Varese, 10-11 Marzo 2016

Come trattare il paziente con Trombosi distali

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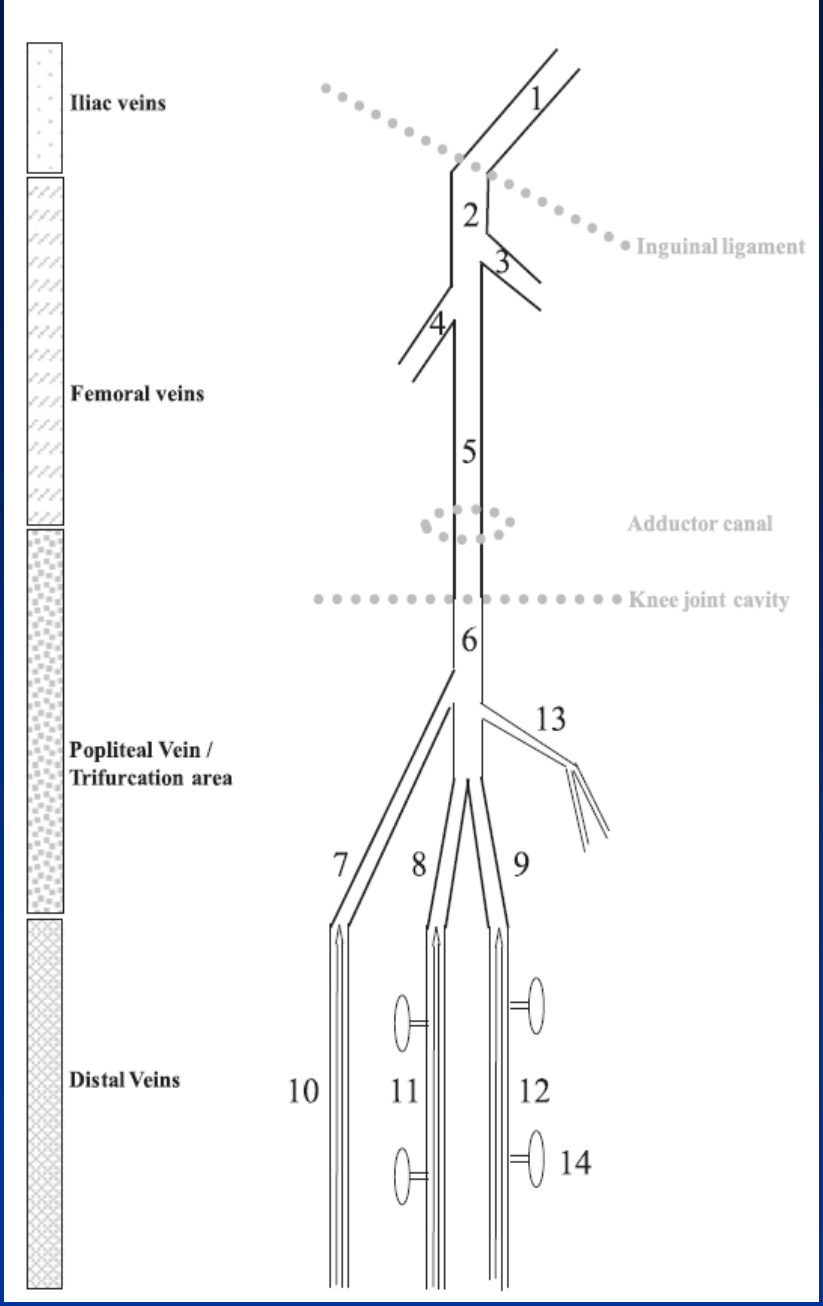

Schematic representation of leg veins

1, External iliac vein;
2, common femoral vein;
3, greater saphenous vein;
4, profound femoral vein;
5, (superficial) femoral vein;
6, popliteal vein;
7, anterior tibial confluent segment;
8, posterior tibial confluent segment;
9, peroneal confluent segment;
10, anterior tibial veins;
11, posterior tibial veins;
12, peroneal veins;
13, gastrocnemius muscle veins (medial head);
14, soleus muscle veins.

Clinical Characteristics of Patients with Isolated Calf Vein Thrombosis in a Large Teaching Hospital

Santin Brian,[1] B. Fries Richard,[2] and Satiani Bhagwan[2]

Int J Vasc Med 2011

Table 3: Location of calf DVTs.

