Ultrasound screening for distal vein thrombosis is not beneficial after major orthopedic surgery. A randomized controlled trial. Thromb Haemost 2003; 90: 949–54.
68. Barnes R. Is anticoagulation indicated for postoperative or spontaneous calf vein thrombosis? In: Veith F, editor. Current clinical problems in vascular surgery. St. Louis, Missouri: Quality Medical Publishing Inc; 1993.
69. Solis MM, Ranval TJ, Nix ML et al. Is anticoagulation indicated for asymptomatic postoperative calf vein thrombosis? J Vasc Surg 1992; 16: 414–8; discussion 418–9.
70. Vaccaro JP, Cronan JJ, Dorfman GS. Outcome analysis of patients with normal compression US examinations. Radiology 1990; 175: 645–9.
71. Heijboer H, Buller HR, Lensing AW et al. A comparison of real-time compression ultrasonography with impedance plethysmography for the diagnosis of deep-vein thrombosis in symptomatic outpatients. N Engl J Med 1993; 329: 1365–9.
72. Sarpa MM, LM. Villemure P. et al. Significance of a negative duplex scan in patients suspected of having acute deep venous thrombosis of the lower extremity. J Vasc Tech 1989; 13: 224–226.
73. Bernardi E, Prandoni P, Lensing AW et al. D-dimer testing as an adjunct to ultrasonography in patients with clinically suspected deep vein thrombosis: prospective cohort study. The Multicentre Italian D-dimer Ultrasound Study Investigators Group. Bmj 1998; 317: 1037–40.
74. Cogo A, Lensing AW, Koopman MM et al. Compression ultrasonography for diagnostic management of patients with clinically suspected deep vein thrombosis: prospective cohort study. BMJ 1998; 316: 17–20.
75. Perrier A, Desmarais S, Miron MJ et al. Non-invasive diagnosis of venous thromboembolism in outpatients. Lancet 1999; 353: 190–5.
76. Wells PS, Anderson DR, Bormanis J et al. Value of assessment of pretest probability of deep-vein thrombosis in clinical management. Lancet 1997; 350: 1795–8.
77. Kraaijenhagen RA, Piovella F, Bernardi E et al. Simplification of the diagnostic management of suspected deep vein thrombosis. Arch Intern Med 2002; 162: 907–11.
78. Birdwell BG, Raskob GE, Whitsett TL et al. The clinical validity of normal compression ultrasonography in outpatients suspected of having deep venous thrombosis. Ann Intern Med 1998; 128: 1–7.
79. Elias A, Mallard L, Elias M et al. A single complete ultrasound investigation of the venous network for the diagnostic management of patients with a clinically suspected first episode of deep venous thrombosis of the lower limbs. Thromb Haemost 2003; 89: 221–7.
80. Schellong SM, Schwarz T, Halbritter K et al. Complete compression ultrasonography of the leg veins as a single test for the diagnosis of deep vein thrombosis. Thromb Haemost 2003; 89: 228–34.
81. Stevens SM, Elliott CG, Chan KJ et al. Withholding anticoagulation after a negative result on duplex ultrasonography for suspected symptomatic deep venous thrombosis. Ann Intern Med 2004; 140: 985–91.
82. Wells PS, Hirsh J, Anderson DR et al. Accuracy of clinical assessment of deep-vein thrombosis. Lancet 1995; 345: 1326–30.
83. Bressollette L, Nonent M, Oger E et al. Diagnostic accuracy of compression ultrasonography for the detection of asymptomatic deep venous thrombosis in medical patients--the TADEUS project. Thromb Haemost 2001; 86: 529–33.
84. Oger E. Incidence of venous thromboembolism: a community-based study in Western France. EPI-GETBP Study Group. Groupe d'Etude de la Thrombose de Bretagne Occidentale. Thromb Haemost 2000; 83: 657–60.
85. Meissner MH, Caps MT, Bergelin RO et al. Early outcome after isolated calf vein thrombosis. J Vasc Surg 1997; 26: 749–56.
86. Monreal M, Martorell A, Callejas JM et al. Venographic assessment of deep vein thrombosis and risk of developing post-thrombotic syndrome: a prospective study. J Intern Med 1993; 233: 233–8.
87. Lindner DJ, Edwards JM, Phinney ES et al. Long-term hemodynamic and clinical sequelae of lower extremity deep vein thrombosis. J Vasc Surg 1986; 4: 436–42.
88. Perone N, Bounameaux H, Perrier A. Comparison of four strategies for diagnosing deep vein thrombosis: a cost-effectiveness analysis. Am J Med 2001; 110: 33–40.
