

# IL TROMBO RESIDUO

MITO O REALTA'?

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# Venous Thromboembolism (VTE)

Include deep-vein thrombosis (DVT) and pulmonary embolism (PE)

- Third most common cardiovascular disease after the myocardial infarction and the ischemic stroke
- Incidence 1.0-1.6 per 1000/year
- Prevalence 200.000-250.000 new cases/year (USA)
- Important cause of mortality and of morbidity

# “Qualitative” CUS

- CUS is a **qualitative** method providing informations as 0/1, yes/no, +/-
- CUS allows to sensitively investigate only patients with a 1st suspect of DVT
- If a **Come fare a riconoscere e** objective DVT is **aggiudicare una TVP recidiva?**
- CUS is the tool of choice for diagnosis of recurrence in patients with a suspect of a contralateral DVT, but not of an ipsilateral DVT (because of high RTM incidence and of potential high rates of false positive scans)
- Other parameters, as changes in the thrombus lenght, Doppler flow, or intraluminal US appearance (“fresh”, “stabilized”, “organized”) still have not been validated

# The “residual thrombus mass”

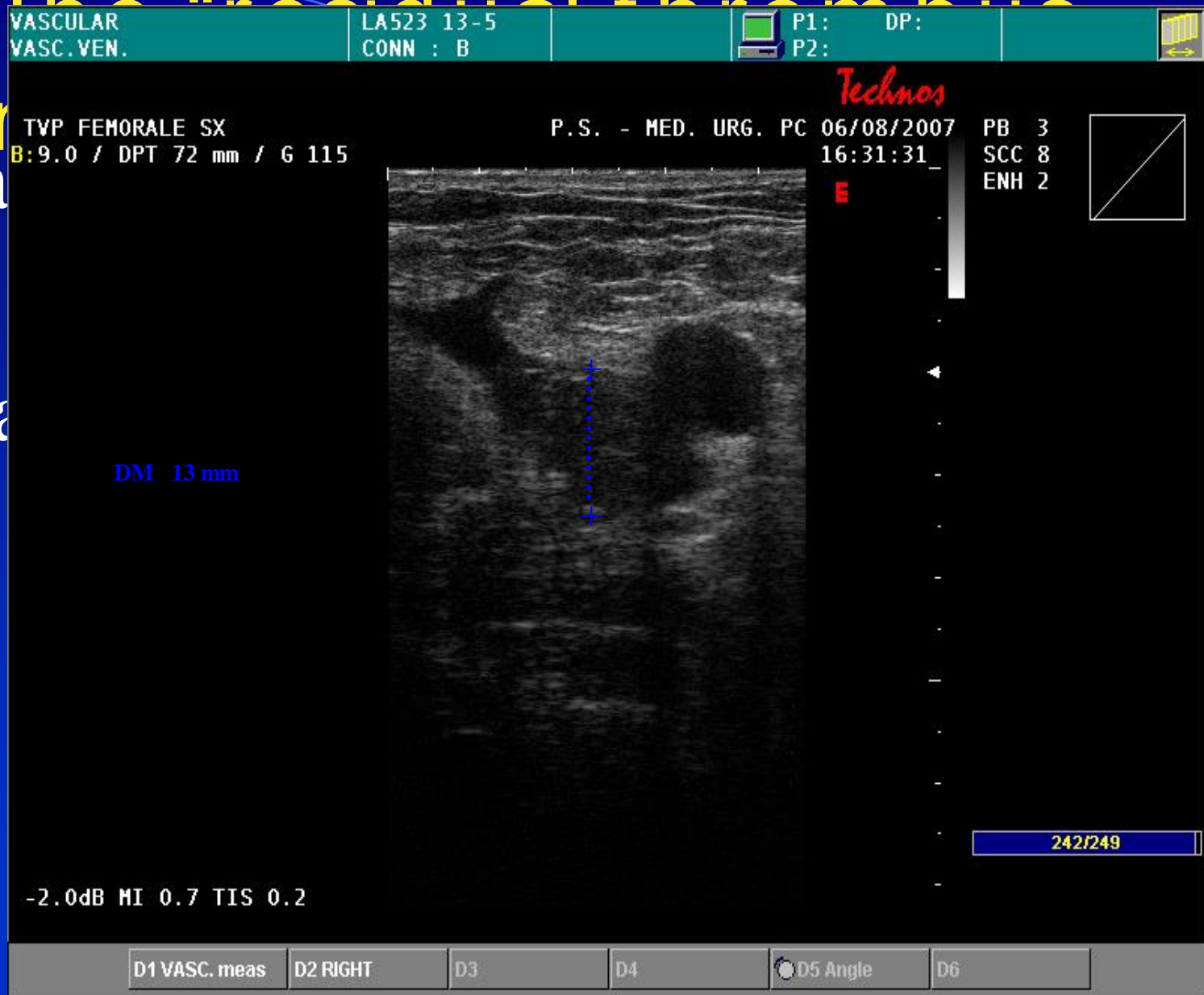
To resolve this issue some Authors suggested to use CUS as a **quantitative method**

- measuring the thickness of the thrombus at the time of the first diagnosis
- measuring the thickness of the residual thrombus mass during follow-up (after 1, 3, 6 and 12 months)

by means of a full compression of the veins, mainly common femoral and popliteal veins (or where visible) using as index the diameter variation of the vessel as explored in transverse scan

*P Prandoni, Circulation 1993;Piovella F, Haematologica 2002;  
Prandoni P Thromb Haemost 2002*

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*Prandoni P, 1993; Heijboer H, 1992; Piovella F, 2002*

# Pathophysiology

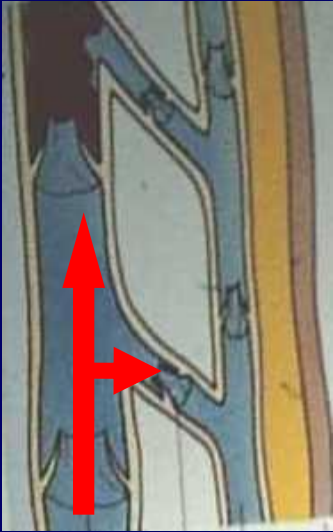
- Damage to delicate venous valves by the thrombus itself or by associated inflammatory mediators, which causes valvular reflux
- Residual venous obstruction because of incomplete thrombus clearance and impaired venous return



Increased venous pressure (venous hypertension) with reduced muscle perfusion, increased tissue permeability and the associated clinical manifestations

