ANTICOAGULANTI NELLE TROMBOSI VENOSE DISTALI

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MANAGEMENT OF CALF VEIN THROMBOSIS

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DISTAL DVT: PRACTICAL CLINICAL ISSUES

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Distal DVT: my talk today

- Epidemiology and natural history
- Diagnosis
- Treatment

Distal DVT: my talk today

- Epidemiology and natural history
- (Diagnosis)
- Treatment

Distal DVT: my talk today

- Epidemiology and natural history
- (Diagnosis)
- Treatment

Distal DVT: practical clinical issues

- Natural history
- Diagnosis
- Treatment

Isolated calf deep vein thrombosis in the community setting: the Worcester Venous Thromboembolism study

Frederick A. Spencer · Aimee Kroll · Darleen Lessard · Cathy Emery · Alla V. Glushchenko · Luigi Pacifico · George Reed · Joel M. Gore · Robert J. Goldberg

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Abstract The prevalence of isolated calf deep vein thrombosis (DVT) in the community setting is relatively unexplored. Confusion remains with regards to its management and contemporary natural history. The purpose of this investigation was to describe the number of cases of calf DVT in the community, use of early management strategies, and rates of venous thromboembolism (VTE) recurrence and major bleeding. The medical records of residents of the Worcester (MA) metropolitan area with ICD-9 codes consistent with potential VTE during 4 study years (1999/2001/2003/2005) were validated by trained nurses. Patient demographic/clinical characteristics,

Electronic supplementary material The online version of this article (doi: 10.1007/s11239-011-0670-x) contains supplementary material, which is available to authorized users.

F. A. Spencer · A. V. Glushchenko Department of Medicine, McMaster University Medical School, treatment practices, and outcomes were evaluated. Isolated calf DVT was diagnosed in 166 (11.1%) of 1,495 patients with lower extremity DVT. Patients with calf DVT were less likely to be discharged on anticoagulants or with an IVC filter than patients with proximal DVT (84.1 vs. 92.3%). The rates of VTE recurrence and pulmonary embolism did not differ significantly between patients with calf DVT and proximal DVT at 6 months (11.0 vs. 8.7%, 2.6 vs. 1.8%, respectively). Patients with calf DVT had higher adjusted risk of early (14-day) VTE recurrence/ extension (OR 2.34, 95% CI 1.01-5.44). Patients with calf DVT had lower rates of major bleeding at 6 months compared to patients with proximal DVT (5.2 vs. 9.3%, P = 0.04). Rates of recurrent VTE and major bleeding following calf DVT in the community are much higher than in randomized clinical trials of patients with proximal or calf DVT. Further study of management strategies for isolated calf DVT is needed.

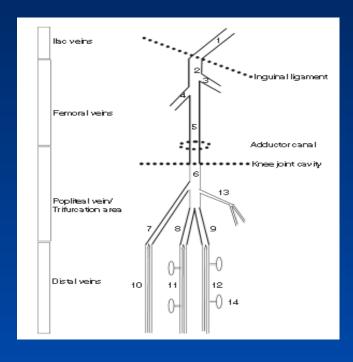
Baseline	patio	ent cl	haract	teri	st	CS
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Multicenter
Redvanced Study
for a ThromboEmbolism
Registry

Verso, Th Res, 2012

	N	%
Gender male	1056	49.8
Mean Age	59.3 <u>+</u> 18	3.1 yrs
Age classes:		
<u><</u> 40 yrs	424	20
41-60 yrs	529	25
61-80 yrs	943	44.5
≥ 81 yrs	223	10.5
Site distribution of lower limb DVT		
Bilateral	114	5.9
Proximal	1602	83.7
Distal	170	8.9
Inferior vena cava	50	2.6

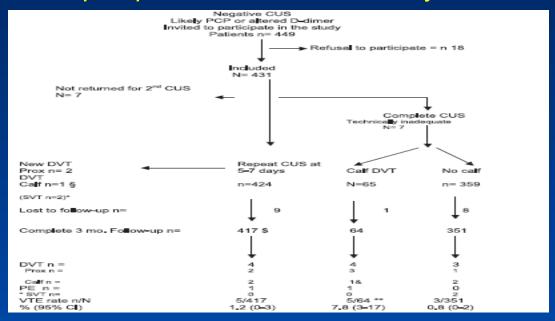
Distal DVT: prevalence



- 7 11% of patients with suspected PE
- 4 15% of patients with suspected DVT
- 9% 60% of patients with confirmed DVT

