Canadian Venous Thromboembolism
Clinical Trials and Outcomes Research Network

DISTAL DEEP VEIN THROMBOSIS
AN UNRESOLVED PROBLEM?

Vicky Tagalakis, MD, FRCPC
Associate Professor of Medicine, McGill University
Division of Internal Medicine, and Centre for Clinical Epidemiology of the Lady Davis Institute for Medical Research
Jewish General Hospital

Centre of Excellence in Thrombosis and Anticoagulation Care

Hôpital général juif
Jewish General Hospital

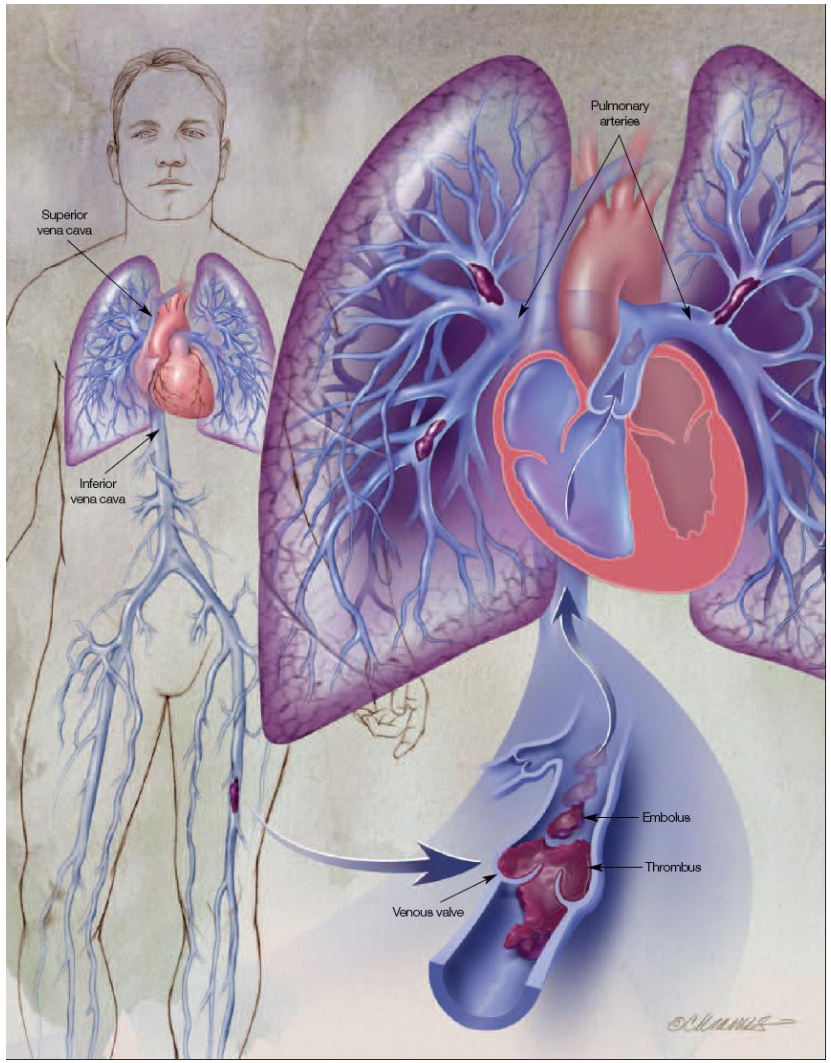
McGill UNIVERSITY

Conflits d'intérêts potentiels

- Membre d’un conseil consultatif
  - Pfizer, Bayer, Leo Pharma
- Membre d’un service de conférenciers
  - Pfizer, Sanofi, Leo Pharma
- Subventions
  - CIHR
  - Sanofi

Aims

1. To understand the prevalence and prognosis of isolated distal deep vein thrombosis in comparison to that of proximal vein deep vein thrombosis
2. To review the results of the newly published CACTUS study and the management of isolated distal DVT



The epidemiology of venous thromboembolism (VTE) is well characterized and based primarily of proximal deep vein thrombosis (DVT) and pulmonary embolism (PE)

- VTE Incidence: 1-2/1000 persons per year
- 2/3 DVT and 1/3 PE presentation
- 50% risk of PE if untreated proximal DVT
- 6% of proximal DVT patients and 10% of PE patients will die within one month
- 25% of PE cases present as fatal PE
- 75-80% of PE patients have DVT (mainly asymptomatic)
- Chronic complications
  - Recurrence 2-30% per year (PE and proximal DVT)
  - Post thrombotic syndrome (25-30%) (proximalDVT)
  - Pulmonary hypertension (0.5%)