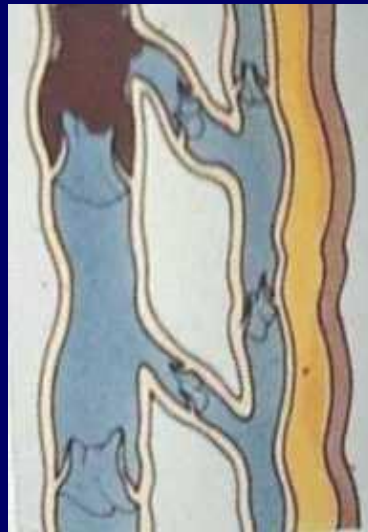
## C.V.I. - Persistent Thrombus

### Early Phase

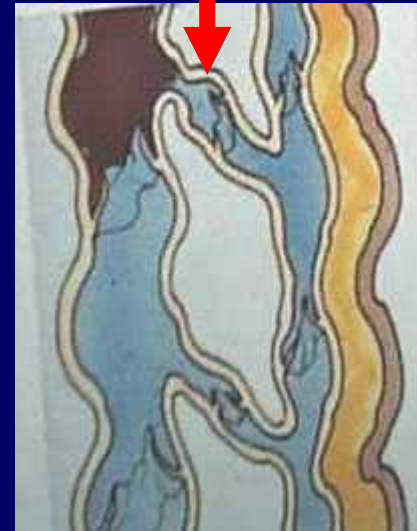


Pressure  
Overload

Early balanced  
dilation of superficial  
venous wall



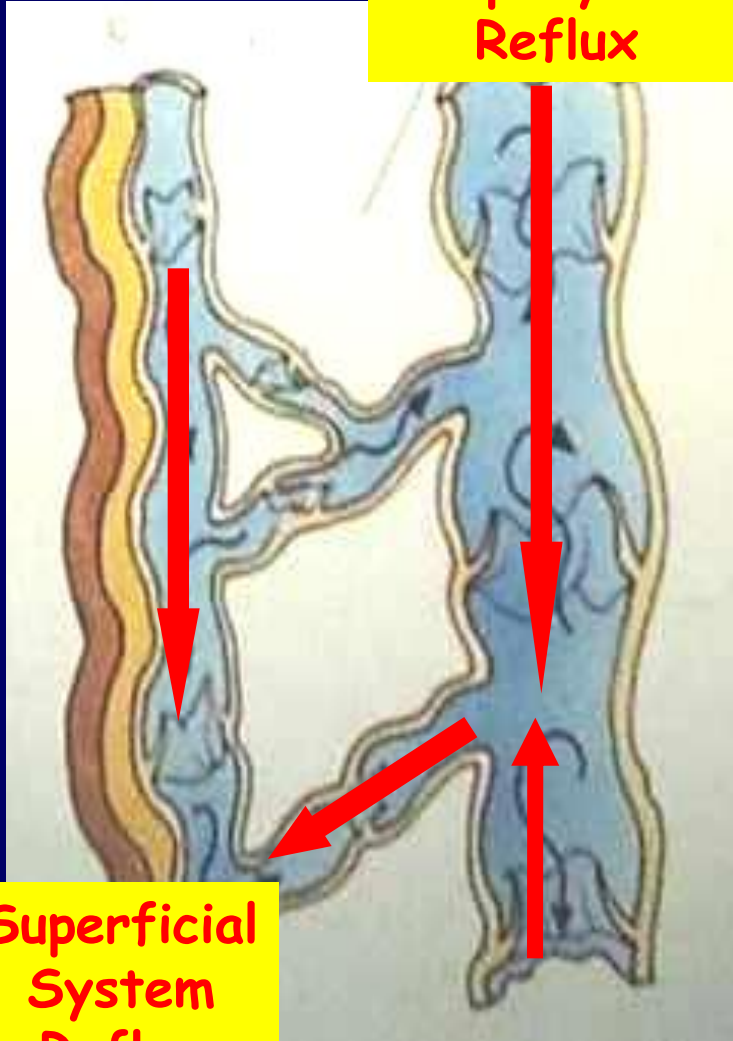
Critical Step  
Involvement of  
Perforator Veins



Secondary, unbalanced  
Post-Thrombotic Varicose Veins  
Obstruction and Small Reflux

## C.V.I. - Recanalisation of the Thrombus

Deep System  
Reflux



Superficial  
System  
Reflux

Critical Step  
Involvement of  
Perforator Veins

Stasis

Volume  
Overload

Passive Venous  
Hypertension

Big Reflux

Faster Evolution if the  
original thrombus was  
involving the perforator v.

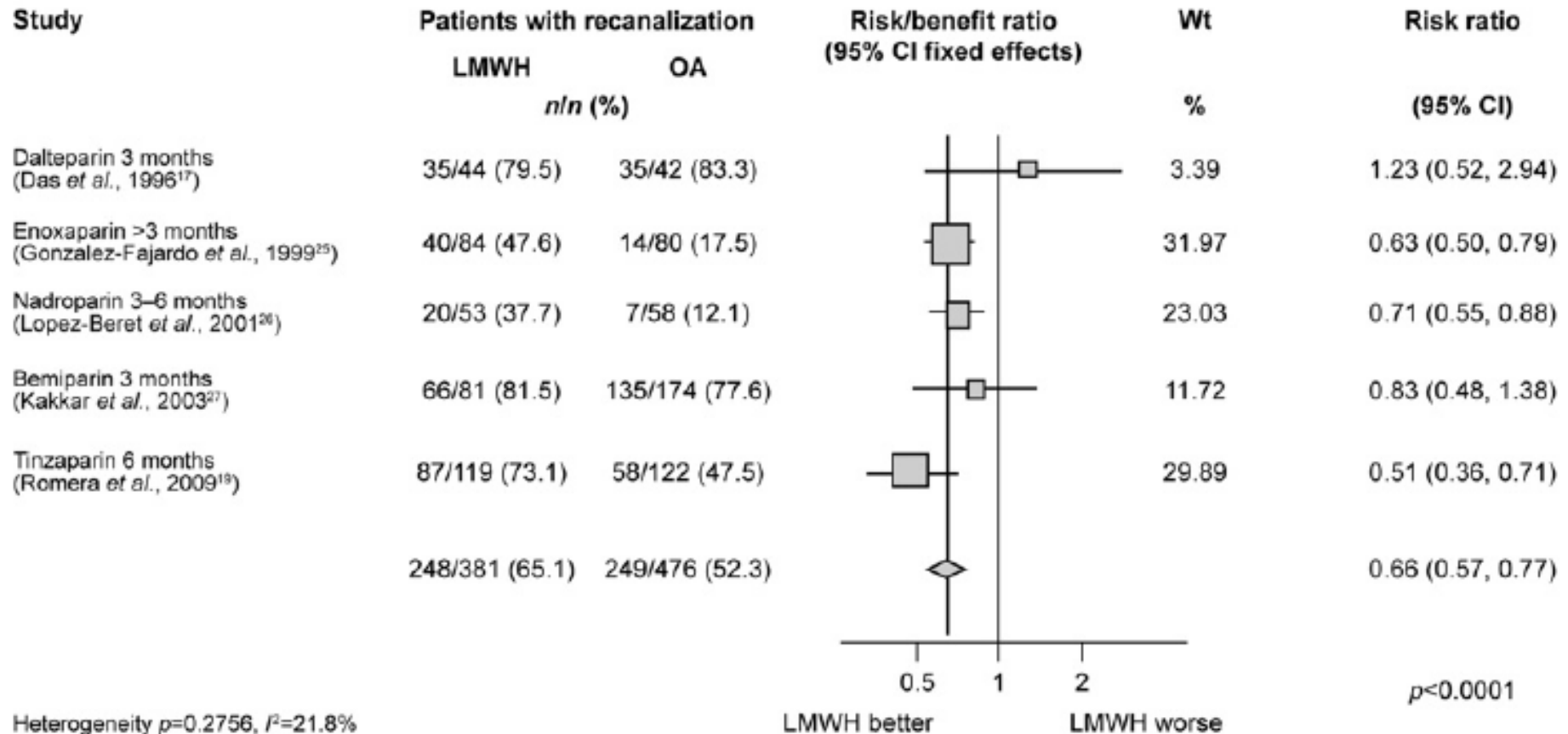


# Risk factors for PTS: Present during follow-up

Risk factor	Author, year	Risk estimate	Strength/ Consistency of risk association
Poor INR control			++
	Chitsike <i>et al</i> , 2012	OR: 1.84 (95% CI: 1.13-3.01) ; INR < 2 for > 20% of the time	
	van Dongen <i>et al</i> , 2005	OR: 2.71 (95% CI: 1.44-5.10); TTR < 50%	

