



ATBV

GRUPPO DI STUDIO ATEROSCLEROSI, TROMBOSI, BIOLOGIA VASCOLARE



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Brescia

Le *dieci* cose da non dimenticare dell'embolia polmonare

Iseo, 10 novembre 2018

Iseo, 10 novembre 2018

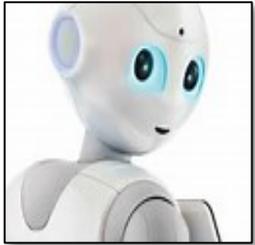
La prima

La memoria

I grandi maestri



In futuro potremmo forse trovarci di fronte ad osservazioni come questa: “In un cardiologo di 100 anni che ritornava a casa da un congresso un sensore collocato nella vena iliaca sinistra ha rivelato un incremento del tasso del frammento protrombinico 1+2. Un controllo per l’identificazione di un’eventuale trombofilia, eseguito alla porta di imbarco all’inizio del viaggio, era risultato negativo. Un aumento dell’espressione locale dei recettori t-PA endoteliali mediante agopuntura ha ripristinato il normale equilibrio emocoagulativo ... e il paziente ha potuto raggiungere Marte senza ulteriori problemi...” (Case Reports: New Trends in Managing Economy Class Syndrome. Eur Heart J, 2050).



Considerate la vostra semenza:...

Considerate la vostra semenza:...

Inferno, canto XXVI (vv.112-120)

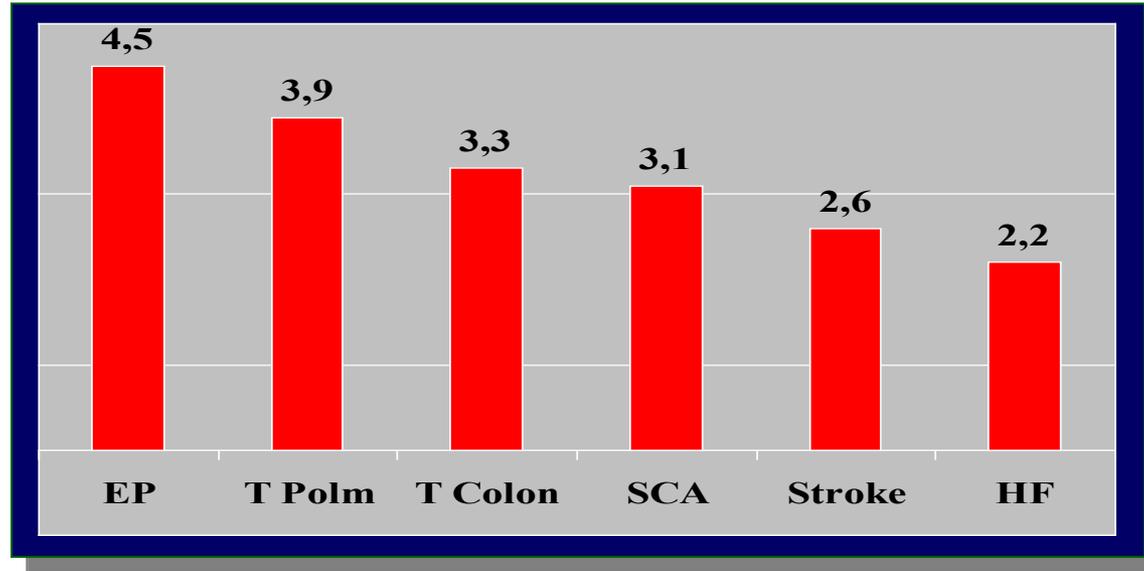
Inferno, canto XXVI (vv.112-120)

La seconda

La misura

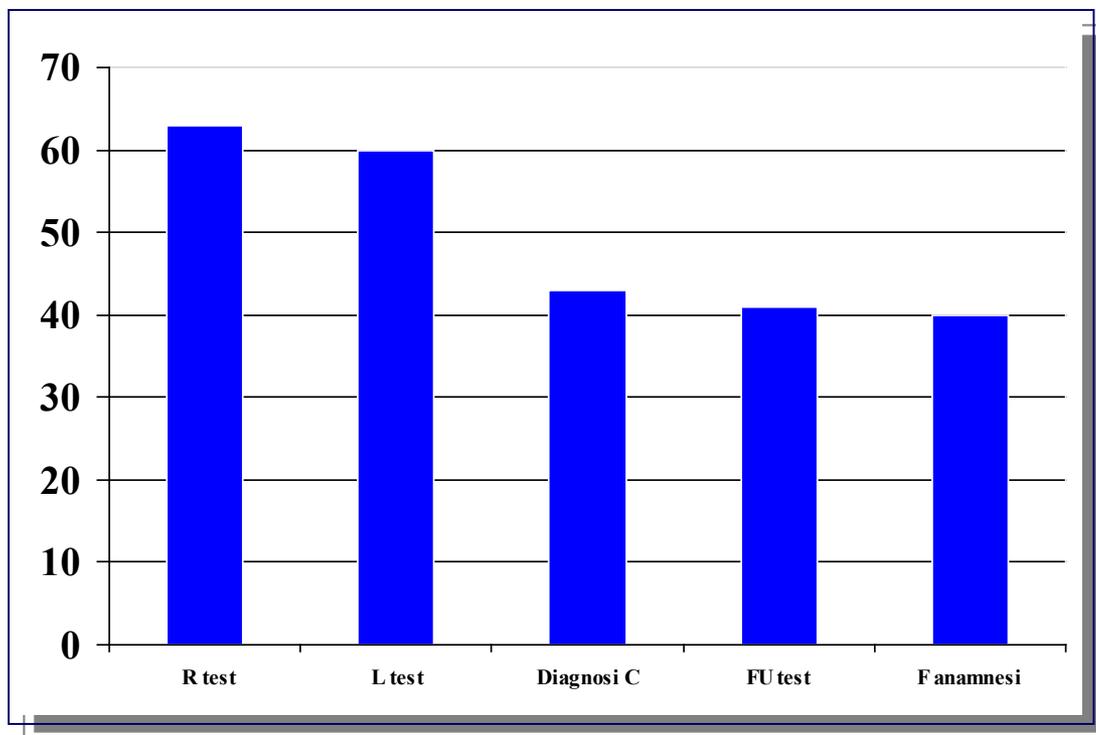
Diagnostic Error in Medicine

Analysis of 583 Physician-Reported Errors



Diagnostic Error in Medicine

Analysis of 583 Physician-Reported Errors



Analisi dei processi

7%

As estimated on the basis of an epidemiological model, over 317 000 deaths were related to VTE in six countries of the European Union (with a total population of 454.4 million) in 2004.² Of these cases, 34% presented with sudden fatal PE and 59% were deaths resulting from PE that remained undiagnosed during life; only 7% of the patients who died early were correctly diagnosed with PE before death.

The prevalence of confirmed PE in patients undergoing diagnostic work-up because of suspicion of disease has been rather low (10–35%) in large series.^{99,100,113,116,197}

10%-35%

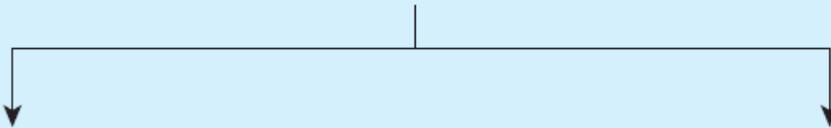
La terza

Il pensiero

Suspected PE without shock or hypotension



Assess clinical probability of PE
Clinical judgment or prediction rule^a



WELLS, PERC...

As the post-test (e.g. after computed tomography) probability of PE depends not only on the characteristics of the diagnostic test itself but also on pre-test probability, this has become a key step in all diagnostic algorithms for PE.



indici di *probabilità*

test *diagnostici*

test *prognostici*



indici di *probabilità*

Wells rule	Original version ¹⁵
Previous PE or DVT	1.5
Heart rate ≥ 100 b.p.m.	1.5
Surgery or immobilization within the past four weeks	1.5
Haemoptysis	1
Active cancer	1
Clinical signs of DVT	3
Alternative diagnosis less likely than PE	3

Clinical probability	
Three-level score	
Low	0-1
Intermediate	2-6
High	≥ 7
Two-level score	
PE unlikely	0-4
PE likely	≥ 5

Indice di Wells

indici di *probabilità*

The pulmonary embolism rule out criteria (PERC rule)*

Age <50 years

Heart rate <100 bpm

Oxyhemoglobin saturation $\geq 95\%$

No hemoptysis

No estrogen use

No prior DVT or PE

No unilateral leg swelling

No surgery/trauma requiring hospitalization within the prior four weeks

DVT: deep venous thrombosis; PE: pulmonary embolus; bpm: beats per minute.

* This rule is only valid in patients with a low clinical probability of PE (gestalt estimate <15 percent).

In patients with a low probability of PE who fulfill all eight criteria, the likelihood of PE is low and no further testing is required. All other patients should be considered for further testing with sensitive D-dimer or imaging.

Le regole di PERC

test *diagnostici*

D-dimero

TAC

Scintigrafia

(*Ecocardiogramma*)



test *prognostici*

TAC

Scintigrafia

Ecocardiogramma

ECG

Esami ematochimici

Parametri emodinamici

Score di rischio

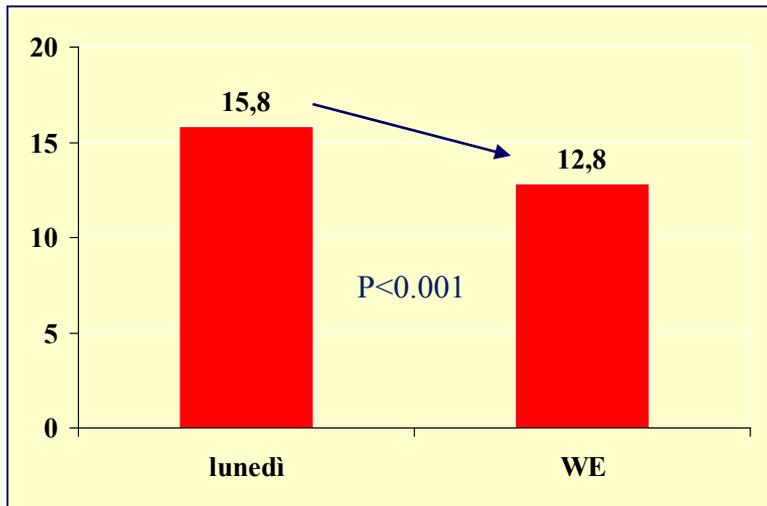
indici di *indicibilità*

?

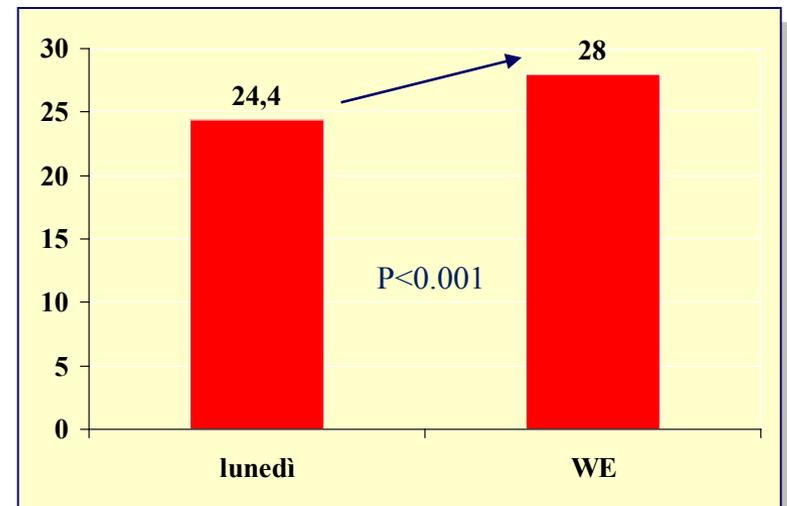
?

indici di *indicibilità*

Ricoveri per EP



Mortalità per EP



La quarta

La certezza

8.1.1 Diagnosis of pulmonary embolism in pregnancy

Exposure of the foetus to ionizing radiation is a concern when investigating suspected PE during pregnancy; although this concern is largely overruled by the hazards of missing a potentially fatal diagnosis. This is particularly true for pregnant patients with suspected high-risk PE. Moreover, erroneously assigning a diagnosis of PE to a pregnant woman is also fraught with risks, since it unnecessarily exposes the mother and foetus to the risks of anticoagulant treatment and will impact on delivery plans, future contraception, and thromboprophylaxis during future pregnancies. Therefore, investigations should aim at diagnostic certainty.