Diagnosis of DVT

1. Pre-test clinical probability
2. High sensitivity D-dimer assay
3. Venous compression ultrasound

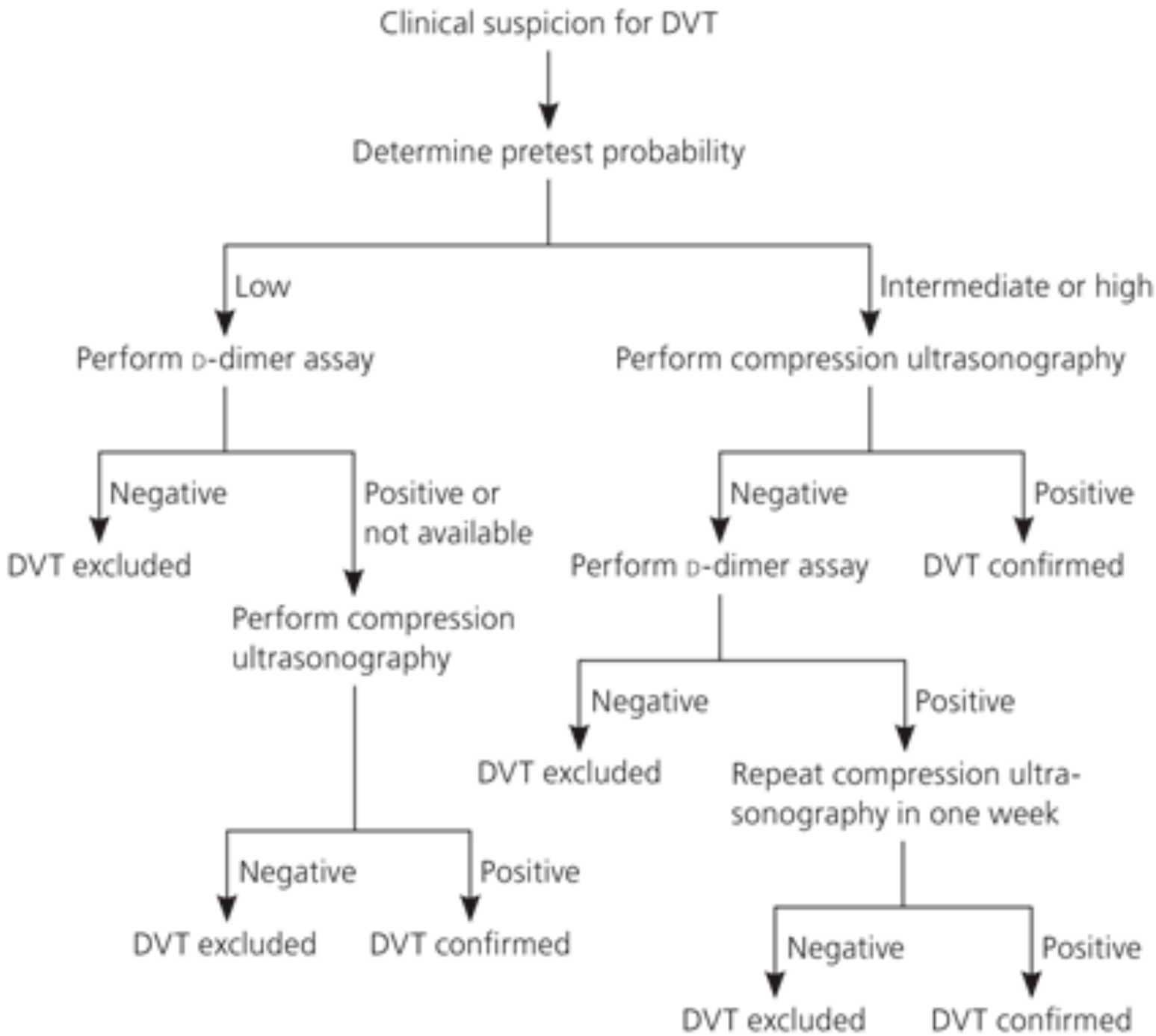
Wells Criteria for Probability of DVT

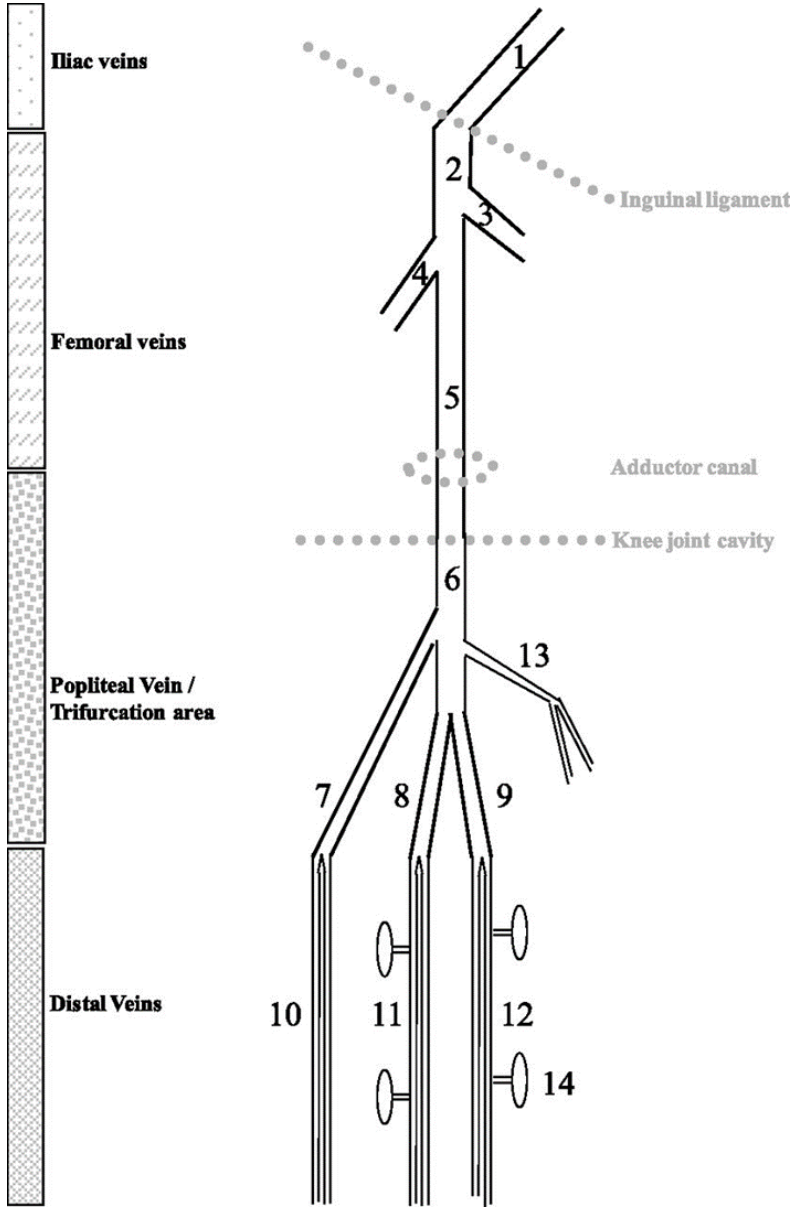
	Clinical Hx/Sign	Criteria	Points
1.	Malignancy	receiving active treatment for cancer OR have received treatment for cancer in past 6 mo. OR are receiving palliative care for cancer	1.0
2.	Limb immobilization	Paralysis OR Paresis OR Recent casting of lower extremity	1.0
3.	Patient immobilization	bedrest (except access to BR) ≥ 3 days OR surgery in previous 4 weeks	1.0
4.	Localized tenderness	Along distribution of deep venous system	1.0
5.	Entire leg swollen		1.0
6.	Calf swelling	>3cm when compared with asymptomatic leg Measured 10cm below the tibial tuberosity	1.0
7.	Pitting edema	Greater in the symptomatic leg	1.0
8.	Collateral superficial veins dilated	Non-varicose veins	1.0
9.	Alternative Dx as likely or more likely than that of DVT	No specific criteria – use Hx, Physical, CXR, EKG, and labs to decide	-2.0

LOW PROB
≤ 0 points

MOD PROB
1 or 2 points

HIGH PROB
>3 points


Clinical suspicion for DVT
Determine pretest probability
Low
Intermediate or high
Perform D-dimer assay
Perform compression ultrasonography
Negative
Positive or not available
Negative
Positive
DVT excluded
Perform compression ultrasonography
Perform D-dimer assay
DVT confirmed
Negative
Positive
Negative
Positive
DVT excluded
DVT confirmed
DVT excluded
Repeat compression ultrasonography in one week
Negative
Positive
DVT excluded
DVT confirmed



Palareti et al Thrombo Haemost 2010; 104(5) : 1063-1070

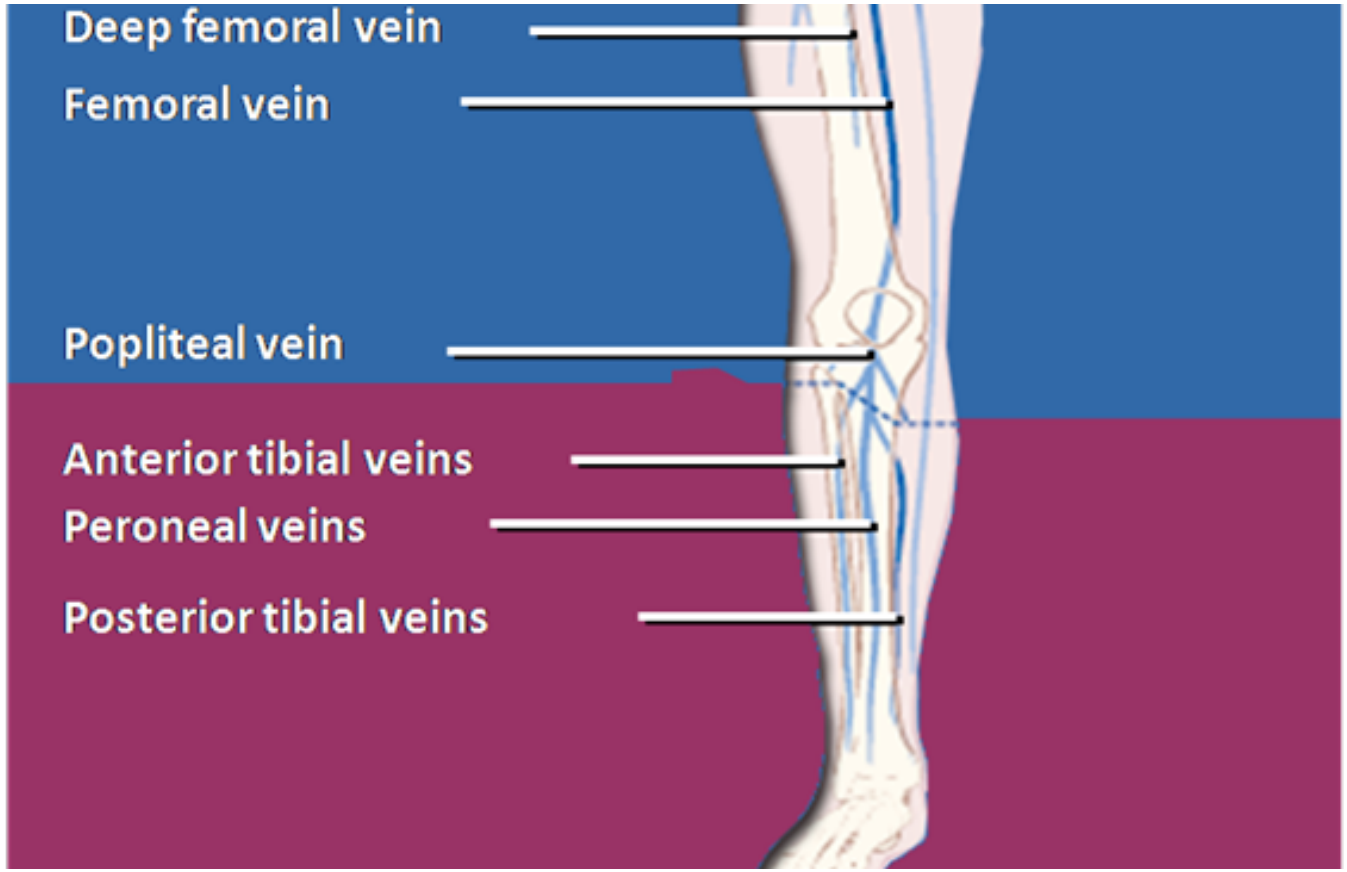
Isolated distal DVT

- Deep veins below the knee
  - Peroneal
  - Posterior tibial
  - Anterior tibial
- Calf muscle veins
  - Gastrocnemius
  - Soleal