Location	*N*	Percent
Right	66	55
Left	42	35
Bilateral	11	9
Muscular calf vein	16	13
Anterior tibial vein	0	0
Posterior tibial vein	17	14
Peroneal vein	39	32
Gastrocnemius vein	26	22
Soleal vein	7	6
Tibial trunk	12	10

The OPTIMEV study: a French, multicenter, prospective, observational study of inpatients and outpatients referred to vascular medicine physicians for clinically suspected VTE and followed for 3 years
(Galanaud et al., JTH 2014)

DVT at baseline = 1643
- Proximal = 43.2%
- Distal = 56.8%

Performance and safety of diagnosis with CUS

Serial Proximal CUS (rapid)

Reference	Prevalence of DVT (%)	Three-month thromboembolic risk [% (95% CI)][a]
Birdwell *et al.* [18]	16	0.6 (0.1–2.1)
Cogo *et al.* [14]	24	0.7 (0.3–1.2)
Bernardi *et al.* [15]	28	0.4 (0–0.9)
Wells *et al.* [16]	16	0.6 (0.1–1.8)
Perrier *et al.* [19]	24	2.6 (0.2–4.9)
Kraaijenhagen *et al.* [17]	22	0.7 (0.3–1.6)
Pooled estimate	23	0.6 (0.4–0.9)

Single Complete CUS

Reference	Patients (*n*)	Prevalence of DVT [*n* (%)]		Three-month thromboembolic risk Single proximal and distal CUS
		Proximal	Distal	
Elias *et al.* [22]	623	112 (55)	92 (45)	0.5 (0.1–1.8)
Schellong *et al.* [23]	1646	121 (44)	154 (56)	0.3 (0.1–0.8)
Stevens *et al.* [24]	445	42 (69)	19 (31)	0.8 (0.2–2.3)
Subramaniam *et al.* [25]	526	49 (43)	64 (57)	0.2 (0.01–1.3)
Pooled estimate	3240	324 (50)	329 (50)	0.3 (0.1–0.6)

(Modified from Righini & Bounameaux, Curr Opin Pulm Med 2008)

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

Bernardi et al., JAMA 2008

Main results of the randomized study (by Bernardi et al., JAMA 2008)

	Rapid Serial CUS no. 1045	Single Complete CUS no. 1053
DVT [*n* (%)]	231 (22.1)	278 (26.4)
Proximal	231	213
Distal	0	65
Three-month thromboembolic risk [% (95% CI)]	0.9 (0.3–1.8)	1.2 (0.5–2.2)

New Technologies, Diagnostic Tools and Drugs

Evolution of untreated calf deep-vein thrombosis in high risk symptomatic outpatients: The blind, prospective CALTHRO study

Gualtiero Palareti[1]; Benilde Cosmi[1]; Gianfranco Lessiani[2]; Giuseppina Rodorigo[1]; Giuliana Guazzaloca[1]; Carlotta Brusi[1]; Lelia Valdré[1]; Eleonora Conti[1]; Michelangelo Sartori[1]; Cristina Legnani[1]

Clinical evolution at 3 month follow-up

	Simplified CUS 417	Calf DVT 64 (15.1%)	No calf DVT 359	p
Outcomes at 3 mo: 1 PE; 2 Prox. DVT; 2 Calf DVT	5 (1.2%)	5 (7.8%) [3 (4.7%)]*	3 (0.8%)	0.003

* excluding the 2 subjects in whom DVT was picked at the 2nd CUS

Treatment of IDDVT

Accepted Manuscript

Antithrombotic Therapy for VTE Disease: CHEST Guideline

Clive Kearon, MD, PhD, Elie A. Akl, MD, MPH, PhD, Joseph Ornelas, PhD, Allen Blaivas, DO, FCCP, David Jimenez, MD, PhD, FCCP, Henri Bounameaux, MD, Menno Huisman, MD, PhD, Christopher S. King, MD, FCCP, Timothy Morris, MD, FCCP, Namita Sood, MD, FCCP, Scott M. Stevens, MD, Janine R.E. Vintch, MD, FCCP, Philip Wells, MD, Scott C. Woller, MD, Col. Lisa Moores, MD, FCCP