D-dimero → TC polmonare:

“Piccolo difetto di riempimento endoluminale sub occludente, da riferire a trombo a livello della diramazione dell’arteria polmonare per il segmento apicale del lobo superiore di destra”.

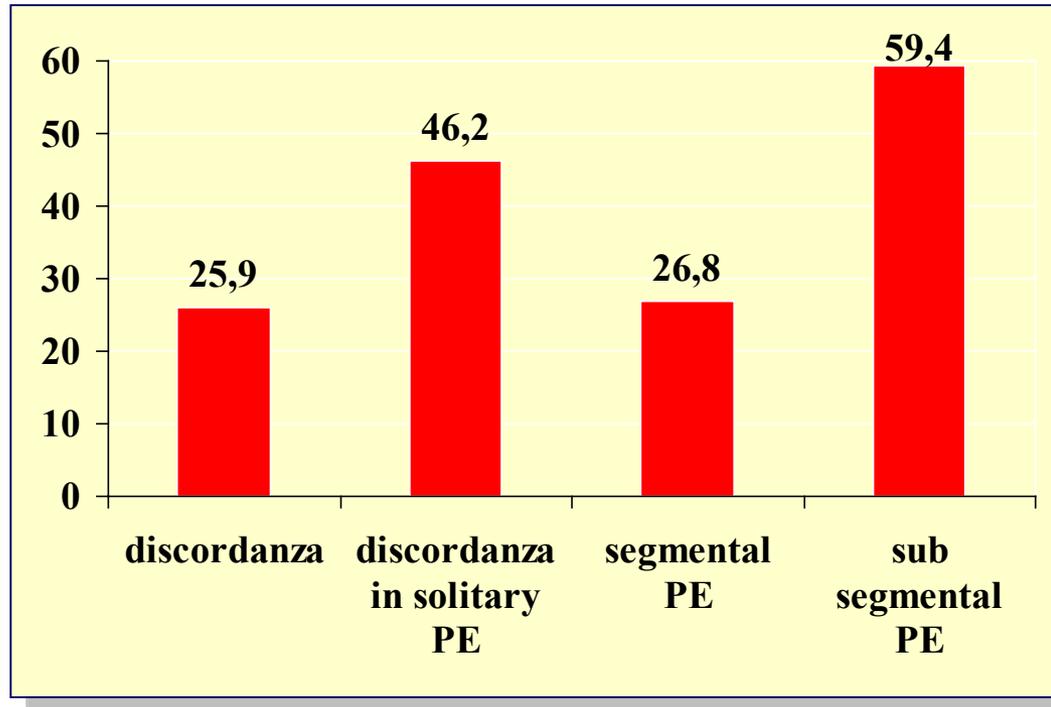


Carico di un NOAC e dimissione immediata?
Carico di un NOAC e ricovero?
Ricovero previo bolo di eparina non frazionata?
Altro?

Da noi, pochi mesi fa...

Da noi, pochi mesi fa...

discordanza nella diagnosi (TAC) di embolia polmonare



Hutchinson BD et al. Am J Roentgenol 2015;205:271

Hutchinson BD et al. Am J Roentgenol 2015;205:271



Un filtro sbagliato, eccessivamente duro...

Per cortesia del dr Dore, Pavia

PER CORTESIA DEL DR DORE, PAVIA

Una pillola e via? ...

Multidisciplinary Pulmonary Embolism Response Teams

David M. Dudzinski, MD, JD; Gregory Piazza, MD, MS



1 Within 30 minutes, a team consisting of representatives from Vascular Medicine, Interventional Cardiology, Cardiothoracic Surgery, Pulmonology, Echocardiography, and Radiology convened to evaluate the patient's case and review the imaging studies.

Una pillola e via? Sì, se...

Circulation 2016;133:98-103

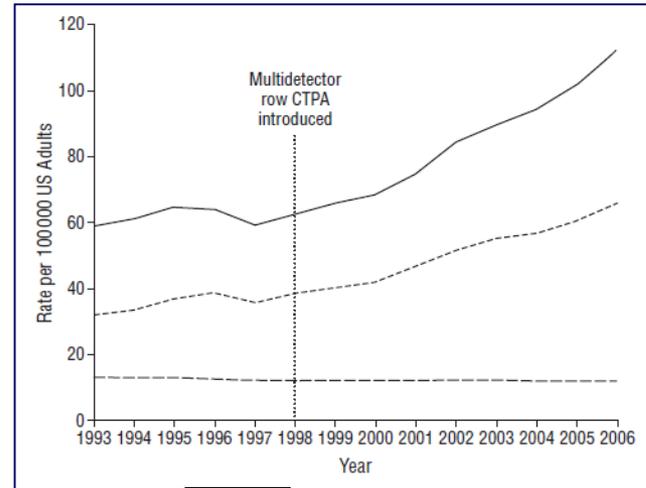
Circulation 2016;133:98-103

La quinta

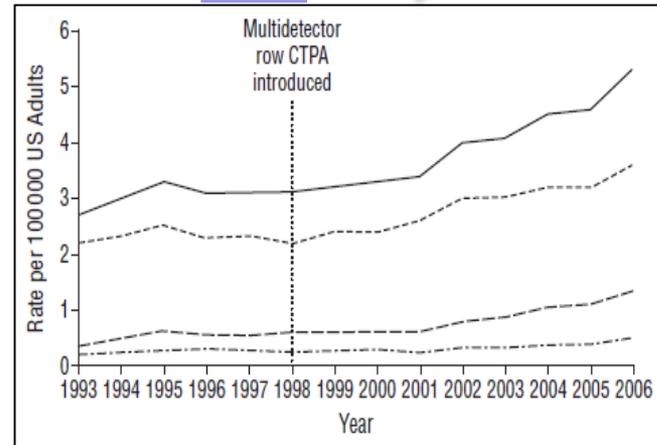
L'ossessione



overdiagnosis

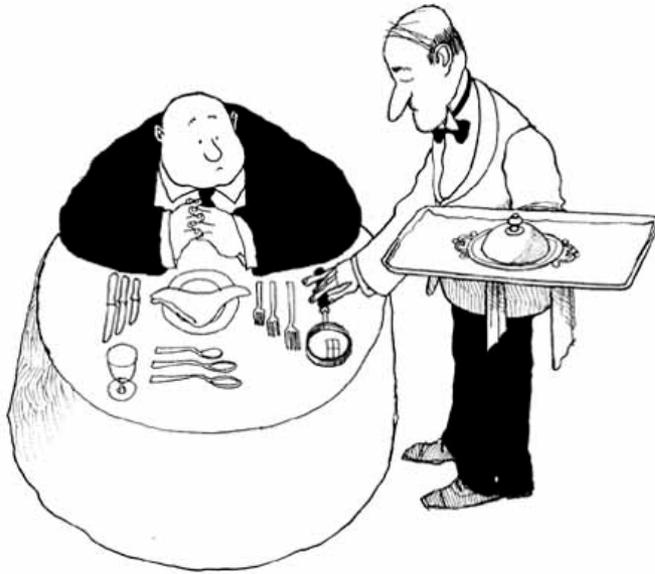


1998

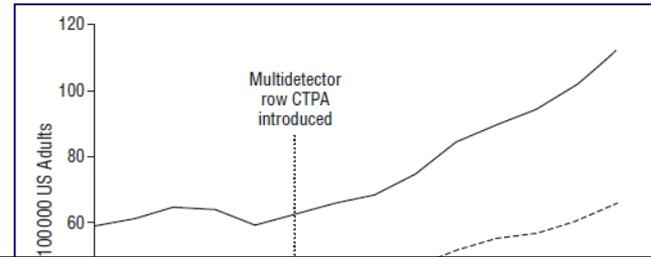


Weiner R.S. et al. Arch Intern Med 2011;171

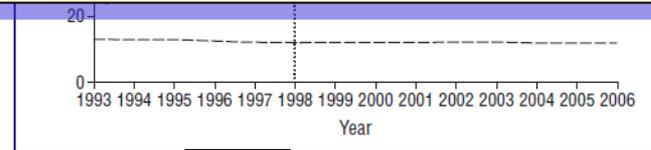
Weiner R.S. et al. Arch Intern Med 2011;171



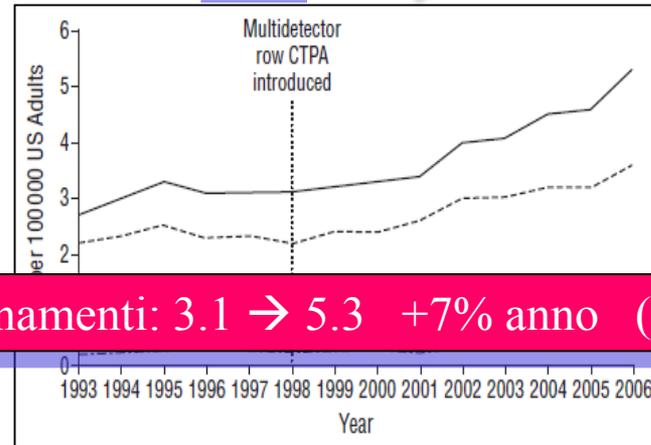
overdiagnosis



Mortalità, in 8 anni: 12.3% → 11.9% ns



1998



Sanguinamenti: 3.1 → 5.3 +7% anno (p<0.001)

Weiner R.S. et al. Arch Intern Med 2011;171

Weiner R.S. et al. Arch Intern Med 2011;171

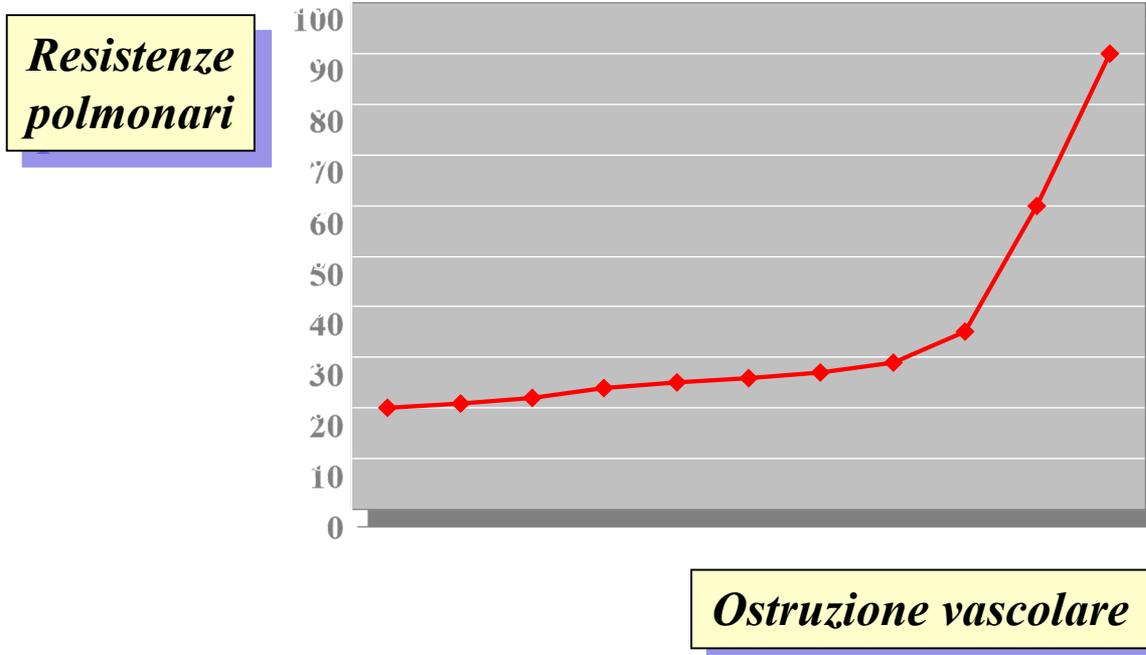


In addition to the papers cited by Wiener, one prospective study performed CT pulmonary angiography on asymptomatic patients on the first day after total hip arthroplasty or total knee arthroplasty.² One of 27 and 11 of 21 patients in the hip and knee replacement groups, respectively, had filling defects on their scan (not only restricted to ISSPE). All asymptomatic patients with filling defects were discharged without anticoagulation and none had an additional diagnosis of venous thromboembolism at three months' follow-up.