Vein distribution among 282 limbs of 251 patients with iDDVT

Location	No of limbs
Peroneal	115 (41%)
Soleal	109 (39%)
Posterior Tibial	105 (37%)
Gastrocnemius	79 (28%)

J Vasc Surg 1999;30:787-793



Prevalence of isolated distal DVT

- Variability of prevalence in part explained by the following

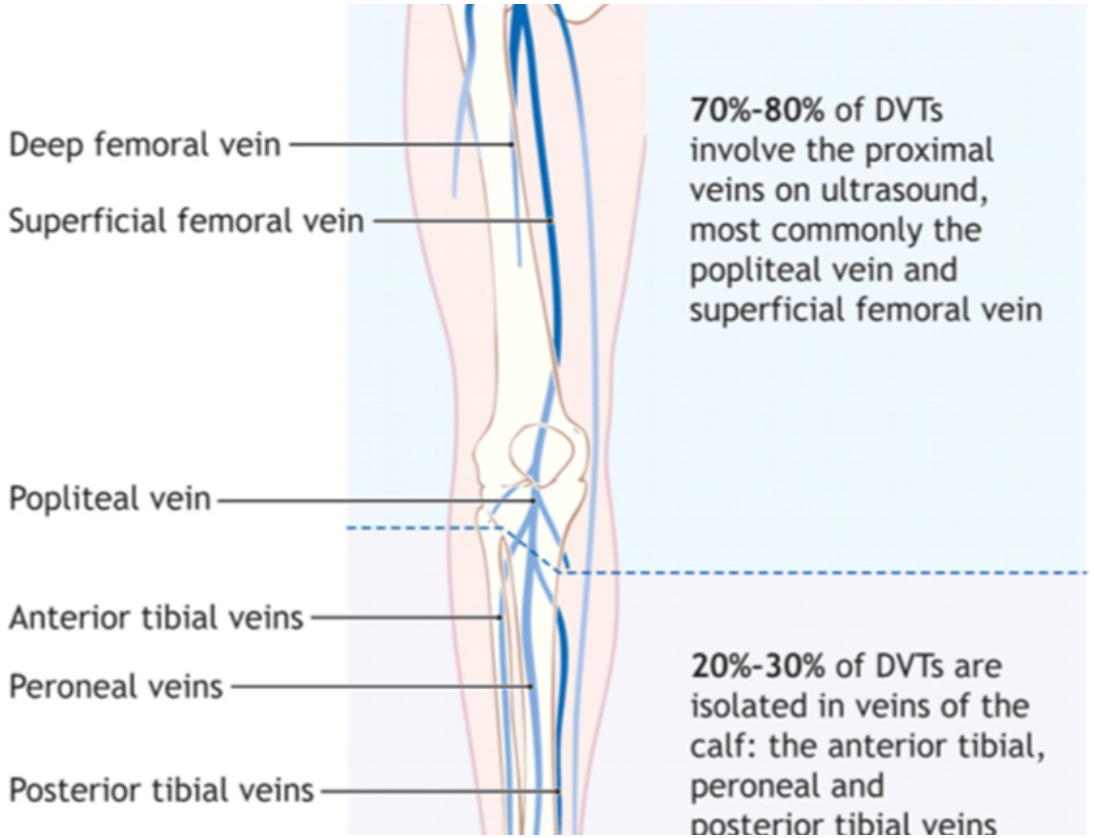
1. Type of compression ultrasound (CUS) diagnostic studies
   - proximal CUS vs. whole leg CUS

2. Clinical setting
   - Asymptomatic surgical or medical patients examined for DVT in clinical studies
   - Symptomatic patients examined for suspected DVT or PE
   - Confirmed PE and looking for embolic source

In patients with suspected DVT and examined with whole leg CUS

Prevalence of DVT by location

- Inpatients
  - 20% distal; 80% proximal
- Outpatients
  - 50-70% distal; 30-50% proximal



Rhigini et al, J Thromb Haemost 2007;5(1) 55-59

Prevalence of proximal and distal DVT in in- and outpatients for suspected DVT of lower limbs and/or PE (A) or in patients with diagnosed DVT of the lower limbs (B)

Table 1 Results of studies reporting the prevalence of proximal deep vein thrombosis (DVT) or isolated distal deep vein thrombosis (IDDVT) in the total population of in- or outpatients examined for suspected deep vein thrombosis of lower limbs and/or pulmonary embolism (A), or in patients with diagnosed DVT of lower limbs (B)

Author	Design of study	Population type	Diagnostic criteria	Population examined	Total VTE	Proximal DVT		IDDVT		Annotations
						A %	B %	A %	B %	
Schulman [14]	Prospective multicenter,	Cohort with diagnosed VTE	Venography for DVT suspicion		790		56.1		43.9	
Mattos [47]	Retrospective	In- & outpatients with suspected DVT	Complete ultrasound	655 (limbs)	159 DVTs	16.2	66.7	8.1	33.3	
Bendick [48]	Prospective	Patients with suspected PE	Complete ultrasound	507	79 DVTs	8.9	57.0	6.7	43.0	
Warwick [2]	Retrospective	Patients symptomatic for DVT after total knee replacement	Venography in 119 pts	1000	89 DVTs	1.5	16.9	7.4	83.1	
Kazmers [8]	Retrospective	In- & outpatients with suspected DVT	Complete ultrasound	3096	457 DVTs	10.9	74.2	3.8	25.8	
Labropoulos [49]	Retrospective	In- & outpatients with suspected DVT	Complete ultrasound	5250	742 DVTs	9.3	66.2	4.8	33.8	
Oger [50]	Prospective, epidemiological, 320 000 subjects for 1 year	Community-based population in western France	Complete ultrasound		423		63		37	
Pinede [15]	Prospective multicenter	Cohort with diagnosed VTE	Complete ultrasound or venography		703		64.2		35.8	
Eichinger [51]	Prospective multicenter	Cohort with diagnosed VTE	Complete ultrasound or venography		349		59.9		40.1	
Elias [27]	Prospective	Outpatients	Complete ultrasound	623	204 DVTs	18	54.9	14.8	45.1	
Schellong [28]		In- & outpatients with suspected DVT	Complete ultrasound	1646	275 DVTs	7.3	44	9.3	56	
Stevens [29]	Prospective	NA	Complete ultrasound	445	61 DVTs	9.4	68.8	4.3	31.2	
Subramaniam [30]	Prospective	Outpatients	Complete ultrasound	526	113 DVTs	9.3	43.4	12.2	56.6	
Seinturier [6]	Retrospective	In- and outpatients with DVT	Complete ultrasound		1913 DVTs		53.2		46.8	
Subramaniam [52]	Prospective	Outpatients	Complete ultrasound	309	67 DVTs	8.7	40.3	12.9	59.7	
Bernardi [36]	Prospective, randomized*	Outpatients	Complete ultrasound	1053	278 DVTs	20.2	76.6	6.2	23.4	
Palareti [53]	Prospective multicenter	Cohort with diagnosed VTE	CUS or complete ultrasound, or venography		1772 DVTs		90.4		9.6	
Gibson [37]	Prospective, randomized*	NA	Complete ultrasound	264	99 DVTs	23.1	61.6	14.4	38.4	Patients with DVT unlikely and normal DD were excluded
Sevestre [54]	Retrospective	NA	Complete ultrasound	3871	1023 DVTs	11.7	44.4	14.7	55.6	
Righini [55]	Prospective	Patients with suspected PE	Complete ultrasound	541	112 PE	9.8	47.3	10.9	52.7	Only patients with high clinical probability or altered DD were included
Palareti [10]	Prospective	Outpatients	Complete ultrasound	424				15.3		Patients with proximal DVT and those with unlikely and normal DD were excluded

VTE, venous thromboembolism; NA, not available; CUS, compression ultrasonography limited to proximal deep veins; PE, pulmonary embolism; DD, D-dimer. *The patients included in these two studies were randomized to receive an ultrasonography investigation limited to the proximal veins or to the whole leg veins; the data shown in the table refer to the results recorded in the group randomized to a complete ultrasonography examination.