# LMWH vs VKA for prevention in PTS: Venis recanalisation

**B**



# 8 – Possible risk factors for SPT

## Residual thrombus

Risk factor	Author, year	Risk estimate	Strength/ Consistency of risk association
Residual thrombus			+
	Vedovetto et al., 2013	RR: 1.92 (95% CI: 1.39-2.64) residual thrombus alone, 1.83 (95% CI 1.26-2.66) residual thrombus + popliteal valve reflux. Popliteal valve insufficiency after 6 months neither predicts the occurrence of PTS nor increases its rate in association with residual thrombosis	
	Comerota et al, 2012	Direct linear correlation of Villalta score with residual thrombus (P = .0014).	
	Galanaud et al, 2012	OR:2.1 (95% CI : 1.1-3.7)	
	Tick et al, 2010	RR: 1.6 (95% CI 1.0-2.5); proximal veins	
	Prandoni et al., 2005	RR : 1.56 (95% CI 1.01–2.45); common femoral and the popliteal vein	

# Pathophysiology

- Damage to delicate venous valves by the thrombus itself or by associated inflammatory mediators, which causes valvular reflux
- Residual venous obstruction and presence of incomplete thrombus clearance **RECURRENCE** impaired venous return



Increased venous pressure (venous hypertension) with reduced muscle perfusion, increased tissue permeability and the associated clinical manifestations

# The Diagnostic Value of Compression Ultrasonography in Patients with Suspected Recurrent Deep Vein Thrombosis

Paolo Prandoni<sup>1</sup>, Anthonie WA Lensing<sup>2</sup>, Enrico Bernardi<sup>1</sup>, Sabina Villalta<sup>1</sup>, Paola Bagatella<sup>1</sup>, Antonio Girolami<sup>1</sup> for the DERECUS Investigators Group

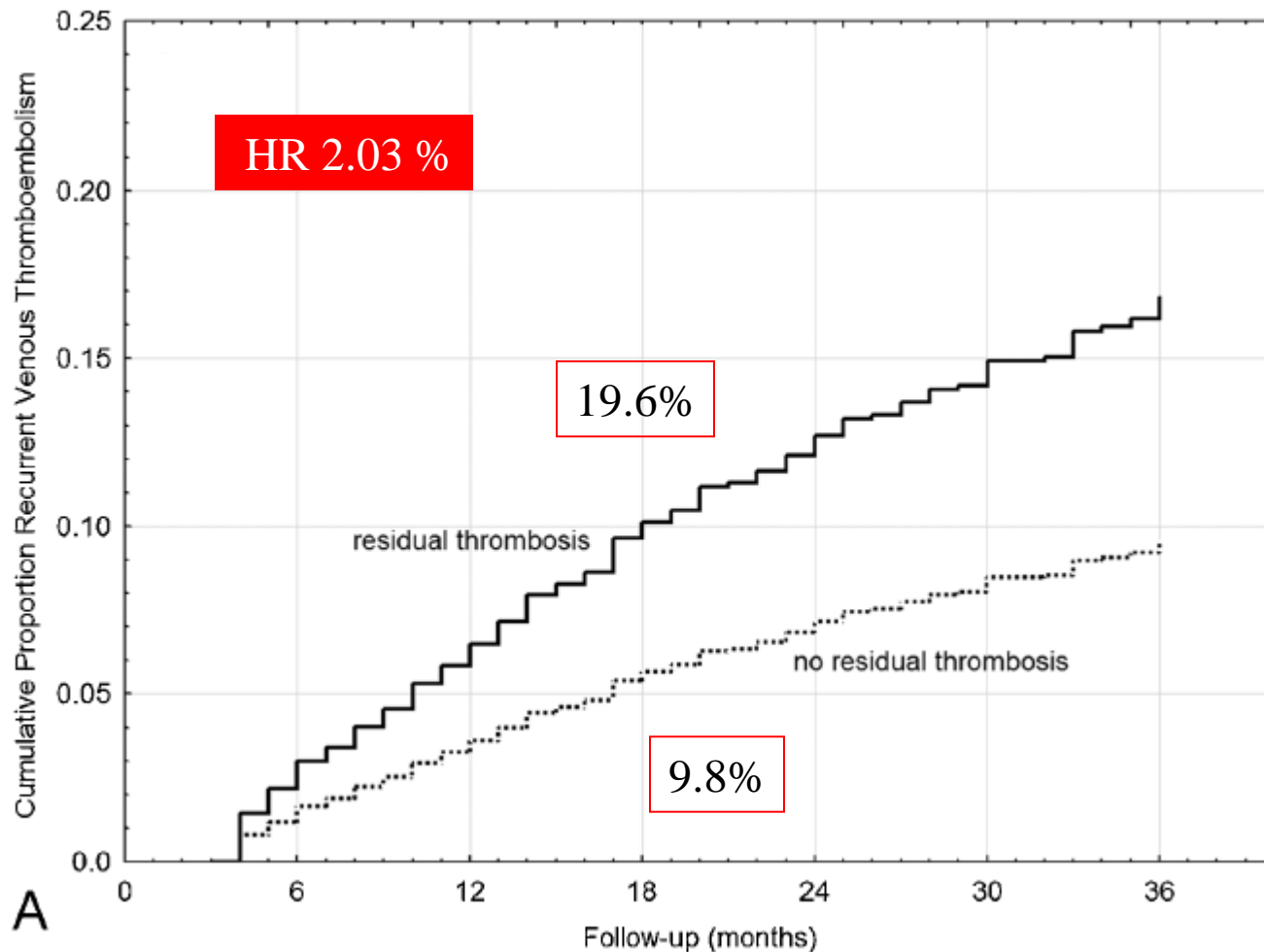
<sup>1</sup>Department of Medical and Surgical Sciences, 2nd Chair of Internal Medicine, University of Padua Medical School, Padua, Italy; <sup>2</sup>The Center for Vascular Medicine, Academic Medical Center, University of Amsterdam, The Netherlands

