

**Scelta più appropriata del  
farmaco antitrombotico**

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# **9º Corso Incontri Pratici Di Ematologia**

**SAVONA**  
**9-10-11 novembre 2017**  
Hotel NH Darsena  
Via Chiode 9

**Responsabile scientifico del progetto**

Dott. Rodolfo TASSARA  
S.C. Medicina Interna, Savona.



## **Il sottoscritto Dott. Marco Scudeletti**

dichiara che negli ultimi due anni ha avuto i seguenti rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario:

**NESSUNO**

Il Dott. Marco Scudeletti non si trova pertanto in una situazione di conflitto di interessi rispetto all'evento ai sensi e per gli effetti dell'Accordo Stato-Regioni del 5 /01/2009



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**sanitario:**

**NESSUNO**

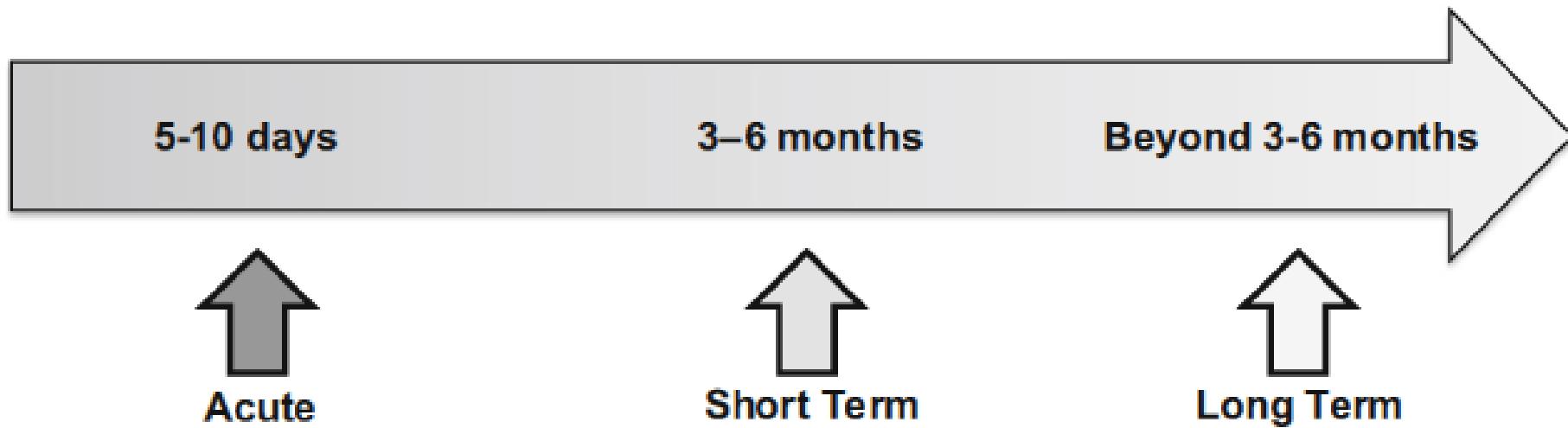
**Il Dott. Marco Scudeletti non si trova pertanto in una situazione di conflitto di interessi rispetto all'evento ai sensi e per gli effetti dell'Accordo Stato-Regioni del 5 /01/2009**



# Di cosa parliamo

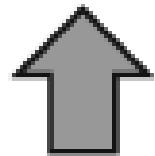
<b>Incidenza/anno/1000 persone</b>	<b>0.75 – 2.69</b>
	<b>2.0 - 7.0 (età &gt; 70 aa.)</b>
<b>% Mortalità a 30 giorni</b>	<b>10.6</b>
<b>% Mortalità a 1 anno</b>	<b>23</b>
<b>Recidiva %</b>	<b>25 a 10 aa., (picco a 6 mesi 11%)</b>
<b>Complicanze</b>	<b>s. post-trombotica (20-50%)</b> <b>Ipertensione polmonare</b>

# Le fasi del trattamento della TEV



# Terapia fase acuta e breve termine

5-10 days



Acute  
IV Heparin  
SQ LMWH  
SQ Fondaparinux  
DOAC

3–6 months

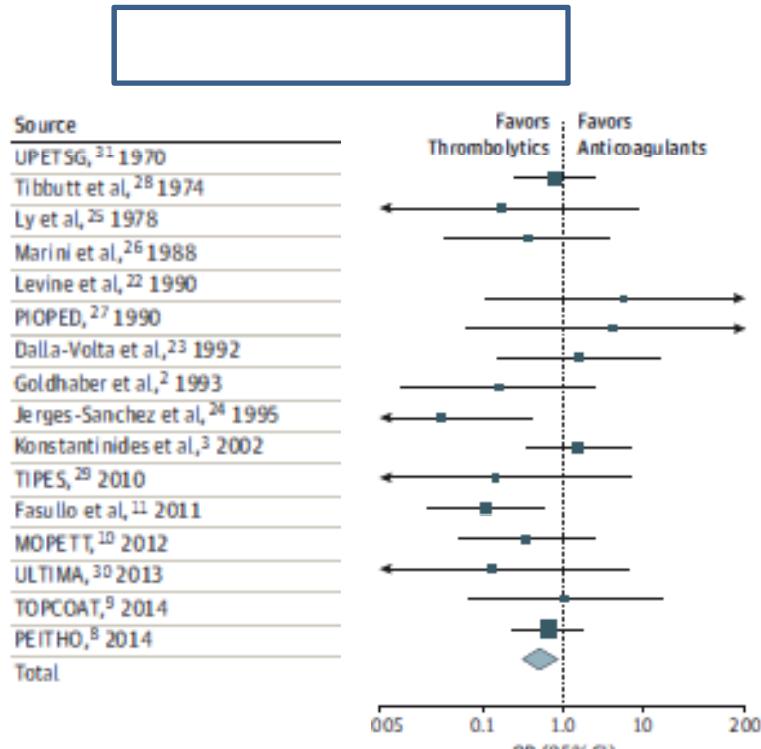


Short Term  
Warfarin  
SQ LMWH (in cancer)  
DOAC



# Thrombolysis for PE and risk of all cause mortality, MB, and ICH: a meta-analysis

(S. Chatterjee et al., JAMA 2014)



Outcome of Interest (No. of Studies Reporting)	No. of Events/No. of Patients, Absolute Event Rate (%)		No. Needed to Treat or Harm	P Value
	Thrombolytic Group	Anticoagulant Group		
All-cause mortality (16)	23/1061 (2.17)	41/1054 (3.89)	NNT = 59	.01
Major bleeding (16) <sup>a</sup>	98/1061 (9.24)	36/1054 (3.42)	NNH = 18	<.001
ICH (15)	15/1024 (1.46)	2/1019 (0.19)	NNH = 78	.002
Recurrent PE (15)	12/1024 (1.17)	31/1019 (3.04)	NNT = 54	.003
Age > 65 y				
All-cause mortality (5)	14/673 (2.08)	24/658 (3.65)	NNT = 64	.07
Major bleeding (5) <sup>a</sup>	87/673 (12.93)	27/658 (4.10)	NNH = 11	<.001
Age ≤ 65 y				
All-cause mortality (11)	9/388 (2.32)	17/396 (4.29)	NNT = 51	.09
Major bleeding (11) <sup>a</sup>	11/388 (2.84)	9/396 (2.27)	NNH = 176	.89
Intermediate-risk PE				
All-cause mortality (8)	12/866 (1.39)	26/889 (2.92)	NNT = 65	.03
Major bleeding (8) <sup>a</sup>	67/866 (7.74)	20/889 (2.25)	NNH = 18	<.001

> Rischio MB e ICH

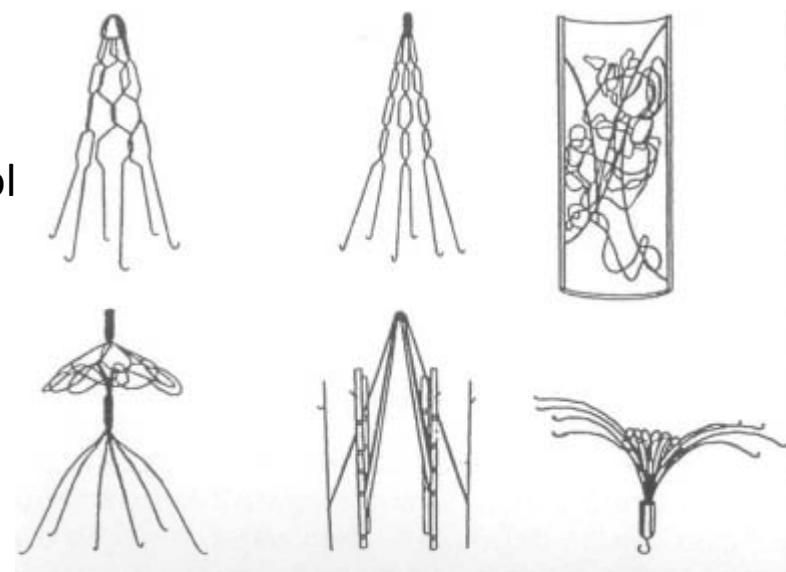
Rischio MB e mortalità età < 65

Efficace anche in EP stabile

# Filtro cavale

**Indicazione principale:** controindicazione assoluta a scoagulazione in TEV acuta con alto rischio di estensione

- Altre (IIb, livello C\*):
  - inefficacia t. scoagulante
  - p. sottoposto a EAP
  - chirurgia addomino-pelvica in pregresso TEV
  - donna gravida con TVP prossimale e rischio embol
  - p. politraumatizzato
- Usare filtri rimovibili e rimuoverli appena la t. scoagulante può essere ripresa,



## **Guidance for the treatment of DVT and PE**

M.B. Streiff et al., J Thomb Thrombolysis  
2016

- **LMWH**

## **Initial treatment**

C. Kearon et al., Chest 2016 (IA)  
LG AIOM 2016 (IA)

- **UHF**

< emivita di LMWH  
Manovre periprocedurali  
Alto rischio sanguinamento  
Pesi estremi  
IRC IV stadio (ClCr <30 mL/min.)

## **DOACs**

Apixaban o Rivaroxaban (IB)  
LMWH (5-10 gg) e poi Dabigatran o  
Edoxaban (IB)

- **Fondaparinux**

Emivita lunga (17-21h)

Unpredictable response

Narrow therapeutic window  
(INR range 2-3)

Routine coagulation monitoring

Frequent dose adjustments

Warfarin therapy has several limitations that make it difficult to use in practice

Slow onset/offset of action

Numerous food-drug interactions

Numerous drug-drug interactions

Risk of Bleeding Complications

- Warfarin was #1 in 2003 and 2004 in the number of mentions of “deaths for drugs causing adverse effects in therapeutic use”
- Warfarin caused 6% of the 702,000 ADEs treated in the ED/year; 17% required hospitalization

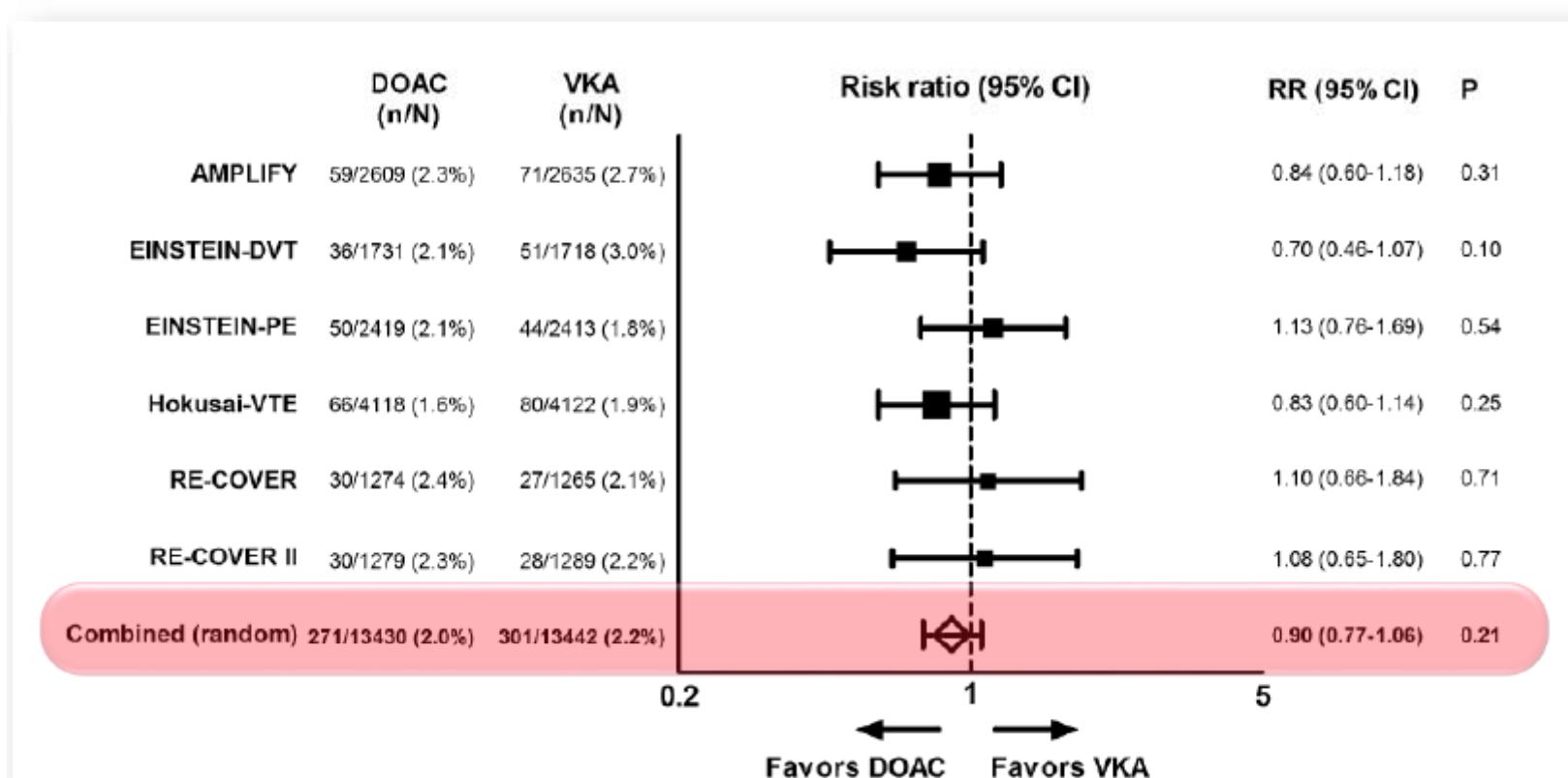
# Efficacia e sicurezza dei DOACs nel trattamento della TEV