Palareti G, Schellong S. Isolated distal deep vein thrombosis: what we know and what we are doing. *J Thromb Haemost* 2012;

Prevalence of isolated DVT varies according to patient population

- Prevalence of isolated DVT in symptomatic patient populations undergoing whole leg CUS
  - In patients with suspected PE: 7-11%
  - In patients with suspected DVT: 4-20%
  - In patients with confirmed DVT: 23-59%

Palereti J Thromb Haemost. 2006;10:11-9

Same risk factors but differentially distributed

- Isolated distal DVT: transient > irreversible risk factors
- Proximal DVT: irreversible > transient risk factors

	Proximal DVT vs control patients OR [CI 95%]	Distal DVT vs control patients OR [CI 95%]	Distal DVT vs Proximal DVT OR [CI 95%]
Age [51 – 75] *vs.* ≤ 50 years	1.3 [1.0 – 1.7]*	1.2 [1.0 – 1.5]	0.9 [0.7 – 1.2]
Age >75 *vs.* ≤ 50 years	2.0 [1.5 – 2.6]**	1.1 [0.9 – 1.4]	0.5 [0.4 – 0.7]**
Men *vs.* Women	2.1 [1.8 – 2.6]**	1.5 [1.3 – 1.7]**	0.6 [0.5 – 0.9]**
Transient risk factors for venous thromboembolism			
Bed confinement, yes *vs.* no	2.3 [1.8 – 3.0]**	2.0 [1.6 – 2.5]**	0.8 [0.6 – 1.1]
Recent plaster immobilisation of the lower limb(s), yes *vs.* no	2.6 [1.5 – 4.4]**	5.4 [3.9 – 7.7]**	2.2 [1.3 – 3.8]**
Recent travel, yes *vs.* no	2.1 [1.2 – 3.6]**	4.1 [2.8 – 6.2]**	1.7 [1.0 – 2.8]*
Recent surgery (≤ 45 days), yes *vs.* no	1.3 [1.0 – 1.8]	2.3 [1.9 – 2.9]**	1.8 [1.3 – 2.5]**
Congestive heart failure or respiratory insufficiency, yes *vs.* no	3.0 [2.1 – 4.4]**	1.5 [1.0 – 2.2]	0.6 [0.4 – 0.9]*
Acute infectious disease, yes *vs.* no	1.2 [0.6 – 2.2]	0.8 [0.5 – 1.5]	0.7 [0.3 – 1.6]
Pregnancy or post partum <6 weeks, yes *vs.* no	1.4 [0.7 – 3.0]	0.6 [0.3 – 1.2]	0.4 [0.1 – 1.1]
Chronic risk factors for venous thromboembolism			
Personal history of DVT or PE, yes *vs.* no	2.4 [1.9 – 2.9]**	1.8 [1.5 – 2.1]**	0.8 [0.6 – 1.0]
Family history of DVT or PE, yes *vs.* no	1.4 [1.1 – 1.8]**	1.4 [1.1 – 1.7]**	1.0 [0.8 – 1.4]
Active cancer, yes *vs.* no	3.2 [2.5 – 4.1]**	1.5 [1.2 – 1.9]**	0.5 [0.4 – 0.7]**
Varicose veins, yes *vs.* no	0.7 [0.5 – 0.9]**	0.9 [0.8 – 1.1]	1.3 [1.0 – 1.7]
Oral contraception, yes *vs.* no	5.0 [3.1 – 8.1]**	4.0 [2.6 – 5.9]**	0.7 [0.4 – 1.1]
Hormone replacement therapy, yes *vs.* no	0.9 [0.3 – 2.3]	1.7 [0.9 – 3.1]	1.6 [0.6 – 4.6]
Obesity (BMI > 30 kg/m^2), yes *vs.* no	0.9 [0.7 – 1.2]	0.8 [0.7 – 1.1]	0.9 [0.7 – 1.3]

*p<0.05; **p<0.01
BMI: body-mass index; CI: confidence interval; DVT: deep-vein thrombosis; PE Pulmonary embolism; OR: odds ratio
OR were calculated using random intercept multivariable logistic regression models adjusting for anticoagulant therapy at inclusion and inpatient versus out-patient status.

Galanaud et al Thromb Haemost 2009;102:493-5000

There is debate regarding the diagnosis and management of isolated distal DVT

- Limited performance of whole leg CUS to diagnose distal DVT
- Prognosis is more benign than that of proximal DVT
- Lack of methodologically robust management/treatment studies of isolated distal DVT

There is debate regarding the diagnosis and management of isolated distal DVT

- Limited performance of whole leg CUS to diagnose distal DVT
  - Sensitivity 50-75% and specificity 90-95%[1] compared to 97% and 98% respectively for proximal DVT
    - Higher false positive rate than for proximal DVT
    - Increasing numbers of patients exposed to full dose anticoagulation
  - Alternative strategy of limited proximal CUS has been shown to be as safe as whole leg CUS regarding 3-month VTE risk in untreated patients with IDDVT
- Prognosis is more benign than that of proximal DVT
- Lack of management/treatment studies of isolated distal DVT with methodologic issues

1. Kearon et al Ann Intern Med 1998

Natural history based on proximal CUS studies
Proximal extension and risk of of VTE at 3 months

Table 1 Performances and safety of proximal compression ultrasonography for diagnosing DVT in outcome management studies. Distal DVTs were not searched for in these studies

Source, year	Patients (*n*)	Incidence of DVT (%)	Proportion of proximal DVTs detected by the second CUS % (95% CI)	3-month thromboembolic risk, % (95% CI)*
Birdwell *et al.*[15], 1998	405	16	2 (0.8–4.2)	0.6 (0.1–2.1)
Cogo *et al.*[11], 1998	1702	24	0.9 (0.3–1.2)	0.7 (0.3–1.2)
Bernardi *et al.*[12], 1998	946	28	5.7 (1.9–12.8)	0.4 (0–0.9)
Wells *et al.*[13], 1997	593	16	1.8 (0.3–5.2)	0.6 (0.1–1.8)
Perrier *et al.*[16], 1999	474	24	NA*	2.6 (0.2–4.9)
Kraaijenhagen *et al.*[14], 2002	1756	22	3 (1.9–5.2)	0.7 (0.3–1.6)
Pooled estimate	5876	23	NA	0.6 (0.4–0.9)

*During 3-month follow-up in patients left untreated after normal proximal compression ultrasonography.
DVT, deep vein thrombosis; CUS, compression ultrasonography; NA, not applicable.
NA*: In the study by Perrier *et al.*, only one CUS limited to proximal veins was realized in patients with a positive ELISA D-dimer measurement.

J Thromb Haemost 2007;5:55-59

Natural history based on whole leg CUS
Risk of VTE at 3 months in non-treated patients

Table 2 Performances and safety of a single proximal and distal compression ultrasonography for diagnosing DVT in outcome management studies

		Incidence of DVT %, (*n*)			3-month thromboembolic risk, % (95% CI) *
Source, year	Patients (*n*)	All *n* (%)	Proximal *n* (%)	Distal *n* (%)	Single proximal and distal CUS
Elias *et al.*[18], 2003	623	204 (33)	112 (55)	92 (45)	0.5 (0.1–1.8)
Schellong *et al.*[19], 2003	1646	275 (17)	121 (44)	154 (56)	0.3 (0.1–0.8)
Stevens *et al.*[20], 2004	445	61 (14)	42 (69)	19 (31)	0.8 (0.2–2.3)
Subramaniam *et al.*[21], 2005	526	113 (22)	49 (43)	64 (57)	0.2 (0.01–1.3)
Pooled estimate	3240	653 (20)	324 (50)	329 (50)	0.3 (0.1–0.6)

*During 3-month follow-up in patients left untreated after a normal complete (proximal and distal) compression ultrasonography.
NA, not applicable; DVT, deep vein thrombosis.

J Thromb Haemost 2007;5:55-59

FAUT-IL LES TRAITER ? ETUDES DIAGNOSTIQUES

Etude	Patients (n)	TVP (dont distales) prévalence (%)	Risque à trois mois (%, IC à 95%)
Echo-doppler proximal sérié			
Cogo,1998	1702	24 (0)	**0.7 (0.3-1.2)**
Birdwell, 1988	404	16 (0)	**0.6 (0.1-2.1)**
Bernardi, 1998	946	28 (0)	**0.4 (0-0.9)**
Wells, 1997	593	16 (0)	**0.6 (0.1-1.8)**
Kraaijenhagen, 2002	1756	22 (0)	**0.7 (0.3-1.6)**
Total	**5876**	**23 (0)**	**0.5 (0.2-0.7)**
Un seul écho-doppler proximal et distal			
Elias, 2003	623	36 (45)	**0.5 (0.1-1.8)**
Schellong, 2003	1646	17 (56)	**0.3 (0.1-0.8)**
Stevens, 2004	445	14 (31)	**0.8 (0.2-1.3)**
Subramaniam, 2005	526	22 (57)	**0.2 (0.01-1.3**
Total	**3240**	**20 (50)**	**0.3 (0.1-0.6)**

Righini, Thromb Haemost 2006 ; 95 : 56-64.