Palareti, J Thromb Haemost, 2012

Evolution of untretaed calf DVT in high risk symptomatic outpatients: the blind prospective CALTHRO study



Palareti, Thromb Haemost, 2010

MASTER REGISTRY Isolated calf deep vein thrombosis (IC-DVT)

IC-DVT: 240/1772 (13.5%)

IC (%)	Prox.(%)) p-value	
15.0	5.5	<0.0001	
49.6	41.1	0.016	
10.8	20.4	<0.001	
24.6	19.9	ns	
	15.0 49.6 10.8	15.0 5.5 49.6 41.1 10.8 20.4	15.0 5.5 <0.0001 49.6 41.1 0.016 10.8 20.4 <0.001

Palareti, Int Angiol, 2008

Evolution of untretaed calf DVT in high risk symptomatic outpatients: the blind prospective CALTHRO study

Subjects included = 431 Subjects with technically inadequate calf examination = 7 Subjects evaluated = 424							
	Calf DVT 65 (15.3%)	No calf DVT 359 (84.7%)	Р				
Clinical evolution at 3 month follow-up, no. (%) Primary outcomes (DVT or PE)	5 (7.8) 3 (4.7)*	3 (0.8) 3 (0.8)	0.003 0.049				
Secondary outcomes (SVT) Symptoms in the affected leg Improved or absent (%) 54 (84.4) 321 (91.5) 0.841 Stable (%) 5 (7.8) 24 (6.8) Worsened (excluded subjects with thrombotic complications) (%) 0 1 (0.3) Lost at follow-up 1 8							
* excluding the 2 subjects in whom DVT was picked at the 2nd CUS.							

Palareti, Thromb Haemost, 2010

Should we be looking for and treating isolated calf vein thrombosis?

Author/year	Population	Sample size	Diagnostic method	Follow-up	PE rate
Lagerstedt et al (1985) ⁴⁰	Symptomatic medical patients	28	Isotopic uptake confirmed by ascending phlebography	90 days	1/28 (3.6%)
Solis et al (1992) ⁴¹	Inpatient combination of postoperative hip and knee arthroplasty patients. Physician led follow-up	28	Ascending venography with follow-up CUS	Unclarified	0/28 (0%)
Pellegrini et al (1993) ⁴²	Postoperative hip arthroplasty patients nested within prophylaxis RCT	24	Blinded contrast venogram	33 days (22 to 52)	4/24 (16.7%)
Oishi <i>et al</i> (1994) ⁴³	Asymptomatic postoperative THR/TKR patients	41	CUS	6 months	0/41 (0%)
Masuda et al (1998) ⁴⁴	Retrospective outpatient cohort managed by attending physician	26	CUS	6 months	0/26 (0%)
Schwarz et al (2001) ⁴⁵	Low-risk ambulatory patients with isolated calf muscle thrombus	32	$\frac{\text{CUS}}{\text{CUS}} = (0-16.7\%)$	3 months	0/32 (0%)
Labropoulos et al (2002) ⁴⁶	Symptomatic medical and surgical inpatients and outpatients	29	CUS (0-10.77	(up to 11) months	1/29 (3.4%)
Dorr et al (2007) ⁴⁷	Postoperative hip and knee arthroplasty patients nested within prophylaxis RCT	25	Single CUS at 24 h postoperatively	6 months	0/25 (0%)
Lautz et al (2009) ⁴⁸	Retrospective cohort of inpatients and outpatients with ICMVT who received at least one follow-up CUS	406	CUS	7.5 (up to 11) months	7/119 (5.9%)
Schwarz et al (2010) ³⁸	Low-risk ambulatory patients with isolated calf muscle thrombus	53	CUS	3 months	0/53 (0%)
Palareti et al (2010) ³⁷	Symptomatic outpatients with confirmed IDDVT	65	CUS	3 months	1/64 (1.6%)
Horner et al (2014) ³⁶	Symptomatic ambulatory emergency department patients	35	CUS	3 months	1/35 (2.9%)

Data are presented as mean (SD), median (IQR) or n/N (percentage) as seen. Diagnostic method refers to original method of diagnosis for IDDVT. Acute PE was confirmed by either VIQ or CTPA testing. Variable follow-up periods are reported as median

TCPA, CT pulmonary angiogram; CUS, compression ultrasound; TCMVT, isolated calf muscle vein thrombosis; IDDVT, isolated distal (calf) deep vein thrombosis; RCT, randomised controlled trial; THR, total hip replacement; TKR, total knee replacement; V/Q, ventilation/perfusion.