TABLE 1 Efficacy and Safety of NOACs for the Treatment of VTE: Results From Clinical Trials							
Trial Name (Ref. #)	Design	Treatments	Duration (months)	Patients	TTR (%)	Efficacy Outcome	Safety Outcome
RE-COVER, 2009 (37)	DB	Enoxa/dabigatran (150 mg bid) Enoxa/warfarin	6	2,539 acute VTE	60	Recurrent VTE or VTE-related death: 2.4% enoxa/dabigatran, 2.1% enoxa/warfarin	Major/clinically relevant nonmajor bleeding: 5.6% dabigatran, 8.8% warfarin
RE-COVER II, 2011 (38)	DB	Enoxa/dabigatran (150 mg bid) Enoxa/warfarin	6	2,539 acute VTE	57	Recurrent VTE or fatal PE: 2.3% dabigatran, 2.2% warfarin	Major/clinically relevant nonmajor bleeding: 5.0% dabigatran, 7.9% warfarin
EINSTEIN-DVT, 2010 (39)	Open-label	Rivaroxaban (15 mg bid for 3 weeks, then 20 mg od) Enoxaparin/VKA	3, 6, or 12	3,449 acute DVT	58	Recurrent VTE: 2.1% rivaroxaban, 3.0% enoxa/warfarin	Major/clinically relevant nonmajor bleeding: 8.1% rivaroxaban, 8.1% enoxa/warfarin
EINSTEIN-PE, 2012 (40)	Open-label	Rivaroxaban (15 mg bid for 3 weeks, then 20 mg od) Enoxa/VKA	3, 6, or 12	4832 acute PE	63	Recurrent VTE: 2.1% rivaroxaban, 1.8% enoxa/VKA	Major/clinically relevant nonmajor bleeding: 10.3% rivaroxaban, 11.4% enoxa/VKA
AMPLIFY, 2013 (41)	DB	Apixaban (10 mg bid for 7 days, then 5 mg bid) Enoxa/warfarin	6	5,395 acute VTE	61	Recurrent VTE or VTE-related death: 2.3% apixaban, 2.7% enoxa/VKA	Major bleeding: 0.6% apixaban, 1.8% enoxa/warfarin
Hokusai, 2013 (42)	DB	LMWH/edoxaban (60 mg od or 30 mg od) UFH or LMWH/warfarin	>12	8,292 acute VTE	63	Recurrent VTE: 3.2% enoxa/edoxaban, 3.5% enoxa/warfarin	Major/clinically relevant nonmajor bleeding: 8.5% enoxa/edoxaban, 10.3% enoxa/warfarin

# VTE Recurrence

## DOACs vs VKAs

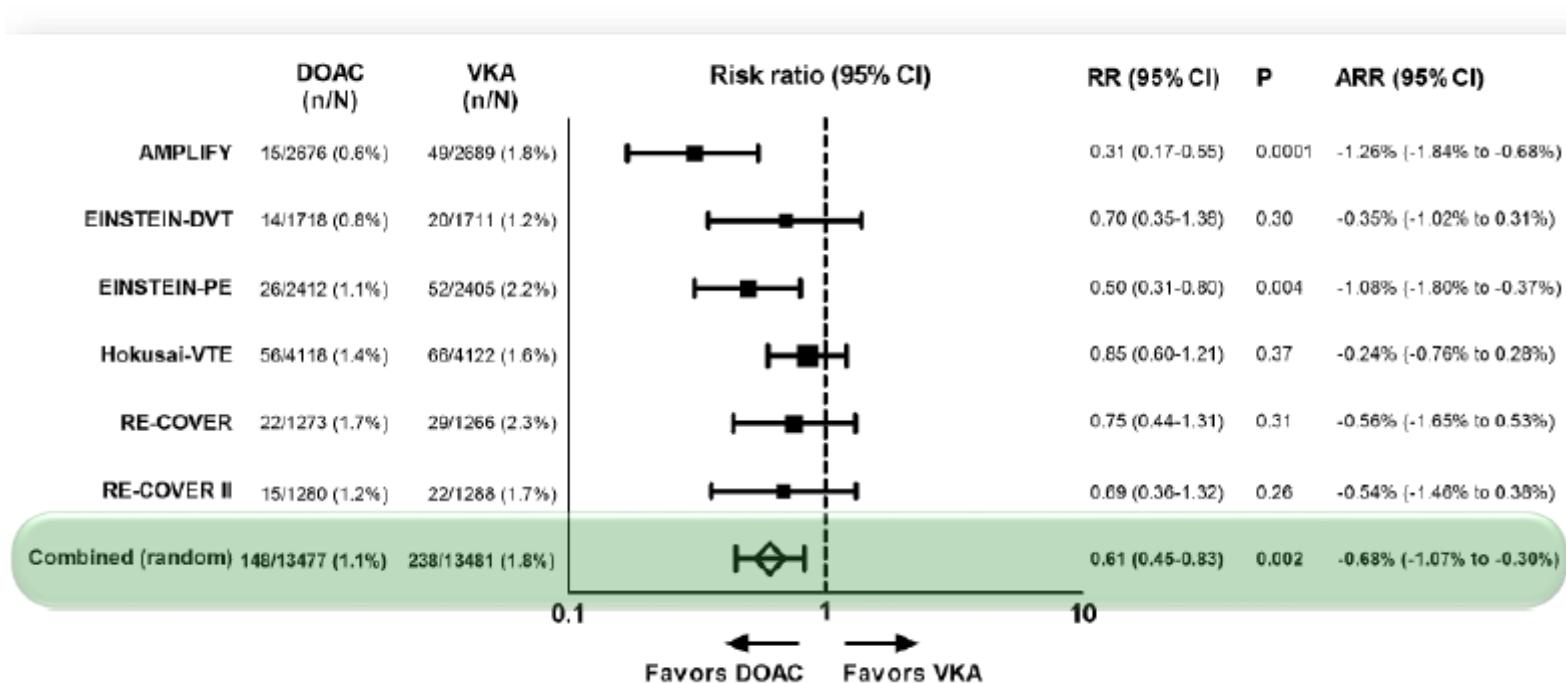
### First recurrent VTE or VTE-related death



Van Es et al. Blood 2014

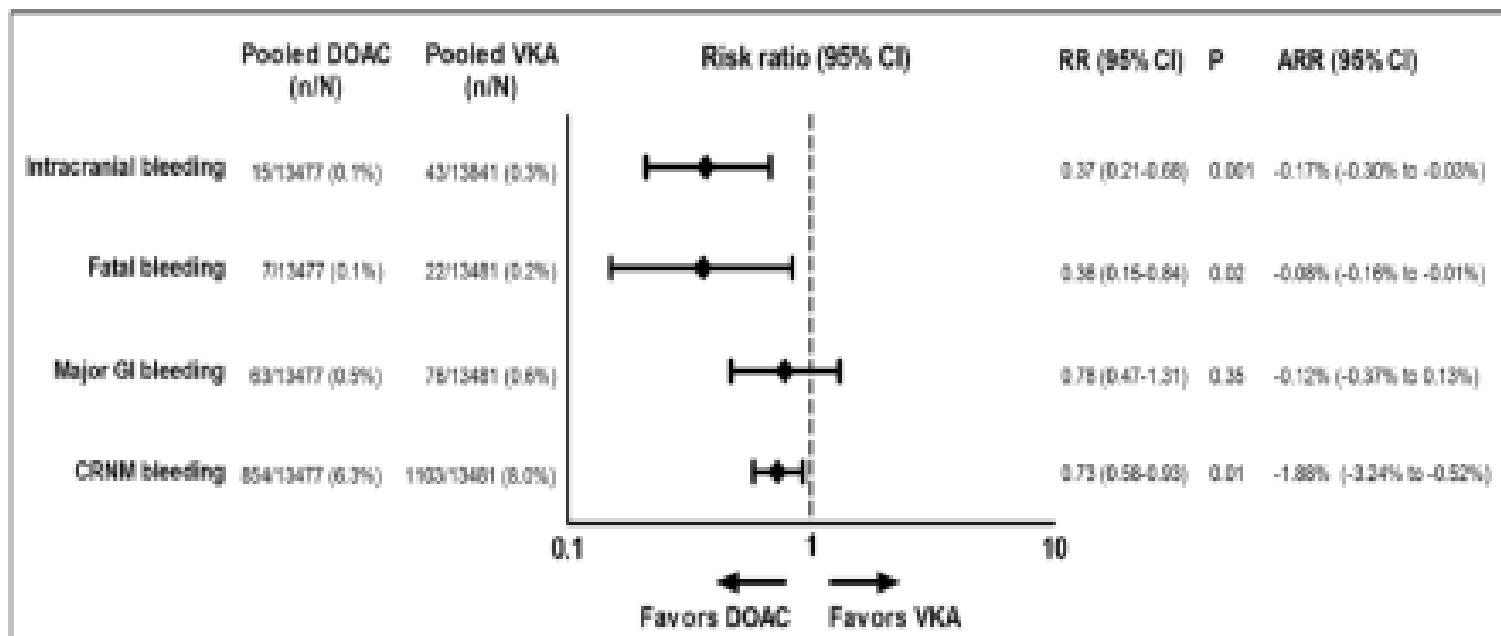
# Major Bleeding

## Major bleeding



Van Es et al. Blood 2014

# Other End Points

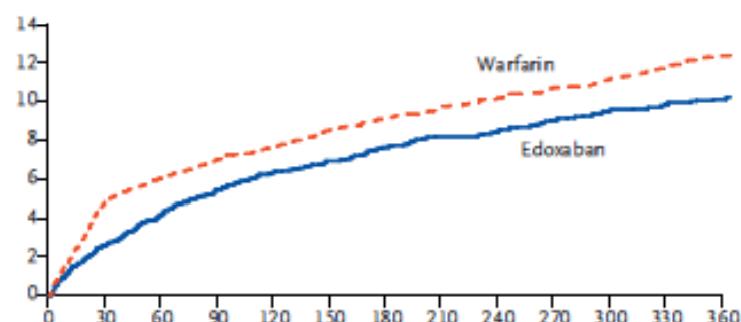
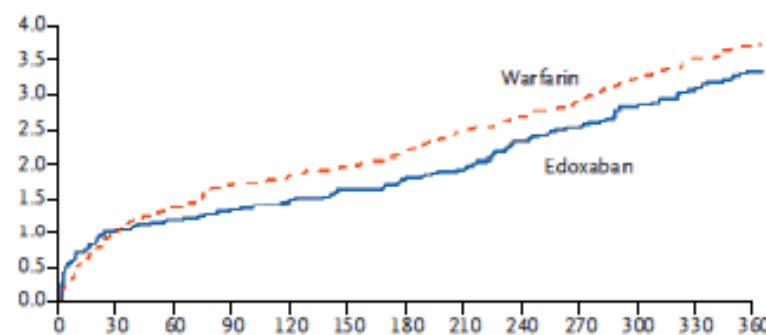


Van Es et al. Blood 2014

# Edoxaban versus warfarin for the treatment of symptomatic VTE

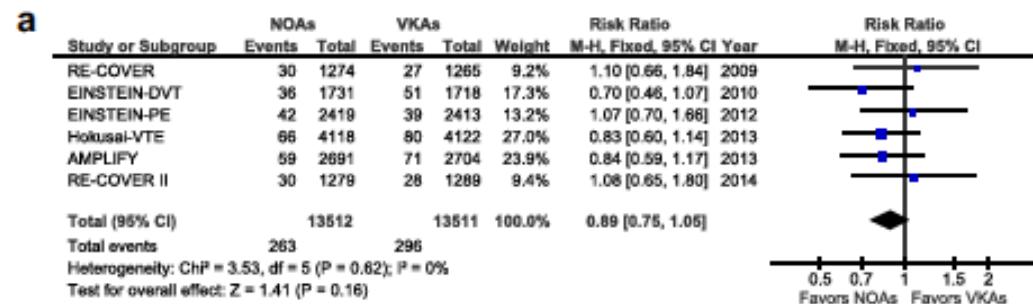
The Okusai-VTE Investigators  
(HR Buller et al., NEJM 2013)