The ACCP Chest Guidelines favor not looking for isolated distal DVT

- The ACCP guidelines discourage routine whole-leg US examinations (ie, including the distal veins) in patients with suspected DVT, thereby reducing how often isolated distal DVT is diagnosed.
- The rationale for not routinely examining the distal veins if proximal DVT has been excluded is that:
  - other assessments may already indicate that isolated distal DVT is either unlikely to be present or unlikely to cause complications if it is present (eg, low clinical probability of DVT, D-dimer is negative)
  - if these conditions are not met, a repeat US examination of the proximal veins can be done after a week to detect possible DVT extension and the need for treatment;
  - false-positive findings for DVT occur more often with US examinations of the distal compared with the proximal veins

Reference 1, 73, 74

There is debate regarding the diagnosis and management of isolated distal DVT

- Limited performance of CUS to diagnose distal DVT

- Prognosis of iDDVT is more benign than that of proximal DVT
  - Proximal extension of untreated iDDVT into popliteal vein
  - Rate of recurrence
  - PE risk
  - Mortality

- Lack of methodologically robust management/treatment studies of isolated distal DVT

Rates of proximal extension proximally in untreated patients with iDVVT

VERY VARIBALE
0-29%

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%)

Thromb Haemost 2006; 95: 56–64

Natural history based on proximal CUS studies
Proximal extension and risk of of VTE at 3 months

Table 1 Performances and safety of proximal compression ultrasonography for diagnosing DVT in outcome management studies. Distal DVTs were not searched for in these studies

Source, year	Patients (*n*)	Incidence of DVT (%)	Proportion of proximal DVTs detected by the second CUS % (95% CI)	3-month thromboembolic risk, % (95% CI)*
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J Thromb Haemost 2007;5:55-59

Proximal extension rate is low

In summary

- Proximal extension rate historically ……..8-15%[1]
- Proximal extension indirectly determined from clinical studies assessing safety of proximal serial CUS…… 1-5.7%
- Certain factors have been shown to be associated with higher rates of proximal extension

Righini, Thromb Heamost 2006;95:56-64

Risk factors for proximal extension

- Positive d-dimer
- Cancer
- Thrombus close to proximal veins
- No reversible provoking factor
- History of prior VTE
- Inpatient status
- Extensive thrombus
  - >5cm, involves multiple veins, >7mm in diameter

There is debate regarding the diagnosis and management of isolated distal DVT

- Limited performance of CUS to diagnose distal DVT

- Prognosis is more benign than that of proximal DVT
  - Proximal extension of untreated iDDVT into popliteal vein: 1-5.7%
  - Rate of recurrence:
  - PE risk
  - Mortality

- Lack of methodologically robust management/treatment studies of isolated distal DVT

Low rate of recurrence: based on a recent patient-level meta-analysis of 7 studies

Table 3 Recurrent venous thromboembolism: mode of recurrence

Initial diagnosis		Pulmonary embolism (±DVT)	Proximal DVT (without PE)	Calf DVT (without PE)
Any recurrence (DVT or PE)				
1 year	Cumulative recurrence (95% CI)	7.4% (5.7–9.5)	8.4% (6.9–10.2)	None
3 years	Cumulative recurrence (95% CI)	14.7% (11.7–18.4)	15.6% (13.0–18.7)	0.9% (0.1–6.3)
	Annual recurrence (95% CI)	5.4 per 100 pt-years (4.4–6.6)	6.1 per 100 pt-years (5.2–7.2)	0.5 per 100 pt-years (0.1–2.2)
5 years	Cumulative recurrence (95% CI)	22.0% (16.3–29.8)	26.4% (20.5–34.1)	7.6% (3.0–18.9)
	Annual recurrence (95% CI)	5.1 per 100 pt-years (4.2–6.2)	6.0 per 100 pt-years (5.2–7.0)	1.0 per 100 pt-years (0.4–2.5)
Recurrence as pulmonary embolism				
1 year	Cumulative recurrence (95% CI)	3.7% (2.6–5.4)	1.3% (0.8–2.1)	None
3 years	Cumulative recurrence (95% CI)	7.2% (5.2–10.0)	2.5% (1.6–4.0)	1.2% (0.2–8.2)
	Annual recurrence (95% CI)	2.6 per 100 pt-years (2.0–3.5)	0.9 per 100 pt-years (0.6–1.4)	0.3 per 100 pt-years (0.0–1.9)
5 years	Cumulative recurrence (95% CI)	10.6% (7.2–15.7)	3.6% (1.8–7.3)	1.2% (0.2–8.2)
	Annual recurrence (95% CI)	2.5 per 100 pt-years (1.9–3.3)	0.9 per 100 pt-years (0.6–1.3)	0.2 per 100 pt-years (0.0–1.5)

DVT, deep vein thrombosis; PE, pulmonary embolism.

Baglin T, Douketis J Thrombo Haemost 2010 8(11) 2436-2442

The cumulative rate of recurrent VTE after cessation of anticoagulation was 4.7-fold higher in patients with proximal compared to isolated distal DVT

Table 4 Risk factors for recurrent venous thromboembolism

Initial diagnosis	Risk of any recurrence (DVT or PE)
PE vs. any DVT alone	HR 0.96 (95% CI, 0.75–1.24; $P = 0.758$) LR = 76.29 ($P < 0.001$)
PE vs. proximal DVT alone	HR 0.85 (95% CI, 0.66–1.10; $P = 0.211$) LR = 96.84 ($P < 0.001$)
Proximal DVT vs. distal DVT (±PE)	HR 4.20 (95% CI, 1.78–9.92; $P = 0.001$) LR = 68.20 ($P < 0.001$)
Proximal DVT vs. distal DVT alone	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	HR 3.55 (95% CI, 2.17–5.81; $P < 0.001$) LR = 41.88 ($P < 0.001$)
PE vs. proximal DVT alone	HR 3.10 (95% CI, 1.87–5.13; $P < 0.001$) LR = 45.14 ($P < 0.001$)
Proximal DVT vs. distal DVT alone	HR 4.46 (95% CI, 0.59–33.88; $P = 0.149$) LR = 45.14 ($P < 0.001$)

Patients with DVT confined to the calf are at lower risk of overall recurrence and at low risk of recurrence as PE. The risk of any recurrence of VTE was 4-fold lower compared with patients with symptomatic proximal DVT or PE and the absolute risk of recurrence as PE was only 0.2% per year, with a cumulative recurrence of 1.2% after 5 years of follow-up.

Baglin T, Douketis J Thrombo Haemost 2010 8(11) 2436-2442

Rate of recurrence following treated isolated distal DVT

- OPTIMEV study
- Prospective observational study that followed 749 patients diagnosed with iDDVT or proximal isolated DVT for 3 years and assessed rates of recurrence after cessation of anticoagulation
  - iDDVT group (n=259): 2.7% per patient-year (95% CI: 1.9-3.8)
  - Proximal isolated DVT group (n=490): 5.2% per patient-year (95% CI: 3.6-7.6)

J Thromb Haemost 2014; **12**: 436–43.