Horner, Em Med J, 2014

Should we be looking for and treating isolated calf vein thrombosis?

Table 2 Studies asset	ssing local and total propagation in patients with untreated IDDVT					
Author/year	Population	Sample size	Diagnostic method	Duration of follow-up for primary endpoint	Local propagation rate	Total propagation rate
Lagerstedt et al (1985) ⁴⁰	Symptomatic medical patients	28	Isotope uptake then phlebography	90 days	Unreported	5/28 (17.9%)
Lohr et al (1991) ⁵³	Symptomatic medical and surgical inpatients	75	CUS	3 months	13/75 (17.3%)	24/75 (32.0%)
Lohr et al (1995) ⁵⁴	Mostly symptomatic surgical and medical inpatients (59.4%)	192	CUS	4 weeks	32/192 (16.7%)	53/192 (28%)
Schwarz et al (2001) ⁴⁵	Symptomatic outpatients with isolated calf muscle vein thrombosis (ICMVT)	32	CUS	3 months	8/32 (25%)	8/32 (25%) *
Macdonald et al (2003)55	Mostly symptomatic surgical and medical inpatients (68.6%) with ICMVT	135	CUS	3 months	18/135 (13.3%)	22/135 (16.3%)
Lautz et al (2009) ⁴⁸	Retrospective cohort of inpatients and outpatients with ICMVT who received at least one follow-up CUS	406	CUS	7.5 (11) months	21/406 (5.2%)	66/406 (16.3%)
Schwarz et al (2010) ³⁸	Low-risk ambulatory patients with isolated calf muscle thrombus	53	CUS	3 months	1/53 (1.9%)	2/53 (3.8%)
Palareti et al (2010) ³⁷	Symptomatic outpatients	65	CUS	3 months	1/64 (1.6%)	4/64 (6.3%)

Data are presented as mean (SD), median (IQR) or n/N (percentage) as seen. Local propagation refers to that confined to the calf veins, below the popliteal fossa. Total propagation rate refers to any propagation of thrombus above or below the popliteal trifurcation

*Patients in this study were immediately given therapeutic LMWH on diagnosis of extension to the deep calf veins. This may explain the notably low rate of proximal extension. CUS, compression ultrasound; IDDVT, isolated distal (calf) deep vein thrombosis; LMWH, low molecular weight heparin.

Symptomatic ambulatory emergency department patients

Horner et al (2014)36

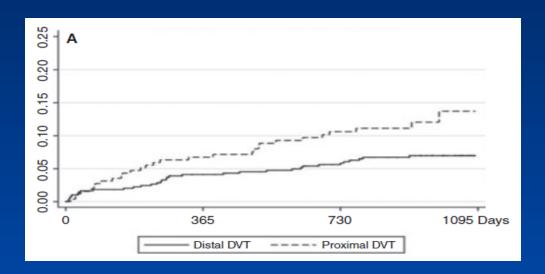
The second second

Horner, Em Med J, 2014

3.8-32%

Long term VTE recurrence

Distal vs Proximal



Galanaud, JTH, 2014

Profonde vs Muscolari

Recidive a 3 mesi follow up

Optimev Study

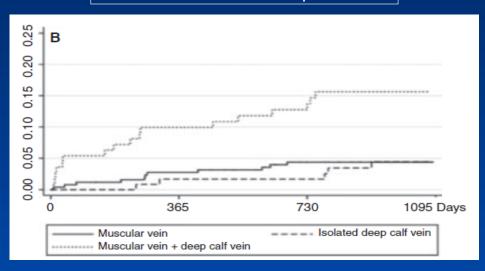
Outcome	DCVT (n = 222) No. (%)	MCVT (n = 390) No. (%)	DCVT vs MCVT OR (95% CI)
Death	9 (4.1)	15 (3.8)	0.98 (0.24-4.11)
Recurrent VTE	3 (1.4)	6 (1.5)	0.98 (0.24-4.11)
Major bleeding	1 (0.5)	0 (0)	

CI, Confidence interval; OR, odds ratio; VTE, venous thromboembolism.

