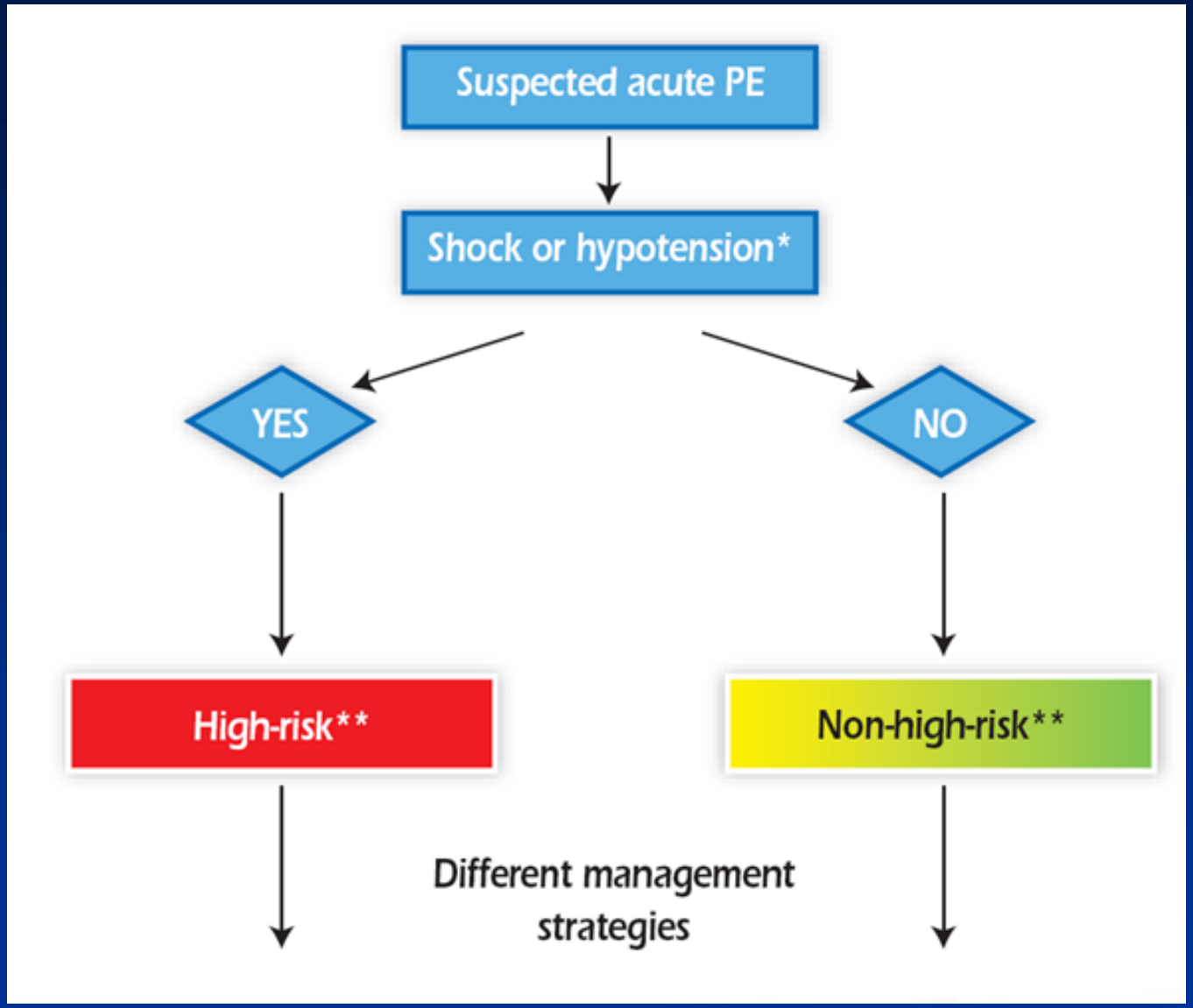
SISET; Cremona 19 Settembre 2016

TEV: Terapia e durata del trattamento

Gualtiero Palareti
Malattie Cardiovascolari
Università di Bologna

Cosa fare dopo la iagnosi di EP e/o TVP

A) Con presentazione come EP


Suspected acute PE
Shock or hypotension*
YES
NO
High-risk**
Non-high-risk**
Different management strategies

Management of Massive and Submassive Pulmonary Embolism, Iliofemoral Deep Vein Thrombosis, and Chronic Thromboembolic Pulmonary Hypertension : A Scientific Statement From the American Heart Association

Michael R. Jaff, M. Sean McMurtry, Stephen L. Archer, Mary Cushman, Neil Goldenberg, Samuel Z. Goldhaber, J. Stephen Jenkins, Jeffrey A. Kline, Andrew D. Michaels, Patricia Thistlethwaite, Suresh Vedantham, R. James White, Brenda K. Zierler and on behalf of the American Heart Association Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation, Council on Peripheral Vascular Disease, and Council on Arteriosclerosis, Thrombosis and Vascular Biology

Circulation 2011, 123:1788-1830: originally published online March 21, 2011

Definition for *massive PE:*

Acute PE with sustained hypotension (SBP ≤ 90 mm Hg for > 15 min or requiring inotropic support, not due to a cause other than PE), pulselessness, or persistent profound bradycardia (heart rate 40 bpm with signs or symptoms of shock).

Management of Massive and Submassive Pulmonary Embolism, Iliofemoral Deep Vein Thrombosis, and Chronic Thromboembolic Pulmonary Hypertension : A Scientific Statement From the American Heart Association

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Circulation 2011, 123:1788-1830: originally published online March 21, 2011

Recommendations for Fibrinolysis for Acute PE

1. Reasonable for patients with massive acute PE and acceptable risk of bleeding complications *(Class IIa, B)*

2. To be considered for patients with submassive acute PE judged to have clinical evidence of adverse prognosis (new hemodynamic instability, worsening respiratory insufficiency, severe RV dysfunction, or major myocardial necrosis) and low risk of bleeding complications *(Class IIb, C)*.

3. Not recommended for patients with low-risk PE *(Class III; Level of Evidence B)*

Thrombolysis for PE: Contraindications

Absolute

- History of haemorrhagic stroke or stroke of unknown origin
- Ischaemic stroke in previous 6 months
- Central nervous system neoplasms
- Major trauma, surgery, or head injury in previous 3 weeks

The NEW ENGLAND JOURNAL of MEDICINE

2014

ORIGINAL ARTICLE

Fibrinolysis for Patients with Intermediate-Risk Pulmonary Embolism

Guy Meyer, M.D., Eric Vicaut, M.D., Thierry Danays, M.D., Giancarlo Agnelli, M.D., Cecilia Becattini, M.D., Jan Beyer-Westendorf, M.D., Erich Bluhmki, M.D., Ph.D., Helene Bouvaist, M.D., Benjamin Brenner, M.D., Francis Couturaud, M.D., Ph.D., Claudia Dellas, M.D., Klaus Empen, M.D., Ana Franca, M.D., Nazzareno Galiè, M.D., Annette Geibel, M.D., Samuel Z. Goldhaber, M.D., David Jimenez, M.D., Ph.D., Matija Kozak, M.D., Christian Kupatt, M.D., Nils Kucher, M.D., Irene M. Lang, M.D., Mareike Lankeit, M.D., Nicolas Meneveau, M.D., Ph.D., Gerard Pacouret, M.D., Massimiliano Palazzini, M.D., Antoniu Petris, M.D., Ph.D., Piotr Pruszczyk, M.D., Matteo Rugolotto, M.D., Aldo Salvi, M.D., Sebastian Schellong, M.D., Mustapha Sebbane, M.D., Bozena Sobkowicz, M.D., Branislav S. Stefanovic, M.D., Ph.D., Holger Thiele, M.D., Adam Torbicki, M.D., Franck Verschuren, M.D., Ph.D., and Stavros V. Konstantinides, M.D., for the PEITHO Investigators*