Comparison of VTE recurrence after cessation of anticoagulants in patients with iDDVT vs. proximal DVT according to the type of VTE recurrence

Table 2 Comparison of the incidences of first VTE recurrence between isolated distal and isolated proximal DVT patients after stopping anticoagulants according to the type of recurrence

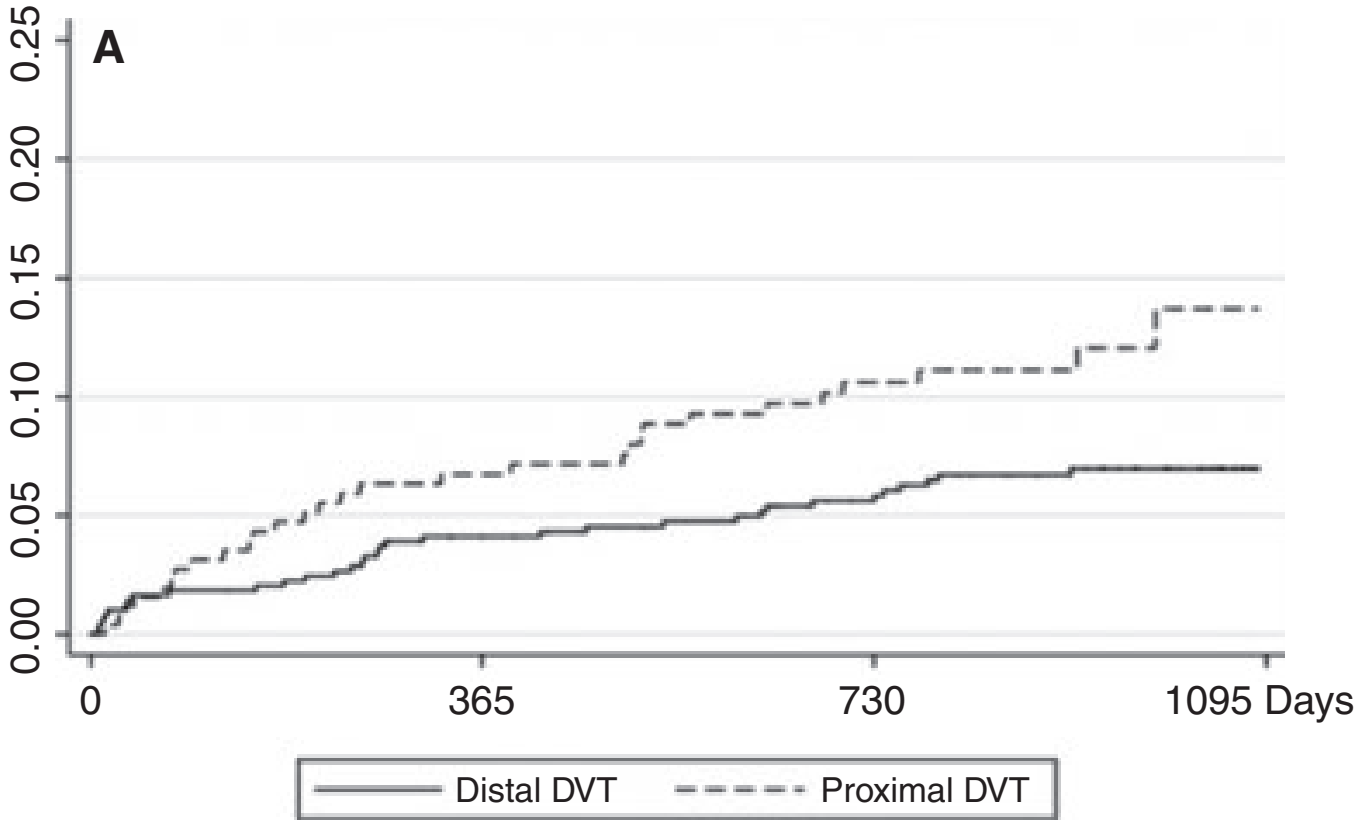
	Distal DVT, HR (95% CI) (N = 490)	Proximal DVT, HR (95% CI), (N = 259)	Proximal vs. distal DVT, HR (95% CI)
Any recurrent VTE event	2.7 (1.9–3.8) (n = 33)	5.2 (3.6–7.6) (n = 29)	1.8 (1.1–3.0)*
Distal DVT	1.5 (0.9–2.3) (n = 18)	0.7 (0.3–1.8) (n = 4)	0.5 (0.2–1.4)
Proximal DVT	0.3 (0.1–0.9) (n = 4)	3.4 (2.2–5.3) (n = 19)	9.7 (3.3–28.5)*
PE	0.9 (0.5–1.6) (n = 11)	1.0 (0.5–2.3) (n = 6)	1.1 (0.4–3.0)

Values are percentages per patient-year (95% CI) (number of events) with calculation of the hazard ratio (HR) and 95% CI (fourth column).CI, confidence interval; DVT, deep vein thrombosis, PE, pulmonary embolism; VTE, venous thromboembolism. *$P \leq 0.050$.

J Thromb Haemost 2014; **12**: 436–43.

OPTIMEV STUDY

- The risk of recurrence decreased over time for iPDVT and iDDVT and the difference between the two groups remained the same
- iPDVT vs iDVT
  - 7.2% vs. 4.0 % per patient-year at year 1
  - 3.0% vs. 1.7% per patient-year at year 3



J Thromb Haemost 2014; **12**: 436–43.

Risk factors for recurrence after stopping anticoagulation in patients with iDDVT

Table 3 Predictive factors and incidence of VTE recurrence after stopping anticoagulants in the case of isolated distal DVT (univariate and multivariate analyses, incidence of VTE recurrence)

	Univariate analysis, HR (95% CI)	Multivariate analysis, HR (95% CI)*	Incidence of VTE recurrence, % PY (95% CI)
Age			
≤ 50 years (ref)	–	–	0.9 (0.3–2.3)
> 50 years	−8.9 (3.0–26.8)†	−3.7 (1.0–10.6)	3.8 (2.6–5.5)
Gender			
Female sex (ref)	–	–	3.3 (2.2–4.9)
Male sex	−0.6 (0.3–1.3)	–	2.0 (1.1–3.6)
Status at index event			
Outpatient (ref)	–	–	2.8 (1.9–4.1)
Inpatient	−0.9 (0.4–2.1)	–	2.5 (1.2–5.3)
Risk factors associated with index DVT‡			
Major transient risk factor (ref)	–	–	1.44 (0.7–2.9)
Unprovoked DVT	−2.6 (1.2–5.9)†	−3.1 (1.4–6.9)	3.8 (2.6–5.6)
Anatomical characteristics of index DVT			
Deep calf DVT (ref)	–	–	1.6 (0.7–3.9)
Muscular DVT§	−1.0 (0.3–2.7)	–	1.7 (0.9–3.0)
Ultrasonographic characteristics of index DVT			
Number of venous segments thrombosed			
Single unilateral thrombosis (ref)	–	–	1.8 (1.1–2.9)
Multiple unilateral thromboses	−2.4 (1.1–5.0)†	−2.9 (1.4–6.1)	4.9 (3.1–7.8)
Bilateral DVT	4.8 (1.8–13.3)†	4.0 (1.4–11.1)	8.9 (3.7–21.4)
Clot diameter under compression			
≤ 7 mm (ref)	–	–	3.1 (2.1–4.5)
> 7 mm	−0.7 (0.3–1.6)	–	2.2 (1.0–4.5)
Anticoagulant treatment > 90 days	0.6 (0.3–1.3)	–	–

J Thromb Haemost 2014; **12**: 436–43.

There is debate regarding the diagnosis and management of isolated distal DVT

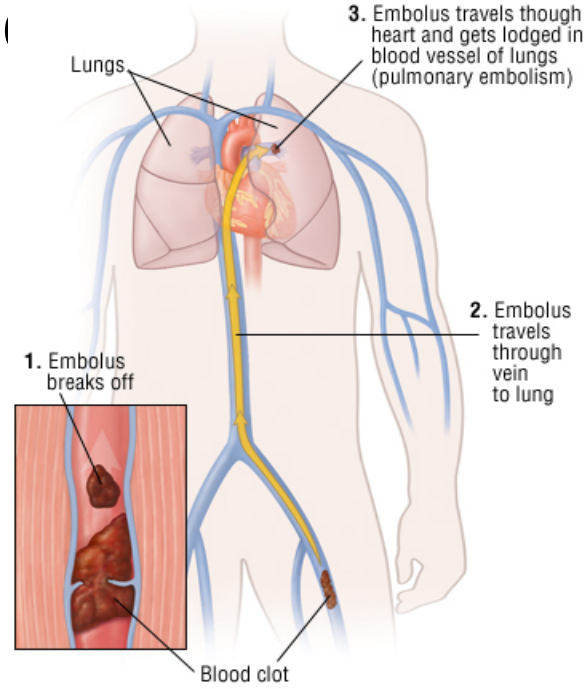
- Limited performance of CUS to diagnose distal DVT

- Prognosis is more benign than that of proximal DVT
  - Proximal extension of untreated iDDVT into popliteal vein: 1-5.7%
  - Rate of recurrence: low and 4-5-fold less than proximal DVT
  - PE risk
  - Mortality

- Lack of methodologically robust management/treatment studies of isolated distal DVT

Pulmonary embolism risk

- Distinguish studies in which iDDVT was diagnose in patients with PE vs. studies in which PE was detected during surveillance of patients with diagnosed iDDVT
- CALTHRO study
  - 1 of 64 patients with untreated iDDVT (1.6%) developed a PE during 3 month follow up
- Recent systematic review reported a 0-6.3% risk at 3 months with no deaths attributable to PE



Palareti et al Thrombo Haemost 2010; 104(5) : 1063-1070

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- Limited performance of CUS to diagnose distal DVT

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  - Proximal extension into popliteal vein: 1-5.7%
  - Rate of recurrence: low and 4-5-fold less than proximal DVT
  - PE risk: 0-6.3% if iDDVT not treated
  - Mortality

- Lack of methodologically robust management/treatment studies of isolated distal DVT

Death higher in patients with proximal vs. distal DVT

Table 5: Three month clinical outcomes (multivariate analysis).