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Clive Kearon, MD, PhD, Elie A. Akl, MD, MPH, PhD, Joseph Ornelas, PhD, Allen Blaivas, DO, FCCP, David Jimenez, MD, PhD, FCCP, Henri Bounameaux, MD, Menno Huisman, MD, PhD, Christopher S. King, MD, FCCP, Timothy Morris, MD, FCCP, Namita Sood, MD, FCCP, Scott M. Stevens, MD, Janine R.E. Vintch, MD, FCCP, Philip Wells, MD, Scott C. Woller, MD, Col. Lisa Moores, MD, FCCP

2016

In patients with an IDDVT provoked by surgery or by a nonsurgical transient risk factor,

- we suggest treatment with AC for 3 months
over treatment of a shorter period (Grade 2C),
- we recommend treatment with AC for 3 months over treatment of a longer time-limited period (e.g. 6, 12 or 24 months) (Grade 1B),
- we recommend treatment with AC for 3 months over extended therapy (no scheduled stop date) (Grade1B).

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2016

Whether and How to Prescribe Anticoagulants to Patients with IDDVT

The rationale for not routinely examining the distal veins:
(1) other assessment (e.g. low clinical probability; D-dimer is negative);
(2) a repeat US of the proximal veins can be done after a week
(3) false-positive findings for DVT occur

Accepted Manuscript

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2016

If the calf veins are imaged and IDDVT is diagnosed,
two management options:

1) treat patients with AC therapy;
2) do not treat patients with AC therapy unless extension of their DVT is detected on a follow-up US examination (e.g. after one and two weeks)

Accepted Manuscript

Antithrombotic Therapy for VTE Disease: CHEST Guideline

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2016

In patients with acute IDDVT of the leg and

(i) without severe symptoms or risk factors for extension, we suggest serial imaging of the deep veins for 2 weeks over AC (Grade 2C),

(ii) with severe symptoms or risk factors for extension, we suggest AC over serial imaging of the deep veins (Grade 2C).

Isolated distal deep vein thrombosis: efficacy and safety of a protocol of treatment. Treatment of Isolated Calf Thrombosis (TICT) Study

R. PARISI [1], A. VISONÀ [2], G. CAMPORESE [3], F. VERLATO [3], G. LESSIANI [4], P. L. ANTIGNANI [5], G. PALARETI [6] and Intersocietary Working Group on Distal Deep Vein Thrombosis

EVENTS DURING TREATMENT:

10/171 PTS (5.8%) had complications:

5 (2.9%) proximal DVT (all unprovoked IDDVT

the remaining extension of IDDVT

No major bleeding; 1.7% minor bleeding

EVENTS DURING 3 MO. FOLLOW-UP

5 complications: (3 developed cancer)

4 proximal DVT (3 had an unprovoked IDDVT)

IDDVT treatment: current management in symptomatic pts
(Angiologia, Bologna)

- Idiopathic IDDVT
  Therapeutic LMWH followed by oral anticoagulation (2.0-3.0 INR) for 3 months, elastic stocking
- Secondary IDDVT
  Therapeutic IDDVT for 1 week, half dose for 3 weeks, elastic stocking

Anticoagulant therapy for symptomatic distal DVT: the CACTUS randomized placebo-controlled trial

(Righini et al., XXV ISTH Congress Toronto, abstract)