PEITHO study (NEJM 2014):

- Death or hemodynamic decompensation occurred in 2.6% in the TG as compared with 5.6% in the PG (OR, 0.44; CI, 0.23 to 0.87; P = 0.02)

- Extracranial bleeding in 6.3% in the TG and in 1.2% in the PG (P<0.001)

- Stroke occurred in 2.4% in the TG and in 0.2% in the PG hemorrhagic (P = 0.003)

- By day 30, 2.4% in the TG and 3.2%) in the PG had died (P = 0.42)

Terapia del TEV

B) Con presentazione come TVP o come EP non da trombolisare

Fase acuta:
Immediata anticoagulazione

QUANDO

- Appena fatta la diagnosi di TVP/EP
- Anche in attesa di diagnosi se alta probabilità clinica
- Dopo aver escluso controindicazioni assolute agli anticoagulanti

Controindicazioni assolute agli anticoagulanti

- Grave emorragia in atto
- Recente intervento neurochirurgico o recente emorragia del SNC
- Grave diatesi emorragica congenita o acquisita
- Necessità di urgente chirurgia o manovra invasiva

Cosa fare in caso di controindicazione assoluta agli anticoagulanti

- Filtro cavale

Permanente: in caso di tumore o controindicazione prevedibilmente lunga

Rimuovibile: in caso di controindicazione prevedibilmente di durata limitata

Tempi e terapie del TEV

Initiale e per 3-6 mesi
(breve durata)

Fondap.
LMWH
UFH
DOAC

AVK
DOAC
(LMWH)

Prevenzione secondaria
(lunga durata, indefinita)

AVK
DOAC
(LMWH)

Terapia da iniziare appena fatta la diagnosi (anche prima se alta PC e diagnosi non disponibile immediatamente) usando dosi terapeutiche

Terapia iniziale del TEV

Due diverse modalità

A) Terapia parenterale immediata,
embricata con terapia orale

B) Terapia direttamente con farmaci orali

Terapia iniziale del TEV (1)

A) Terapia parenterale immediata, embricata con terapia orale;

- Eparina non-frazionata: da usare solo in EP emodinamiche in previsione di trombolisi
- LMWH (se enoxaparina 1000 UI sc/10 Kg, 2 volte al dì)
- Fondaparinux (Arixtra) 7,5 mg sc 1 volta al dì (per pesi tra 50 e 100 Kg); 5 mg se < 50 Kg; 10 mg se > 100 Kg

Terapia iniziale del TEV (2)

Embricazione tra farmaci parenterali e quelli orali

- Se AVK: iniziare subito AVK e controllare INR (3°-4° giornata), sospendere farmaco parenterale dopo non meno di 5 gg e dopo 2 gg consecutivi con INR > 2.0

- Se Dabigatran (Pradaxa) iniziare 150 mg 2 volte al dì dopo 5-10 gg e sospendere subito il farmaco parenterale

- Se Edoxaban (Lixiana) iniziare 60 mg 1 volta al dì dopo 7-9 gg e sospendere subito il farmaco parenterale (30 mg se Kg < 60 e CrCl 30-50 ml/min)

Terapia iniziale del TEV (3)

- B) Terapia direttamente con farmaci orali

- Rivaroxaban (Xarelto) 15 mg, 2 volta al dì per 21 giorni, poi 20 mg 1 volta al dì (riduzione della dose a 15 mg x 1 se alto rischio emorragico)
- Apixaban (Eliquis) 10 mg 2 volte al dì per 7 giorni, poi ridurre a 5 mg 2 volte al dì
  (dose ridotta a 2,5 mg x 2 se età >=80 a.,
  peso <= 60 kg, Cr >= 1,5 mg/dl)

Controindicazioni per DOAC

- Gravidanza
- Allattamento
- Insuff. Ren. Grave Cl Creat <15 ml/min (dabigatran < 30 ml/min)
- Insuff. Epatica (Xarelto: Child-Pugh B e C)
- Diatesi emorragica

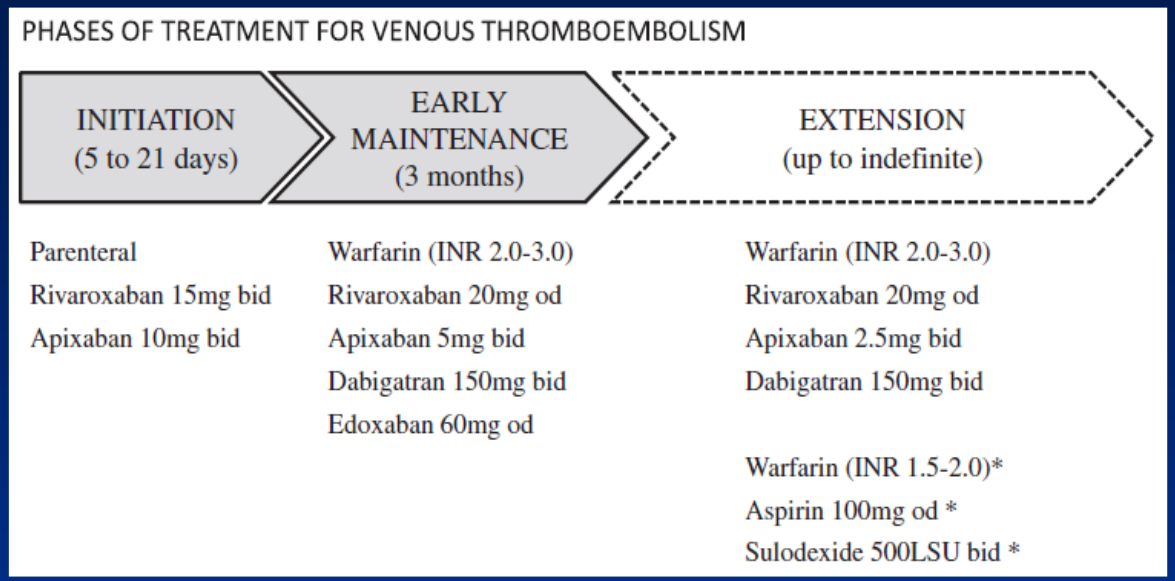
Non ci sono solo le recidive

Tab. 1 The complications of deep vein thrombosis (DVT)

progression of DVT	• Phlegmasia coerulea dolens • Phlegmasia alba dolens → loss of limb
destruction of venous valves or failure of thrombus to resolve	• venous insufficiency (post-thrombotic syndrome) → venous ulcers
pulmonary embolism	• death • pulmonary hypertension
recurrent venous thromboembolism	any of the above