Characteristic	All Patients		Patients with Pulmonary Embolism	
	Edoxaban (N=4118)	Warfarin (N=4122)	Edoxaban (N=1650)	Warfarin (N=1669)
<b>Age</b>				
Mean — yr	55.7±16.3	55.9±16.2	57.1±16.6	57.4±16.5
≥75 yr — no. (%)	560 (13.6)	544 (13.2)	278 (16.8)	271 (16.2)
Male sex — no. (%)	2360 (57.3)	2356 (57.2)	863 (52.3)	875 (52.4)
<b>Weight — no. (%)</b>				
≤60 kg†	524 (12.7)	519 (12.6)	204 (12.4)	215 (12.9)
>100 kg	611 (14.8)	654 (15.9)	251 (15.2)	275 (16.5)
Creatinine clearance ≥30 to ≤50 ml/min — no. (%)†	268 (6.5)	273 (6.6)	116 (7.0)	120 (7.2)
Patients receiving 30 mg of edoxaban at randomization — no. (%)†	733 (17.8)	719 (17.4)	308 (18.7)	308 (18.5)
<b>Anatomical extent of qualifying event — no. (%)‡</b>				
Limited	—	—	128 (7.8)	123 (7.4)
Intermediate	—	—	679 (41.2)	682 (40.9)
Extensive	—	—	743 (45.0)	778 (46.6)
Not assessable	—	—	100 (6.1)	86 (5.2)
Concomitant DVT — no. (%)	—	—	410 (24.8)	404 (24.2)
Baseline NT-proBNP — no. (%)				
Patients with measurement	—	—	1484 (89.9)	1505 (90.2)
Patients with level ≥500 pg/ml	—	—	454 (27.5)	484 (29.0)
Right ventricular dysfunction — no./total no. (%)§	—	—	172/498 (34.5)	179/504 (35.5)



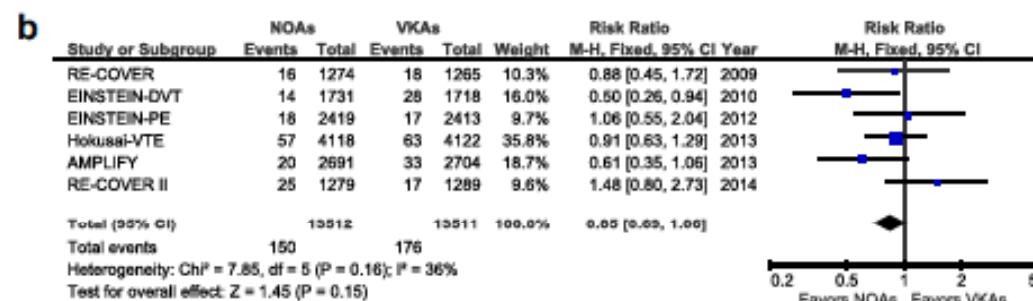
# Efficacy and safety of DOACs in the treatment and secondary prevention of TEV: a systematic review and meta-analysis of phase III

Prevenzione  
recidiva TEV

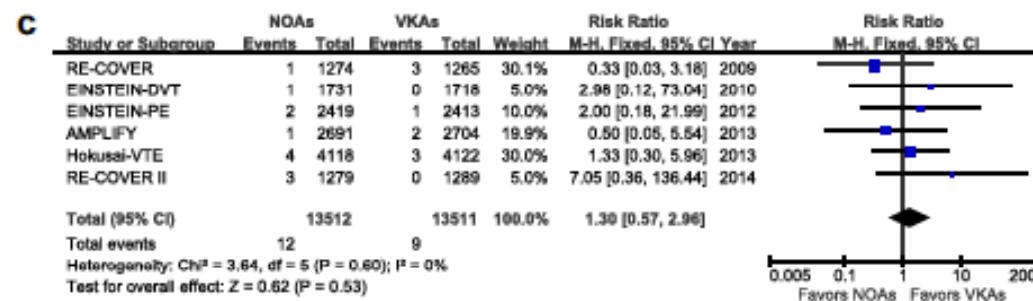


17 trials  
38.000 p.