## Subgroup analysis

US findings	Pts	DVT
Non- compressibility of a previous normal(ized) vein	10	10
Enlargement of thrombus mass > 4 mm	28	28
Enlargement of thrombus mass ≤ 4 mm	8	4

# The Impact of Residual Thrombosis on the Long-Term Outcome of Patients with Deep Venous Thrombosis Treated with Conventional Anticoagulation

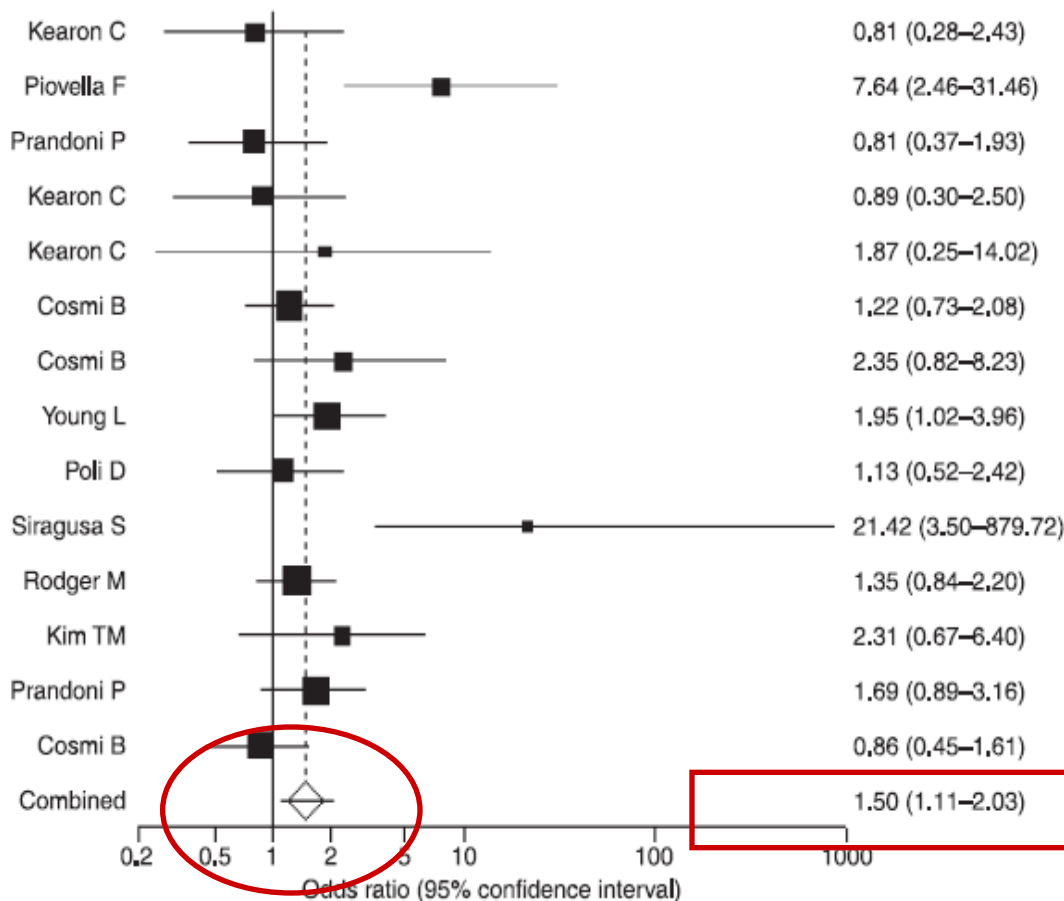
Paolo Prandoni, MD, PhD<sup>1</sup> Anthonie W. A. Lensing, MD, PhD<sup>2</sup> Martin H. Prins, MD, PhD<sup>3</sup>  
Raffaele Pesavento, MD<sup>1</sup> Andrea Piccioli, MD<sup>1</sup> Maria T. Sartori, MD<sup>1</sup> Daniela Tormene, MD<sup>1</sup>  
Marta Milan, MD<sup>1</sup> Valentina Vedovetto, MD<sup>1</sup> Franco Noventa, MD<sup>1</sup> Sabina Villalta, MD<sup>4</sup>  
Job Harenberg, MD, PhD<sup>5</sup>



## IN FOCUS

# Residual vein obstruction to predict the risk of recurrent venous thromboembolism in patients with deep vein thrombosis: a systematic review and meta-analysis

M. CARRIER,\*† M. A. RODGER,\*† P. S. WELLS,\*† M. RIGHINI‡§ and G. LE GAL¶



Only unprovoked  
DVT + Stop OAT

OR  
1.24 (0.9 -1.7)

# Residual venous thrombosis as predictive factor for recurrent venous thromboembolism in patients with proximal deep vein thrombosis: a systematic review

	RVT present		RVT absent		Odds Ratio		Odds Ratio M-H, Fixed, 95% CI	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		
<b>Malignancy</b>								
Cosmi <i>et al</i> (2005b)	16	51	5	37	3.3%	2.93 [0.96, 8.90]		
Siragusa (2009)	11	47	1	42	0.7%	12.53 [1.54, 101.84]		
<b>Subtotal (95% CI)</b>		<b>98</b>		<b>79</b>	<b>4.0%</b>	<b>4.55 [1.76, 11.79]</b>		
Total events	27		6					
Heterogeneity: Chi <sup>2</sup> = 1.50, df = 1 (P = 0.22); I <sup>2</sup> = 33% Test of overall effect: Z = 3.12 (P = 0.002)								
<b>Unprovoked</b>								
Cosmi <i>et al</i> (2005a)	41	225	26	174	19.9%	1.27 [0.74, 2.17]		
Cosmi <i>et al</i> (2010)	17	151	32	246	17.9%	0.85 [0.45, 1.59]		
Rodger <i>et al</i> (2008)	45	231	32	221	21.8%	1.43 [0.87, 2.35]		
Siragusa (2008)	25	92	1	78	0.7%	28.73 [3.79, 217.76]		
<b>Subtotal (95% CI)</b>		<b>699</b>		<b>719</b>	<b>60.3%</b>	<b>1.50 [1.12, 2.01]</b>		
Total events	128		91					
Heterogeneity: Chi <sup>2</sup> = 11.75, df = 3 (P = 0.008); I <sup>2</sup> = 74% Test of overall effect: Z = 2.69 (P = 0.007)								
<b>Mixed</b>								
Piovella <i>et al</i> (2002)	16	129	4	122	3.0%	4.18 [1.36, 12.87]		
Poli <i>et al</i> (2008)	14	105	18	153	10.5%	1.15 [0.55, 2.44]		
Prandoni <i>et al</i> (2002)	30	252	9	61	10.6%	0.78 [0.35, 1.74]		
Prandoni <i>et al</i> (2009)	19	79	27	189	10.0%	1.90 [0.98, 3.67]		
Siragusa <i>et al</i> (2008)	63	312	2	206	1.6%	25.81 [6.24, 106.75]		
<b>Subtotal (95% CI)</b>		<b>877</b>		<b>731</b>	<b>35.7%</b>	<b>2.61 [1.84, 3.69]</b>		
Total events	142		60					
Heterogeneity: Chi <sup>2</sup> = 24.78, df = 4 (P < 0.0001); I <sup>2</sup> = 84% Test of overall effect: Z = 5.39 (P < 0.00001)								
<b>Total (95% CI)</b>		<b>1674</b>		<b>1529</b>	<b>100.0%</b>	<b>2.02 [1.62, 2.50]</b>		
Total events	297		157					
Heterogeneity: Chi <sup>2</sup> = 43.51, df = 10 (P < 0.0001); I <sup>2</sup> = 77% Test of overall effect: Z = 6.35 (P < 0.00001) Test for subgroup differences: Chi <sup>2</sup> = 5.48, df = 2 (P = 0.06); I <sup>2</sup> = 64%								