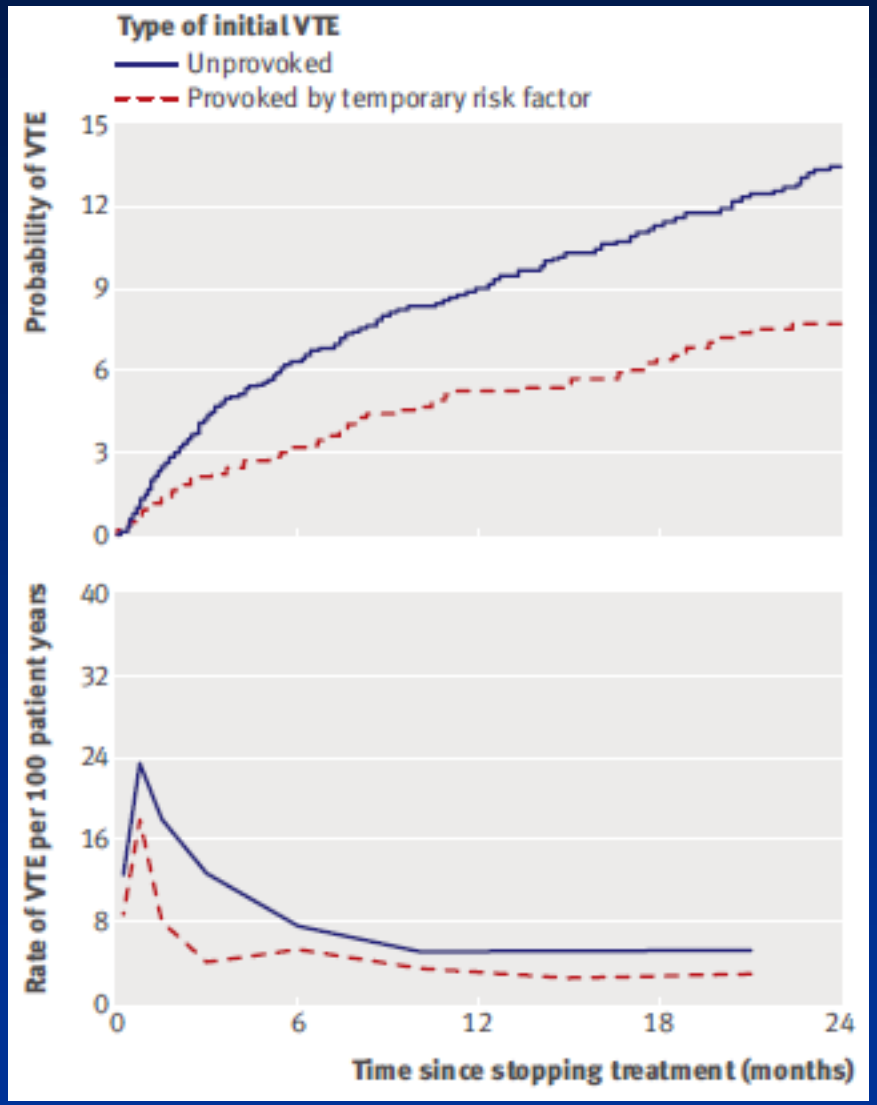
Da Schulman 2008

From Blondon & Bounameaux, Circulation 2015



Initial → Long-Term → Extended

From Kearon et al., Chest 2016



Boutitie et al. BMJ 2011

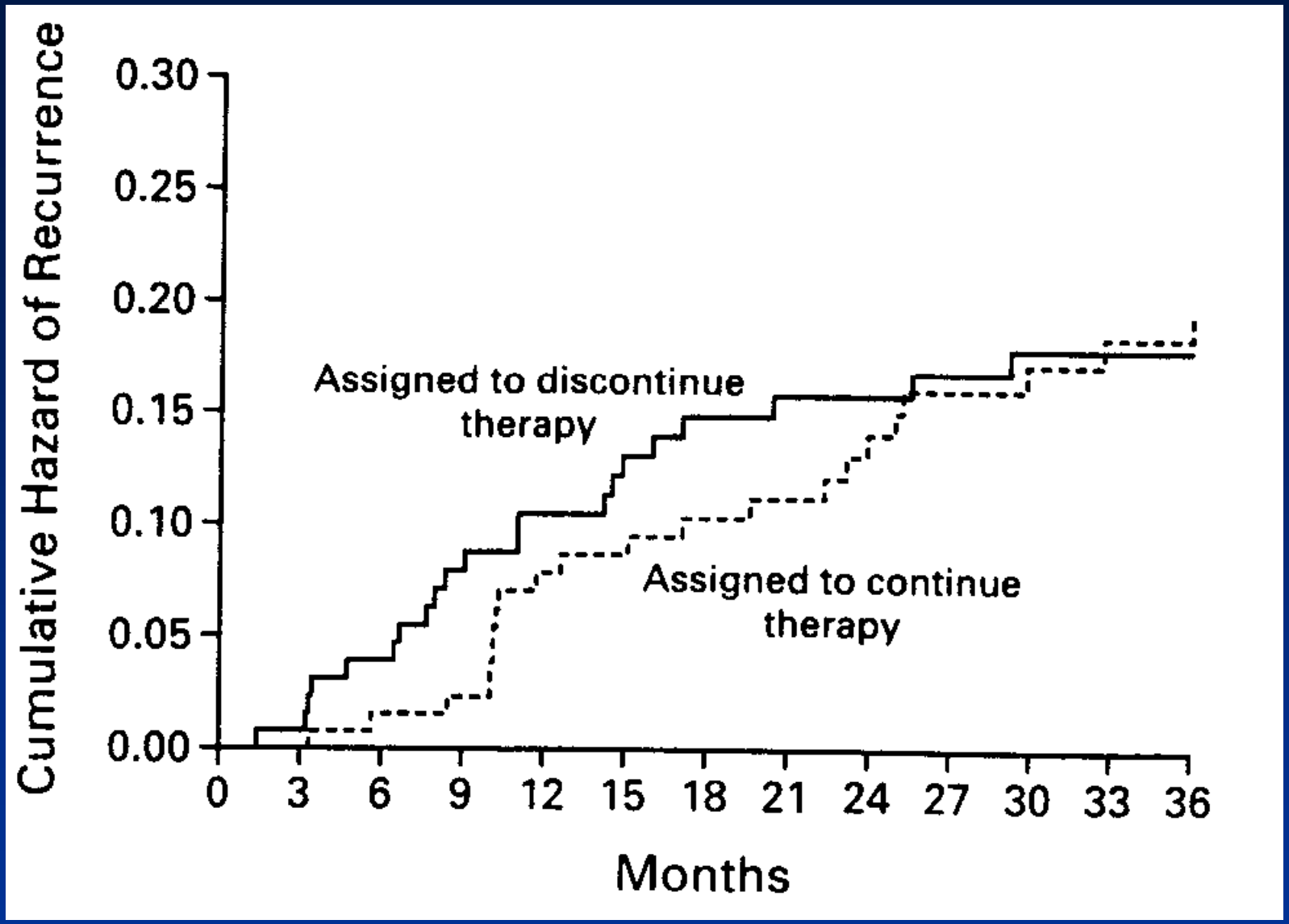
adjusted for age, sex, study, length of treatment before stopping anticoagulant, and location of initial VTE

Risks of VTE and of its treatment

- Recurrences= 17,5% (at 2 y); 24,6% (at 5 y); about 30% (at 10 y)
- VKAs (INR > 2.0) highly effective with a risk reduction 90%
- Major bleeding during VKAs = 1-2%
  fatal 0,25% **(ISCOAT study, Lancet 1996)**

La Durata: fattori da considerare

1. Qualsiasi sia la sua durata, la terapia AC protegge fin quando è in corso, ma non dopo la sua interruzione
2. Qual è il livello di recidive che può essere accettato per non dare AC?
3. Come valutare il rischio di recidiva?