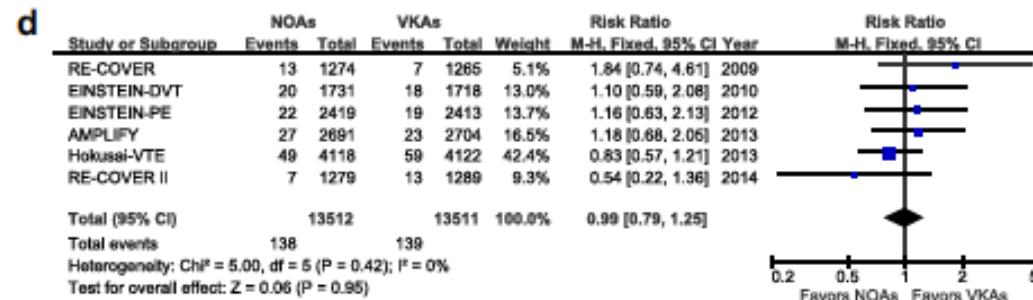
Prevenzione  
recidiva VTD



Prevenzione  
recidiva EP  
fatale

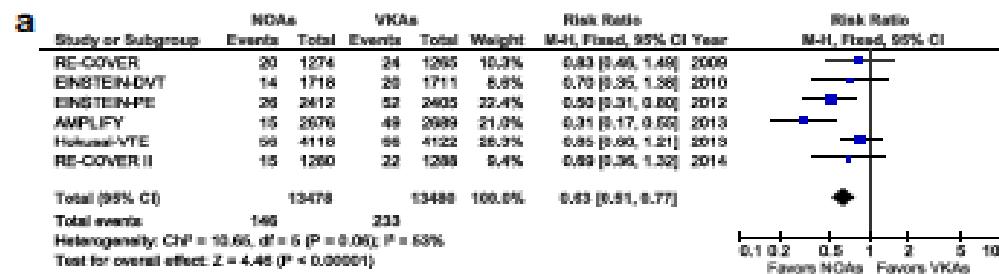


Prevenzione  
recidiva EP non  
fatale

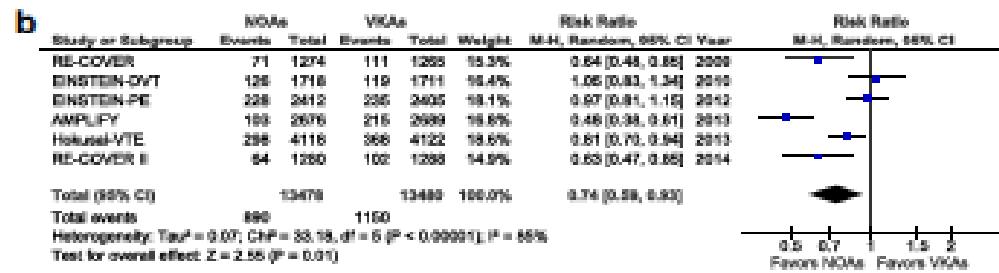


SK Kakkos et al.,  
Eur J Vasc. Endovasc.  
Surg. 2014

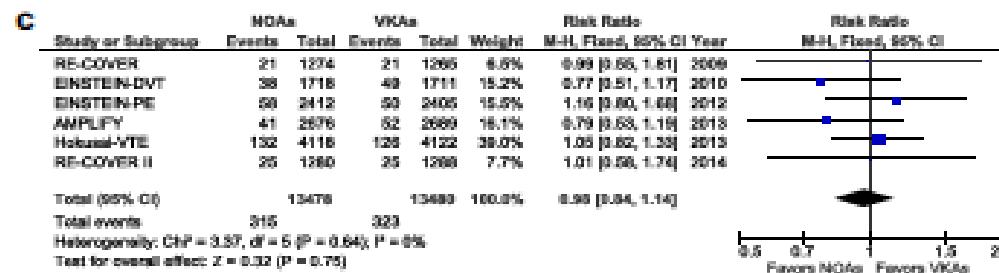
## Major bleeding



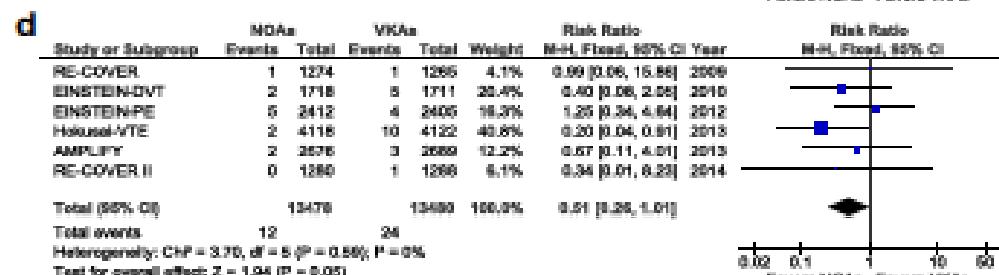
## CRNMB



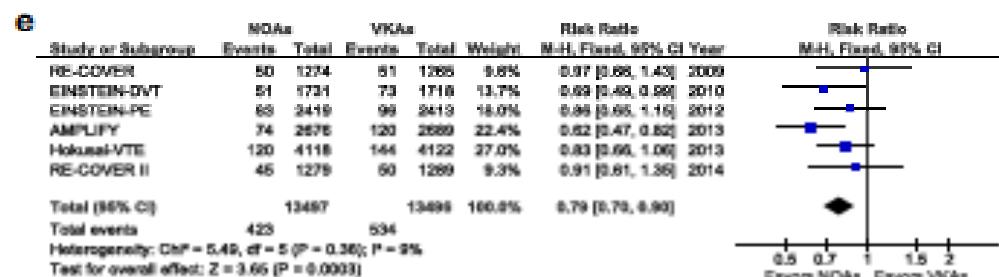
## Mortalità per tutte le cause



## Morte per sanguinamento

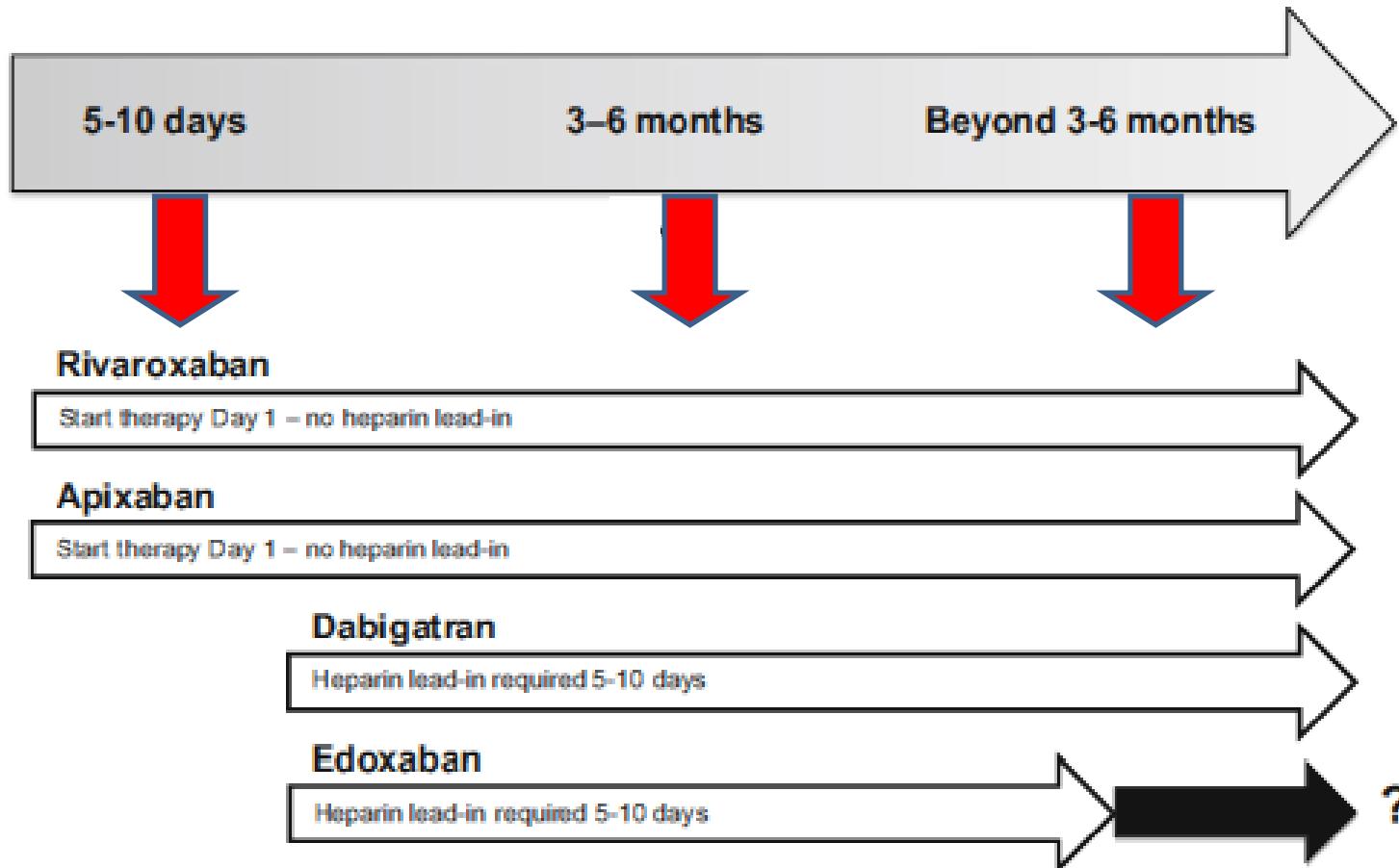


## Beneficio clinico netto



SK Kakkos et al.,  
Eur J Vasc. Endovasc.  
Surg. 2014

# Come si usano i DOACs?



# Rispettare le dosi registrative

## Razionale per il trattamento intensificato

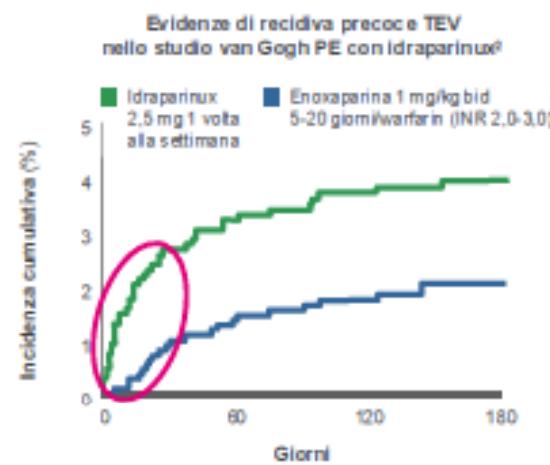
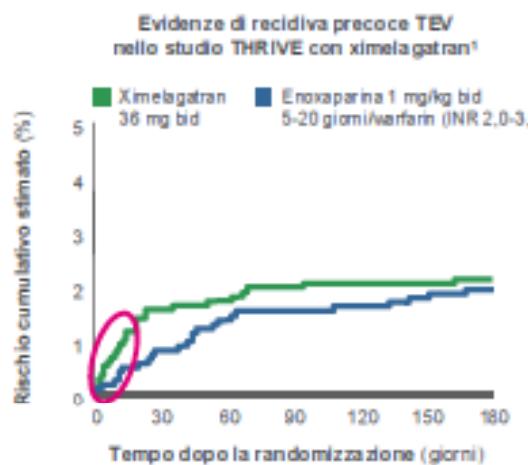
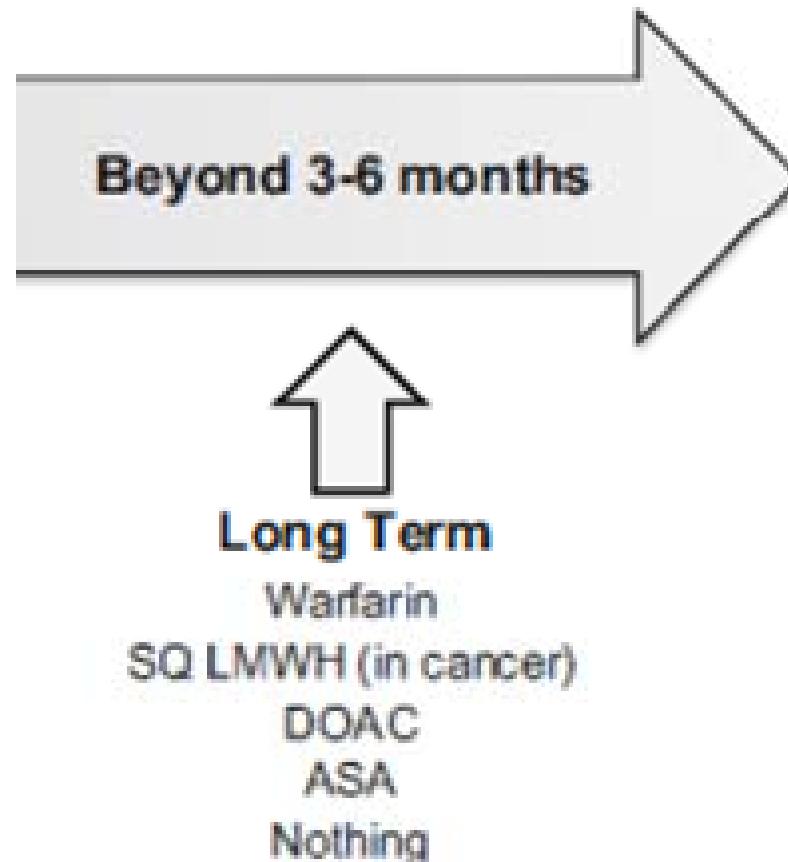


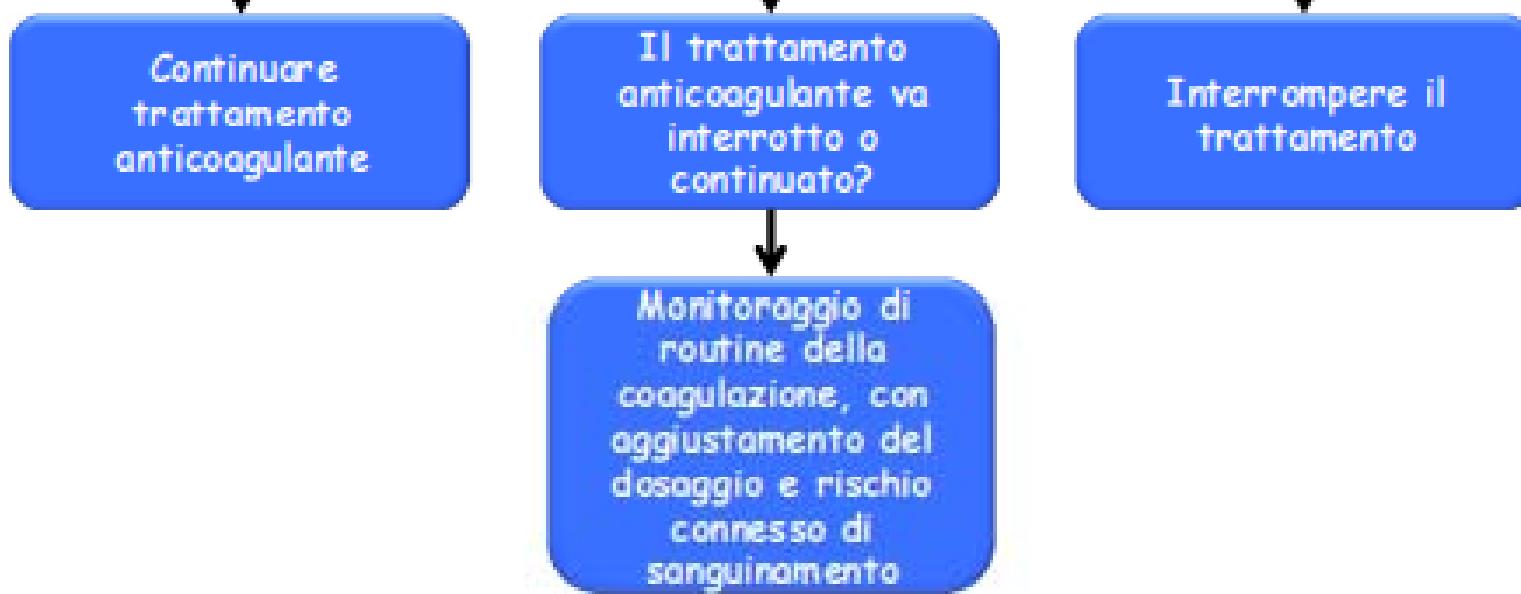
TABLE 2 Licensed direct oral anticoagulant dosing regimens for treatment of venous thromboembolism

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
run-in period	LMWH for at least 5 days	15 mg BID for 21 days	10 mg BID for 7 days	LMWH for at least 5 days
subsequent dosing	150 mg BID	20 mg OD	5 mg BID	60 mg OD
renal adjustment	110 mg BID if $\geq 80$ years old or moderate renal impairment	N/A	N/A	30 mg OD if CrCl 15–50 mL/min; weight < 60 kg or potent P-gp inhibitors

# Trattamento esteso



**Trattamento per l'evento tromboembolico venoso iniziale  
6 o 12 mesi di trattamento anticoagulante**



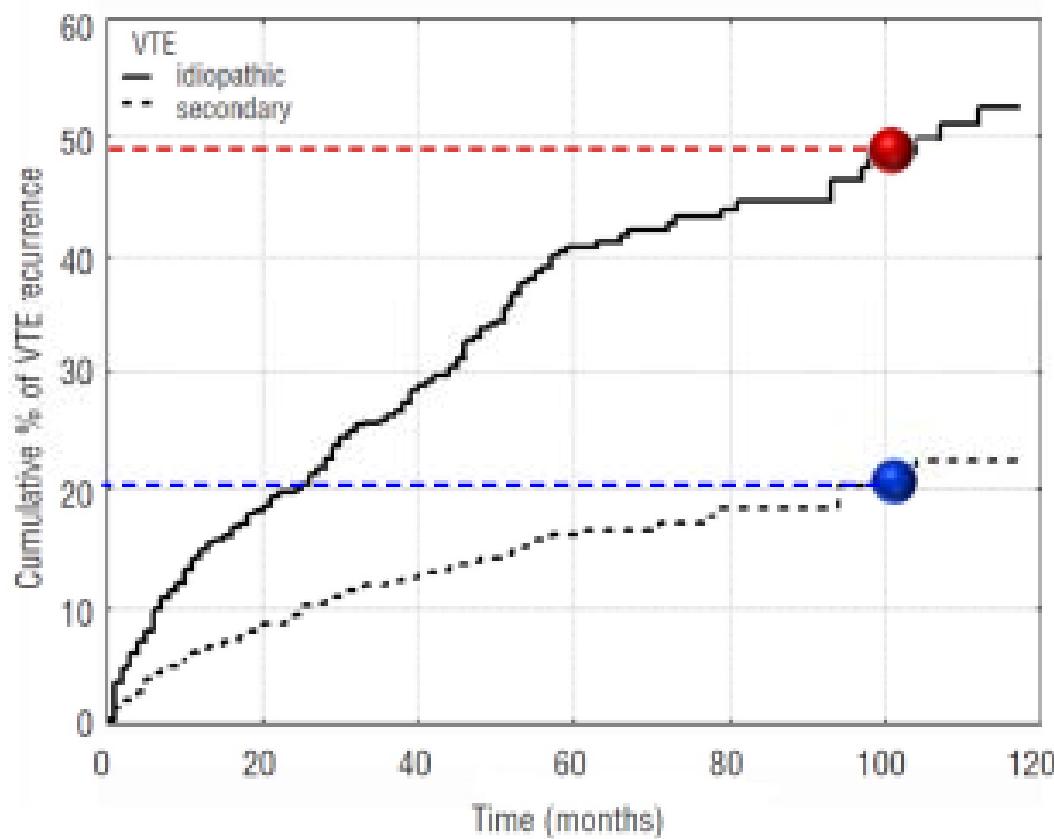
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**The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1,626 patients**

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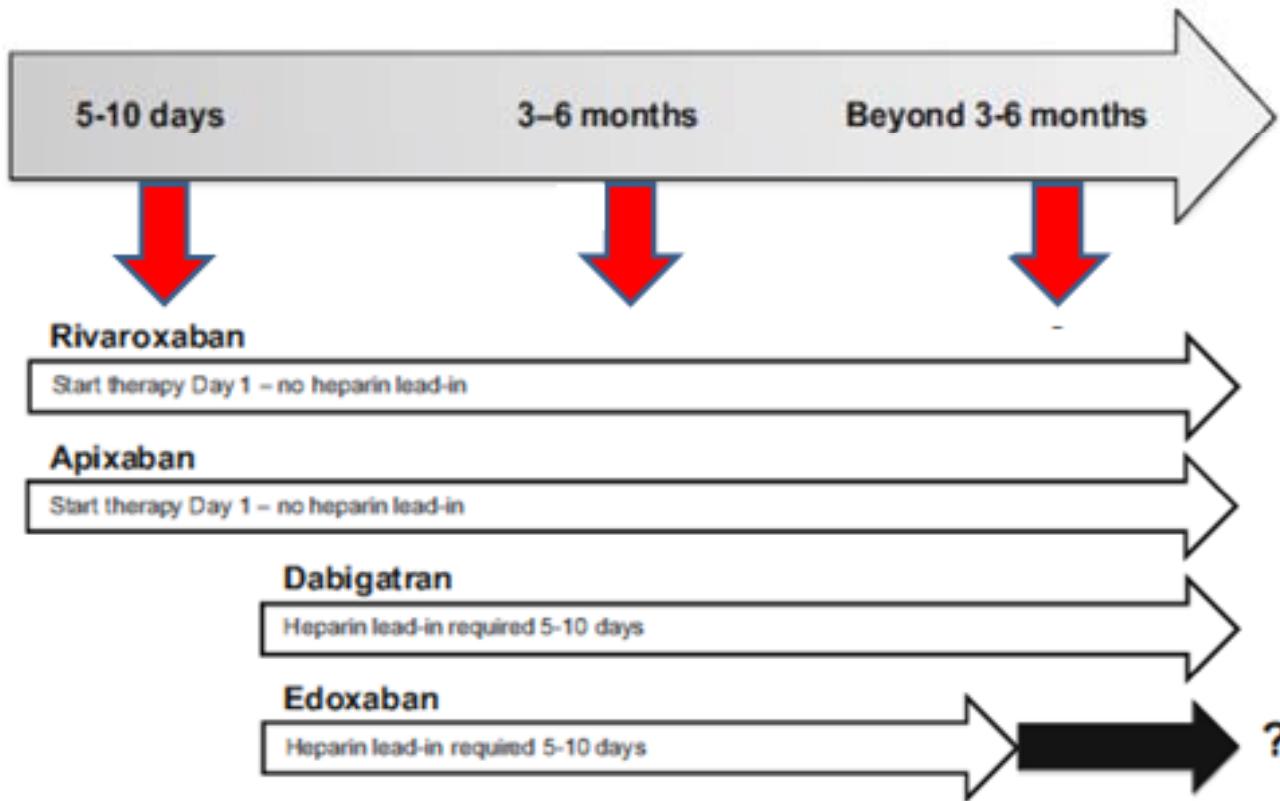
**Figure 3.** Cumulative incidence of recurrent thromboembolism separately in patients with idiopathic (unprovoked) and secondary VTE.