	Proximal DVT vs control patients, OR [CI 95%]	Distal DVT vs control patients, OR [CI 95%]	Distal DVT vs Proximal DVT, OR [CI 95%]
Recurrent VTE	-***	-***	0.8 [0.4 – 1.8]
Major bleeding	3.4 [0.8 – 15.3]	2.1 [0.5 – 9.0]	0.8 [0.3 – 2.4]
Death	3.7 [2.0 – 6.6]**	2.0 [1.1 – 3.5]*	0.6 [0.4 – 0,9]*

DVT: deep vein thrombosis VTE: venous thromboembolism, OR: odds ratio, CI: confidence interval *p<0.05; **p<0.01; ***Patients with a recurrent venous thromboembolism during the three-month study period were excluded from the analysis (considered as false negative at the first examination). OR were calculated using a Cox model adjusting for sex, age, anticoagulant therapy duration and in-patient versus outpatient status.

J Thromb Haemost 2014; **12**: 436–43.

There is <u>debate</u> regarding the diagnosis and management of isolated distal DVT

- Limited perf
- Prog
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  - PE
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- Lack s of isola

SHOULD WE TREAT DISTAL DVT?

There is debate regarding the diagnosis and management of isolated distal DVT

- Limited performance of CUS to diagnose distal DVT
- Prognosis is more benign than that of proximal DVT
  - Proximal extension into popliteal vein: 1-5.7%
  - Rate of recurrence: low and 4-5-fold less than proximal DVT
  - PE risk: 0-6.3% if iDDVT not treated
  - Mortality: considerable less than proximal DVT
- Lack of methodologically robust management/treatment studies of isolated distal DVT: treat or not to treat?

ESSAIS THÉRAPEUTIQUES

- Un seul essai randomisé, en ouvert
  - 51 patients, diagnostic par phlébographie
  - Héparine IV à l'hôpital pendant 5 jours et contention veineuse pour tous
  - Randomisation entre warfarine ou pas de warfarine
- Risque thromboembolique à 3 mois
  - 0 / 23 dans le groupe héparine + warfarine
  - 8 / 28 dans le groupe héparine sans relais
- Limites
  - Patients à haut risque (antédécents de TVP 20% des cas, 50% des récidives)
  - Pas d'adjudication des récidives
  - Hospitalisation, alitement

Lagerstedt, Lancet 1985 ; 326 : 515-8. *PERMISSION Gregoire Le GAL*

Anticoagulant therapy for symptomatic calf deep vein thrombosis (CACTUS): a randomised, double-blind, placebo-controlled trial

Prof Marc Righini, MD, Jean-Philippe Galanaud, MD, Hervé Guenneguez, MD, Dominique Brisot, MD, Antoine Diard, MD, Pascale Faisse, MD, Marie-Thérèse Barrellier, MD, Claudine Hamel-Desnos, MD, Christine Jurus, MD, Olivier Pichot, MD, Myriam Martin, MD, Prof Lucia Mazzolai, MD, Clarisse Choquenet, MD, Sandrine Accassat, MD, Helia Robert-Ebadi, MD, Prof Marc Carrier, MD, Prof Grégoire Le Gal, MD, Bernadette Mermilllod, Jean-Pierre Laroche, MD, Prof Henri Bounameaux, MD, Prof Arnaud Perrier, MD, Prof Susan R Kahn, MD, Prof Isabelle Quere, MD

The Lancet Haematology

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Study hypothesis and aims

HYPOTHESIS

Withholding anticoagulant treatment in the management of distal DVT is not associated with an increased risk of adverse outcomes

AIM

To assess whether low molecular weight heparin is associated with better outcomes than placebo in the treatment of first symptomatic DVT

Study Methods

Study design

- RCT, double blind, placebo-controlled
- Multicenter (23 centers in Canada, France, and Switzerland)
- Target population
  - 1st, acute, symptomatic, objectively confirmed calf DVT
- Whole leg compression ultrasound
  - Presence of an incompressible venous segment in deep calf veins

Exclusion Criteria
Less than 18 yo
Pregnant
Previous documented VTE
Active or recent (<6 months) cancer
Another indication for longterm anticoagulation
Plts $<100 \times 10^9$
CrCl < 30 ml/min or Cr>180 umol/L
Heparin sensivity
Active or at high risk for bleeding
NSAID use
Extreme weights (<40kg or >115 kg)

Study Methods

- 1:1 randomization
- Nadroparin 171 UI/kg daily vs. placebo injections for 42 days (6 weeks)
- Follow up in-person day 3-7 and at day 42
  - Clinical assessment and whole leg CUS
- Telephone follow up at day 42

Study Outcomes

Efficacy

- Primary efficacy composite outcome at day 42
  - Extension of calf DVT to proximal veins, or
  - Contralateral proximal DVT, or
  - Symptomatic PE
- Secondary outcomes at day 42 and day 90
  - Individual components of the composite outcome

Safety

- Primary safety outcome
  - MB (as per ISTH criteria) or CRNB at day 42 and day 90
- Secondary safety outcomes (day 42 and day 90)
  - Death
  - SAEs
  - PTS (at 1 year; not reported)

Statistical analyses

- Sample size: 286 in each arm
  - 90% power to detect 70% RRR in primary outcome rate
  - Assumed 10% incidence of primary outcome in placebo arm

- Trial stopped early on Nov 1 2014, after 259 included due to slow recruitment and expiration of study drug and lack of funding to manufacture new drug