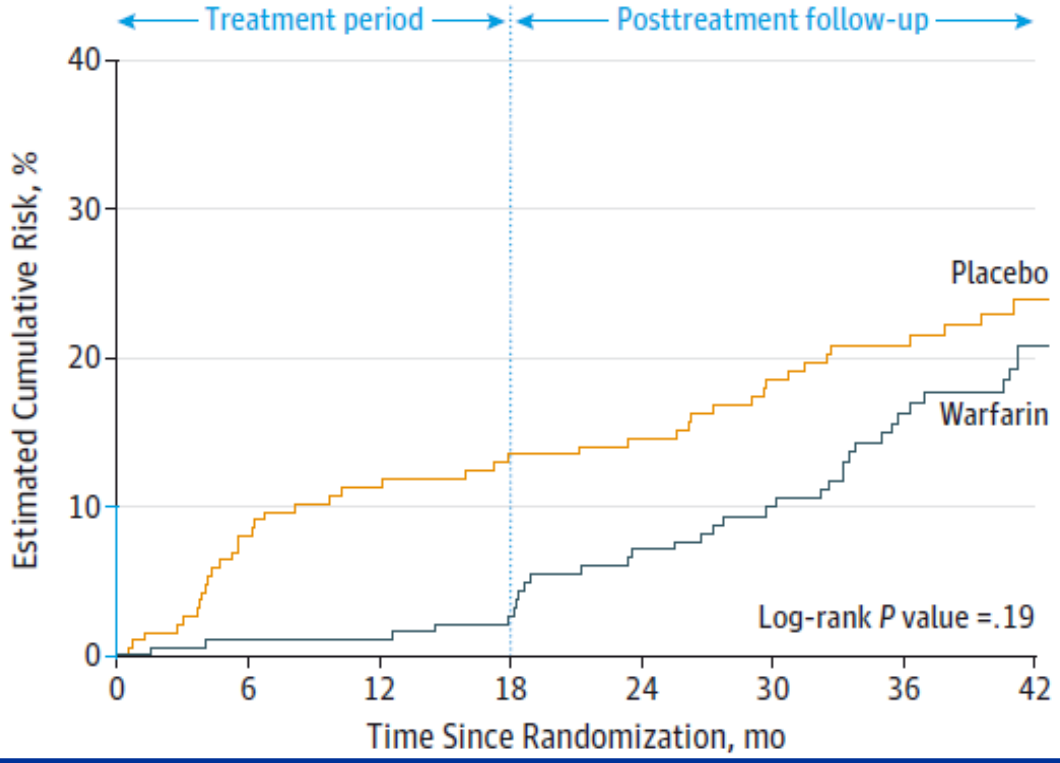


Agnelli et al., NEJM 2001

Six Months vs Extended Oral Anticoagulation After a First Episode of Pulmonary Embolism
The PADIS-PE Randomized Clinical Trial

Couturaud et al.
JAMA 2015

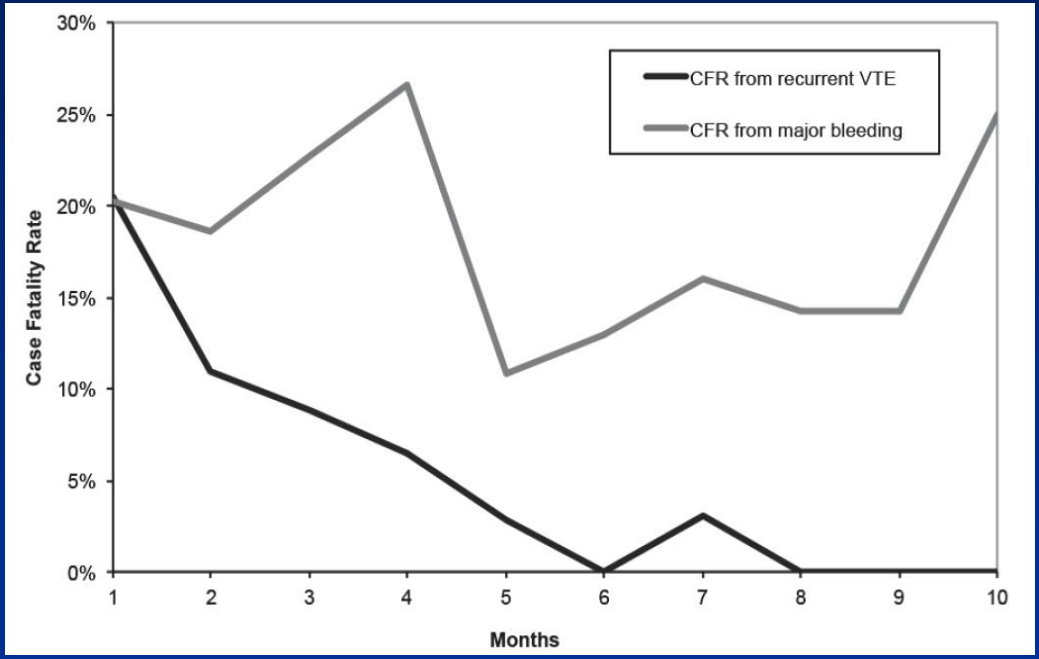
Figure 2. Probability of the Composite Outcome of Recurrent Venous Thromboembolism and Major Bleeding Throughout the Study Period



Dynamics of case-fatalilty rates of recurrent thromboembolism and major bleeding in patients treated for venous thromboembolism

Ramón Lecumberri[1]; Ana Alfonso[1]; David Jiménez[2]; Carmen Fernández Capitán[3]; Paolo Prandoni[4]; Philip S. Wells[5]; Gemma Vidal[6]; Giovanni Barillari[7]; Manuel Monreal[8]; and the RIETE investigators*

T&H 2013



The case-fatality rate of recurrent VTE decreases over time during anticoagulation, while that of major bleeding remains stable

Journal of Thrombosis and Haemostasis, **8**: 2313–2315 DOI: 10.1111/j.1538-7836.2010.03991.x

OFFICIAL COMMUNICATION OF THE SSC

Risk of recurrent venous thromboembolism after stopping treatment in cohort studies: recommendation for acceptable rates and standardized reporting

C. KEARON,* A. IORIO† and G. PALARETI‡ ON BEHALF OF THE SUBCOMMITTEE ON CONTROL OF ANTICOAGULATION OF THE SSC OF THE ISTH

What is an acceptable risk of recurrence after stopping anticoagulant therapy for VTE?

We suggest that a recurrence rate of 5% at 1 year and 15% at 5 years would justify stopping anticoagulant therapy,

Come calcolare il rapporto rischio/beneficio:
(Keeling Br J Haematol 2013)

- Casefatality rate delle recidive = circa 5% (Douketis et al, 2007; Carrier et al, 2010)
- Emorragie fatali durante warfarin = 0,25% anno (Palareti et al, 1996; Linkins et al, 2003; Carrier et al, 2010)
- Un'incidenza di recidive del 5% per anno è il punto di pareggio
- Se i DOAC provocano meno emorragie fatali l'obiettivo di incidenza di recidive può essere più basso

Risk of Recurrence After a First Episode of Symptomatic Venous Thromboembolism Provoked by a Transient Risk Factor

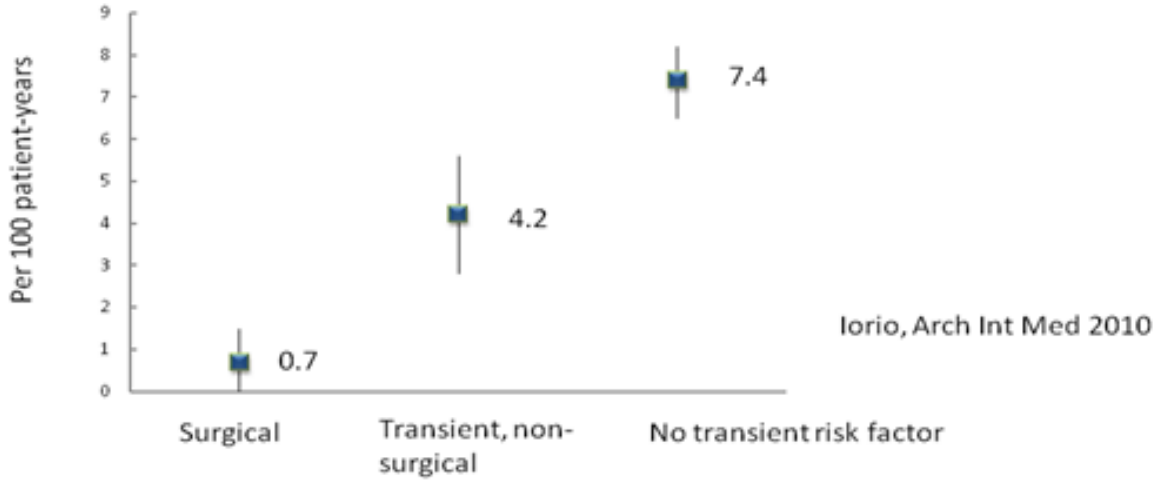
A Systematic Review

Arch Intern Med 2010

Alfonso Iorio, MD; Clive Kearon, MD; Esmeralda Filippucci, MD; Maura Marcucci, MD; Ana Macura, MD; Vittorio Pengo, MD; Sergio Siragusa, MD; Gualtiero Palareti, MD