- 126 pts received nadroparin (170 UI/kg) x 42 d.
- 133 " " placebo

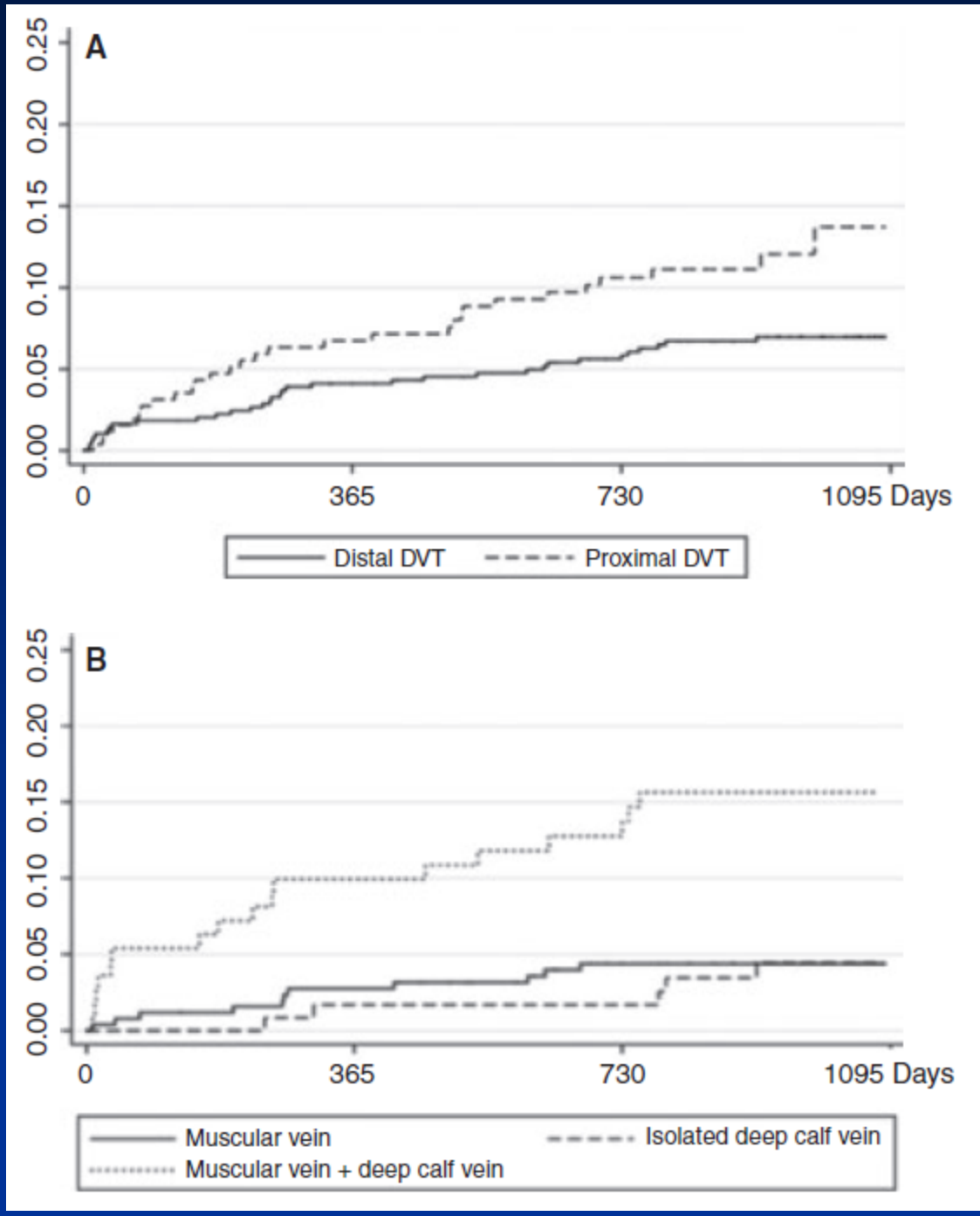
- Outcomes: (at 42 d) nadro = 4 (3.3%); placebo = 7 (5.4%)
- Bleeds (M/NMCR): (at 42 d) nadro = 5 (4.1%) p= 0.03; placebo = 0

The risk of recurrence after treatment of IDDVT

Journal of Thrombosis and Haemostasis, **12**: 436–443 2014

Incidence and predictors of venous thromboembolism recurrence after a first isolated distal deep vein thrombosis