Total OR  
2.02 (1.62 – 2.50)

Tan M, British J of  
Haematology, 2011



# Prognostic significance of residual venous obstruction in patients with treated unprovoked deep vein thrombosis

A patient-level meta-analysis

Variables	Adjusted HR for recurrent VTE (95% CI)	P- value
<b>RVO (present vs absent)</b>	<b>1.32 (1.06- 1.65)</b>	<b>0.015</b>
<b>Age (for 1- year increase)</b>	<b>1.01 (1.00- 1.02)</b>	<b>0.006</b>
<b>Sex (male vs female)</b>	<b>1.49 (1.2- 1.84)</b>	<b>&lt;0.001</b>
<b>Anticoagulation duration before RVO (for 1- day increase)</b>	<b>1.00 (1.00- 1.00)</b>	<b>0.783</b>
<b>Anticoagulation continuation after RVO (yes vs no)</b>	<b>1.08 (0.73- 1.59)</b>	<b>0.712</b>

# Residual Thrombosis on Ultrasonography to Guide the Duration of Anticoagulation in Patients With Deep Venous Thrombosis

## A Randomized Trial

Paolo Prandoni, MD, PhD; Martin H. Prins, MD, PhD; Anthonie W.A. Lensing, MD, PhD; Angelo Ghirarduzzi, MD; Walter Ageno, MD; Davide Imberti, MD; Gianluigi Scannapieco, MD; Giovanni B. Ambrosio, MD; Raffaele Pesavento, MD; Stefano Cuppini, MD; Roberto Quintavalla, MD; and Giancarlo Agnelli, MD, for the AESOPUS Investigators\*

268 pts

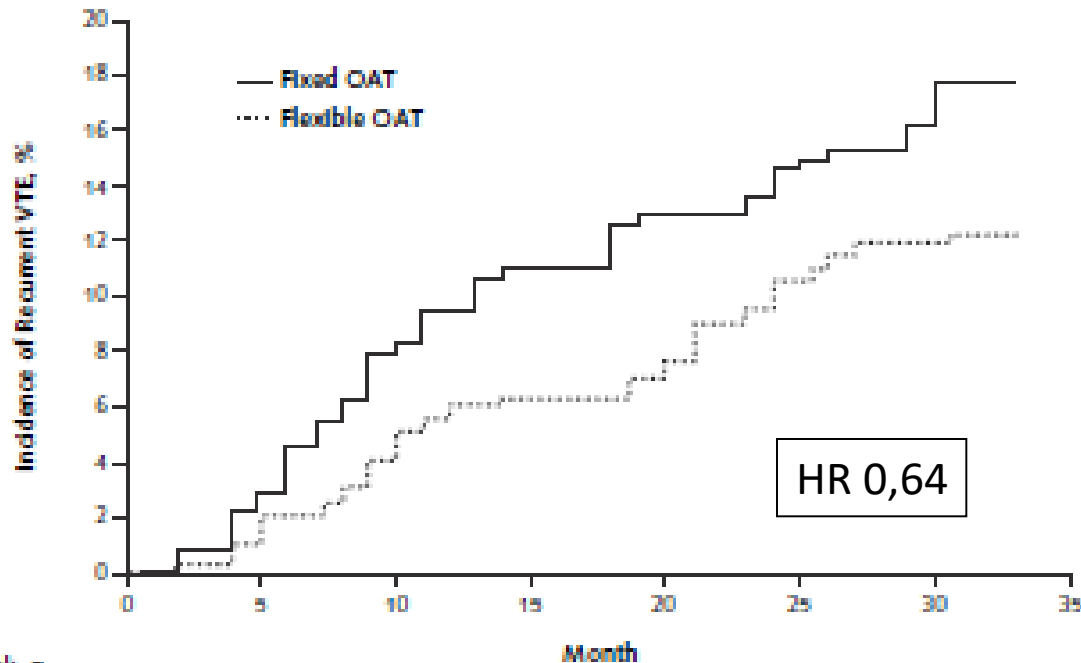
RVT: VTE recurrence

Adj HR 2.4 (95%CI, 1.3 to 4.4)