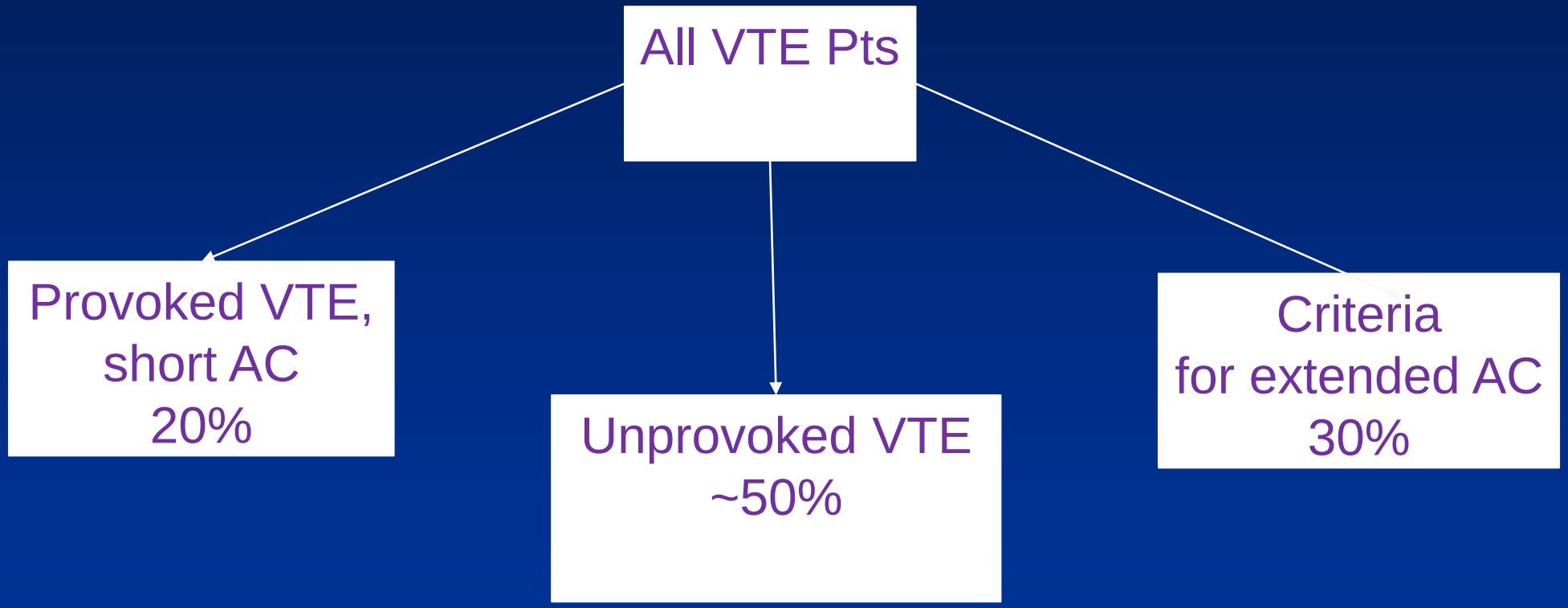
Transient risk factors

- Meta-analysis of 11 studies into incidence of recurrence:
- Incidence of recurrence in first 2 yrs after 1st VT:



Iorio, Arch Int Med 2010

Example of distribution of VTE patients examined for deciding the long-term treatment



Criteri per AC corta

- TEV dopo chirurgia maggiore (entro 3 mesi)
- TEV dopo allettamento prolungato (≥ 4 g)
- TEV dopo trauma maggiore (entro 3 mesi)
- TEV dopo gessi o immobilizzazione (entro 3 mesi)
- TVP distale isolata o TVS

- Alto rischio emorragico

Criteri per AC permanente

- ≥ 2 episodi documentati di TEV (TVP prossimale e/o EP)
- Cancro attivo o malattie ematologiche
- Trombofilia maggiore
- Sindrome da anticorpi antifosfolipidi
- EP con shock o grave e prolungata ipotensione a rischio vitale
- Ipertensione polmonare
- Severa insufficiency cardio-respiratoria (NYHA 3 or 4)
- Altre indicazioni per anticoagulazioen

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

2016

In patients with proximal DVT or PE, we recommend long-term (3 months) anticoagulant therapy over no such therapy (Grade 1B).

“In patients with a first unprovoked proximal DVT of the leg or PE who have a low or moderate bleeding risk, we suggest extended anticoagulant therapy (no scheduled stop date) (Grade 2B)”

Risk Factors for Recurrent VTE

Male sex
Increasing age
Idiopathic VTE/absence of a transient risk factor (ie, bed rest, major surgery, trauma requiring cast, pregnancy/postpartum, oral contraception, hormone replacement therapy)
Multiple VTE
Location of first VTE (PE>proximal DVT>distal DVT)
Abnormal D-dimer level after cessation of anticoagulation
Residual vein thrombosis after anticoagulation
Continued hormonal therapy/estrogen use
Malignancy
Thrombophilias*

2008

Journal of Thrombosis and Haemostasis, **6**: 577–582 DOI: 10.1111/j.1538-7836.2008.02889.x

ORIGINAL ARTICLE

Unprovoked recurrent venous thrombosis: prediction by D-dimer and clinical risk factors

T. BAGLIN,* C. R. PALMER,† R. LUDDINGTON* and C. BAGLIN*

[redacted] Cox proportional hazards modelling of the likelihood of unprovoked recurrent thrombosis. The assumption of proportional hazards was satisfactory by graphical methods

	Hazards ratio	Lower 95% CI	Upper 95% CI	*P* value
Adjusted				
Positive D-dimer	2.00	1.01	3.94	0.046
Age at diagnosis	0.77	0.64	0.92	0.003
Male sex	2.88	1.38	6.01	0.005
First event unprovoked	1.92	0.97	3.78	0.06

*Age at diagnosis is per decade (i.e. hazard ratio relates to each 10-year increase in age).

Annals of Internal Medicine 2009 | ARTICLE

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

A Randomized Trial

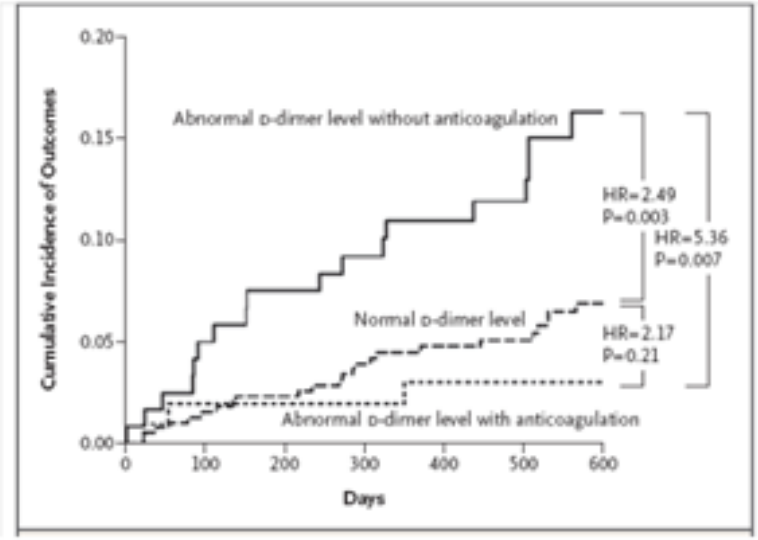
Paolo Prandoni, MD, PhD; Martin H. Prins, MD, PhD; Anthonie W.A. Lensing, MD, PhD; Angelo Ghirarduzzi, MD; Walter Ageno, MD; Davide Imberti, MD; Gianluigi Scannapieco, MD; Giovanni B. Ambrosio, MD; Raffaele Pesavento, MD; Stefano Cuppini, MD; Roberto Quintavalla, MD; and Giancarlo Agnelli, MD, for the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