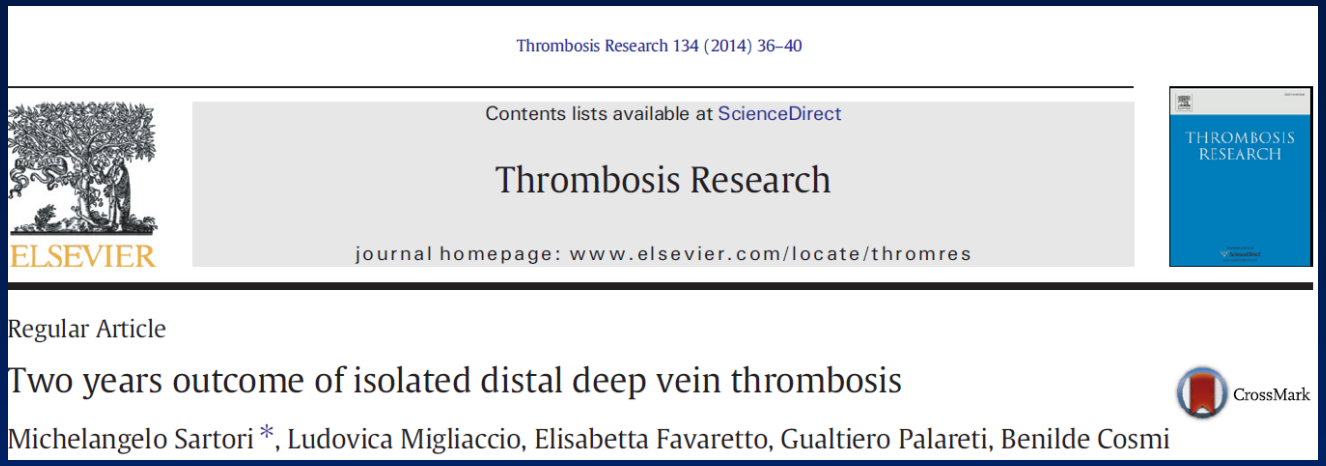
J.-P. GALANAUD,* M.-A. SEVESTRE,† C. GENTY,‡ S. R. KAHN,§ G. PERNOD,‡¶ C. ROLLAND,‡ A. DIARD,** S. DUPAS,† C. JURUS,†† J.-M. DIAMAND,‡‡ I. QUERE,* and J.-L. Bosson‡ FOR THE OPTIMEV-SFMV INVESTIGATORS



Galanaud
JTH 2014

Predictive factors and incidence of VTE recurrence after stopping anticoagulants

	Incidence of VTE recurrence, % PY (95% CI)
Age	
≤ 50 years (ref)	0.9 (0.3–2.3)
> 50 years	3.8 (2.6–5.5)
Gender	
Female sex (ref)	3.3 (2.2–4.9)
Male sex	2.0 (1.1–3.6)
Status at index event	
Outpatient (ref)	2.8 (1.9–4.1)
Inpatient	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	3.8 (2.6–5.6)
Anatomical characteristics of index DVT	
Deep calf DVT (ref)	1.6 (0.7–3.9)
Muscular DVT§	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	4.9 (3.1–7.8)
Bilateral DVT	8.9 (3.7–21.4)
Clot diameter under compression	
≤ 7 mm (ref)	3.1 (2.1–4.5)
> 7 mm	2.2 (1.0–4.5)
Anticoagulant treatment > 90 days	–



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Regular Article

Two years outcome of isolated distal deep vein thrombosis

Michelangelo Sartori *, Ludovica Migliaccio, Elisabetta Favaretto, Gualtiero Palareti, Benilde Cosmi

Results: 90 patients (male 48.9%) enrolled.
At follow-up (24±2 months) = 17 events (18.9%)
3 PE (two in cancer), 4 proximal DVTs (one in cancer) and 10 IDDVT.

Associated with a higher risk of complications
- male sex (HR 4.73 CI95%: 1.55-14.5; p = 0.006)
- cancer (HR 5.47 CI95%: 1.76-17.6; p = 0.003)

Conditions or risk factors for complications after a first IDDVT (1)

Higher risk

- (Axial vs Muscular IDDVT)
- Previous VTE events
- Males
- Age >50 years
- Cancer
- Unprovoked IDDVT
- Secondary IDDVT with persistently hampered mobilisation
- IDDVT involving the popliteal trifurcation
- IDDVT involving >1 calf vein
- IDDVT present in both legs
- Presence of predisposing diseases (e.g. inflammatory bowel diseases)
- Known thrombophilic alterations

Conditions or risk factors for complications after a first IDDVT (2)

Lower risk

- IDDVT secondary to surgery or to other removable risk factors (plasters, immobilisation, trauma, long trip, etc), if complete mobilisation

- IDDVT occurring during contraceptive or replacement hormonal therapy (provided the therapy has been interrupted)

Rivaroxaban for the treatment of symptomatic IDDVT (RIDTS study)

RIDTS study

- **Proposed by: Walter Ageno & Gualtiero Palareti**

- **Study design**
- Phase III, multicenter, randomized, double-blind, placebo-controlled study.