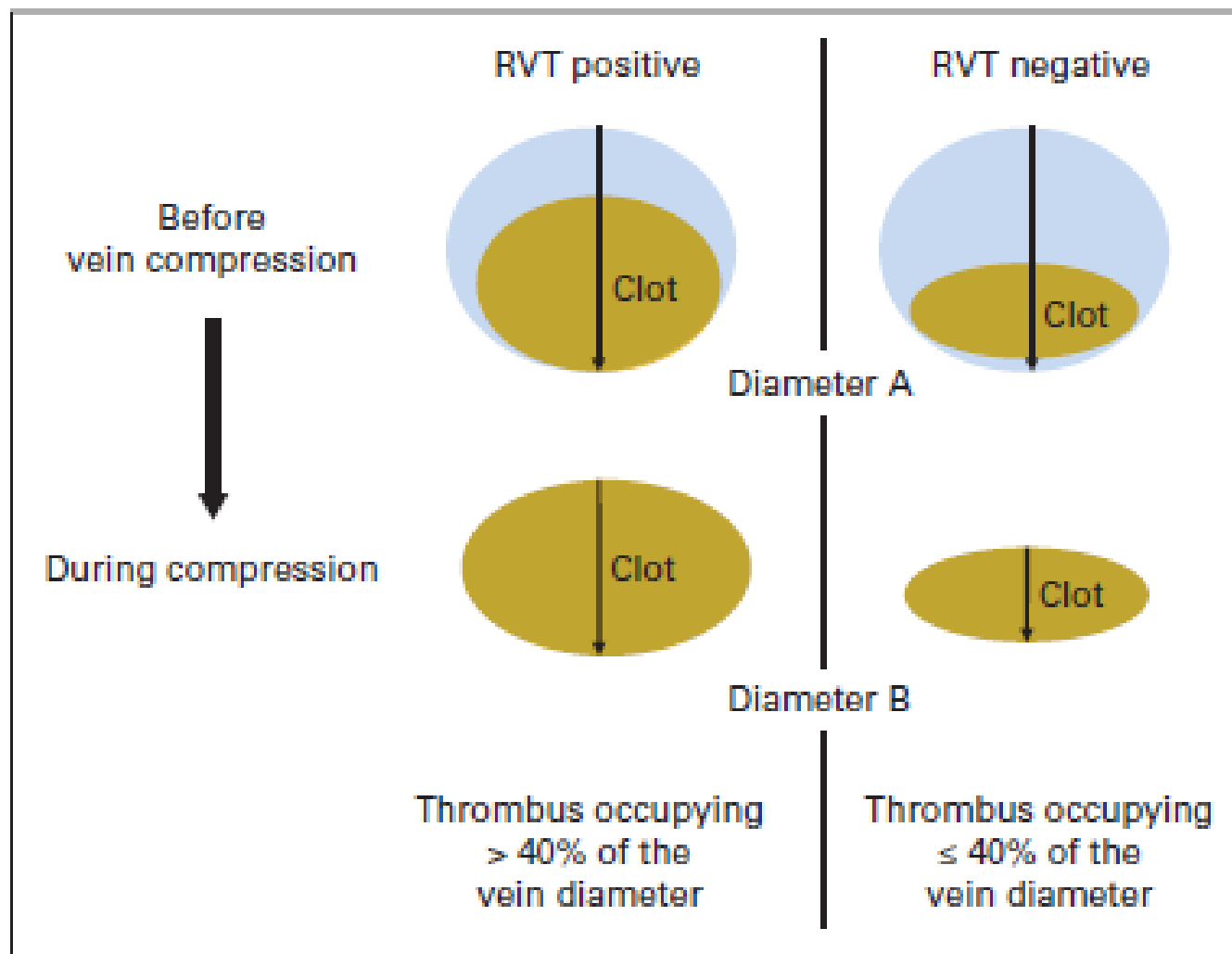
*P* 0.004

*12 events prevented in unprovoked DVT vs 2 in provoked DVT*

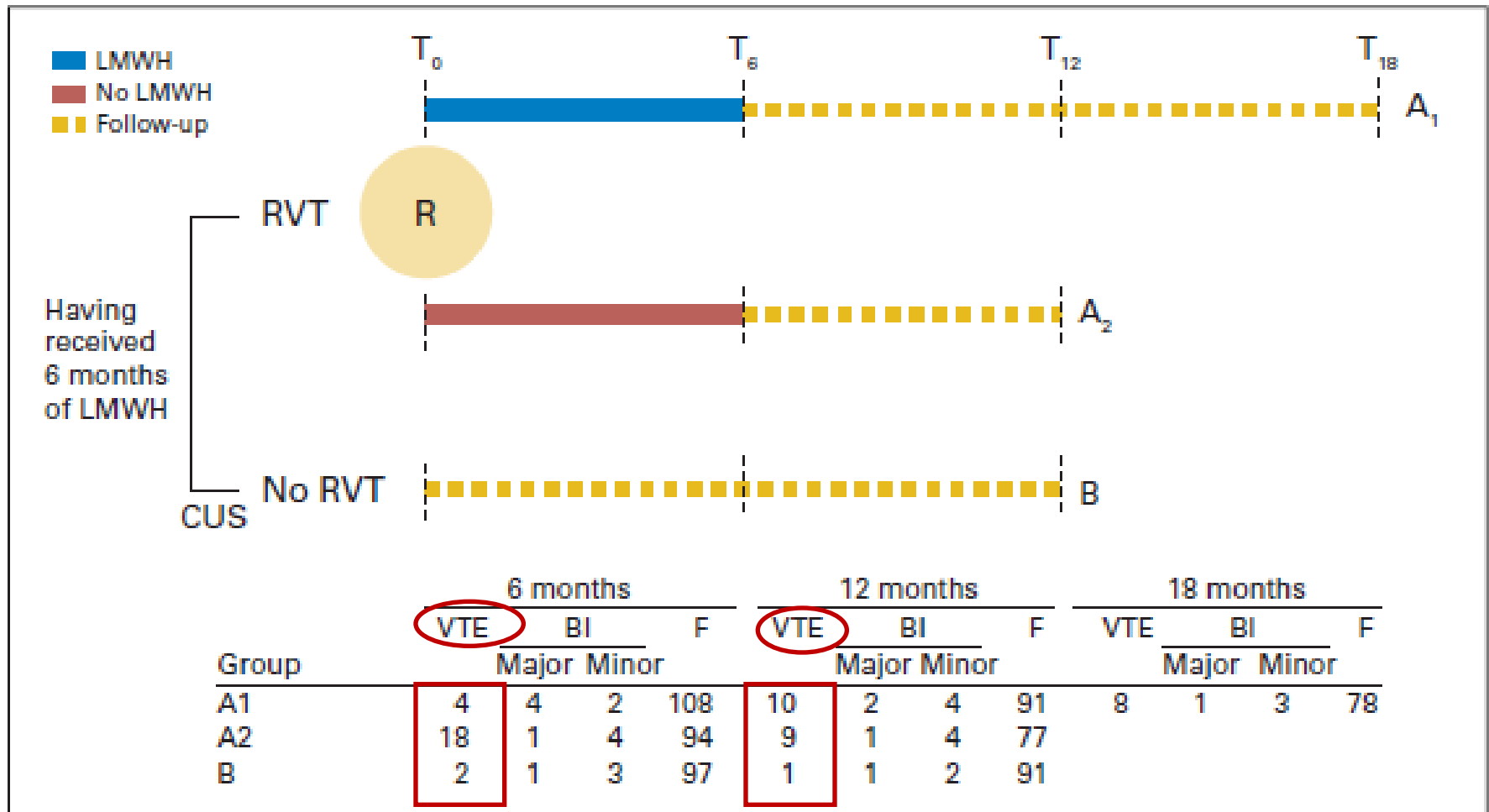
***VTE Recurrence in pts with no RVT 11.9 %***