Table 2. Characteristics of Recurrent Thromboembolism

Characteristic	Patients With Unprovoked DVT		Patients With Secondary DVT	
	Flexible OAT (n = 24)	Fixed OAT (n = 36)	Flexible OAT (n = 8)	Fixed OAT (n = 10)
Relation to vein status, n/n (%)				
Residual thrombosis	–	16/50 (32.0)	–	3/29 (10.3)
Early recanalization	–	20/101 (19.8)	–	7/88 (8.0)

Elevated D-dimer levels after AC is stopped are associated with increased risk of VTE recurrence

D-Dimer and recurrence



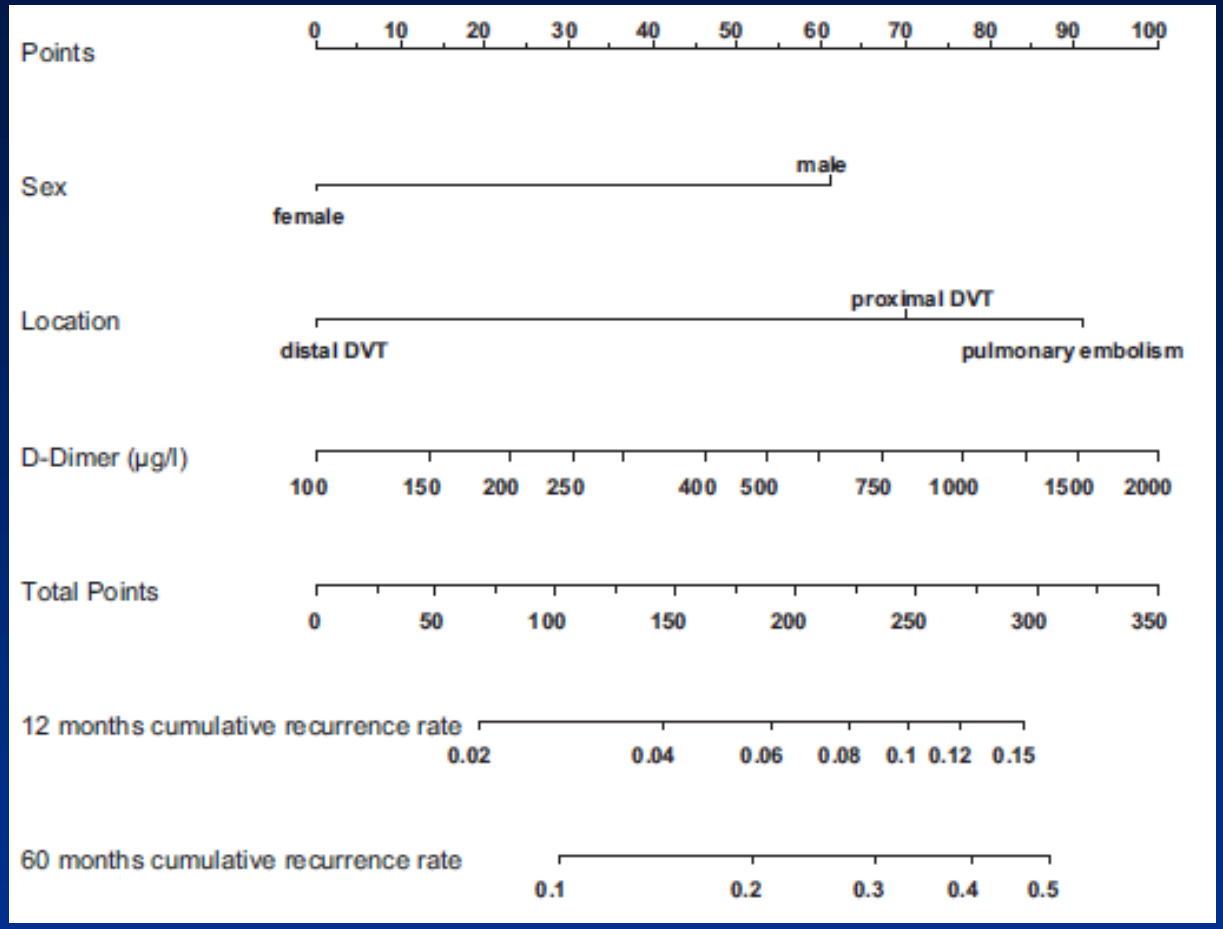
Meta-analysis:

Abnormal D-dimer:
8.9% per year

Normal D-dimer:
3.5% per year

Palareti, NEJM 2006

Verhovsek, Ann Intern Med 2008



The Vienna nomogram to estimate the probability of recurrence (Eichinger et al., Circulation 2010);
recently validated (Marcucci et al., JTH in print)

Journal of Thrombosis and Haemostasis, **10**: 1019–1025

Predicting disease recurrence in patients with previous unprovoked venous thromboembolism: a proposed prediction score (DASH)

A. TOSETTO, * A. IORIO, † M. MARCUCCI, ‡ T. BAGLIN, § M. CUSHMAN, ¶ S. EICHINGER, **
G. PALARETI, †† D. POLI, ‡‡ R. C. TAIT§§ and J. DOUKETIS¶¶

JTH
2012

Individual patient data meta-analysis of 7 prospective studies,
1818 pts

DASH score=	points
Abnormal D-dimer after stopping anticoagulation	2
Age < 50 years	1
Male sex	1
VTE associated with hormonal therapy (in women)	-2