- **Study population**
- Inpatients or outpatients with symptomatic IDDVT of the leg, either secondary or unprovoked

RIDTS study: Inclusion criteria

- DVT in one or more infra-popliteal deep veins.
- Diagnosis by an US extended to the whole deep veins of both legs.
- Diagnosis within 72 hours from inclusion
- Any type of parenteral treatment at therapeutic doses for no > 3 days (maximum accepted doses of LMWH: 6 doses; of fondaparinux: 3 doses).

RIDTS study: Exclusion criteria

- Age < 18 years
- Any absolute contraindication to anticoagulant treatment
- Pregnancy or breast-feeding
- Presence of active cancer
- Concomitant presence of proximal DVT or pulmonary embolism
- Any concomitant indication for long-term anticoagulant treatment
- Creatinine clearance ≤30 ml/min
- Cirrhosis Child-Pugh score B or C
- Liver disease associated with coagulopathy and high risk of bleeding
- Any other contraindication to rivaroxaban as per local SmPC
- Failure to provide written informed consent

RIDTS study: Study design

All patients receive rivaroxaban, 15 mg BID for 3 weeks followed by open label rivaroxaban 20 mg OD for 3 weeks.

At the end of the first 6 weeks of treatment, all patients will be randomized to

A) Long treatment: rivaroxaban 20 mg OD for further 6 weeks

B) Short treatment: placebo for further 6 weeks

Randomization: using an IVRS system implemented to guarantee the balanced and blinded fashion of the two groups

RIDTS study: Follow-up = 2 years

- 1st study visit = 3 weeks (± 2 days): adherence to treatment, symptoms, bleeding or any other clinical event and on concomitant treatments; drug supplying
- 2nd study visit = 6 weeks (± 2 days): US examination of both legs; randomization; rivaroxaban/placebo supplying
- 3rd study visit = 12 weeks (± 3 days): end of treatment; US examination of both legs
- Long-term follow-up every 3 months for the first year and every 6 months thereafter
- For all study visits from month 6 to month 18 a phone contact is accepted,
- Last visit at 24 months, all patients will have US both legs.

RIDTS study: Primary Outcomes (at 2 y)

The primary efficacy outcome (recurrent VTE):
a) progression to the proximal veins;
b) diagnosis of a recurrent DVT (either proximal or distal);
c) symptomatic, objectively documented PE;
d) death for PE (objectively documented or adjudicated if death cannot be confidently attributed to a different cause)

The primary safety outcome (major bleeding)

A pre-specified sub-analysis
the primary outcomes will be compared in specific subgroups defined according to high/low risk conditions

RIDTS study: Secondary Outcomes (2 y)

- Secondary efficacy: incidence of cardiovascular events
- Secondary safety: incidence of clinically relevant non-major bleeding events (CRNMB)
- Residual clot or clot resolution at 3 and 24 months

RIDTS study: Sample Size

- Using data from the OPTIMEV study, it is estimated that with a sample of 550 patients in each group, the study would have at least 80% power to detect a 50% reduction in the rate of the primary efficacy outcome, assuming an incidence of the primary efficacy outcome at one year follow-up of 8% in the placebo group at a two-sided 5% level of significance.

RIDTS study

Più di 30 centri hanno dichiarato la loro disponibilità allo studio

Grazie

Serial rapid proximal CUS

Pros

- Very simple and fast
- Highly accurate for proximal DVT
- No need for particular expertise
- No need for high tech. instrumentation

Cons

- No detection of calf thrombosis
- Need for repeated examination (12.8%, Bernardi 1998)
- Inconvenience and doubts for patients
- Risk of complications before 2nd CUS

Single complete CUS examination

Pros

- Only one examination
- Immediate exclusion or diagnosis of proximal or isolated calf thrombosis
- Possible prevention of PE due to calf DVT
- Possible information for alternative diagnosis

Cons

- Non standard criteria for distal DVT diagnosis
- Greater expertise
- Operator and instrument dependent
- Time-consuming (15-30 more min)
- high proportion of negative examinations (60% to 80%)
- High rate of calf DVTs diagnosed and treated (uncertain their real risk)

Diagnosis of leg DVT in outpatients is still a challenge

- The number of symptomatic subjects referred for suspicion is steeply increasing
- Only 15-20% have the disease
- The best strategy should be rapid and non-invasive
- Efficient to confirm or exclude
- Applicable on a large scale
- Easily available (possibly in Emergency Dept)

Summary of my main points

The examination extended to the calf is highly operator/instrument dependent and currently not sufficiently standardized for routine work

The proximal and complete diagnostic procedures are similarly safe despite the high number of calf DVTs not diagnosed/treated with the former: what is the real clinical importance of diagnosed calf DVTs?