La sesta

La miopia

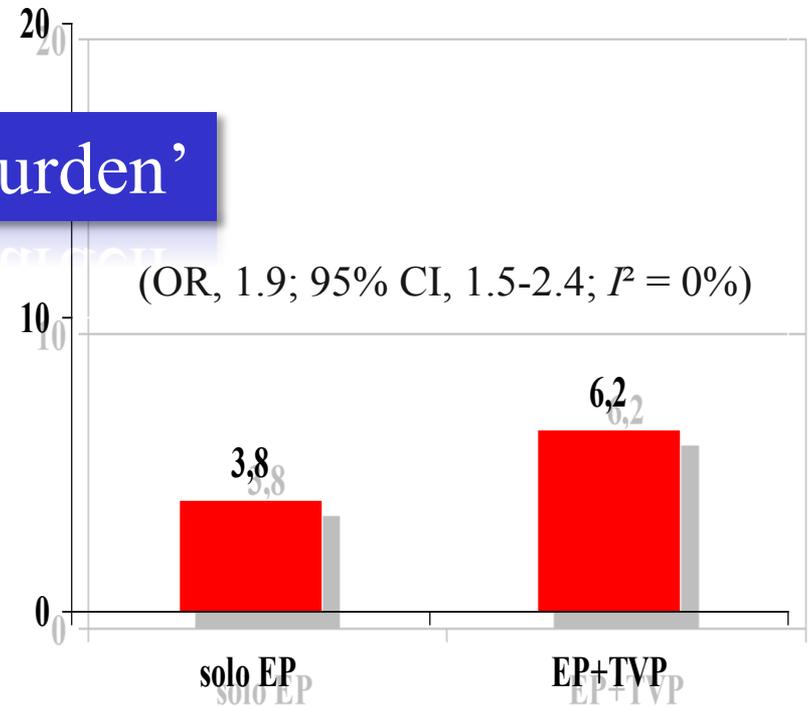
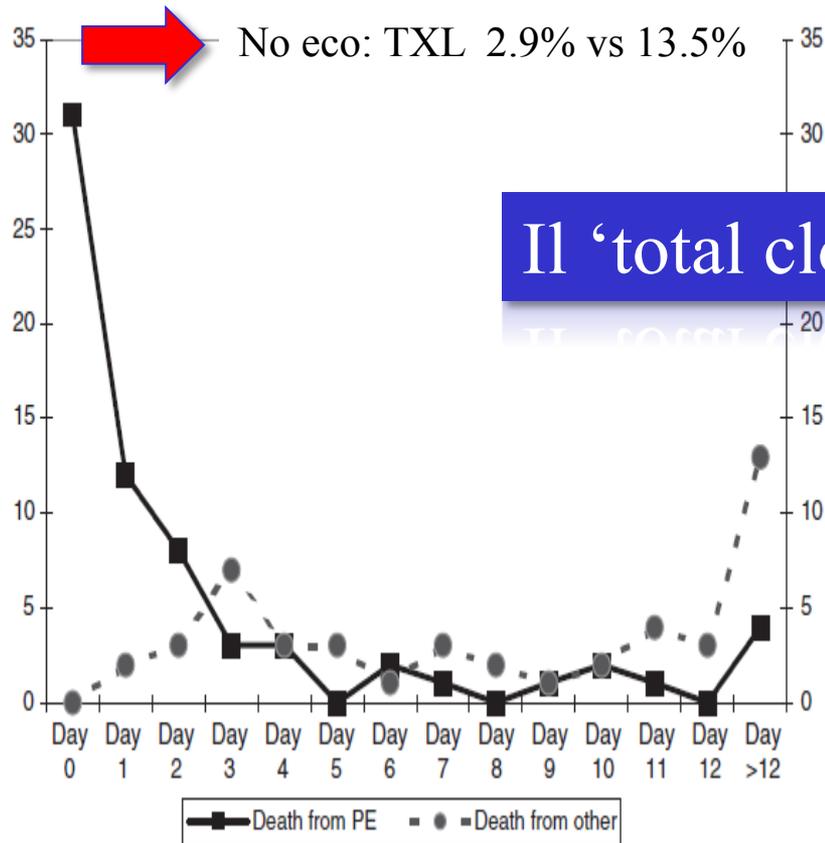
Non esistono embolie polmonari benigne,
ma soltanto prime embolie ben tollerate...



!

1 paziente su 4
non ha l'eco entro 48 h

Metanalisi su EP e TVP:
mortalità a 30 gg per tutte le cause*



IPER Thromb Res 2012;130: 847-852

Becattini C et al. Chest 2016;149(1)192:200

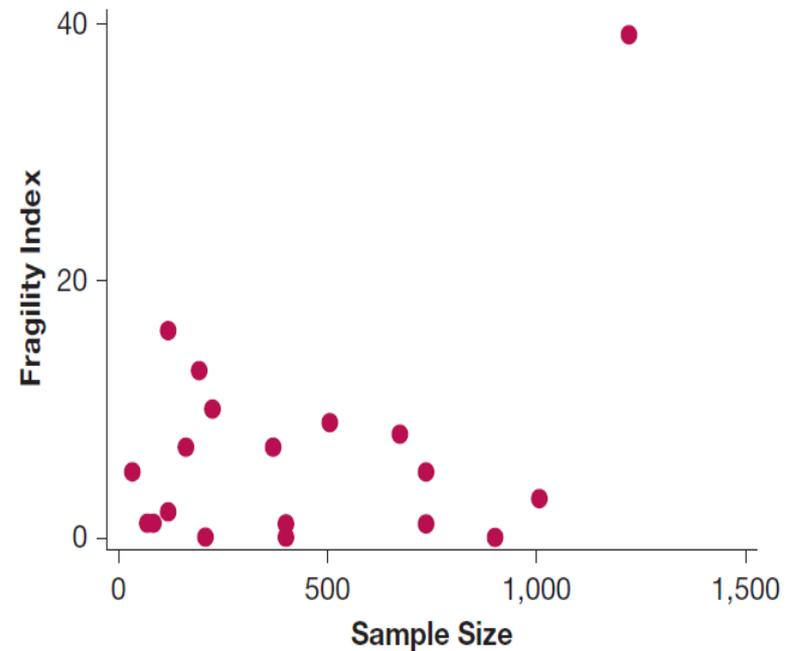
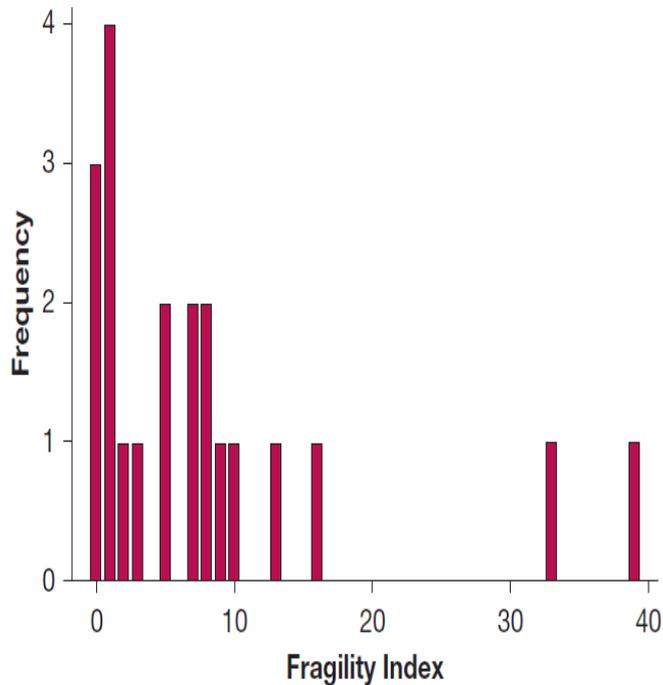
IPER Thromb Res 2012;130: 847-852

Becattini C et al. Chest 2016;149(1)192:200

La settimana

*l'insostenibile leggerezza
dell'evidenza e il pregiudizio*

How Fragile Are Clinical Trial Outcomes That Support the CHEST Clinical Practice Guidelines for VTE?



La fragilità...

Edwards E. et al. Chest 2018;154(3):512-520

Edwards E. et al. Chest 2018;154(3):512-520

Table 9 Classification of patients with acute PE based on early mortality risk

Early mortality risk		Risk parameters and scores			
		Shock or hypotension	PESI class III-V or sPESI >1 ^a	Signs of RV dysfunction on an imaging test ^b	Cardiac laboratory biomarkers ^c
High		+	(+) ^d	+	(+) ^d
Intermediate	Intermediate-high	-	+	Both positive	
	Intermediate-low	-	+	Either one (or none) positive ^e	
Low		-	-	Assessment optional; if assessed, both negative ^e	



ORIGINAL ARTICLE

Fibrinolysis for Patients with Intermediate-Risk Pulmonary Embolism

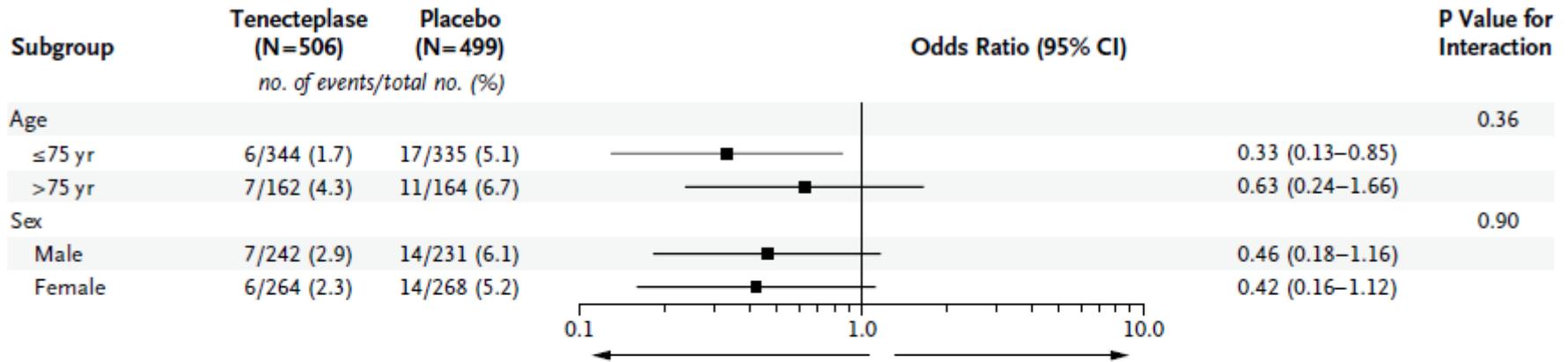
Guy Meyer, M.D., Eric Vicaut, M.D., Thierry Danays, M.D., Giancarlo Agnelli, M.D., Cecilia Becattini, M.D., Jan Beyer-Westendorf, M.D., Erich Bluhmki, M.D., Ph.D., Helene Bouvaist, M.D., Benjamin Brenner, M.D., Francis Couturaud, M.D., Ph.D., Claudia Dellas, M.D., Klaus EMPEROR, M.D., Francesco M. Fenucci, M.D., Nazzareno Galiè, M.D., Annette Geibel, M.D., Samuel G. Harbarth, M.D., David Jimenez, M.D., Ph.D., Matija Kozak, M.D., Christian 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*

Πειθώ

Mayer G. et al. N Engl J Med 10 aprile 2014

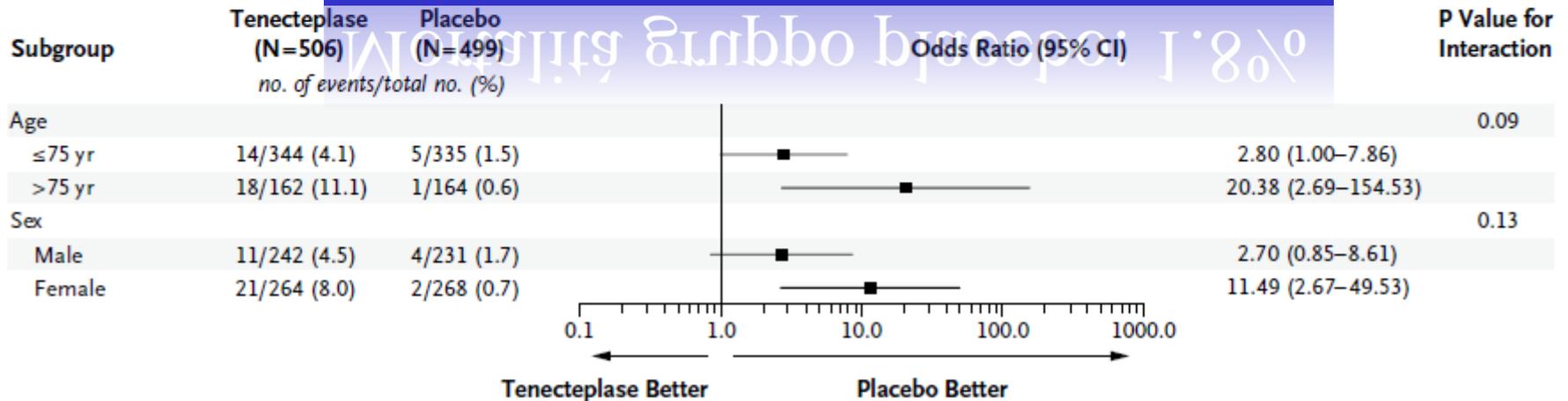
Μαγλι Γ. et al. Ν Engl J Med 10 Απριλίου 2014