Galanaud et al. J Vasc Surg 2010

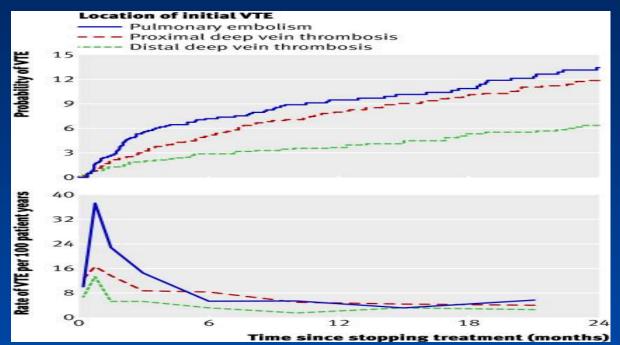
Long term VTE recurrence

Muscular vs Isolated Deep Calf Vein



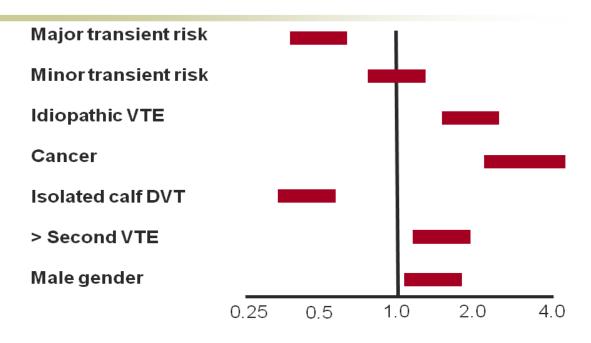
Galanaud, JTH, 2014

Risk of VTE recurrence after OAT stopping according to initial VTE presentation: data from seven trials



Boutitie, BMJ, 2011

Predictors of VTE recurrence



After C. Kearon, unpublished

ORIGINAL ARTICLE

Does the clinical presentation and extent of venous thrombosis predict likelihood and type of recurrence? A patient-level meta-analysis

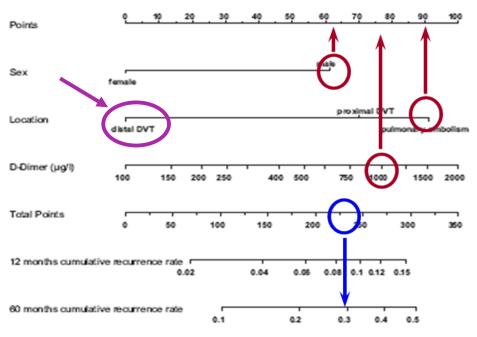
T. BAGLIN,* J. DOUKETIS,† A. TOSETTO,‡ M. MARCUCCI,§ M. CUSHMAN,¶ P. KYRLE,**

G. PALARETI, †† D. POLI, †† R. C. TAIT§§ and A. IORIO§

Initial diagnosis	Risk of any recurrence (DVT or PE)					
PE vs. any DVT alone PE vs. proximal DVT alone Proximal DVT vs. distal DVT (±PE) Proximal DVT vs. distal DVT alone	HR 0.96 (95% CI, 0.75–1.24; $P = 0.758$) LR = 76.29 ($P < 0.001$) HR 0.85 (95% CI, 0.66–1.10; $P = 0.211$) LR = 96.84 ($P < 0.001$) HR 4.20 (95% CI, 1.78–9.92; $P = 0.001$) LR = 68.20 ($P < 0.001$) HR 4.76 (95% CI, 2.06–10.98; $P < 0.001$) LR = 96.84 ($P < 0.001$)					
	Risk of recurrence as PE					
PE vs. any DVT alone PE vs. proximal DVT alone Proximal DVT vs. distal DVT alone	HR 3.55 (95% CI, 2.17–5.81; $P < 0.001$) LR = 41.88 ($P < 0.001$) HR 3.10 (95% CI, 1.87–5.13; $P < 0.001$) LR = 45.14 ($P < 0.001$) HR 4.46 (95% CI, 0.59–33.88; $P = 0.149$) LR = 45.14 ($P < 0.001$)					
	Risk of recurrent PE*					
	All patients	Unprovoked VTE				
PE vs. proximal DVT alone	HR 4.66 (95% CI, 2.70–8.06; P < 0.001)	HR 4.41 (95% CI, 2.47–7.90; P < 0.0				