Journal of Thrombosis and Haemostasis, **10**: 1019–1025

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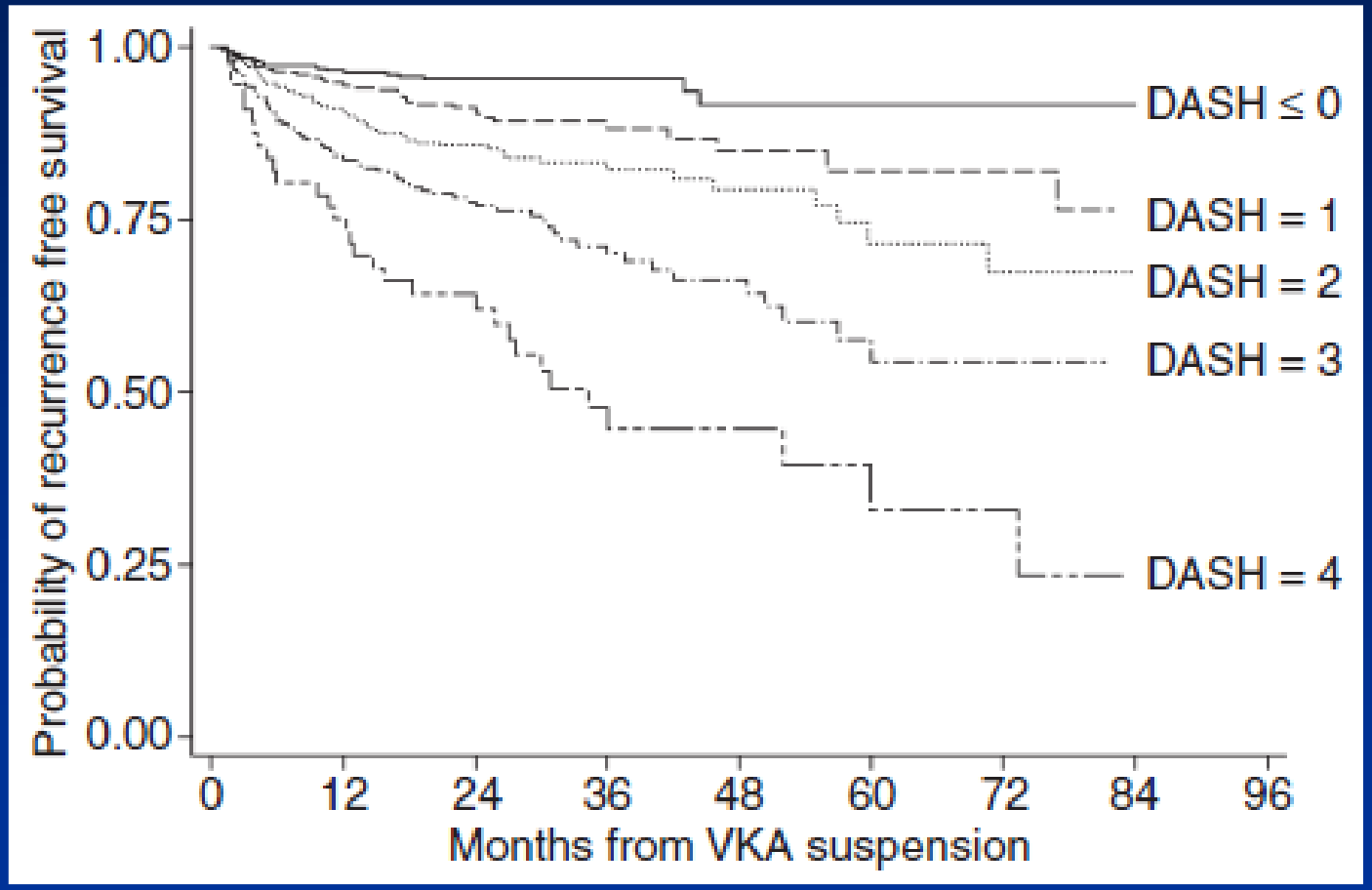
JTH
2012

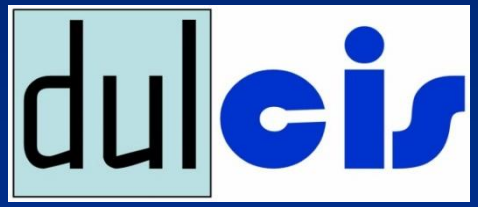


CLINICAL TRIALS AND OBSERVATIONS

D-dimer to guide the duration of anticoagulation in patients with venous thromboembolism: a management study

Gualtiero Palareti,[1] Benilde Cosmi,[1] Cristina Legnani,[1] Emilia Antonucci,[2] Valeria De Micheli,[3] Angelo Ghirarduzzi,[4] Daniela Poli,[2] Sophie Testa,[5] Alberto Tosetto,[6] Vittorio Pengo,[7] and Paolo Prandoni,[8] on behalf of the DULCIS (D-dimer and ULtrasonography in Combination Italian Study) Investigators

Blood 2014



PROCEDURE

- At least 3 mo. of AC
- 1 year AC if RVT in the leg
- Then DD were measured serially for the first 3 mo. after AC withdrawal
- Commercial DD assays
- DD cut-offs specifically determined for sex and age
- AC resumption recommended at first positive DD
- AC stopped definitively in pts with always negative DD

CLINICAL TRIALS AND OBSERVATIONS

Blood 2014

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Clinical events occurred in the investigated patients

	Negative D-dimer, no anticoagulation (n = 528; 829 y)*	Positive D-dimer, anticoagulation refused (n = 109; 171 y)*	Positive D-dimer, anticoagulation resumed (n = 373; 601 y)*
Primary outcomes, n, % (95% CI)	25 (4.7%; 3.2-6.9)	15 (13.8%; 7.9-21.7)§	4 (1.1%; 0.3-2.7)
Incidence per 100 pt-y, % (95% CI)	3.0% (2.0-4.4)	8.8% (5.0-14.1)¶	0.7% (0.2-1.7)
Major bleeding, n, % (95% CI)	0	0	14‡ (3.7%; 2.1-6.2)
Incidence per 100 pt-y, % (95% CI)			2.3% (1.3-3.9)

CLINICAL TRIALS AND OBSERVATIONS

Blood 2014

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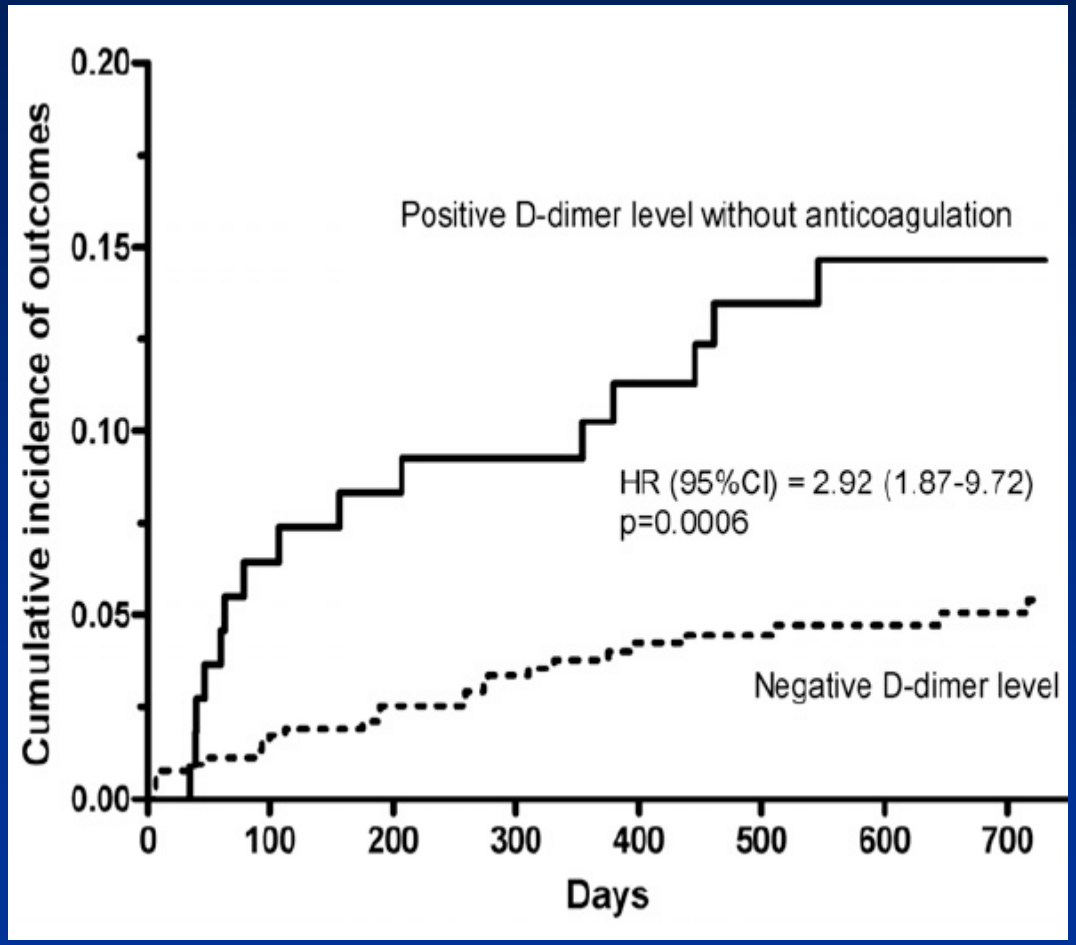
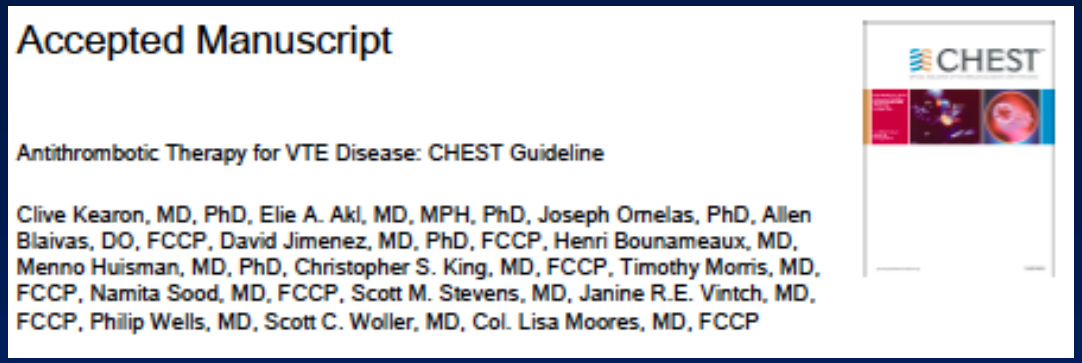