- Intention to Rx analysis

Figure 1. Trial Profile

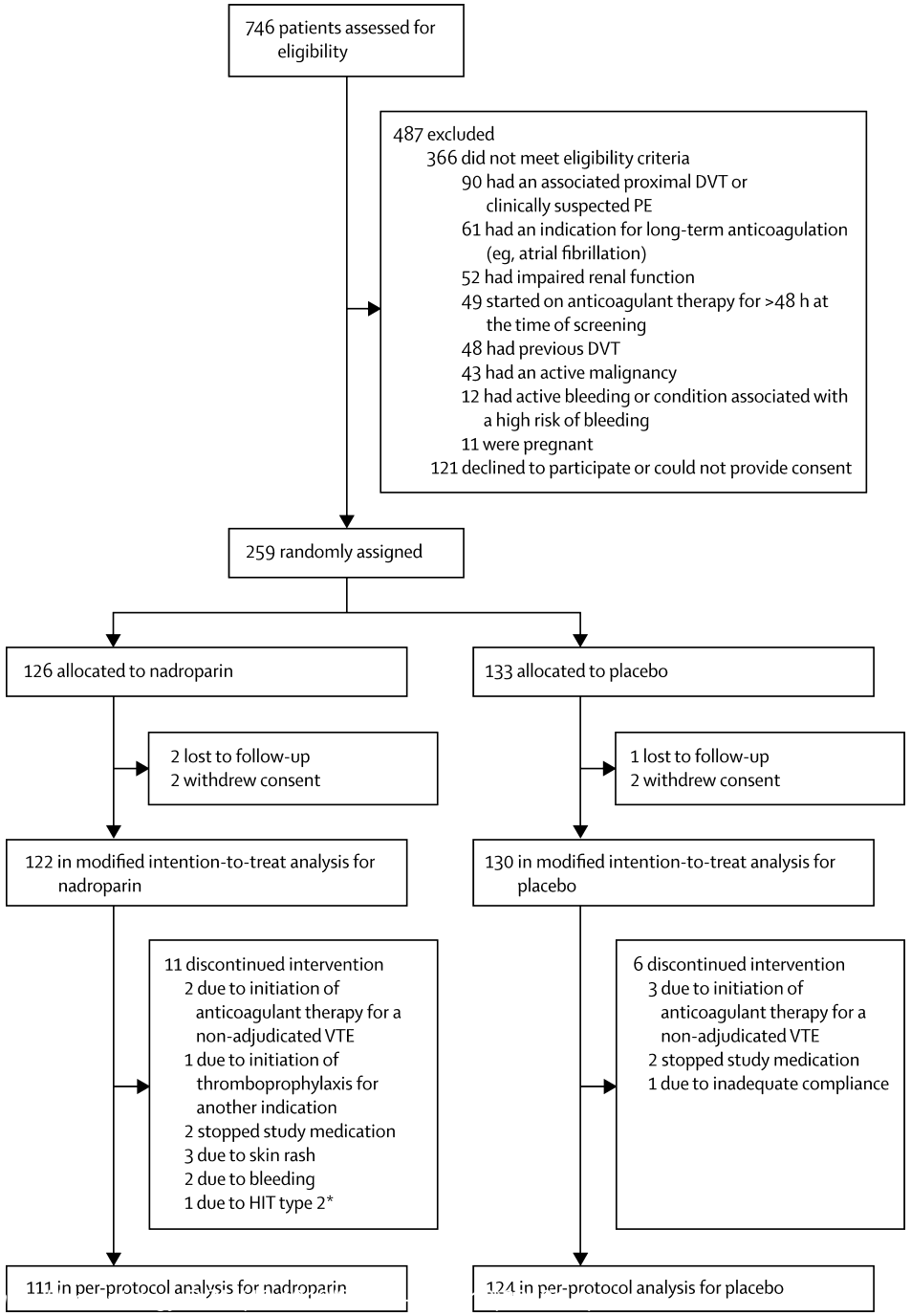

Table 1. Baseline Characteristics

	Nadroparin group (n=126)	Placebo group (n=133)
Women	64 (51%)	63 (47%)
Men	62 (49%)	70 (53%)
Median age (years)	52 (17)	53 (17)
Location of DVT	52 (40–65)	53 (41–68)
Posterior tibial or peroneal vein	61 (48%)	52 (39%)
Gastrocnemius or soleus vein or both	63 (50%)	80 (60%)
Unknown	2 (2%)	1 (1%)
Risk factors		
Familial history of VTE	24 (19%)	24 (18%)
Active malignancy	3 (2%)	2 (2%)
Oestrogen therapy use	21 (17%)	22 (17%)
Surgery	12 (10%)	14 (11%)
Plaster immobilisation	9 (7%)	6 (5%)
Travel >6 h	14 (11%)	20 (15%)
Post partum	2 (2%)	0 (0%)
Bed-rest	14 (10%)	10 (8%)
Concomitant medications		
ECS (compliance >70%)		
Day 7	103/117 (88%)	106/126 (84%)
Day 42	82/110 (75%)	95/122 (78%)
Daily use of aspirin		
Day 1	10/120 (8%)	10/122 (9%)
Day 42	5/112 (4%)	8/123 (7%)
Oral NSAIDs or COX-2 inhibitors		
Day 1	10/120 (8%)	3/131 (2%)
Day 42	4/112 (4%)	1/123 (1%)

Table 1. Efficacy outcomes

	Nadroparin group (n=122)	Placebo group (n=130)	Absolute risk difference (95% CI)	p value
Day 42				
Composite outcome* (primary outcome)	4 (3·3%)	7 (5·4%)	−2·1% (−7·8 to 3·5)	0·54
Proximal DVT	2 (1·6%)	7 (5·4%)	..	..
Pulmonary embolism	2 (1·6%)	0	..	..
Day 90				
Composite outcome*	4 (3·3%)	8 (6·2%)	−2·9% (−8·7 to 2·8)	0·28
Proximal DVT	2 (1·6%)	7 (5·4%)	..	..
Pulmonary embolism	2 (1·6%)	1 (0·8%)	..	..

- DVT extension was detected at the scheduled CUS on day 3-7 in 1 patient in nadroparin gp and 3 in placebo gp
- DVT extension was detected at the scheduled CUS on day day 42 in 1 additional patient in nadroparin gp and 4 in placebo group
- No difference in proportion of outcome between patients with isolated calf muscle DVT and those with a peroneal or PT vein DVT

L'ESSAI CACTUS - RÉSULTATS

Randomisation
(n=259)

Nadroparine
(n=126)

J-42, ITT (n=122)
- TVP prox. ou EP : 4 (3.3%)
- Hémorragies : 5 (4.1%)
- TIH : 1 (0.8%)

J-42, per-protocole
(n=111)
- TVP prox ou EP : 4 (3.6%)

J-90
- Perdus de vue : 0
- Décès non MTEV: 1
- TVP distale sympto : 1, Trt

Placebo
(n=133)

J-42, ITT (n=130)
- TVP prox ou EP : 7 (5.4%)
- Hémorragies : 0 (0.0%)

J-42, per-protocole
(n=124)
- TVP prox ou EP : 7 (5.6%)

J-90
- : 1
- mpto sur l'US à J-42 : 5 (2 traitées)
- TVP distale sympto : 1, Trt
- Embolie pulmonaire : 1

Arrêts de traitement

TIH : 1
Allergie cutanée : 3
Arrêt spontané : 2
Trt d'une MTEV non adjudiquée : 2
Thromboprophylaxie : 1
Hémorragie : 2

Arrêt spontané : 2
Trt d'une MTEV non adjudiquée : 3
Non-compliant: 1

MTEV : - 2,1% (de -7,8 à +2,1%), p 0,54

Hém. : +4,1% (de +0,4 à +9,2%), p 0,03

Results (cont'd)

- Risk of VTE at 90 days after second negative CUS (day 3-7) at proximal level:
  - 3.1% (95% CI: 1.2-7.6%; 4 of 130 pts) in placebo and 2.5% (95% CI 0.8-7%; 3 of 122 pts) in nadroparin

Table. Safety outcome at day 42

	Nadroparin group (n=122)	Placebo group (n=130)	Absolute risk difference (95% CI)	p value
Major bleeding or non-major clinically relevant bleeding	5 (4%)	0	4·1 (0·4 to 9·2)	0·0255
Major bleeding	1 (1%)	0	..	..
Non-major clinically relevant bleeding	4 (3%)	0	..	..
Death	0	0	..	..
Other adverse events				
Skin reactions	3 (2%)	0	..	..
Heparin-induced thrombocytopenia	1 (1%)	0	..	..

Results- Net clinical benefit

- Nadroparin: 9 of 122 patients (7.4 % , 95% CI 3.9-13.4)
- Placebo: 7 of 130 patients (5.4%, 95% CI 2.6-10.7)

- Risk Difference 2%, 955 CI -4.3 to 8.6

Conclusions

- In ***low risk, non-cancer, without prior VTE*** patients with symptomatic distal DVT , nadroparin was not superior to placebo to prevent extension of calf DVT to proximal veins, contralateral DVT, and symptomatic PE and was associated with significantly increased bleeding

- OTHER INTERESTING RESULTS
  - q Low risk of proximal extension or PE after negative second CUS at day 3-7:
    - 4/130 (3.1%) placebo, vs. 3/122 (2.5%) nadroparine
  - q ***CUS surveillance*** seems a reasonable alternative to AC therapy since the risk of VTE at 3 months after a negative serial proximal compression US at day 3-7 was 3.1%

Limitations

- Non-generalizable to cancer patients, patients with prior VTE, inpatients
- Underpowered
  - Early termination due to poor recruitment
  - Had assumed a 10% risk of composite outcome in placebo at 3 months, but observed a 5.4% risk
- Underestimation of 90-day VTE risk
  - patients with distal DVT detected on systematic CUS at day 42 treated with anticoagulation (2/5 all in placebo arm)

ACCP updated 2016

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

- *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.

CHEST 2016; 149(2):315-352

Risk factors for proximal extension

- Positive d-dimer
- Cancer
- Thrombus close to proximal veins
- No reversible provoking factor
- History of prior VTE
- Inpatient status
- Extensive thrombus
  - >5cm, involves multiple veins, >7mm in diameter

ACCP update 2016

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

CHEST 2016; 149(2):315-352

To further consider…..

- We consider thrombosis that is confined to the muscular veins of the calf (ie,, soleus, gastrocnemius) to have a lower risk of extension than thrombosis that involves the axial (ie, true deep; peroneal, tibial) veins.
- Severe symptoms favor anticoagulation, a high risk for bleeding favors surveillance
- The decision to use anticoagulation or surveillance is expected to be sensitive to patient preferences.
- We anticipate that isolated distal DVT that are detected using a selective approach to whole-leg US will often satisfy criteria for initial anticoagulation, whereas distal DVT detected by routine whole-leg US often will not.

CHEST 2016; 149(2):315-352

Conclusion

- Treatment of distal DVT is debated
- Serial proximal CUS is comparable to whole leg CUS in terms of safety
- CACTUS showed no net clinical benefit to a 6-week treatment with LMWH in low risk patients
  - Alternative dose?
  - High risk patients?
  - NOACS?