A Death or Hemodynamic Decompensation



Mortalità gruppo placebo: 1.8%

B Major Extracranial Bleeding



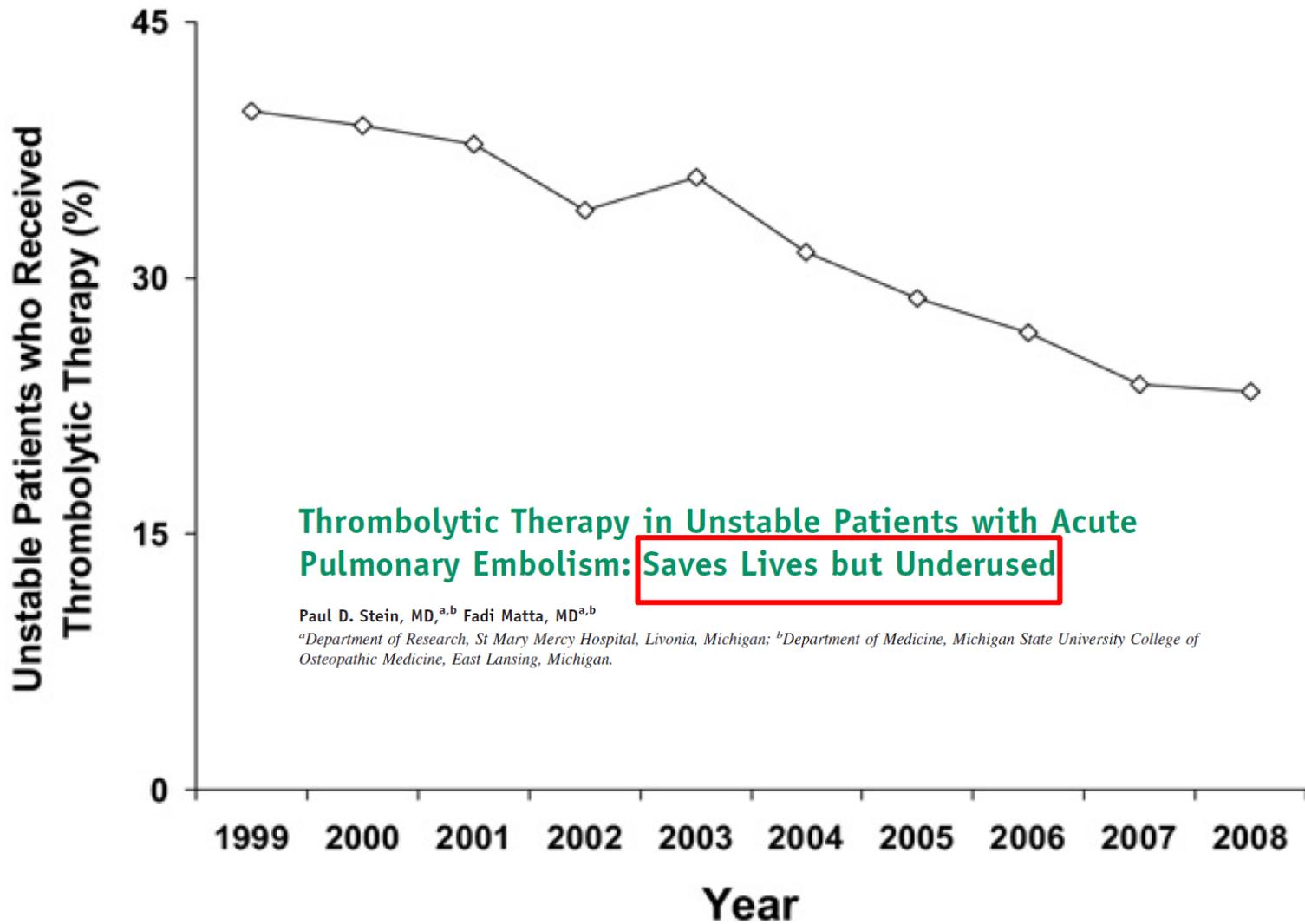
Mayer G. et al. N Engl J Med 10 aprile 2014

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Table 9 Classification of patients with acute PE based on early mortality risk

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Low		-	-	Assessment optional; if assessed, both negative ^e	

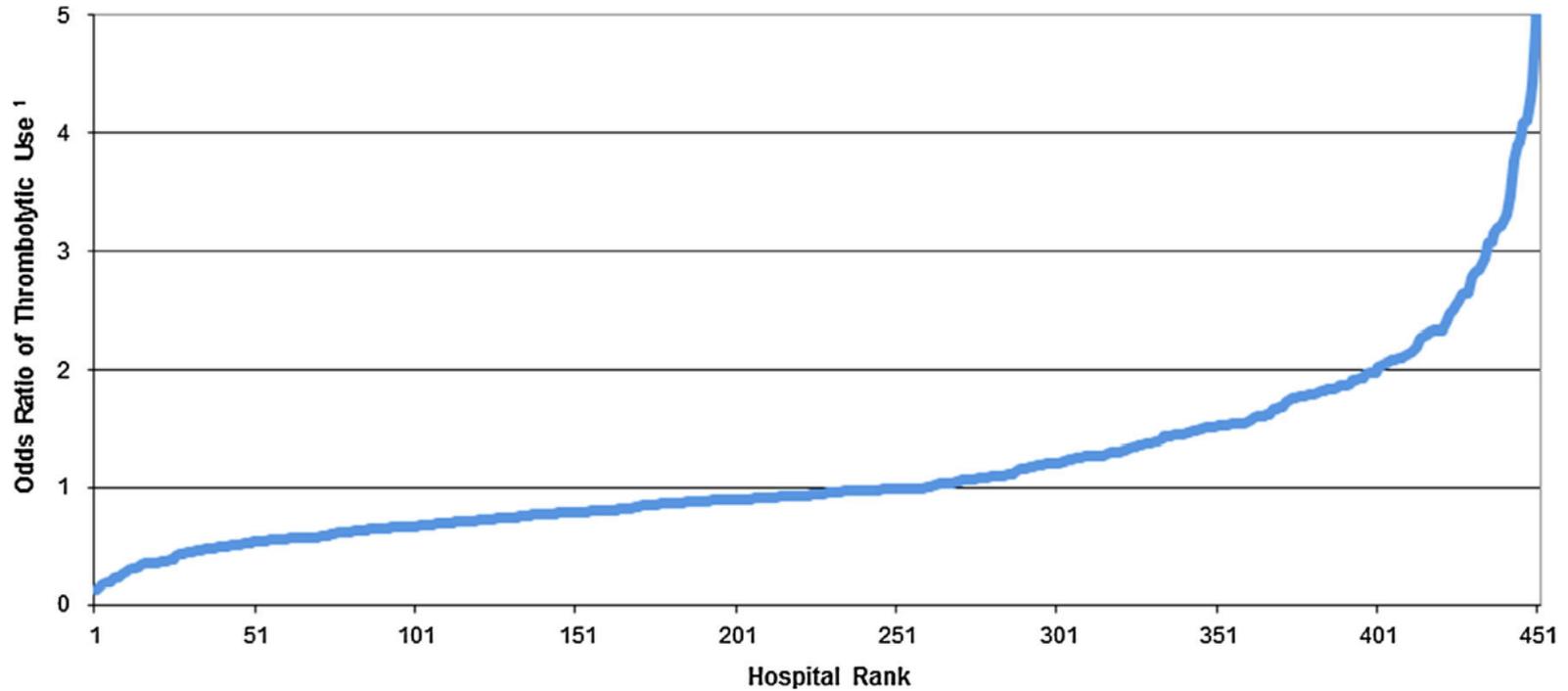




Stein P. et al, Am J Med 2012

Stein P. et al, Am J Med 2012

Hospital variation of thrombolytic use for PE



Bradford M.A. et al. J Thromb Thrombolysis 2016;42

Bradford M.A. et al. J Thromb Thrombolysis 2016;42

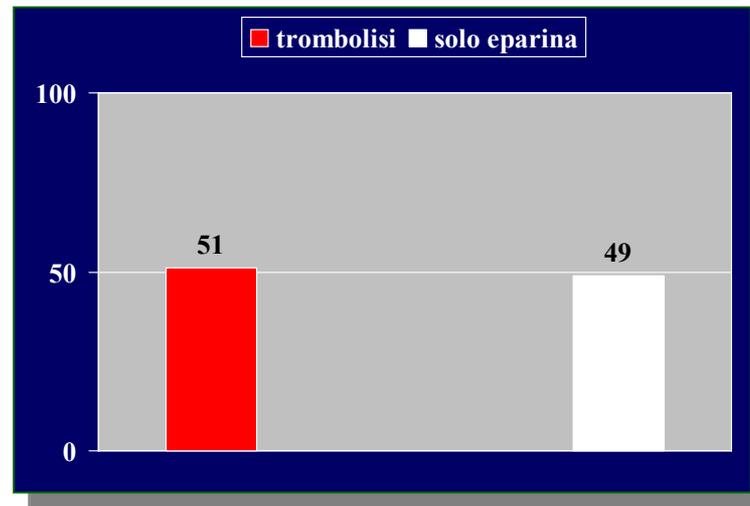


Regular Article

Clinical features and short term outcomes of patients with acute pulmonary embolism. The Italian Pulmonary Embolism Registry (IPER) [☆]

Franco Casazza ^{a,*}, Cecilia Becattini ^b, Amedeo Bongarzone ^a, Claudio Cuccia ^c, Loris Roncon ^d, Giuseppe Favretto ^e, Pietro Zonzin ^d, Luigi Pignataro ^a, Giancarlo Agnelli ^b

pazienti in shock



L'ottava

Non si è mai soli

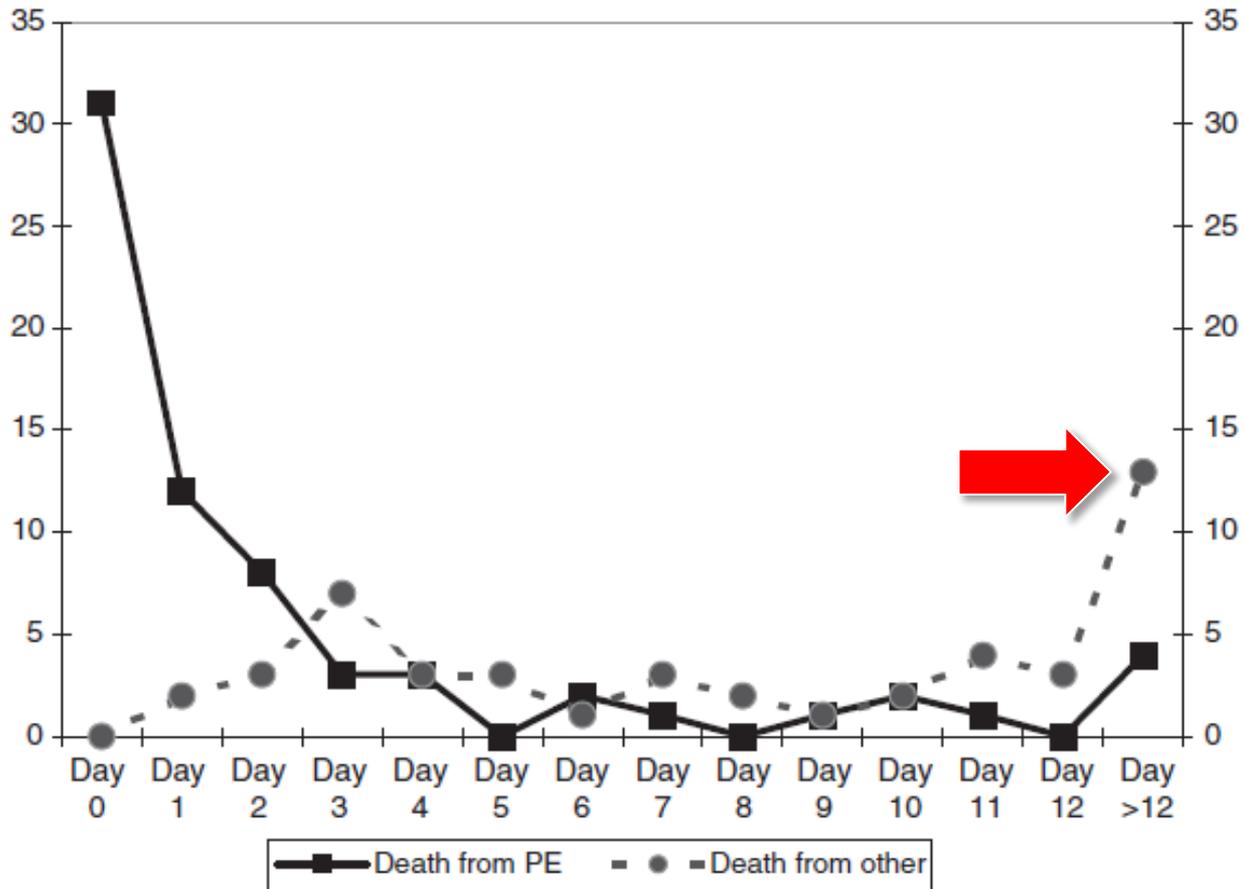
Watching Television and Risk of Mortality From Pulmonary Embolism Among Japanese Men and Women