Clinical research is needed:

- to single out the few calf DVTs that are clinically important
- to standardize calf examination (between centers)

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J.-P. GALANAUD,* M.-A. SEVESTRE,† C. GENTY,‡ S. R. KAHN,§ G. PERNOD,‡¶ C. ROLLAND,‡ A. DIARD,** S. DUPAS,† C. JURUS,†† J.-M. DIAMAND,‡‡ I. QUERE,* and J.-L. Bosson‡ FOR THE OPTIMEV-SFMV INVESTIGATORS

	Distal DVT, HR (95% CI) (N = 490)	Proximal DVT, HR (95% CI), (N = 259)
Any recurrent VTE event	2.7 (1.9–3.8) (n = 33)	5.2 (3.6–7.6) (n = 29)
Distal DVT	1.5 (0.9–2.3) (n = 18)	0.7 (0.3–1.8) (n = 4)
Proximal DVT	0.3 (0.1–0.9) (n = 4)	3.4 (2.2–5.3) (n = 19)
PE	0.9 (0.5–1.6) (n = 11)	1.0 (0.5–2.3) (n = 6)

Values are percentages per patient-year (95% CI)

CALTHRO study: results at f.up

(Palareti et al., T&H 2010)

Clinical evolution at 3 month follow-up, n. (%)			
	Calf DVT 64	No calf DVT 359	p
Primary outcomes 1 PE, 3 prox. DVT, 1 worsened calf DVT	5 (7.8) [3; (4.7)]*	3 (0.8) (3; 0.8)	0.003 0.049
Symptoms - Improved or absent - Stable - Worsened (no DVT)	 54 (84.4) 5 (7.8) 0	 321(91.5) 24 (6.8) 1 (0.3)	0.841

* excluding the 2 subjects in whom DVT was picked at the 2nd CUS

VALUTAZIONE DELLA PROBABILITA' CLINICA PER LA DIAGNOSI DI TVP NEI PAZIENTI AMBULATORIALI SINTOMATICI

- Caratteristiche cliniche (Wells et al, NEJM 2003)

	Punteggio
• Cancro in atto (terapia in corso,o nei 6 mesi precedenti)	1
• Paralisi, paresi o recente immobilizzazione di un arto inf.	1
• Recente allettamento> 3 gg o chirurgia maggiore (12 sett.) in anestesia generale o regionale	1
•	
•Dolorabilità localizzata lungo decorso vene profonde	1
• Edema di tutto l'arto inferiore	1
• Gonfiore di tutto il polpaccio, > 3 cm controlaterale	1
• Edema improntabile (più accentuato nell'arto sintomatico)	1
• Circolo collaterale superficiale (non vene varicose)	1
• Pregresso episodio documentato di TVP/EP	1
• Diagnosi alternativa (verosimile quanto quella di TVP)	-2

- TVP PROBABILE $\geq$ 2 ; TVP IMPROBABILE < 2

Isolated distal deep vein thrombosis: efficacy and safety of a protocol of treatment. Treatment of Isolated Calf Thrombosis (TICT) Study

R. PARISI [1], A. VISONÀ [2], G. CAMPORESE [3], F. VERLATO [3], G. LESSIANI [4], P. L. ANTIGNANI [5], G. PALARETI [6] and Intersocietary Working Group on Distal Deep Vein Thrombosis

The aim of the Treatment of Isolated Calf Thrombosis (TICT) study was to assess the efficacy and safety of a treatment regimen in symptomatic outpatients with ID-DVT a with twice-daily subcutaneous administration of a full dose weight-adjusted of LMWH for one week, followed by a half dose of LMWH administered once-daily for the next three weeks.

CHEST 2012 Supplement
ANTITHROMBOTIC THERAPY AND PREVENTION OF THROMBOSIS, 9TH ED: ACCP GUIDELINES

Antithrombotic Therapy for VTE Disease

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).