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**TABLE 5 Main Results of Phase III Studies With NOACs for Extended Treatment of VTE**

NOAC (Ref. #)	Study	N	Treatment	Duration (months)	Efficacy Outcome	Safety Outcome
Dabigatran (85)	RE-MEDY	2,856	Dabigatran 150 mg bid vs. warfarin (INR 2–3)	18–36	Recurrent VTE: 1.8% with dabigatran, 1.3% with warfarin	Major bleeding: 0.9% with dabigatran, 1.8% with warfarin
	RESONATE	1,343	Dabigatran 150 mg bid vs. placebo	6	Recurrent VTE: 0.4% with dabigatran, 5.6% with warfarin	Major bleeding: 0.3% with dabigatran, 0 with placebo
Rivaroxaban (39)	EINSTEIN-extension	602	Rivaroxaban 20 mg daily vs. placebo	6 or 12	Recurrent VTE: 1.3% with rivaroxaban, 7.1% with placebo	Major bleeding: 0.7% with rivaroxaban, 0 with placebo
Apixaban (86)	AMPLIFY-extension	2,486	Apixaban 2.5 mg bid vs. placebo Apixaban 5 mg twice daily vs. placebo	12	Recurrent VTE and death: 1.7% with apixaban, 8.8% with placebo	Major bleeding: 0.2% with apixaban, 0.5% with placebo
					Recurrent VTE and death: 1.7% with apixaban, 8.8% with placebo	Major bleeding: 0.1% with apixaban, 0.5 % with placebo

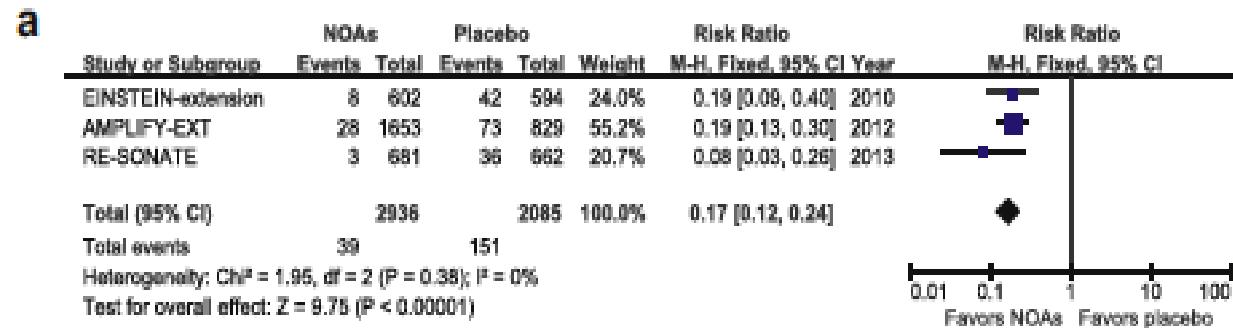


Edoxaban: trattamento esteso TEV

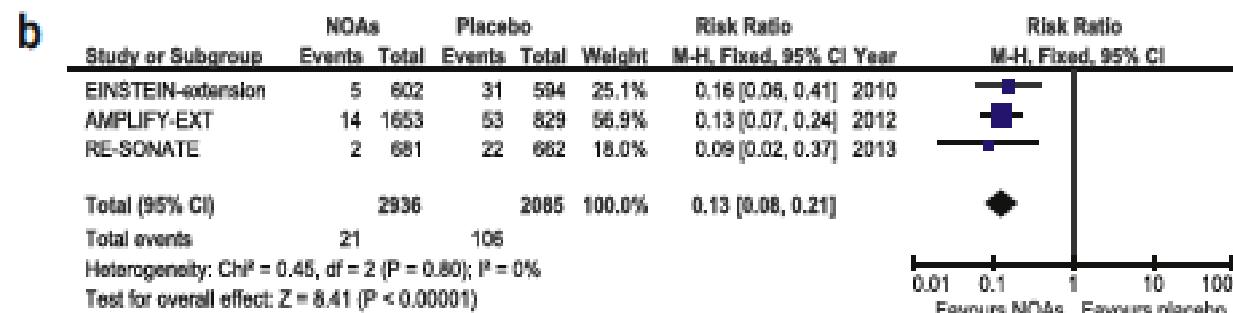
Post-hoc analisi di Hokusai-VTE: efficacia e sicurezza di Edoxaban nel TEV a 3 e 12 mesi: 3633 p. edoxaban vs 3594 warfarin:

Efficacia: 0.3 vs 0.4%

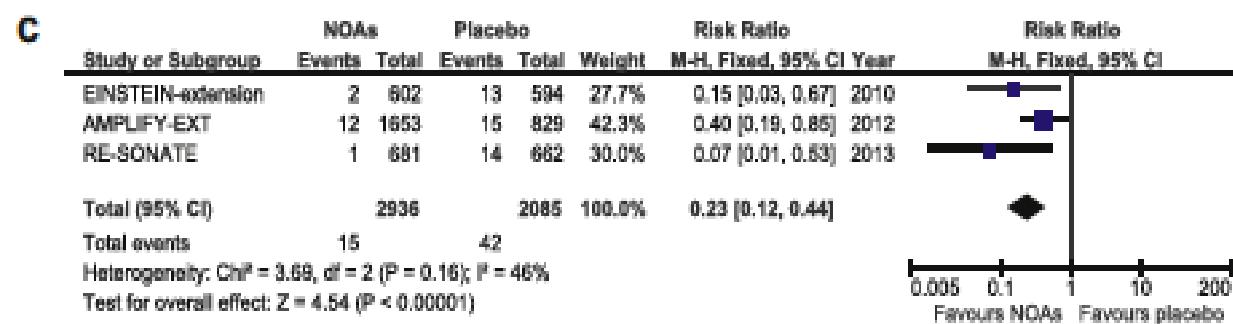
**Recidiva  
TEV**



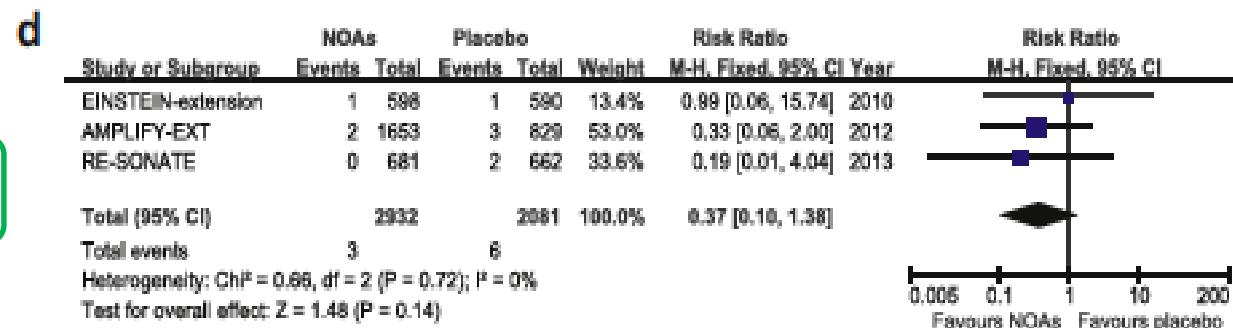
**Recidiva  
DVT**



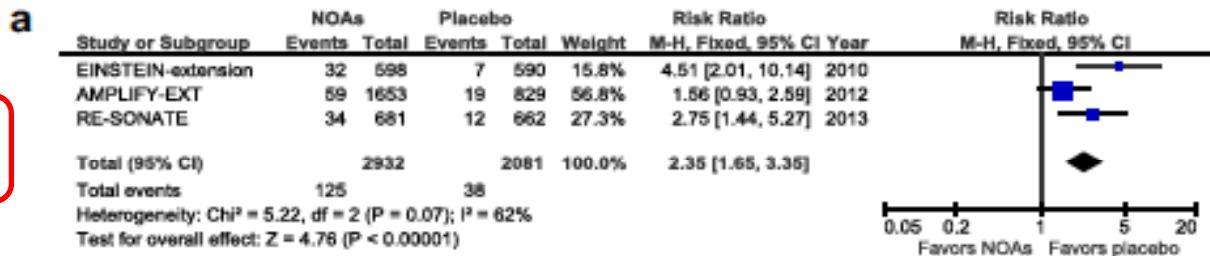
**Recidiva  
EP**



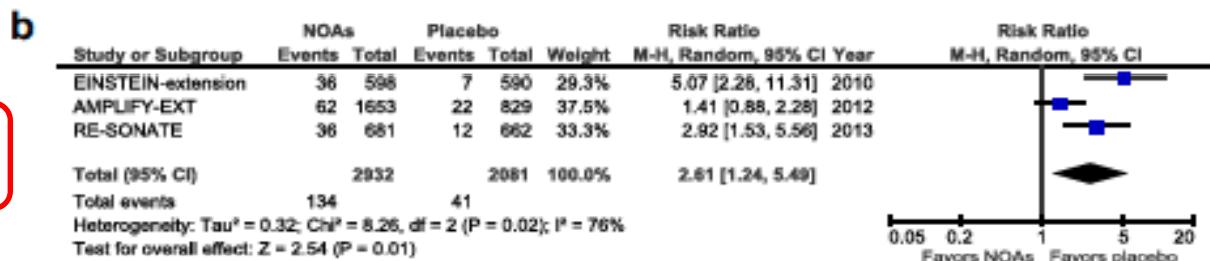
**Recidiva  
EP fatale**



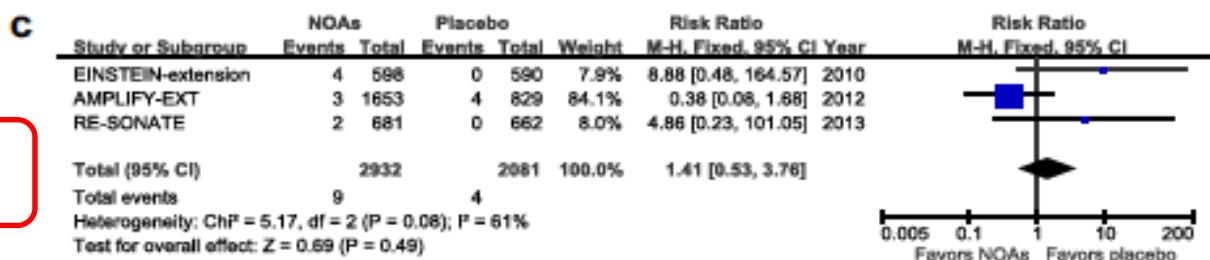
**CRNM**  
DOACs vs placebo



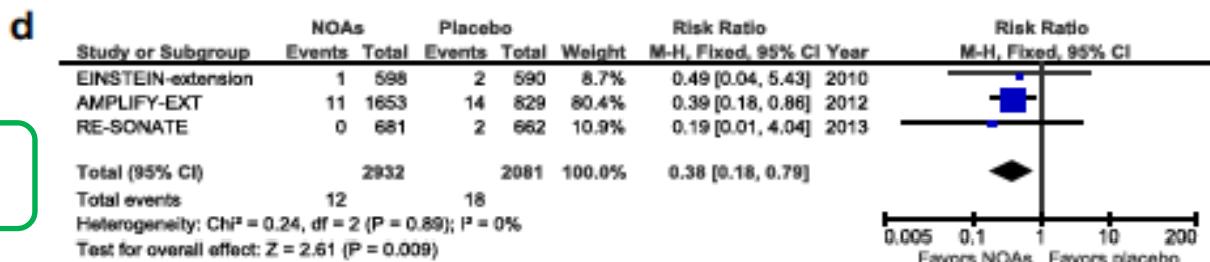
All bleeding  
DOACs vs placebo



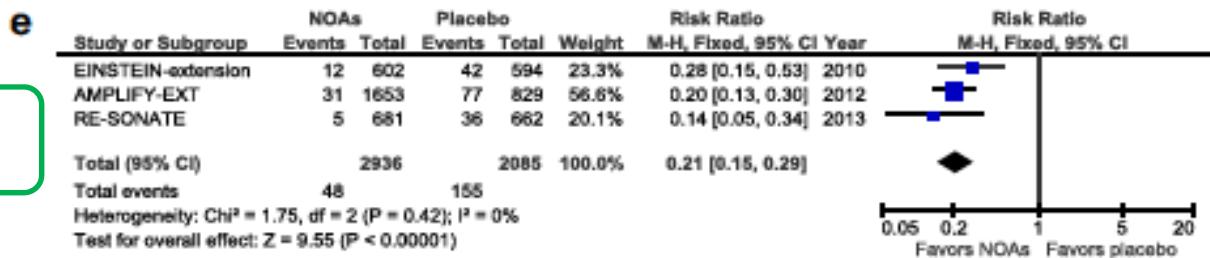
MB  
DOACs vs placebo



All cause mortality rate  
DOACs vs placebo



Net clinical benefit



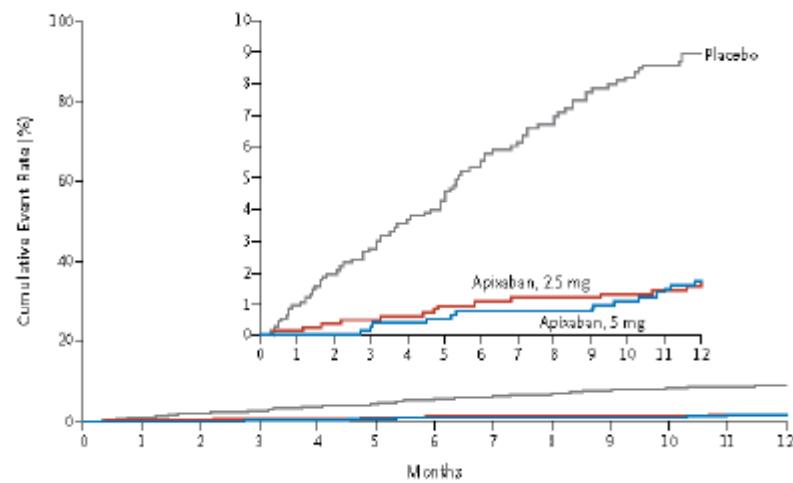
# Amplify Extension Safety

**Table 2.** Clinical Outcomes in the Intention-to-Treat Population during the Intended Active Study Period.\*

Outcome	Apixaban, 2.5 mg (N = 840)	Apixaban, 5 mg (N = 813)	Placebo (N = 829)	Relative Risk (95% CI)		
				Apixaban, 2.5 mg, vs. Placebo	Apixaban, 5 mg, vs. Placebo	Apixaban, 2.5 mg vs. 5 mg
number (percent)						
Recurrent VTE or death from any cause — primary efficacy outcome†	32 (3.8)	34 (4.2)	96 (11.6)	0.33 (0.22–0.48)	0.36 (0.25–0.53)	NA
Recurrent VTE or VTE-related death	14 (1.7)	14 (1.7)	73 (8.8)	0.19 (0.11–0.33)	0.20 (0.11–0.34)	0.97 (0.46–2.02)
Non-VTE-related cardiovascular death, myocardial infarction, or stroke	4 (0.5)	5 (0.6)	11 (1.3)	0.36 (0.11–1.12)	0.47 (0.16–1.33)	0.77 (0.21–2.88)
Recurrent VTE, VTE-related death, myocardial infarction, stroke, or cardiovascular disease-related death	18 (2.1)	19 (2.3)	83 (10.0)	0.21 (0.13–0.35)	0.23 (0.14–0.38)	0.92 (0.48–1.74)
Major bleeding	2 (0.2)	1 (0.1)	4 (0.5)	0.49 (0.09–2.64)	0.25 (0.03–2.24)	1.93 (0.18–21.25)
Clinically relevant nonmajor bleeding	25 (3.0)	34 (4.2)	19 (2.3)	1.29 (0.72–2.33)	1.82 (1.05–3.18)	0.71 (0.43–1.18)
Major or clinically relevant nonmajor bleeding	27 (3.2)	35 (4.3)	22 (2.7)	1.20 (0.69–2.10)	1.62 (0.96–2.73)	0.74 (0.46–1.22)
VTE, VTE-related death, myocardial infarction, stroke, cardiovascular disease-related death, or major bleeding‡	20 (2.4)	20 (2.5)	86 (10.4)	0.23 (0.14–0.37)	0.24 (0.15–0.38)	0.97 (0.52–1.79)

## Amplify Extension Efficacia

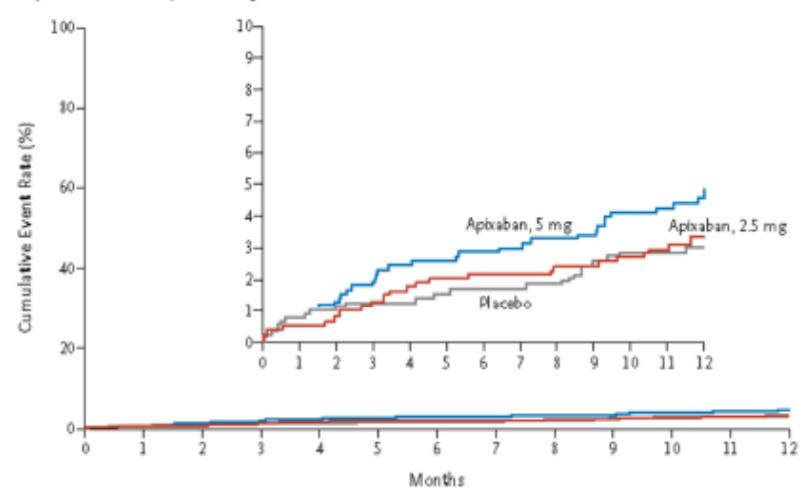
Symptomatic Recurrent VTE or VTE-Related Death



Agnelli et al; NEJM 2013

## Amplify Extension Sicurezza

Major or Clinically Relevant Nonmajor Bleeding



Agnelli et al; NEJM 2013

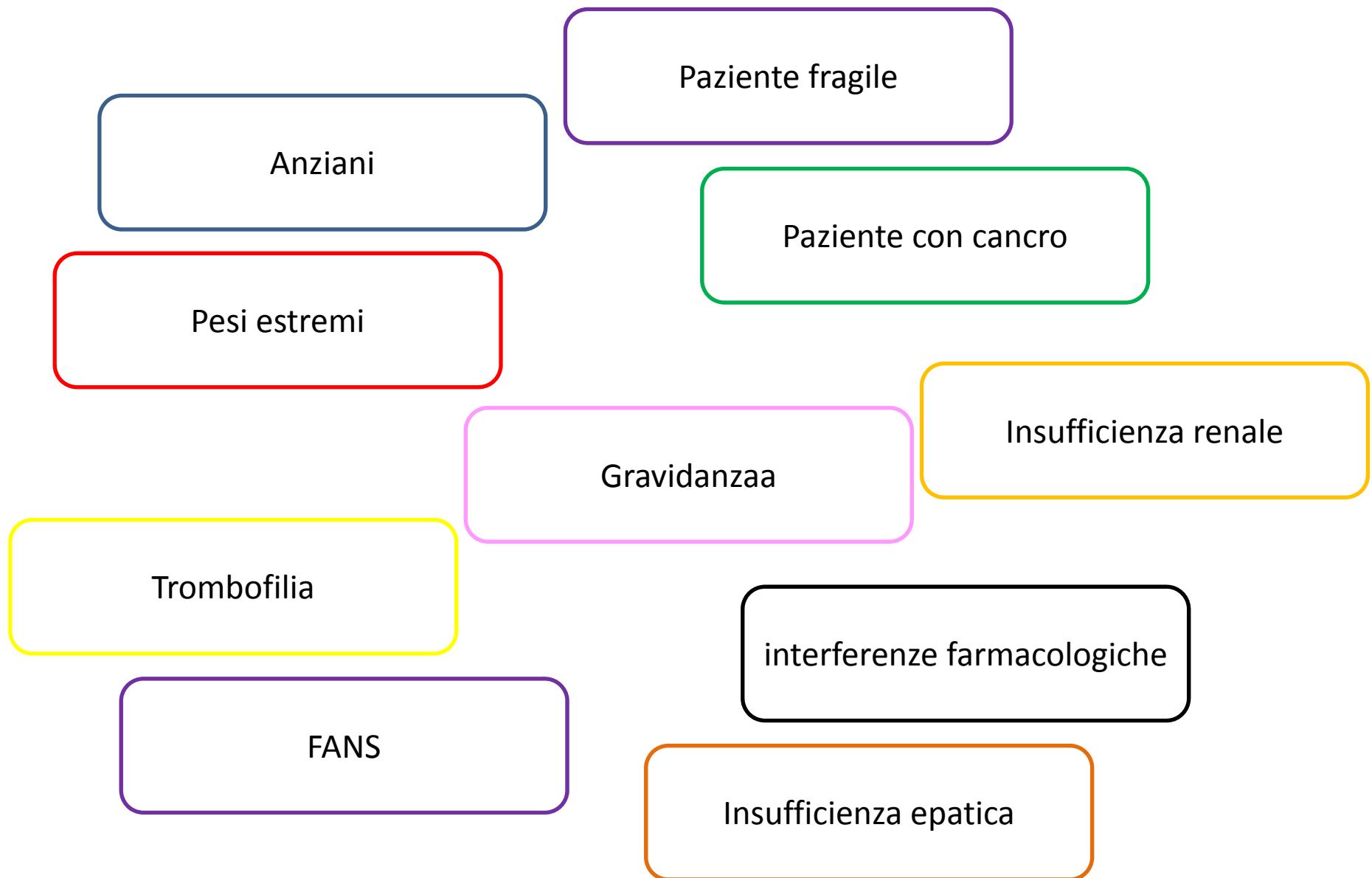
# ....e se il paziente non può o non vuole proseguire l'anticoagulante?

studio	terapia	Follow-up	Recidiva TEV	MB
WARFASA 2012 (402 pazienti randomizzati)	ASA 100 mg/die vs placebo	24.6 mesi	<b>28 vs 43</b> 6.6% vs 11.2% /anno	1 vs 1
ASPIRE 2012* (822 pazienti randomizzati)	ASA 100 mg/die vs placebo	37.2 mesi	<b>57 vs 73</b> 4.8% vs 6.5%/anno	14 vs 8

\*Outcome composito: TEV + IMA + Stroke + Morte CV = -34%

Possibile usare ASA se prevale rischio emorragico su rischio trombotico

# I DOACs vanno bene per tutti?



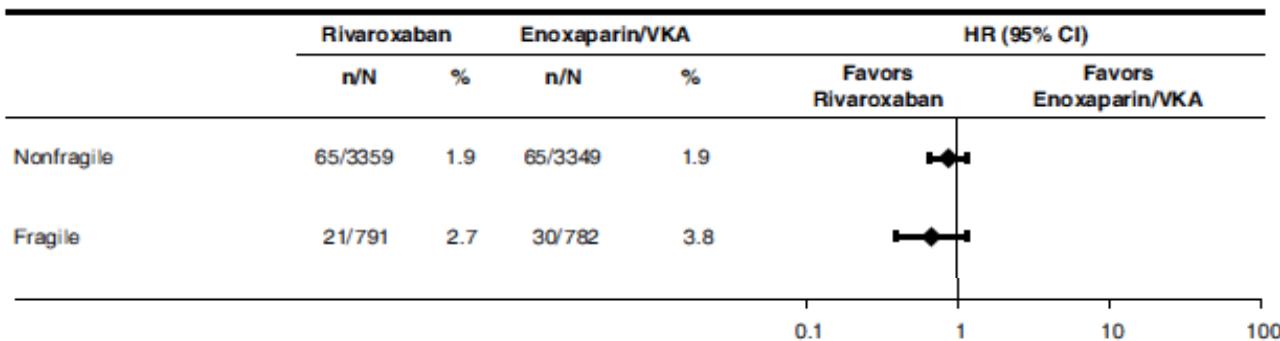
Paziente fragile

Oral rivaroxaban versus standard therapy for the treatment of symptomatic VTE: a pooled analysis of the EINSTEIN-DVT and PE randomized studies  
(MH Prins et al., Thrombosis J. 2013)

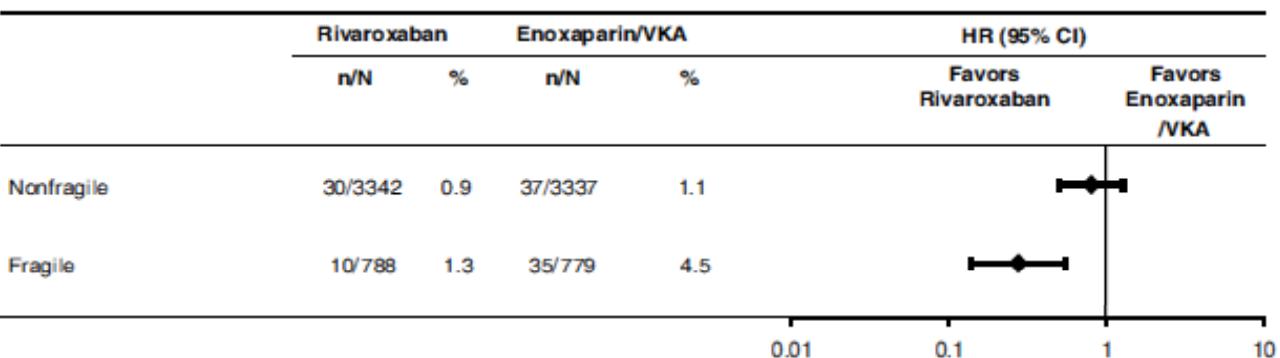
1573 p. (19%) fragili per: **età > 75** (1279), **IR moderata/severa** (649) o **basso peso** (107)