The JACC Study (Japan Collaborative Cohort)

	Time Spent Watching Television, h/d			
	<2.5	2.5–4.9	≥5.0	Increment by 2 h (95% CI), P Value
Cases, n/person-y	19/678 199	27/562 449	13/157 922	
Mortality rate per 100 000 person-y	2.8	4.8	8.2	
Age- and sex-adjusted HR	1.0	1.6 (0.9–2.8)	2.4 (1.2–4.9)	1.3 (1.0–1.8), 0.06
Multivariable HR*	1.0	1.7 (0.9–3.0)	2.5 (1.2–5.3)	1.4 (1.0–1.8), 0.04

Circulation. 2016;134:355–357

Circulation. 2016;134:322–323



IPER Thromb Res 2012;130: 847-852

IPER Thromb Res 2012;130: 847-852

The NEW ENGLAND JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

AUGUST 20, 2015

VOL. 373 NO. 8

Screening for Occult Cancer in Unprovoked Venous Thromboembolism

Marc Carrier, M.D., Alejandro Lazo-Langner, M.D., Sudeep Shivakumar, M.D., Vicky Tagalakis, M.D.,
Ryan Zarychanski, M.D., Susan Solymoss, M.D., Nathalie Routhier, M.D., James Douketis, M.D.,
Kim Danovitch, C.C.R.P., Agnes Y. Lee, M.D., Gregoire Le Gal, M.D., Philip S. Wells, M.D., Daniel J. Corsi, Ph.D.,
Timothy Ramsay, Ph.D., Doug Coyle, Ph.D., Isabelle Chagnon, M.D., Zahra Kassam, M.D., Hardy Tao, M.D.,
and Marc A. Rodger, M.D., for the SOME Investigators*

NEJM 2015; 373(8)

NEJM 2015; 373(8)



- Il 20% dei pazienti con TEV ha una neoplasia
- I pazienti con cancro hanno un rischio di TEV 4-7 volte maggiore
- I pazienti con cancro, sospesa la TAO, hanno rischio di recidiva del 15% anno
- I pazienti con TEV e cancro, in TAO, hanno rischio di emorragia del 15%-20% anno



NAO: la sfida nel paziente con cancro

NAO: la sfida nel paziente con cancro



LMWH > efficacia e sicurezza rispetto agli AVK → LG: 1° scelta
Quali problemi? Iniezioni sottocute Dose in base al peso Rischio di HIT

AVK:

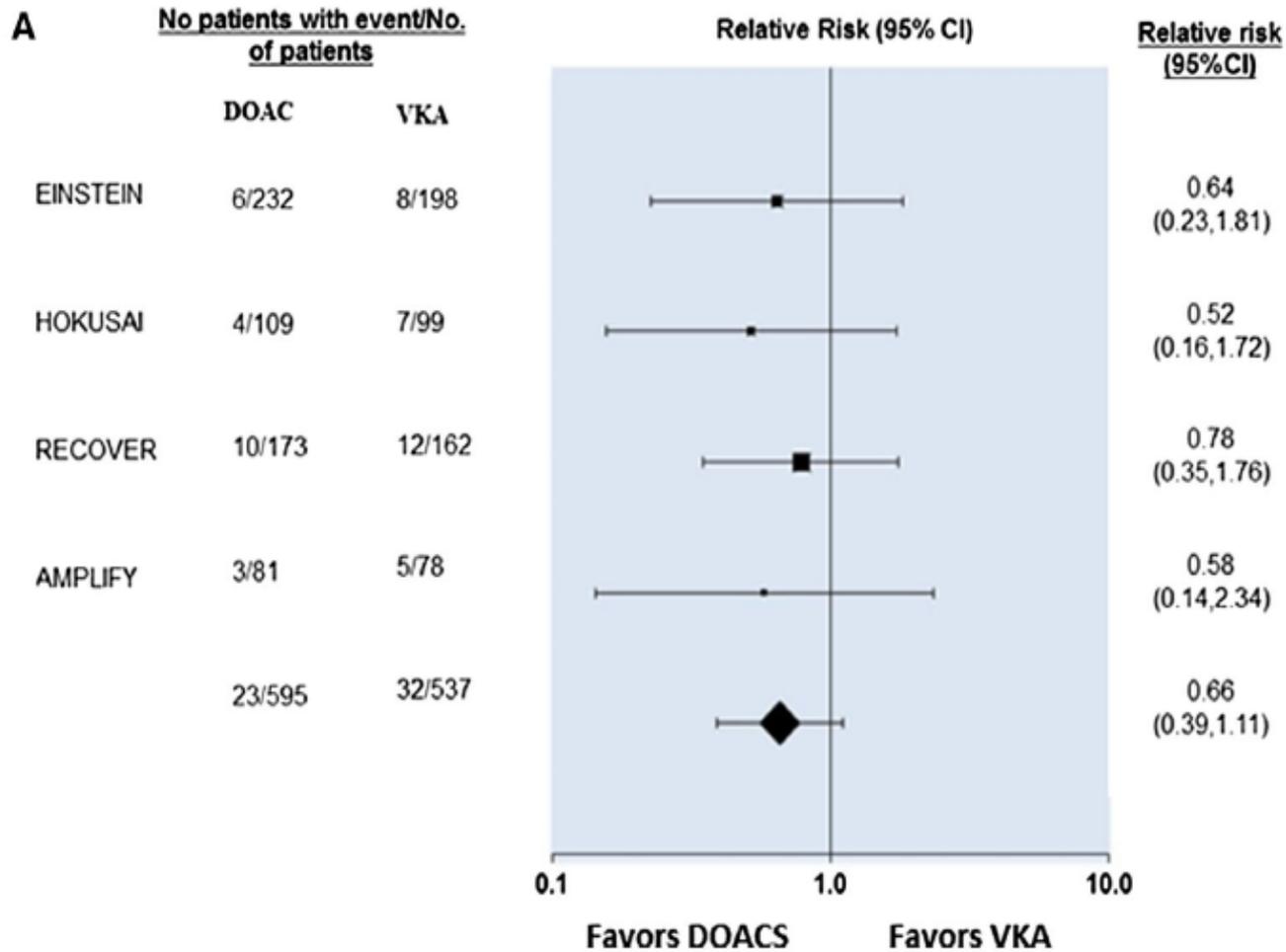
quali problemi? Monitoraggio, interferenze chemioterapici,
ostacolo gestione di procedure invasive

NAO: *quali dati?* 27.000 pazienti in studi di fase III
Cancro: 2.3%-9.4% Cancro attivo: 1227 pazienti
Metanalisi numerose NAO/AVK



NAO: la sfida nel paziente con cancro

NAO: la sfida nel paziente con cancro

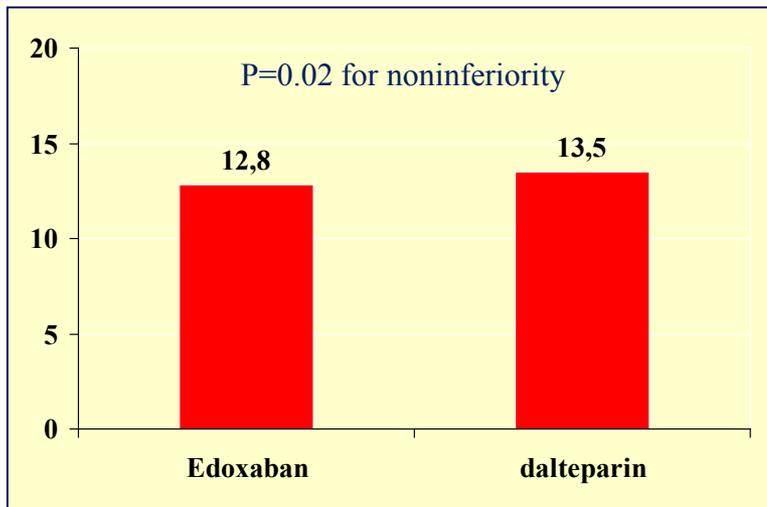


Khorana A. et al. J Thromb Thrombolysis 2016;41:81-91

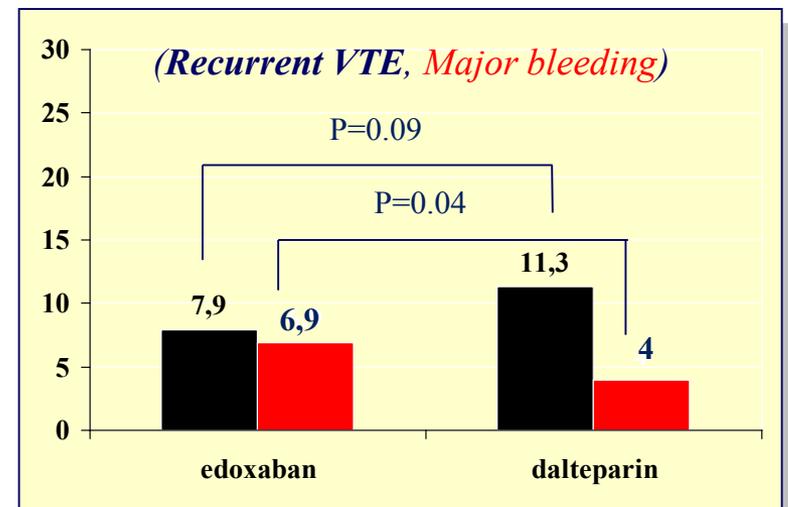
Khorana A. et al. J Thromb Thrombolysis 2016;41:81-91

Hokusai VTE Cancer

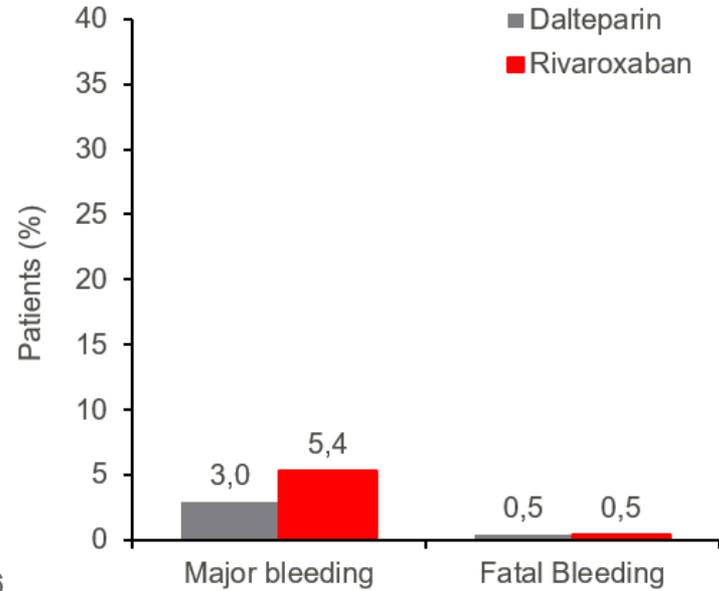
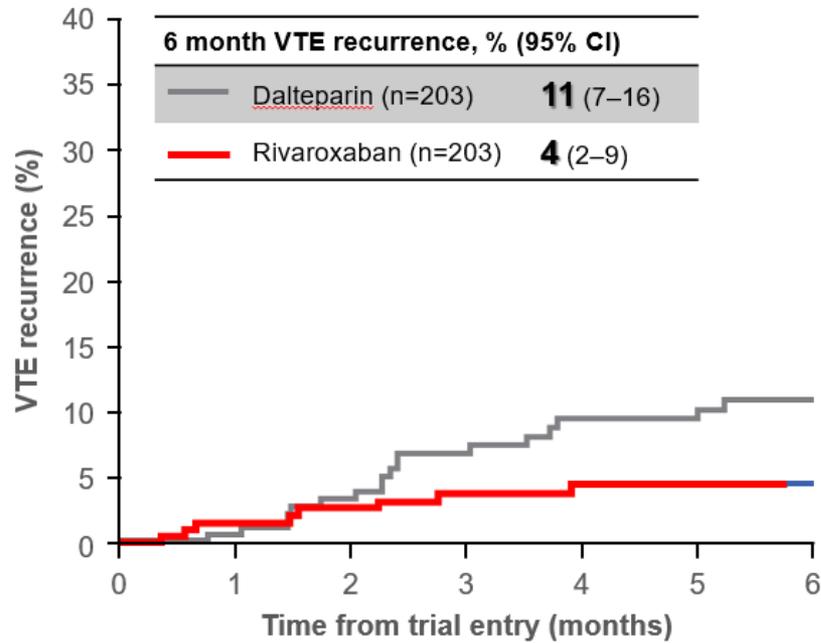
Primary-outcome events