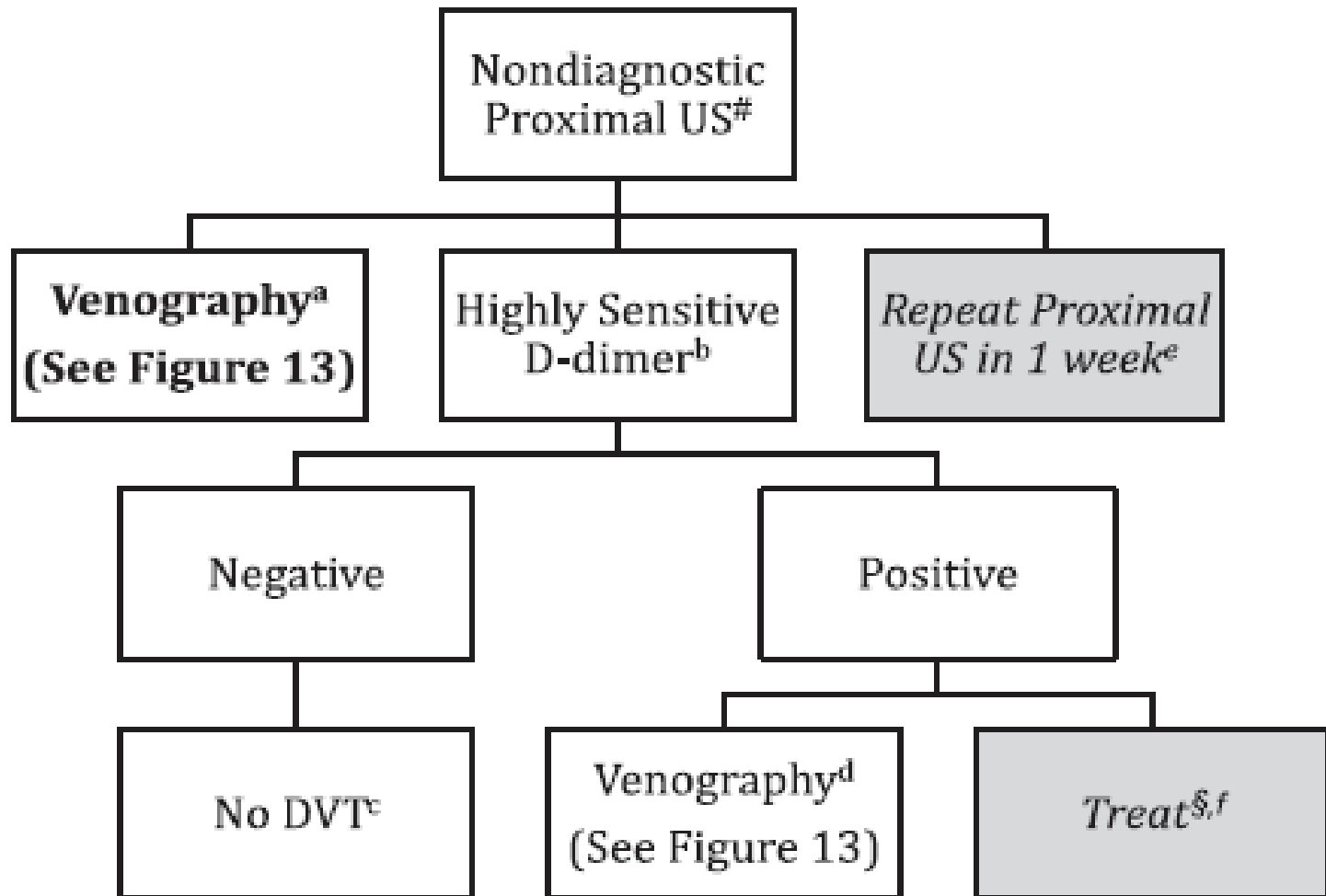
# Evaluation of residual vein thrombosis



# DACUS study

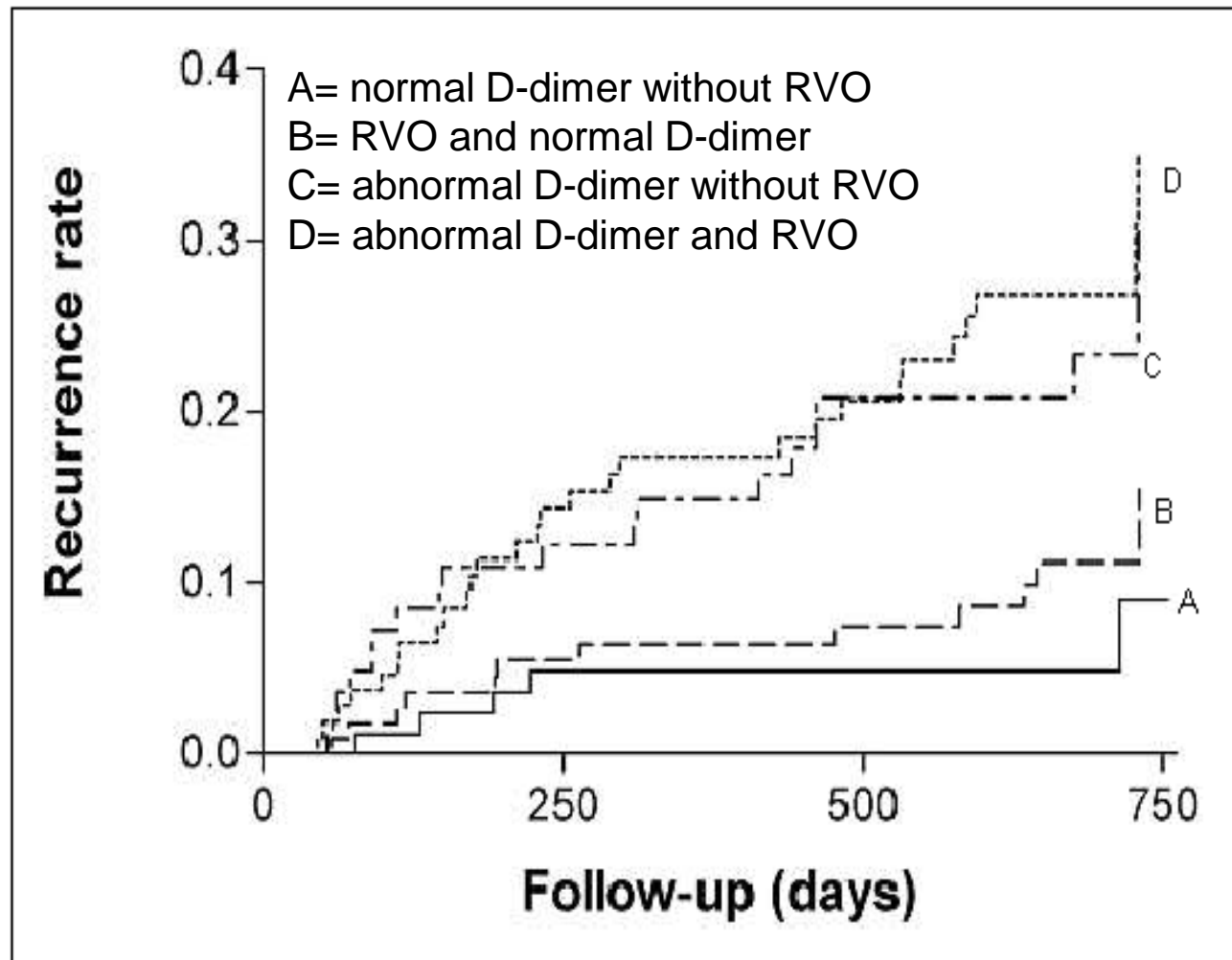


4.3. In patients with suspected recurrent insilat.



venography.