Recidiva TEV: > nei p. fragili vs non fragili

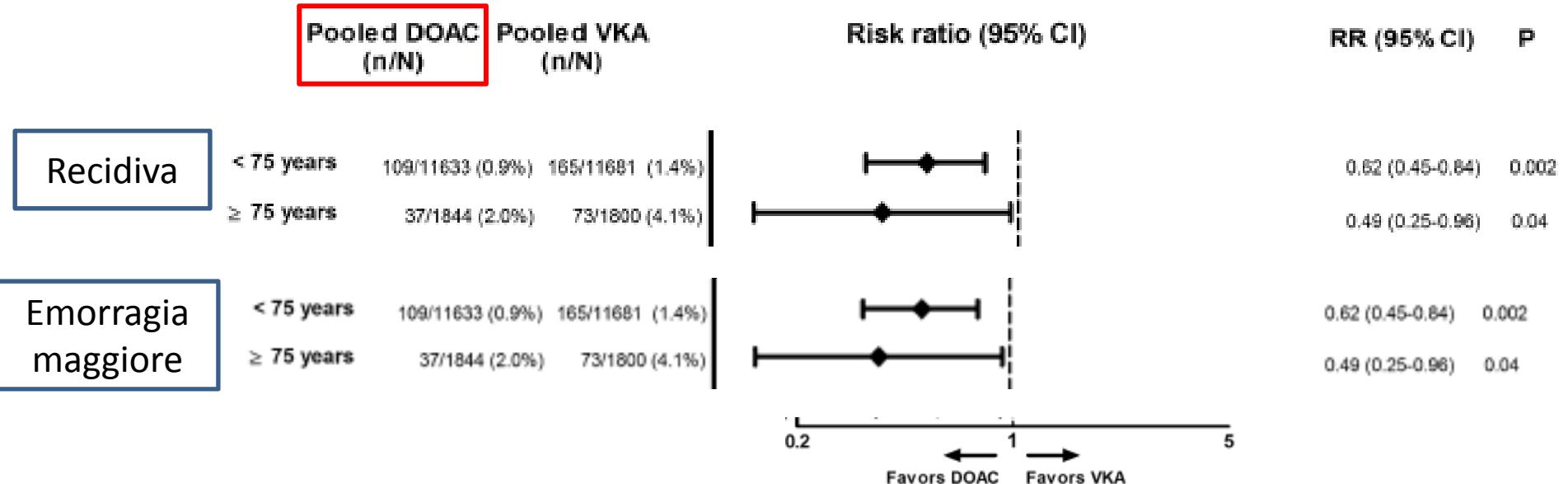
Recidiva %



MB %



## Paziente anziano



N. Van Es et al., Blood 2014

## Pesi estremi

### Recidiva

#### BODY WEIGHT

< 100 kg	57/2146 (2.7%)	62/2157 (2.9%)
≥ 100 kg	278/11354 (2.4%)	305/11262 (2.7%)



### Studi registrativi:

2-13% p. con peso < 50-60 Kg

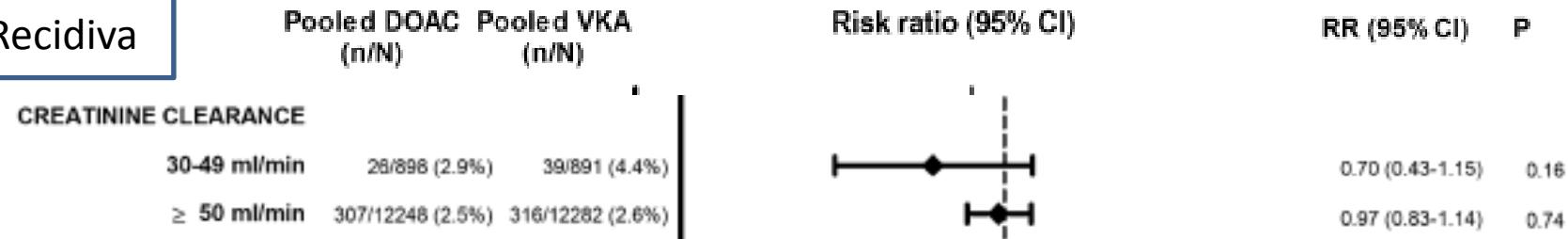
14-19% p. con peso > 100 Kg

30% BMI > 30, 12% con BMI > 35

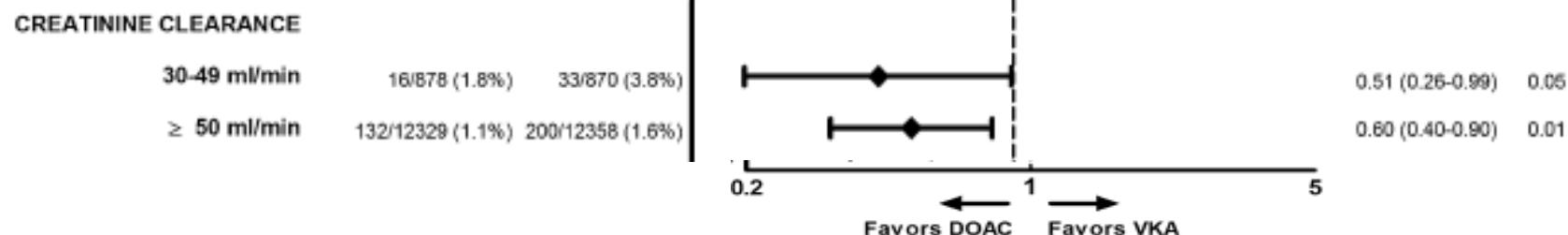
1. Può esserci una differenza di picco di concentrazione , ma non è stato dimostrato impatto clinico
2. Nessuna differenza nel rischio recidiva
3. In attesa di dati più sicuri è raccomandata cautela nel prescrivere DOACs a pesi < 50Kg o > 120 Kg o con BMI > 35

## Insufficienza renale

### Recidiva



### Emorragia maggiore



- Efficacia e riduzione dei sanguinamenti maggiori si mantiene per i pazienti con **età > 75 anni** e con **insufficienza renale moderata**
- Traffico che per Edoxaban, per il TEV non sono stati ridotti i dosaggi nell'insufficienza renale moderata

[Van Es. Blood. 2014](#)

## FANS

<b>Rivaroxaban</b>	ASA si	NR	3.3 vs 6.9%
Vs	ASA no	NR	1.6 vs 2.9%
Enoxa/WF	FANS si	NR	4.7 vs 8.4%
(EINSTEIN-DVT and PE)	FANS no	NR	1.4 vs 2.7%

**Rischio emorragico**

- > + FANS o ASA
- > con ASA
- no differenze fra Riva e enoxa/WF

<b>Dabigatran</b>	ASA si	3.1 vs 2.3	1.0 vs 3.0%
vs	ASA no	2.6 vs 2.4	1.0 vs 1.5%
WF	FANS si	2.8 vs 2.0	1.1 vs 1.0%
(RE-COVER)	FANS no	2.6 vs 2.5	0.9 vs 1.8%

<sup>1.</sup> **Non differenze su recidiva VTE**

**Rischio emorragico**

- Non differenze +- FANS o ASA
- > con ASA e WF
- no differenze fra Dabiga vs WF

Trombofilia

- 2-18% p. arruolati avevano una trombofilia
- Nessuna differenza di efficacia nei trombofilici (studio RE-MEDY S Shulman ASH 2014)
- Fallimenti di dabigatran e rivaroxaban in s. ACA e LAC
- Studi in corso su s.ACA e LAC:
  - rivaroxaban (NCT 02116036) NCT 021572729)
  - apixaban (NCT 02295475)

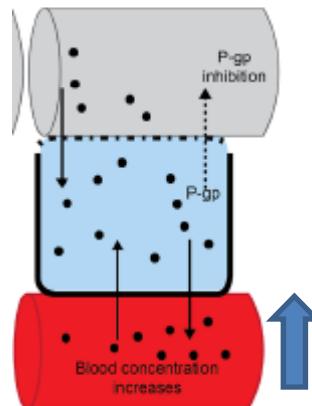
interferenze farmacologiche

- Caratteristiche di trasporto, metabolismo e eliminazione dei DOACs

	P-gp substrate	CYP3A4 substrate (% of drug metabolized via CYP3A4)	% renal elimination
Dabigatran	Yes	No	≈ 80
Rivaroxaban	Yes	Yes (≈ 33) <sup>a</sup>	≈ 33
Apixaban	Yes	Yes (≈ 25) <sup>b</sup>	≈ 25
Edoxaban	Yes	No	≈ 50

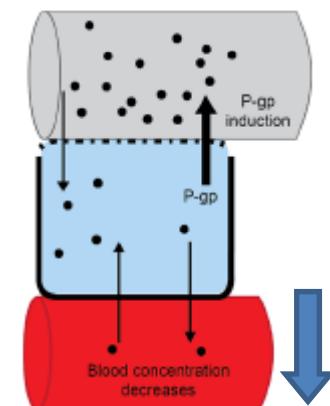
#### P-gp Inhibition

P-gp activity reduced;  
less drug pumped  
back into intestine,  
greater systemic  
exposure.



#### P-gp Induction

P-gp activity increased;  
more drug pumped  
back into intestine,  
less systemic exposure.



## Dabigatran Edoxaban

- Amiodarone
- Carvedilolo/nicardipina
- Clarithromicina/eritromicina
- Ciclosporina/tacrolimus
- Verapamil/Diltiazem
- Ketoconazolo/itraconazolo
- Lapatinib
- Chinidina
- Propafenone
- Tamoxifene
- Antiretrovirali
- Succo di pompelmo

- Barbiturici
- Carbamazepina
- Desametasone
- Fenitoina
- Rifampicina
- Iperico

# Rivaroxaban

# Apixaban

Permeabilità P-gp + forti  
induttori CYP3A4



Permeabilità P-gp e forti  
inibitori di CYP3A4



Permeabilità -gp e  
moderati inibitori  
di CYP3A4



Barbiturici  
Carbamazepina  
Desametasone  
Fenitoina  
Rifampicina  
Iperico

Claritromicina  
Itraconazolo/Ketocona  
zolo/posaconazolo  
Antiretrovirali  
Conivaptan (Vaprisol)  
Iperico

Ciclosporina  
Diltiazem  
Tamoxifene  
verapamil  
dronedarone

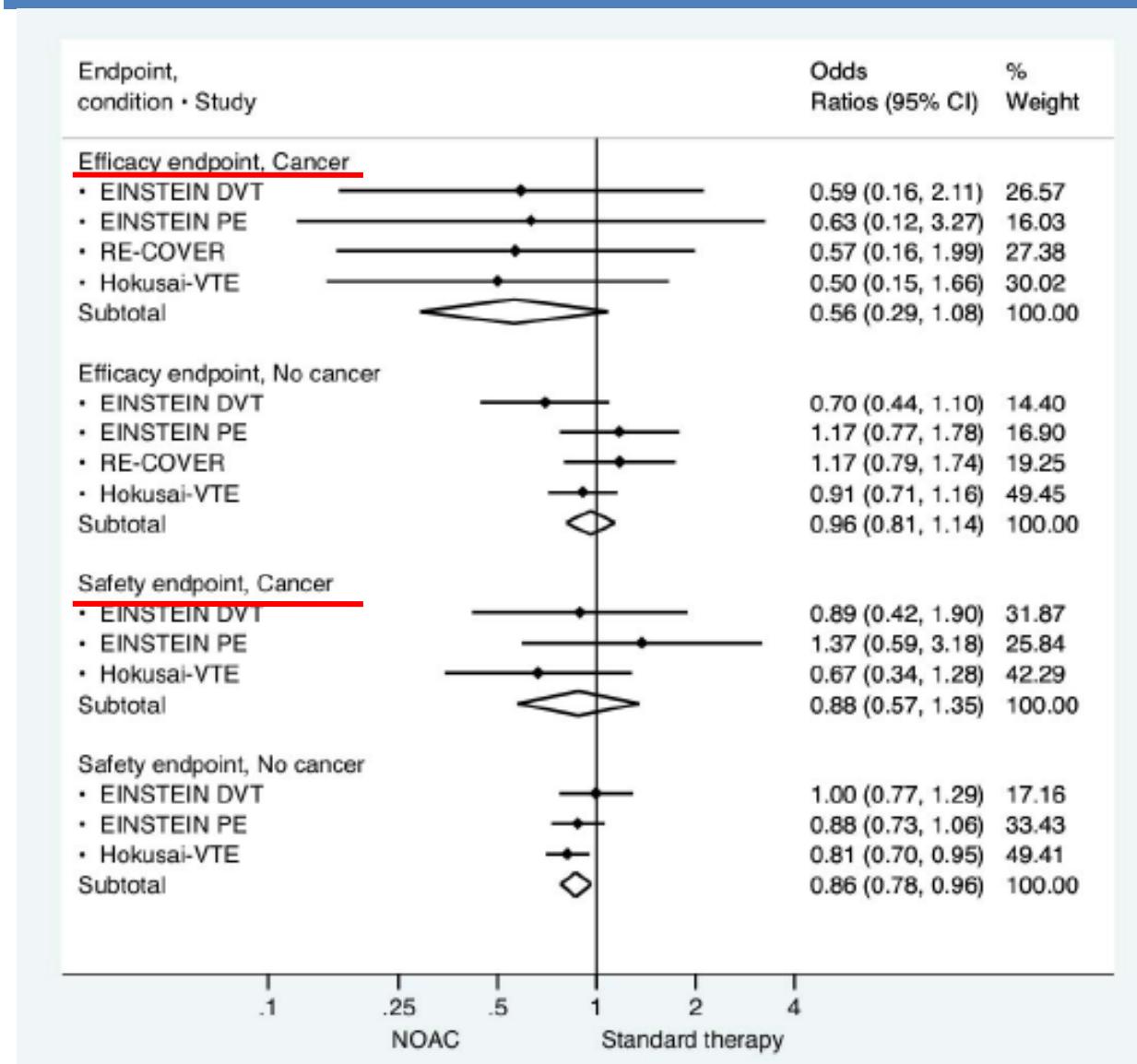
Paziente con cancro

## NOAC VTE trials: Baseline characteristics

	RE-COVER <sup>1#</sup> (Dabigatran)	EINSTEIN DVT <sup>2</sup> (Rivaroxaban)	EINSTEIN PE <sup>3</sup> (Rivaroxaban)	AMPLIFY <sup>4</sup> (Apixaban)	Hokusai-VTE <sup>5</sup> (Edoxaban)
Patients, N	2539	3449	4832	5395	8292
Age (yrs)	55	56	58	57	56
Female (%)	42	43	47	41	43
Creatinine clearance <50 mL/min (%)	NR	7	8	6	7
DVT (%)	69	99	-	65	59
PE±DVT (%)	31	0.6	100	35	40
Unprovoked (%)	NR	62	65	90	65
Cancer (%)	5	6	5	3	9 <sup>†</sup> (2.4%)
Previous VTE	26	19	19	16	18