Secondary-outcome events



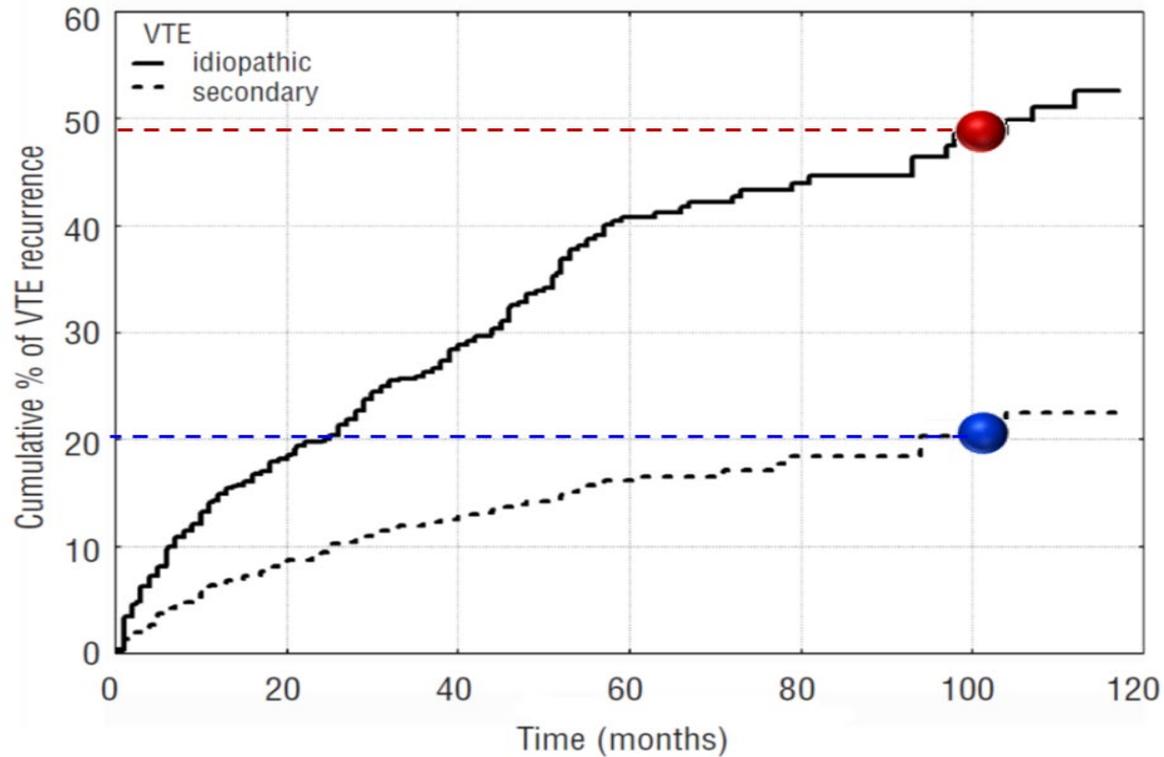
SELECT-D



La nonna

Gli auguri

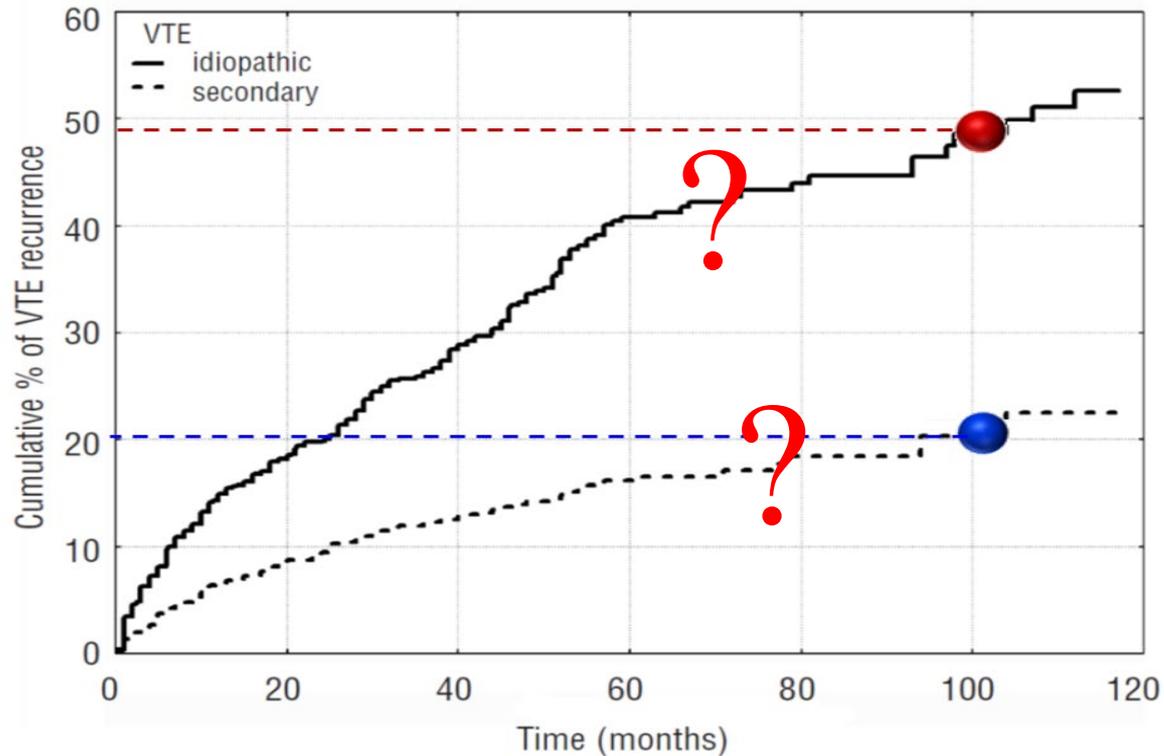
Recidiva di tromboembolismo *dopo sospensione*
dell'anticoagulazione nella TVP o EP (1626 pazienti)



Prandoni P et al. Haematologica 2007

Prandoni P et al. Haematologica 2007

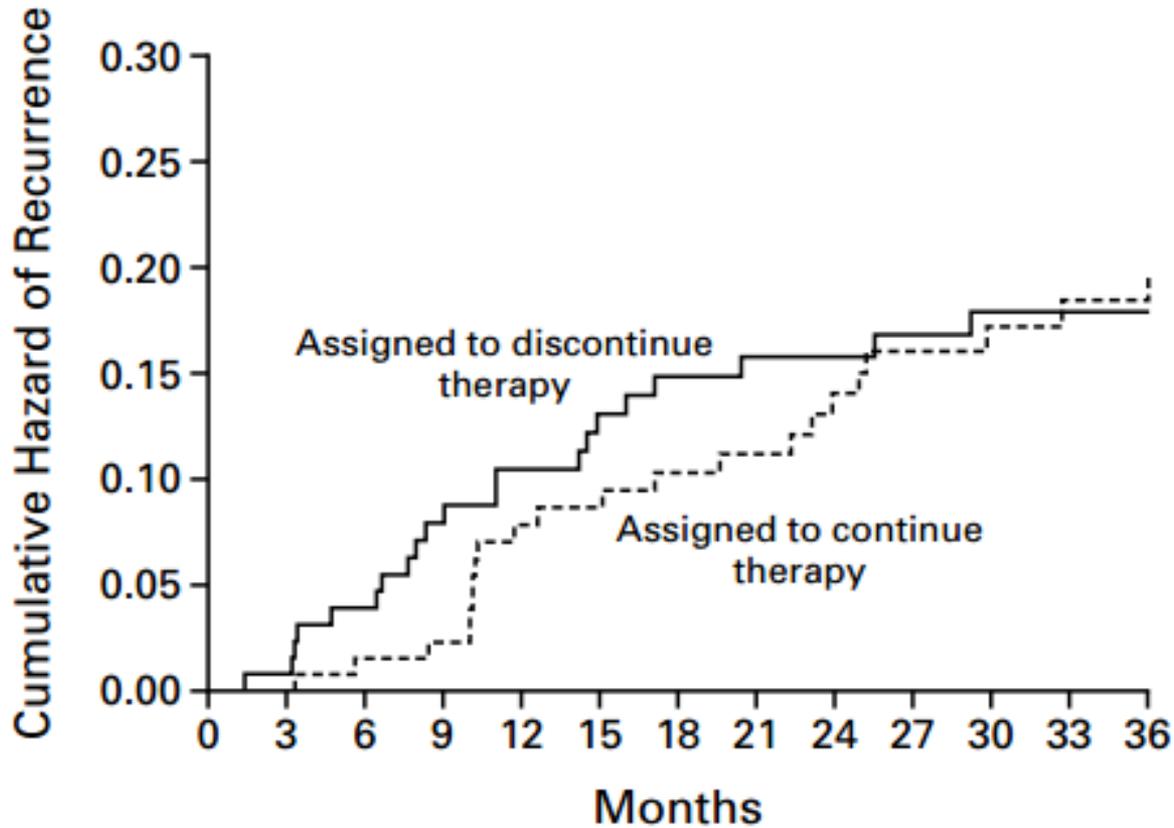
Recidiva di tromboembolismo *dopo sospensione* dell'anticoagulazione nella TVP o EP (1626 pazienti)



Prandoni P et al. Haematologica 2007

Prandoni P et al. Haematologica 2007

THE WARFARIN OPTIMAL DURATION ITALIAN TRIAL



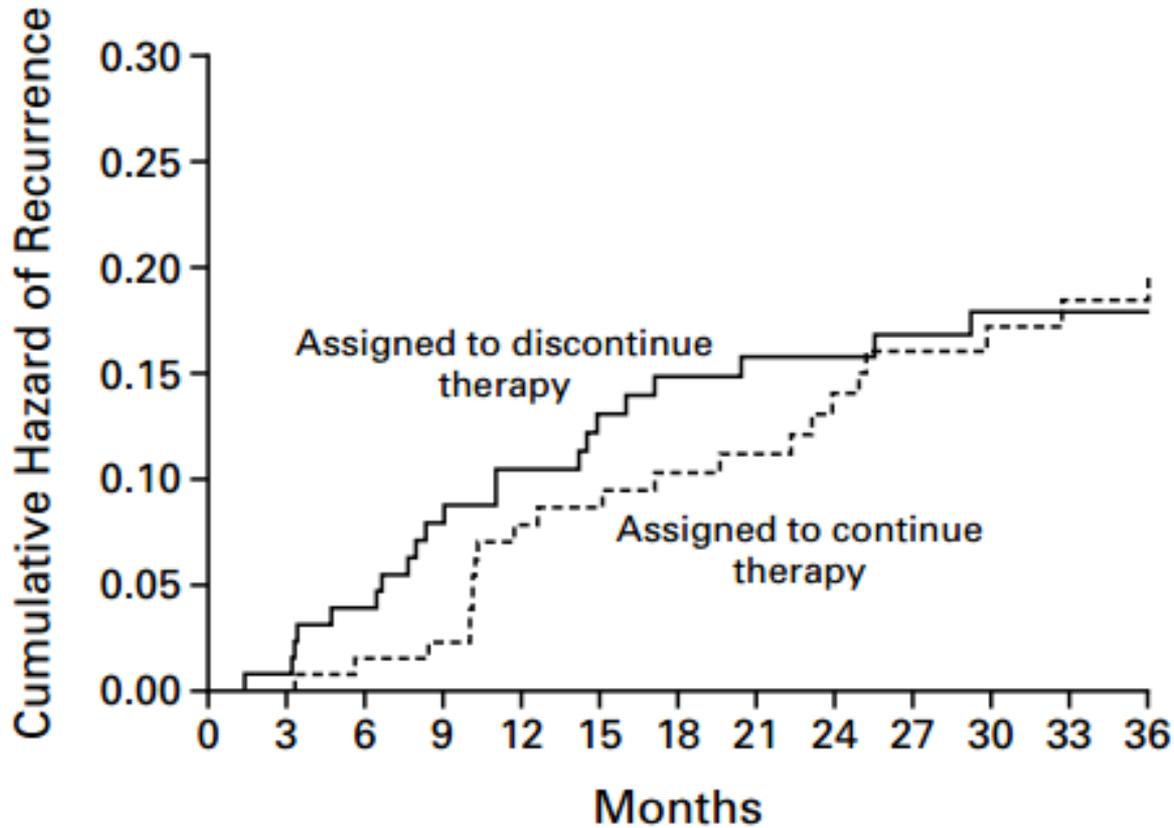
..and *now*?