Baglin, JTH, 2010

Nomogram to estimate cumulative recurrence rates of recurrent VTE by use of sex, location of VTE, and D-dimer



Eichinger, S. et al. Circulation 2010;121:1630-6

Distal DVT: my talk today

- Epidemiology and natural history
- Diagnosis
- Treatment

Diagnostic management of clinically suspected DVT

- Serial compression ultrasound of the proximal veins
 (CUS) (associated with clinical score and D-Dimer)
- Complete US of the entire leg system (alone or associated with Color Doppler)

US of the entire leg venous system

- Several inquiries have shown that ultrasonography of the entire leg vein system (alone or associated with color-Doppler) is by far the most widely employed diagnostic approach to symptomatic patients
- It has a sensitivity for proximal DVT that is fully comparable with that obtained with CUS

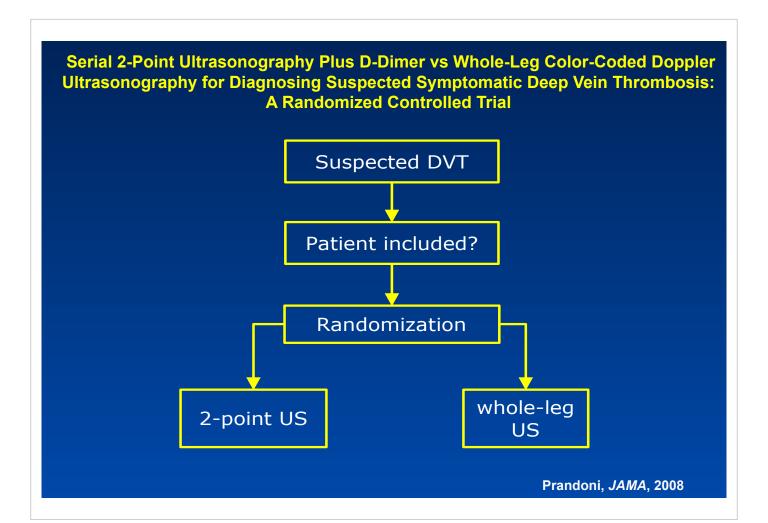
US of the entire leg venous system

- This strategy has the potential to provide the imaging of calf-veins (both distal and muscular veins). However, imaging of calf veins is time-consuming and technically demanding
- Although the negative predictive value of this strategy has been shown to be high in a few studies, the specificity of US diagnosis of calf DVT has not yet been properly investigated
- The clinical implications of calf DVT are unclear, and even more so are those of thrombosis of the muscular veins

Proximal vs. complete US in suspected DVT?

Series	Patients (n)	DVT (di prevale	stal) nce (%)	CUS per 100 patients (n)	3-mo TE Risk (%, 95%CI)
Proximal CUS					
Cogo,1998	1702	24	(0)	176	0.7 (0.3-1.2)
Birdwell, 1988	404	16	(0)	170	0.6 (0.1-2.1)
Bernardi, 1998	946	28	(0)	109	0.4 (0 - 0.9)
Wells, 1997	rial US S	Strata	av.		0.6 (0.1-1.8)
l Kraaijenhagen.	also sat		0.7 (0.3-1.6)		
Pooled estimate • S	unlikely	0.5 (0.2-0.7)			
Drov 4 dietal Cl	unlikely				-1
l Fliae 2003		•	JO 1%	in Cogo et a	0.5 (0.1-1.8)
Schellong, 2003	MJ 1998)			0.3 (0.1-0.8)
Stevens, 2004	445	14	(31)	100	0.8 (0.2-1.3)
Subramaniam, 2005	526	0.2 (0.01-1.3			
Pooled estimate	3240	20	(50)	100	0.3 (0.1-0.6)

Righini M. JTH 2007; 5 (suppl. 1):55-59.