# Cumulative probability of recurrence in pts with idiopathic events according to combination of D-dimer and RVO



# The ***DULCIS study*** (***D-dimer and ULtrasonography in Combination Italian Study***)

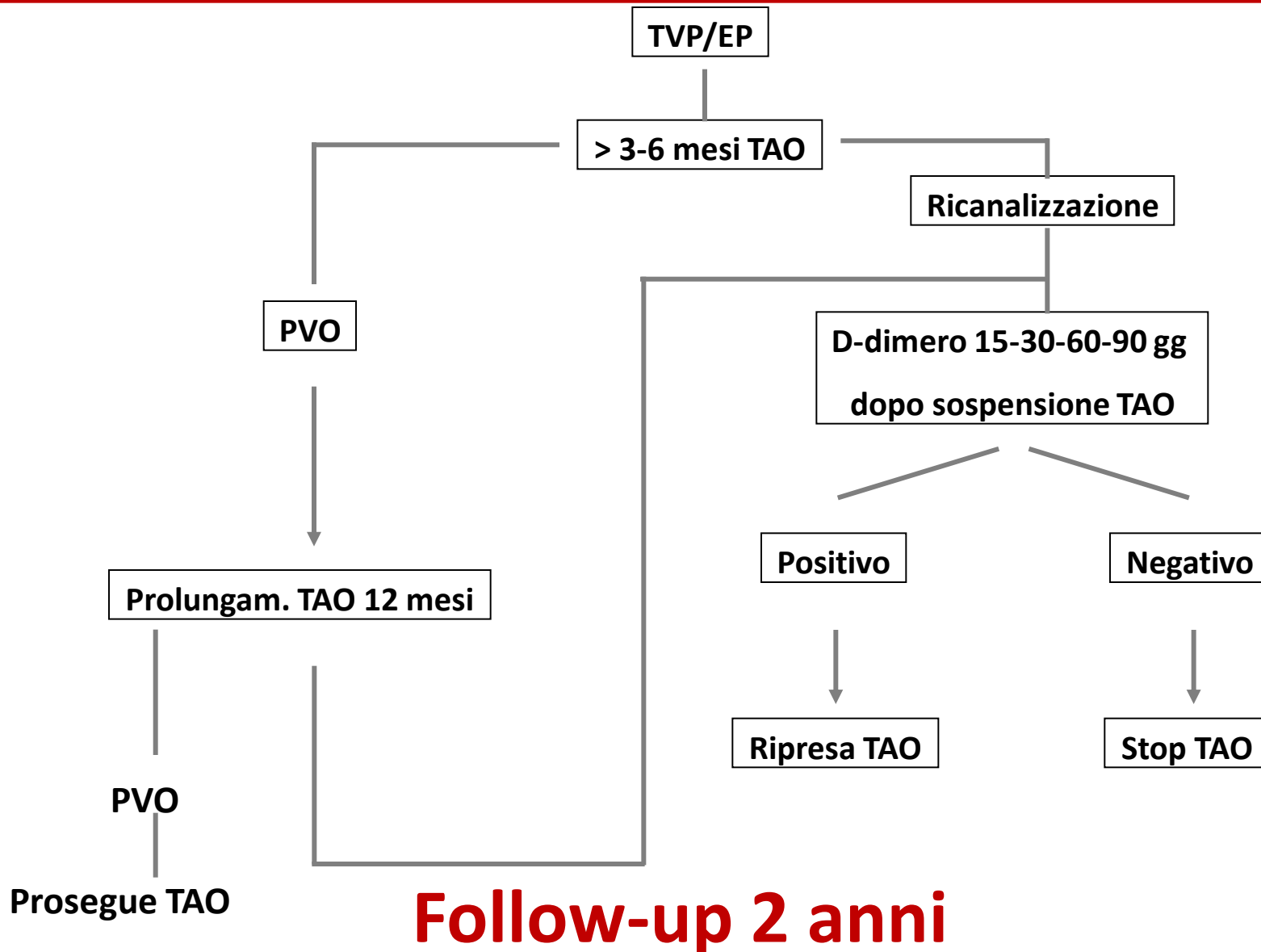
A management study to optimize the duration of anticoagulation after a 1st VTE

## ***Executive Committee:***

Gualtiero Palareti (Bologna), Vittorio Pengo (Padova), Paolo Prandoni (Padova)

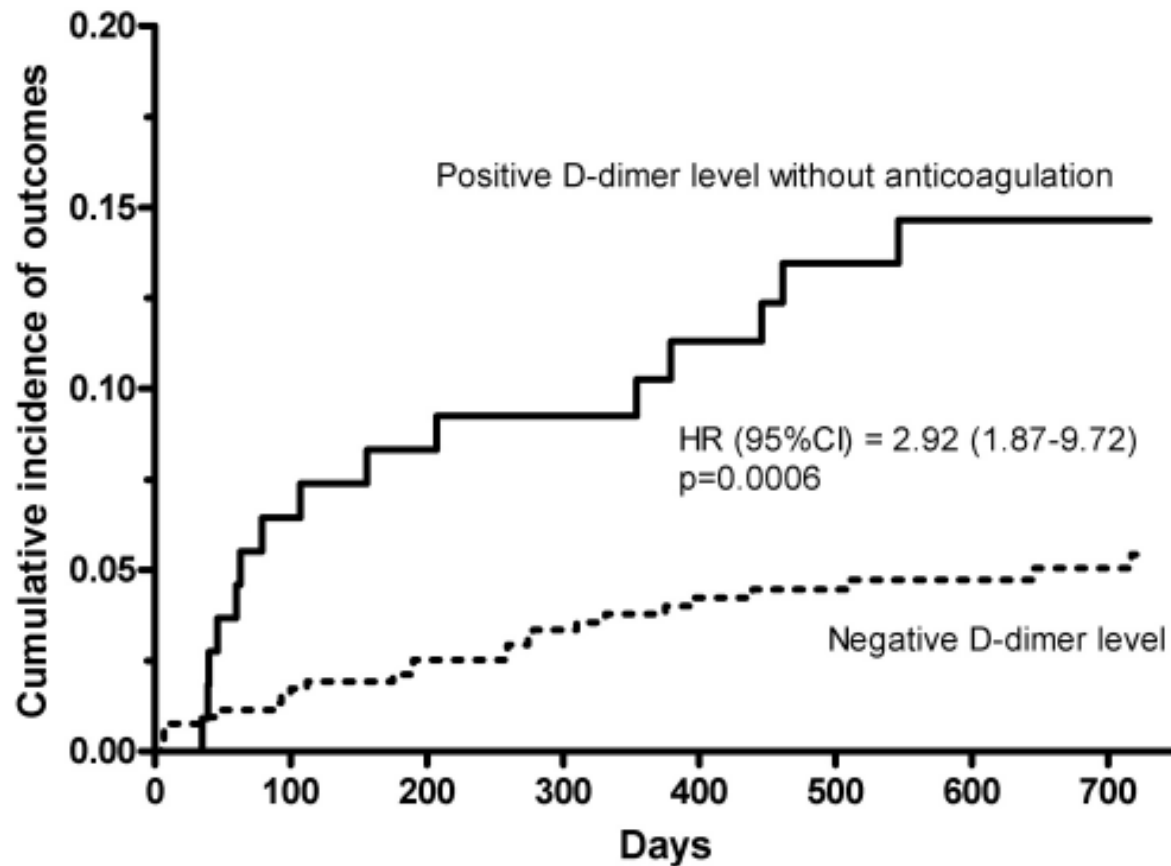
*Blood, 2014*

# Studio DULCIS: flow-chart





# Cumulative event rates for the primary efficacy outcomes



# STUDIO MORGAGNI



**Identificazione della durata  
ottimale della terapia  
anticoagulante nella  
trombosi venosa profonda**

*A cura di Paolo Prandoni, Vittorio  
Pengo, Gualtiero Palareti*

# Studio Morgagni: flow-chart