Agnelli et al. N Engl J Med 2001;345:165-9

Agnelli et al. N Engl J Med 2001;345:165-9

THE **W**ARFARIN **O**PTIMAL **D**URATION **I**TALIAN **T**RIAL



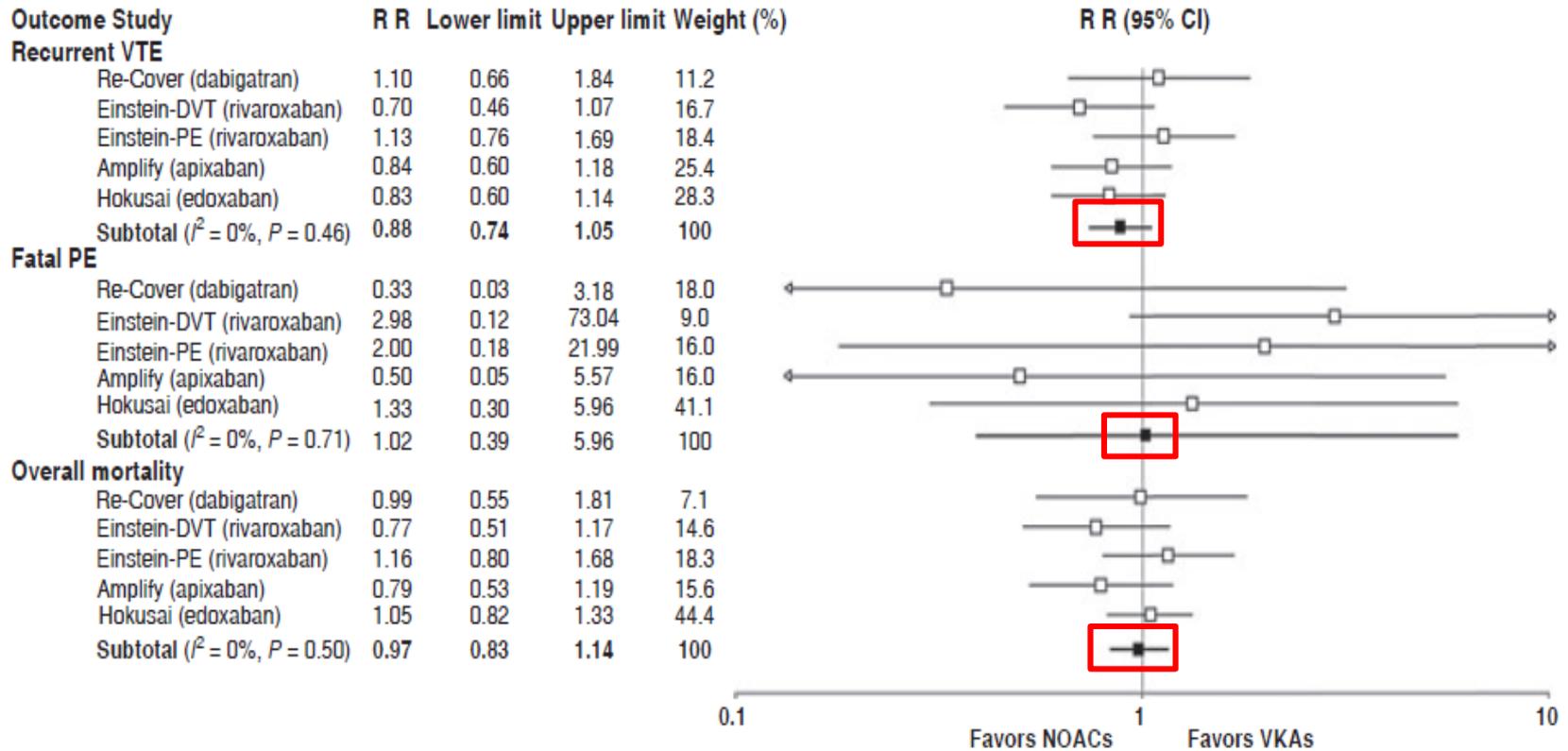
...**NAO!**



Agnelli et al. N Engl J Med 2001;345:165-9

Agnelli et al. N Engl J Med 2001;345:165-9

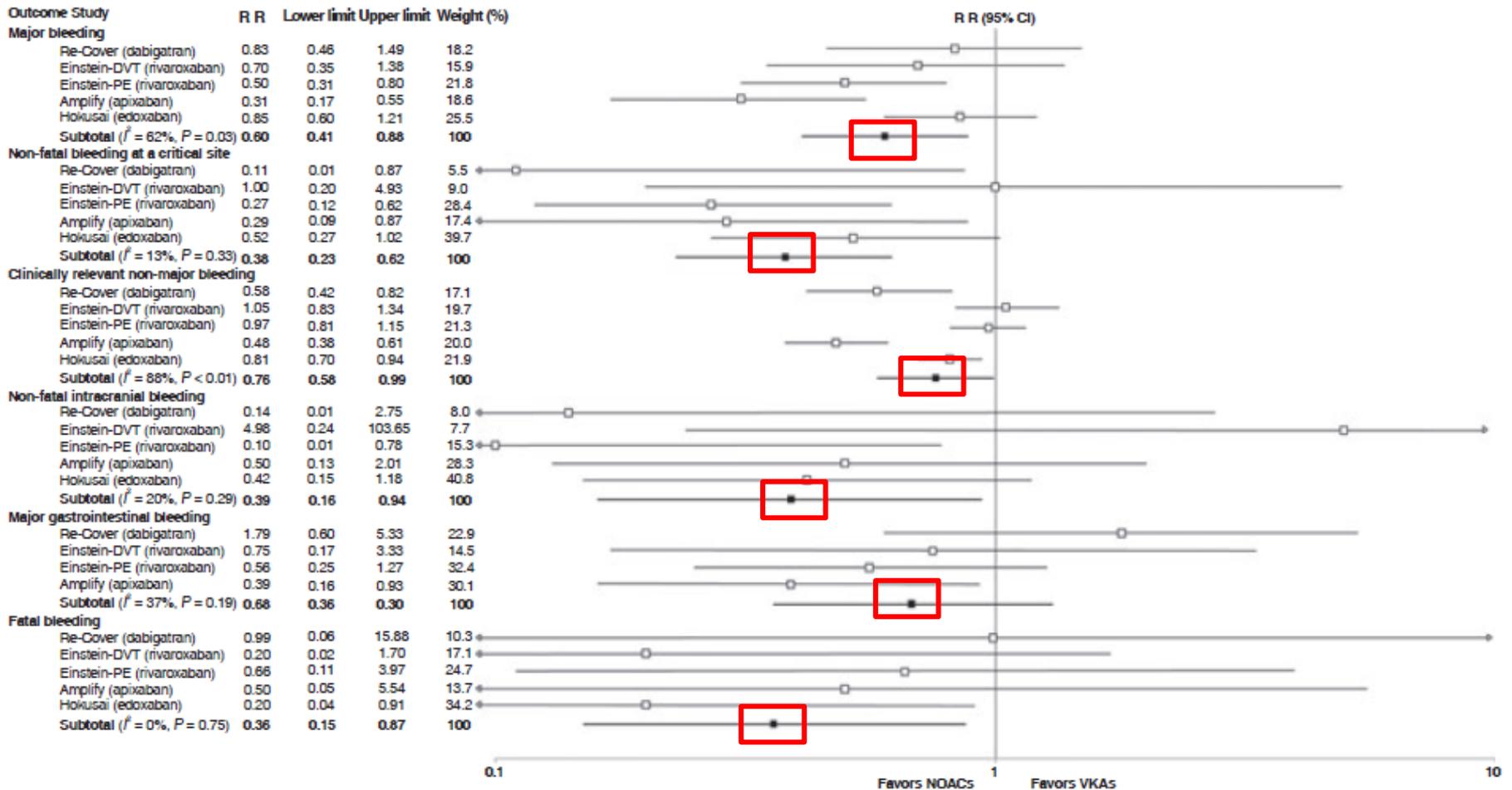
efficacia



Van Der Hulle T. et al. J Thromb Haemost 2014;12:320-8

Van Der Hulle T. et al. J Thromb Haemost 2014;12:320-8

sicurezza



Van Der Hulle T. et al. J Thromb Haemost 2014;12:320-8

Van Der Hulle T. et al. J Thromb Haemost 2014;12:320-8

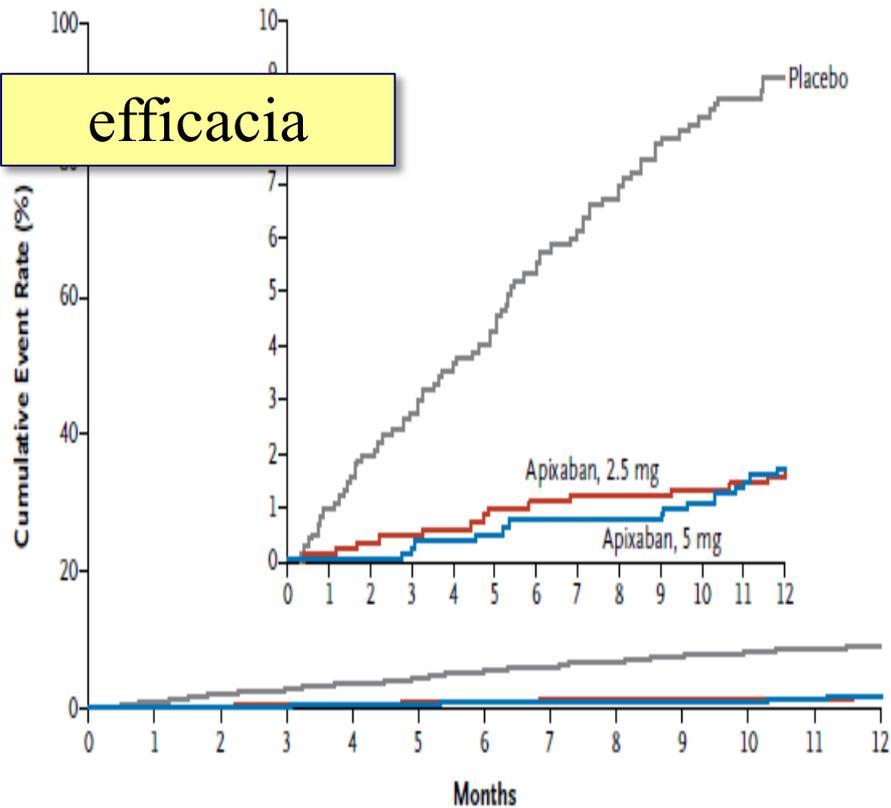
Antithrombotic Therapy for VTE Disease

CHEST Guideline and Expert Panel Report

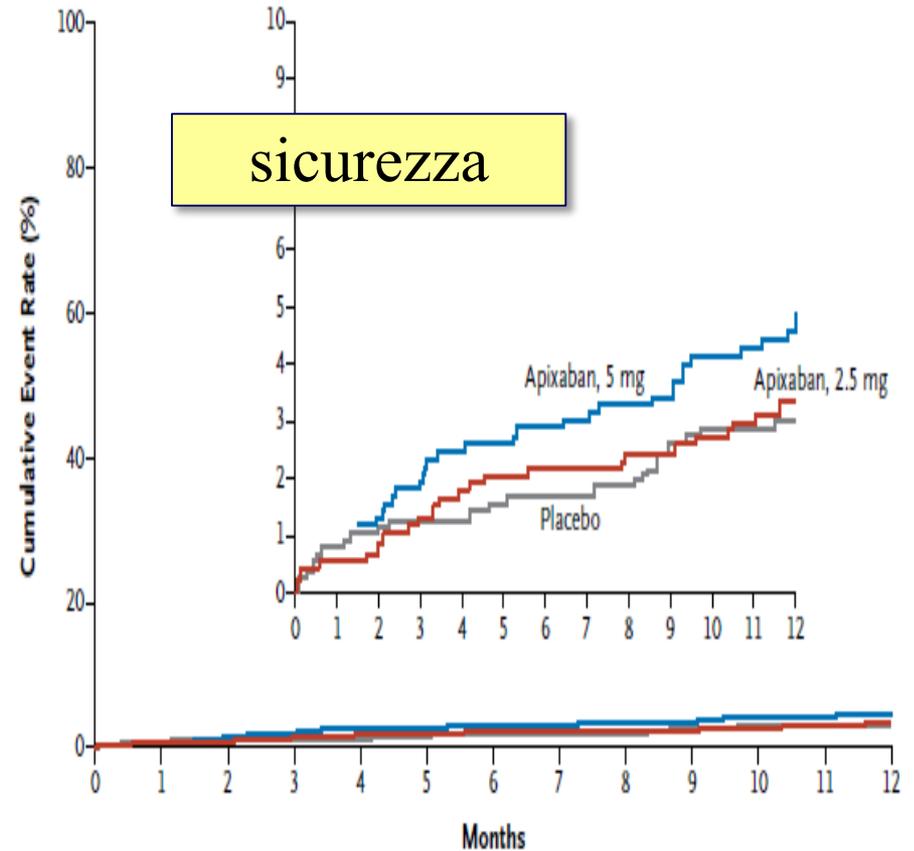
For VTE and no cancer, as long-term anticoagulant therapy, we suggest dabigatran (Grade 2B), rivaroxaban (Grade 2B), apixaban (Grade 2B), or edoxaban (Grade 2B) **over** vitamin K antagonist (VKA) therapy

apixaban nell' *extended VTE* treatment

efficacia



sicurezza

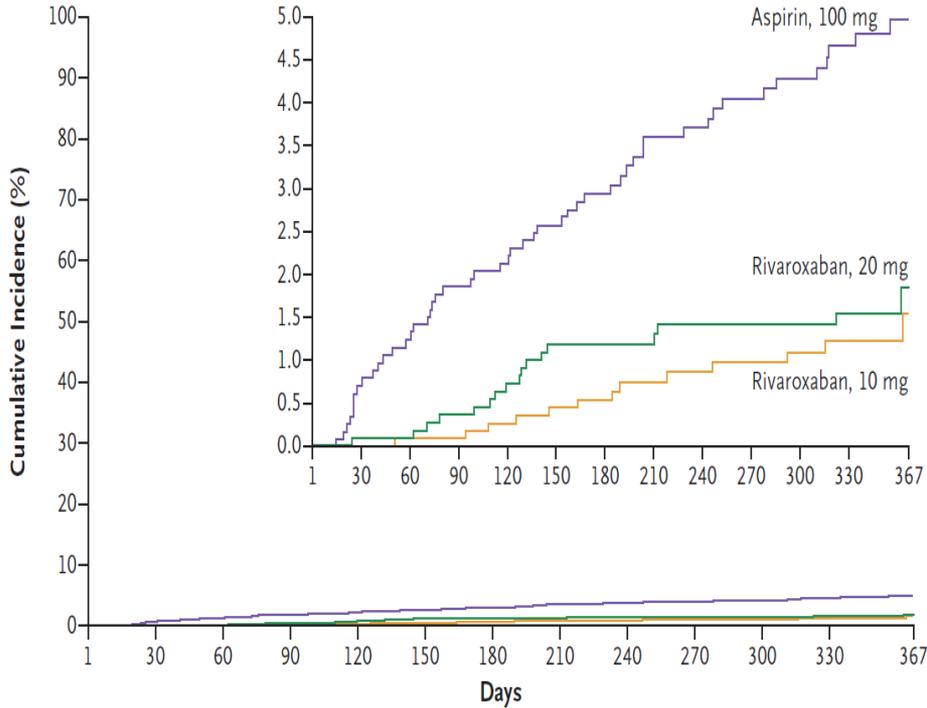