Serial 2-Point Ultrasonography Plus D-Dimer vs Whole-Leg Color-Coded Doppler **Ultrasonography for Diagnosing Suspected Symptomatic Deep Vein Thrombosis:** A Randomized Controlled Trial

Table 2. Distribution and Timing of Venous Thromboembolic Events						
Allocation Group End Points ^a	Timing, d ^b	Diagnostic Method	DVT Site			
Two-point strategy Ipsilateral DVT	10	Ultrasonography	Proximal			
Ipsilateral DVT	12	Ultrasonography	Proximal			
Ipsilateral DVT	7/001 12	Ultrasonography	Isolated calf			
Ipsilateral DVT	7/801	Ultrasonography	Proximal			
Ipsilateral DVT	0.9% 66	Ultrasonography	Proximal			
Contralateral DVT	68	Ultrasonography	Proximal			
Ipsilateral DVT	81	Ultrasonography	Isolated calf			
Whole-leg strategy Pulmonary embolism	2	&Vdot/&Qdot lung scan and computed tomography	NA			
Contralateral DVT	18	Ultrasonography	Isolated calf			
Ipsilateral DVT	42	Ultrasonography	Proximal			
Pulmonary embolism	9/763 48	&Vdot/&Qdot lung scan	NA			
Ipsilateral DVT	54	Ultrasonography	Proximal			
Pulmonary embolism	1.2%	Computed tomography	NA			
Ipsilateral DVT	88	Ultrasonography	Proximal			
Contralateral DVT	88	Ultrasonography	Proximal			
Ipsilateral DVT	92	Ultrasonography	Isolated calf			

Abbreviations: DVT, deep vein thrombosis; NA, not applicable; &Vdot;/&Qdot;, ventilation-perfusion.

^aTwo-point strategy indicates serial 2-point ultrasonography plus D-dimer; whole-leg strategy indicates whole-leg color-coded Doppler ultrasonography.

^bDays from the beginning of follow-up.

Prandoni, JAMA, 2008

Gibson NS, Schellong SM, Kheir DDY, Beyer-Westendorf J, Gallus AS, MrRae S, Schutgens RE, Piovella F, Gerdes VE, Buller HR

Safety and sensitivity of two ultrasound strategies in patients with clinically suspected deep venous thrombosis

A prospective management study

J Thromb Haemost 2009

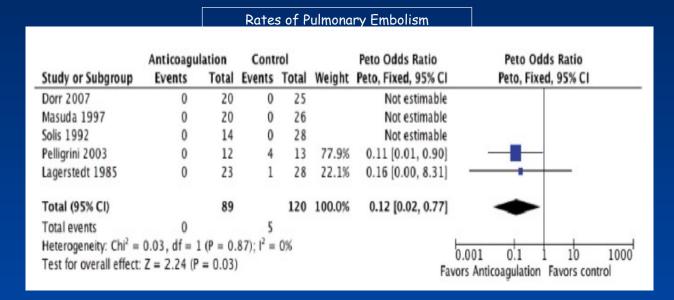
Conclusions of the Erasmus and Dutch Study study

- Both the limited and the extended ultrasonography are safe diagnostic strategies for the management of symptomatic patients with suspected DVT.
- The former is less demanding, but implies the need for one fourth of symptomatic patients to visit the diagnostic center for a second test.
- The latter offers a one-day answer, which is desirable in patients with severe calf complaints, in those with scarce compliance, in travelers, and in people who live far from the diagnostic service, but exposes approximately 1 of every 25 patients to the risk of (unnecessary) anticoagulation, and is more expensive.

Distal DVT: my talk today

- Epidemiology and natural history
- Diagnosis
- Treatment

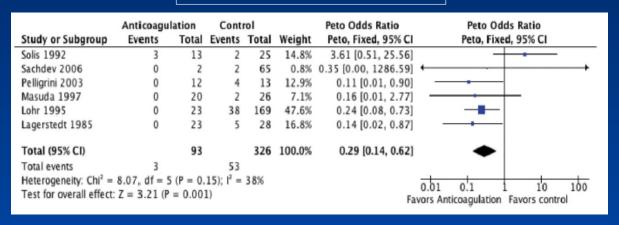
Anticoagulamt therapy in patients with distal DVT



De Martino, J Vasc Surg, 2012

Anticoagulamt therapy in patients with distal DVT

Thrombus propagation to the Popliteal Vein



De Martino, J Vasc Surg, 2012

Should we be looking for and treating isolated calf vein thrombosis?