Duration of anticoagulation after isolated pulmonary embolism

Gualtiero Palareti[1], Benilde Cosmi[2], Emilia Antonucci[3], Cristina Legnani[2], Nicoletta Erba[4], Angelo Ghirarduzzi[5], Daniela Poli[6], Sophie Testa[7], Alberto Tosetto[8], Vittorio Pengo[9] and Paolo Prandoni[10] for the DULCIS investigators[11]

Eur Resp J 2016

	In pts with Neg. D-dimer % (stopped AC)	In pts with Pos. D-dimer % (refused AC)
DVT	4.2% (12/285)	15.1% (8/53)
DVT+symptom. PE	6.2% (6/97)	7.7% (2/26)
Isolated PE	4.8% (7/146)	20.0 % (6/30)


Accepted Manuscript

Antithrombotic Therapy for VTE Disease: CHEST Guideline

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2016

CHEST: Criteria to Help Stratify Risk of Recurrence in Unprovoked Patients at Non-high Risk of Bleeding

Sex

- Men have about a 75% higher (1.75-fold) risk of recurrence compared to women

D-dimer

- A positive D-dimer result measured about one month after stopping AC therapy is associated with about double the risk of recurrence

Chest 2016

TABLE 11] Risk Factors for Bleeding with Anticoagulant Therapy and Estimated Risk of Major Bleeding in Low-, Moderate-, and High-Risk categories[a]

Risk Factors[b]
Age >65 y[184-193]
Age >75 y[184-188,190,192,194-202]
Previous bleeding[185,191-193,198,201-204]
Cancer[187,191,195,198,205]
Metastatic cancer[181,204]
Renal failure[185,191-193,196,199,201,206]
Liver failure[186,189,195,196]
Thrombocytopenia[195,204]
Previous stroke[185,192,195,207]
Diabetes[185,186,196,200,202]
Anaemia[185,189,195,198,202]
Antiplatelet therapy[186,195,196,202,208]
Poor anticoagulant control[189,196,203]
Comorbidity and reduced functional capacity[191,196,204]
Recent surgery[189,209,c]
Frequent falls[195]
Alcohol abuse[191,192,195,202]
Nonsteroidal anti-inflammatory drug[210]

Low risk (no bleeding factors) = 0.8%/y major bleeding
Moderate (one bleeding factor) = 1.6%/y " "
High (two or more factors) = ≥6.5%/y " "

Circulation

American Heart Association.

2014

Aspirin for the Prevention of Recurrent Venous Thromboembolism: The INSPIRE Collaboration

John Simes, Cecilia Becattini, Giancarlo Agnelli, John W. Eikelboom, Adrienne C. Kirby, Rebecca Mister, Paolo Prandoni and Timothy A. Brighton
for the INSPIRE Study Investigators* (International Collaboration of Aspirin Trials for Recurrent Venous Thromboembolism)

The WARFASA and the ASPIRE trials showed that aspirin reduces this risk of recurrence, but they were not individually powered to detect treatment effects for particular outcomes or subgroups.

Year	Events (n/N) Placebo	Aspirin	Event rate (%) Placebo	Aspirin	HR (95% CI)	*P* for trend
1	60/608	31/616	11.0	5.4		0.31
2	25/489	26/531	2.7	2.6		
3	18/378	15/412	1.7	1.3		
4	9/240	9/259	1.0	0.9		
All	112/608	81/616	7.5	5.1		

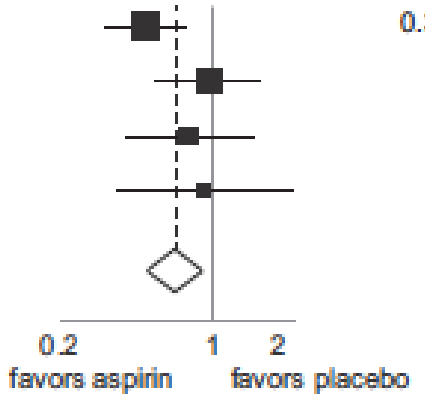

Figure 6. Effects of treatment on venous thromboembolism in each year of follow-up.

32% relative reduction in VTE (HR, 0.68; CI, 0.51–0.90; P=0.008)

Bleeding = 0.7%/y for placebo and 1.1% /y for aspirin

Sulodexide for the Prevention of Recurrent Venous Thromboembolism

The Sulodexide in Secondary Prevention of Recurrent Deep Vein Thrombosis (SURVET) Study: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial

Andreozzi et al.
Circulation 2015

Table 2. Number of Outcome Events According to Study Group

Event	Sulodexide (n=307)	Placebo (n=308)	Hazard Ratio (95% CI)	*P* Value
Recurrent VTE				
Total episodes	15	30	0.49 (0.27–0.92)	0.025
Pulmonary embolism	3	6	0.49 (0.12–1.97)	0.32
Deep vein thrombosis	12	24	0.49 (0.25–0.99)	0.045
Bleeding				
Clinically relevant nonmajor bleeding	2	2	0.97 (0.14–6.88)	0.98

Current options for prevention of VTE recurrence

Risk of recurrent VTE and of clinically relevant bleeding vs placebo

Study	Treatment	Treatment duration (months)	Risk of recurrent VTE vs. placebo		Risk of clinically relevant bleeding vs. placebo	
SURVET	Sulodexide	24	0.4 [0.27–0.92]	p=0.02	0.97 [0.14–6.88]	p=0.98
ASPIRE+WARFASA	Aspirin	24 (48)	0.68 [0.51–0.90]	p=0.008	1.50 [0.72–3.14]	p=0.28
RE-SONATE	Dabigatran	6	0.08 [0.02–0.25]	p<0.01	2.92 [1.52-5.60]	p=0.001
EINSTEIN-EXT	Rivaroxaban	12	0.18 [0.09–0.39]	p<0.001	5.19 [2.13–11.7]	p<0.001
AMPLIFY-EXT	Apixaban (2.5 mg)	12	0.19 [0.11–0.33]	-	1.20 [0.69-2.10]	NA
AMPLIFY-EXT	Apixaban (5 mg)	12	0.20 [0.11–0.34]	-	1.62 [0.96-2.73]	NA

Individual risk assessment

- Low → No AC
- Moderate (?) personal pref. → Sulodex., ASA, AC (?)
- High → AC; preferably low bleed risk → Contraind. to AC= Sulodex., ASA