Agnelli G. et al. N Eng J Med 2013

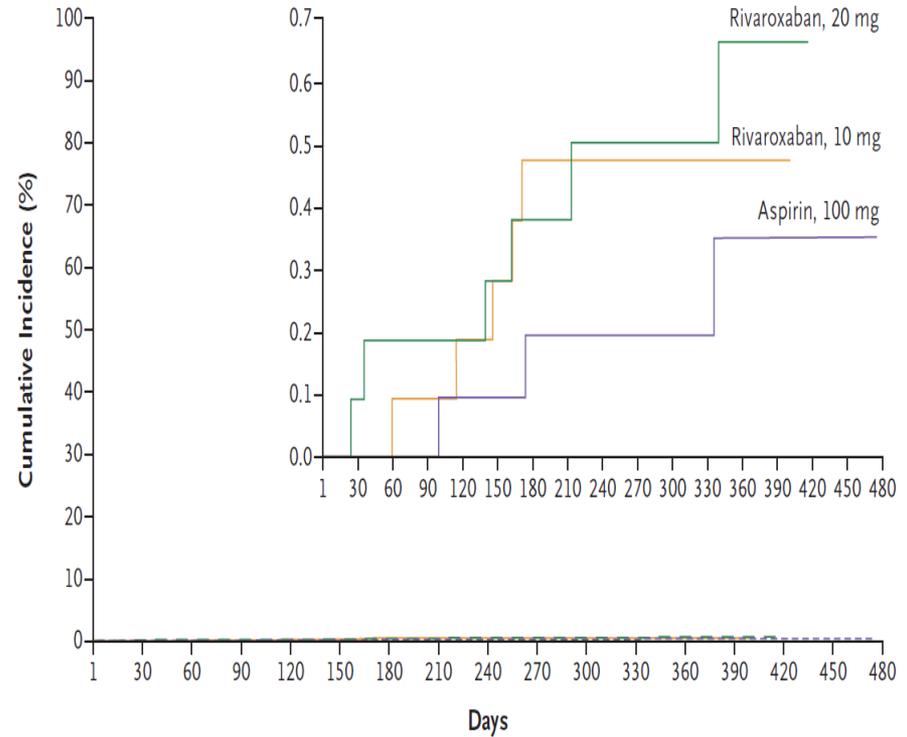
Αgnelli G. et al. N Eng J Med 2013

EINSTEIN CHOICE

fatal or non fatal venous thromboembolism



major bleeding



Weitz JI et al. N Engl J Med 2017; 376: 1211-22.

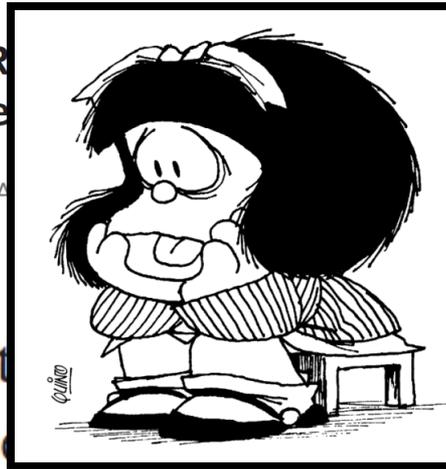
Weitz JI et al. N Engl J Med 2017; 376: 1211-22.

EDITORIALS



Reduced-Intensity R
Ve

Mark A



ention of Recurrent
m

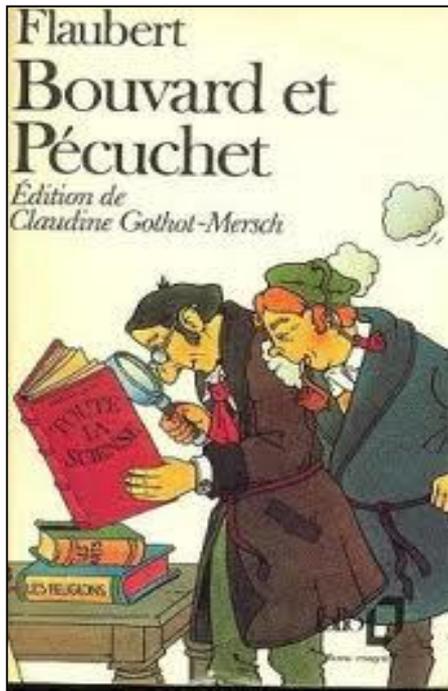
M.D.

In light
rivaroxaban, the
need to be large in order to justify the extension
of therapy.

profile of low-dose
strategy does not

La decima

Prima o poi bisogna pur finire...



*«l'ansia di voler concludere è
una delle più funeste
e sterili manie dell'umanità»*

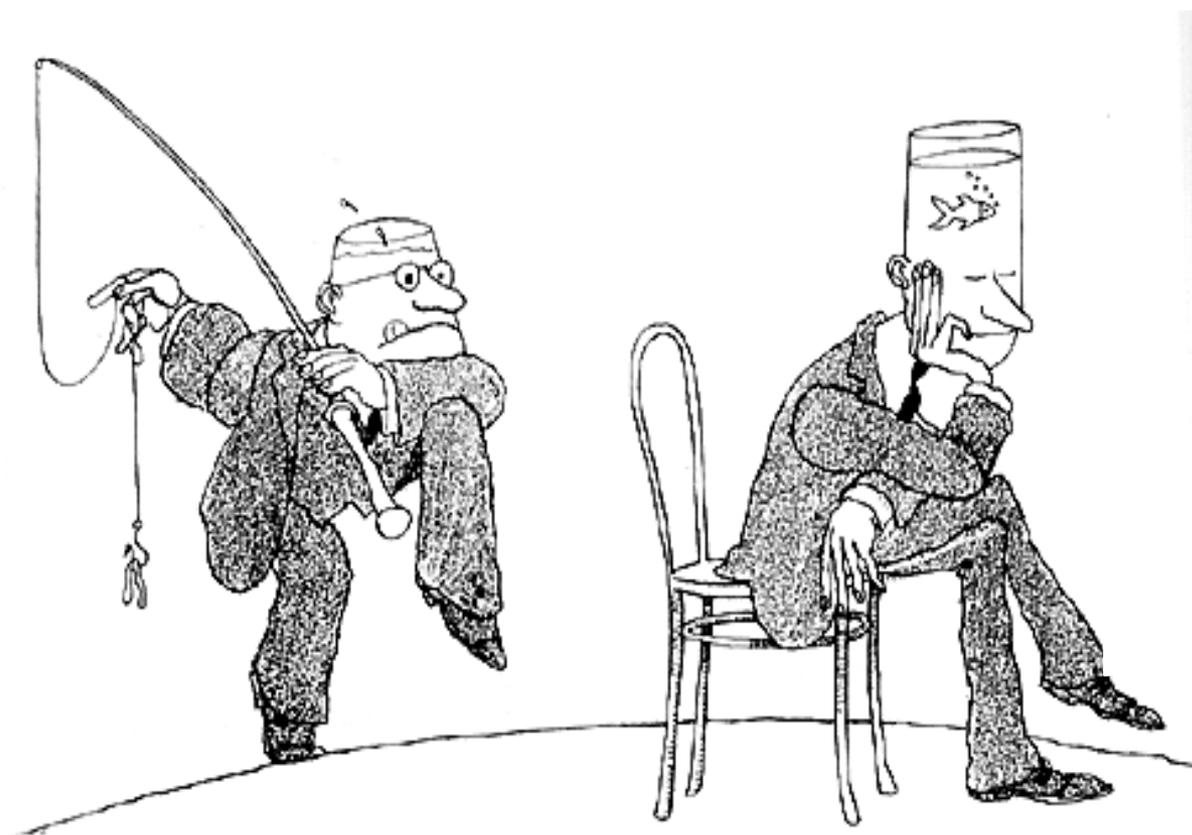
Gustave Flaubert
(1821-1880)

5 cose, da moltiplicar per 2 (che fa 10)

2 cose, da moltiplicar per 5 (che fa 10)

- la diagnosi sia certa
- la prognosi sia definita subito
- la terapia si basi sul peso del rischio
- il follow-up sia strutturato
- l'epicrisi sia obbligatoria





Grazie per l'attenzione

GRAZIE PER L'ATTENZIONE