Table 3 Key risks associated with the management of isolated distal deep vein thrombosis and supporting levels of evidence

Associated complication	Estimated risk	Level of evidence
With conservative management		
Fatal bleeding	0%	1-
Major bleeding	0%	1-
Propagation to the popliteal trifurcation or above	9.1% (95% CI 7.1% to 10.6%)	1_
Acute pulmonary embolism	3.2% (95% CI 0.9% to 5.5%)	1-
All-cause mortality	0.9% (95% CI 0% to 2.3%)	1=
With therapeutic anticoagulation		
Fatal bleeding	0.37% (95% CI 0.36% to 0.38%)	1++
Major bleeding	2.06% (95% CI 2.04% to 2.08%)	1++
Propagation to the popliteal trifurcation or above	1.6% (95% CI 0.1% to 3.0%)	1-
Acute pulmonary embolism	0%	1-
All-cause mortality	0.7% (95% CI 0% to 2.0%)	1-

Estimates from the literature ^{4 35-37} are presented for 3/12 follow-up rates with CIs. Levels of evidence are graded as per the Scottish Intercollegiate Guideline Network recommendations. Bleeding estimates are based on the use of phased anticoagulation and oral vitamin K antagonists only. Major bleeding episodes are standardised as per the definition provided by the International Society for Thrombosis and Haemostasis.⁷⁴

Horner, Em Med J, 2014

Distal DVT: treatment

In patients with acute isolated distal DVT of the leg and without severe symptoms or risk factors for extension *, we suggest serial imaging of the deep veins for 2 weeks over initial anticoagulation (Grade 2C).

In patients with acute isolated distal DVT of the leg and severe symptoms or risk factors for extension *, we suggest initial anticoagulation over serial imaging of the deep veins (Grade 2C).

 positive D -dimer, thrombosis that is extensive or close to the proximal veins (eg, . 5 cm in length, involves multiple veins, . 7 mm in maximum diameter), no reversible provoking factor for DVT, active cancer, history of VTE, and inpatient status.

Kearon, Chest, 2016

Distal DVT: treatment

Remarks:

Patients at high risk for bleeding are more likely to benefit from serial imaging.

Patients who place a high value on avoiding the inconvenience of repeat imaging and a low value on the inconvenience of treatment and on the potential for bleeding are likely to choose initial anticoagulation over serial imaging

Kearon, Chest, 2016

Distal DVT: treatment

- 2.3.1. In patients with acute isolated distal DVT of the leg and without severe symptoms or risk factors for extension *, we suggest serial imaging of the deep veins for 2 weeks over initial anticoagulation (Grade 2C).
 - 2.3.2. In patients with acute isolated distal DVT of the leg and severe symptoms or risk factors for extension *, we suggest initial anticoagulation over serial imaging of the deep veins (Grade 2C).
 - positive D -dimer, thrombosis that is extensive or close to the proximal veins (eg, . 5 cm in length, involves multiple veins, . 7 mm in maximum diameter), no reversible provoking factor for DVT, active cancer, history of VTE, and inpatient status.

Kearon, Chest, 2012

Distal DVT: treatment

- 2.3.3. In patients with acute isolated distal DVT of the leg who are managed with initial anticoagulation, we recommend using the same approach as for patients with acute proximal DVT (Grade 1B)
- 2.3.4. In patients with acute isolated distal DVT of the leg who are managed with serial imaging, we recommend no anticoagulation if the thrombus does not extend (Grade 1B); we suggest anticoagulation if the thrombus extends but remains confined to the distal veins (Grade 2C); we recommend anticoagulation if the thrombus extends into the proximal veins (Grade 1B).

Kearon, Chest, 2012

Distal DVT: treatment

In patients with acute isolated distal DVT of the leg who are managed with initial anticoagulation, we recommend using the same approach as for patients with acute proximal DVT (Grade 1B)

In patients with acute isolated distal DVT of the leg who are managed with serial imaging, we recommend no anticoagulation if the thrombus does not extend (Grade 1B); we suggest anticoagulation if the thrombus extends but remains confined to the distal veins (Grade 2C); we recommend anticoagulation if the thrombus extends into the proximal veins (Grade 1B).

Kearon, Chest, 2016

Distal DVT: treatment

In patients with an isolated distal DVT of the leg provoked by surgery or by a nonsurgical transient risk factor, we suggest treatment with anticoagulation for 3 months over treatment of a shorter period (Grade 2C), we recommend treatment with anticoagulation for 3 months over treatment of a longer time-limited period (e.g. 6, 12 or 24 months) (Grade 1B), and we recommend treatment with anticoagulation for 3 months over extended therapy (no scheduled stop date) (Grade 1B)

Kearon, Chest, 2016