89. Subramaniam RM, Heath R, Chou T et al. Deep venous thrombosis: withholding anticoagulation therapy after negative complete lower limb US findings. Radiology 2005; 237: 348–52.

90. Buller HR, Agnelli G, Hull RD et al. Antithrombotic therapy for venous thromboembolic disease: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004; 126: 401S-428S.
91. Gallus AS, Baker RI, Chong BH et al. Consensus guidelines for warfarin therapy. Recommendations from the Australasian Society of Thrombosis and Haemostasis. Med J Aust 2000; 172: 600–5.
92. Lagerstedt CI, Olsson CG, Fagher BO et al. Need for long-term anticoagulant treatment in symptomatic calf-vein thrombosis. Lancet 1985; 2: 515–8.
93. Illescas FF, Lerclerc J, Rosenthall L et al. Interobserver variability in the interpretation of contrast venography, technetium-99m red blood cell venography and impedance plethysmography for deep vein thrombosis. Can Assoc Radiol J 1990; 41: 264–9.
94. McLachlan MS, Thomson JG, Taylor DW et al. Observer variation in the interpretation of lower limb venograms. AJR Am J Roentgenol 1979; 132: 227–9.
95. Pinede L, Ninet J, Duhaut P et al. Comparison of 3 and 6 months of oral anticoagulant therapy after a first episode of proximal deep vein thrombosis or pulmonary embolism and comparison of 6 and 12 weeks of therapy after isolated calf deep vein thrombosis. Circulation 2001; 103: 2453–60.
96. Macdonald PS, Kahn SR, Miller N et al. Short-term natural history of isolated gastrocnemius and soleal vein thrombosis. J Vasc Surg 2003; 37: 523–7.
97. Hyers TM, Agnelli G, Hull RD et al. Antithrombotic therapy for venous thromboembolic disease. Chest 2001; 119: 176S-193S.
98. Kakkar VV, Howe CT, Flanc C et al. Natural history of postoperative deep-vein thrombosis. Lancet 1969; 2: 230–2.
99. Doouss TW. The clinical significance of venous thrombosis of the calf. Br J Surg 1976; 63: 377–8.
100. Hull R, Hirsh J, Sackett DL et al. Replacement of venography in suspected venous thrombosis by impedance plethysmography and 125I-fibrinogen leg scanning: a less invasive approach. Ann Intern Med 1981; 94: 12–5.
101. Moser KM, LeMoine JR. Is embolic risk conditioned by location of deep venous thrombosis? Ann Intern Med 1981; 94: 439–44.
102. Lohr JM, James KV, Deshmukh RM et al. Allastair B. Karmody Award. Calf vein thrombi are not a benign finding. Am J Surg 1995; 170: 86–90.
103. Oishi CS, Grady-Benson JC, Otis SM et al. The clinical course of distal deep venous thrombosis after total hip and total knee arthroplasty, as determined with duplex ultrasonography. J Bone Joint Surg Am 1994; 76: 1658–63.
104. Schwarz T, Schmidt B, Beyer J et al. Therapy of isolated calf muscle vein thrombosis with low-molecular-weight heparin. Blood Coagul Fibrinolysis 2001; 12: 597–9.
105. Wang CJ, Wang JW, Weng LH et al. Outcome of calf deep-vein thrombosis after total knee arthroplasty. J Bone Joint Surg Br 2003; 85: 841–4.
106. Schulman S, Granqvist S, Juhlin-Dannfelt A et al. Long-term sequelae of calf vein thrombosis treated with heparin or low-dose streptokinase. Acta Med Scand 1986; 219: 349–57.
107. Hull R, Delmore T, Genton E et al. Warfarin sodium versus low-dose heparin in the long-term treatment of venous thrombosis. N Engl J Med 1979; 301: 855–8.
108. Bentley PG, Kakkar VV, Scully MF et al. An objective study of alternative methods of heparin administration. Thromb Res 1980; 18: 177–87.
109. Krupski WC, Bass A, Dilley RB et al. Propagation of deep venous thrombosis identified by duplex ultrasonography. J Vasc Surg 1990; 12: 467–74; discussion 474–5.
110. Lohr JM, Kerr TM, Lutter KS et al. Lower extremity calf thrombosis: to treat or not to treat? J Vasc Surg 1991; 14: 618–23.
111. Astermark J, Bjorgell O, Linden E et al. Low recurrence rate after deep calf-vein thrombosis with 6 weeks of oral anticoagulation. J Intern Med 1998; 244: 79–82.