# NOACs and treatment of VTE in Cancer Patients: A Semi Systematic Review and Meta-Analysis of Safety and Efficacy outcomes (TB Larsen et al., PLOS One 2014)

Metanalisi retrospettiva : 4 studi randomizzati, 19090 p. di cui **759 con cancro**, NOAC vs VKA



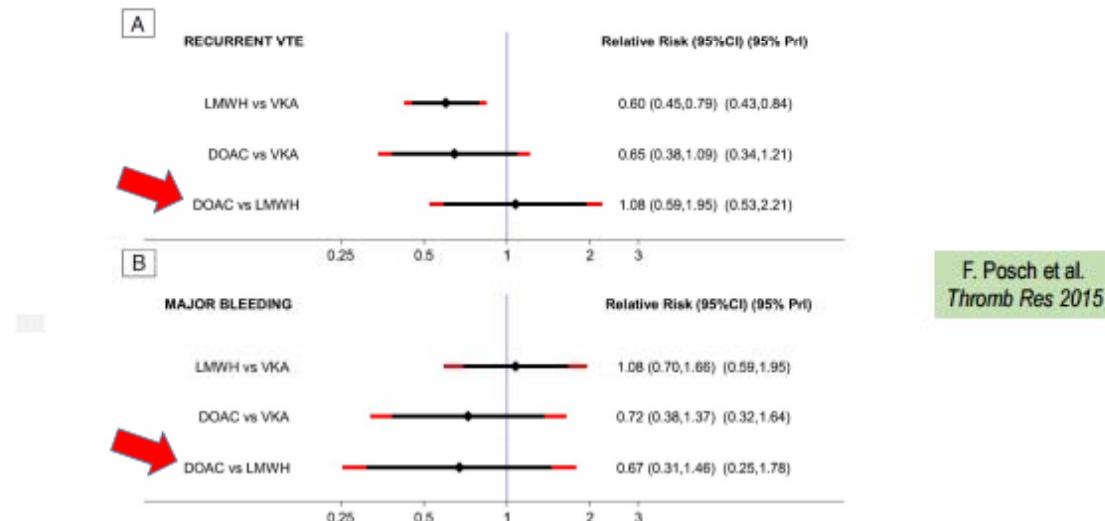
Recidiva TEV  
3.9 vs 6.0%

MC. Vedovati et al.  
Chest 2015

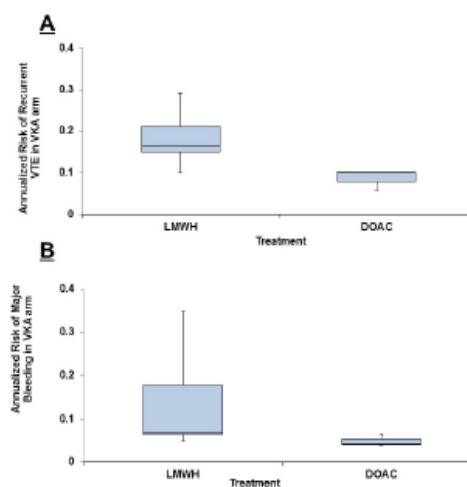
Sanguinamento  
maggiore  
3.2 vs 4.2%

MC. Vedovati et al.  
Chest 2015

## DOACs nei pz con cancro – Network meta-analysis



Selected cancer patient population in DOAC trials?



The higher annualized risk of recurrent VTE and major bleeding in LMWH trials suggests a higher-risk cancer population were enrolled in these studies

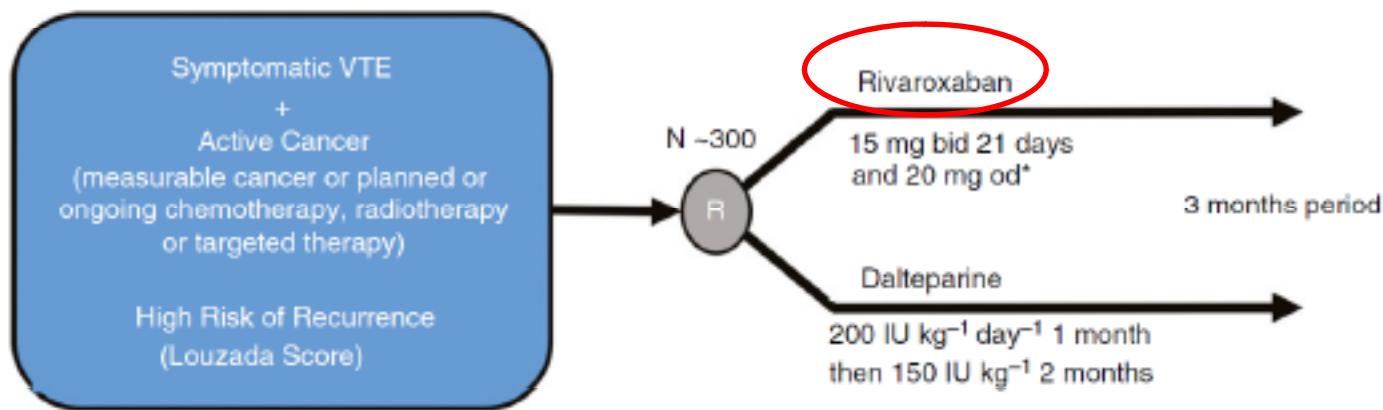


Fig. 1. Overview of the **CASTA DIVA** trial (prospective, multicenter, randomized, open-label, pilot non-inferiority trial with blinded evaluation of endpoints [PROBE]). VTE, venous thromboembolism. [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

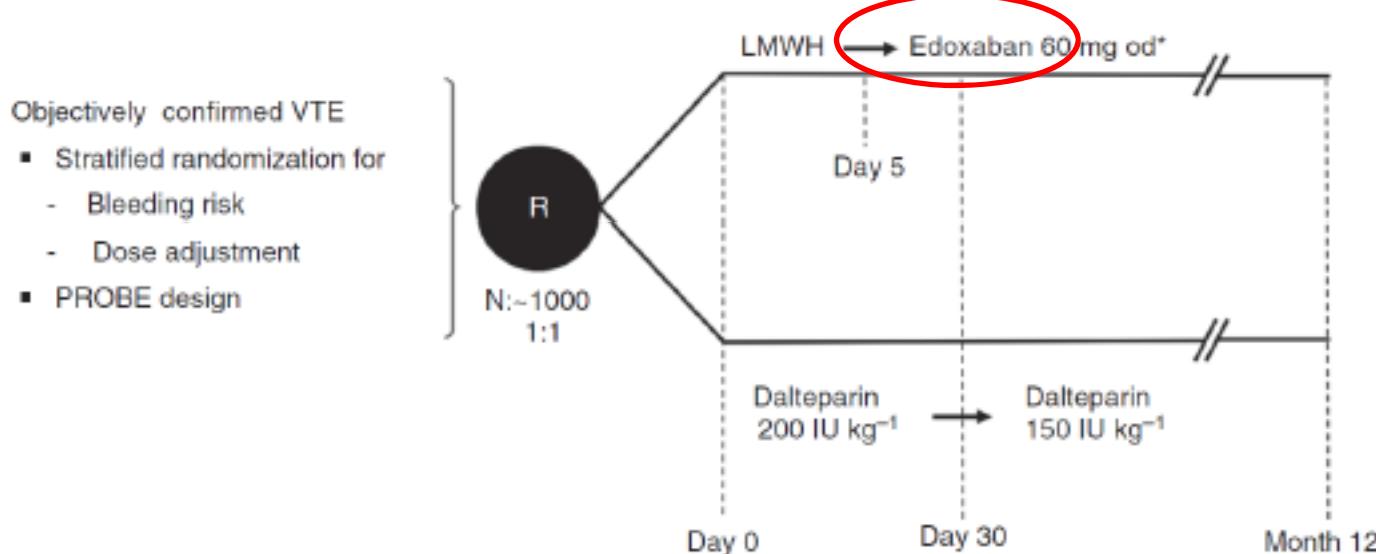
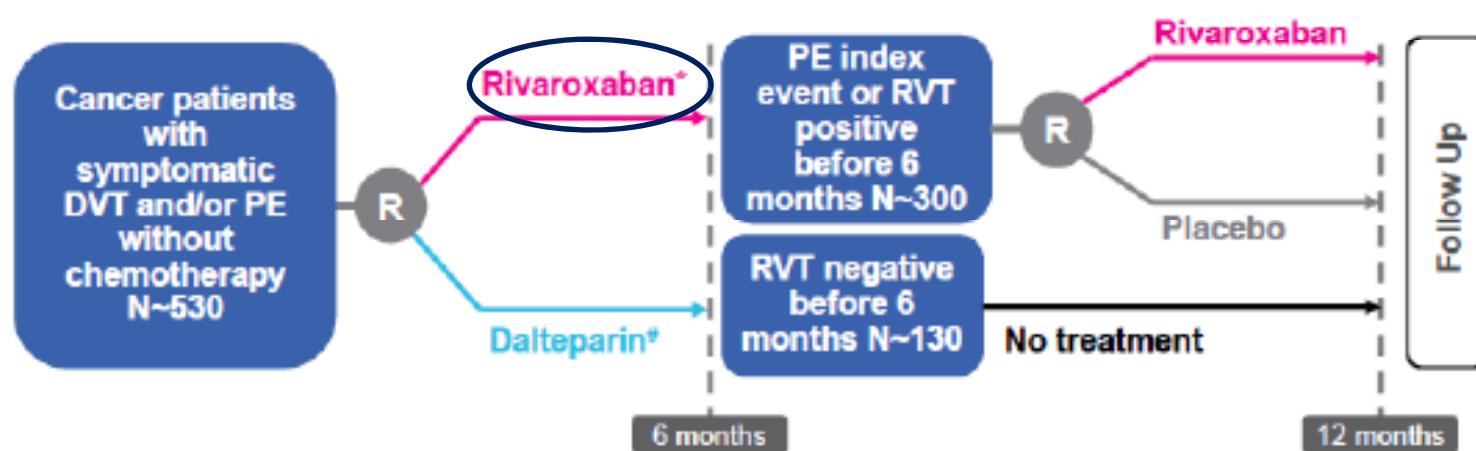


Fig. 2. Overview of the **HOKUSAI VTE-CANCER** trial (prospective, multicenter, randomized, open-label, pilot non-inferiority trial with blinded evaluation of endpoints [PROBE]). \*Dose adjustment to edoxaban 30 mg o.d. in patients with a body weight of 60 kg or less, a creatinine clearance between 30 and 50 mL min<sup>-1</sup> inclusive, or concomitant use of P-gp inhibitors [70]. VTE, venous thromboembolism; LMWH, low-molecular-weight heparin.

## select-d

Rationale: To assess the efficacy and safety of rivaroxaban versus dalteparin for the treatment of VTE in patients with cancer not currently receiving chemotherapy



Short design: Prospective, randomized, open-label, multicentre pilot phase III study

Indication: VTE<sub>x</sub> patients with cancer

FPPV: Q4-13  
LPLV: 16/17

\*15 mg bid for 21 days followed by 20 mg od; for patients with CrCl 30–49 ml/min dosing recommendations as in rivaroxaban SmPC; if a patient's platelet counts falls to <50,000/mm<sup>3</sup>, rivaroxaban should be discontinued until the platelet count recovers to above 50,000/mm<sup>3</sup>; #200 IU/kg od for the first 30 days of treatment followed by 150 IU/kg od; if a patient's platelet count falls to 50,000–100,000/mm<sup>3</sup> the daily dose of dalteparin should be reduced by 2500 IU until platelet count returns to ≥100,000/mm<sup>3</sup>; if a patient's platelet count falls to <50,000/mm<sup>3</sup>, dalteparin should be discontinued until the platelet count recovers to above 50,000/mm<sup>3</sup>

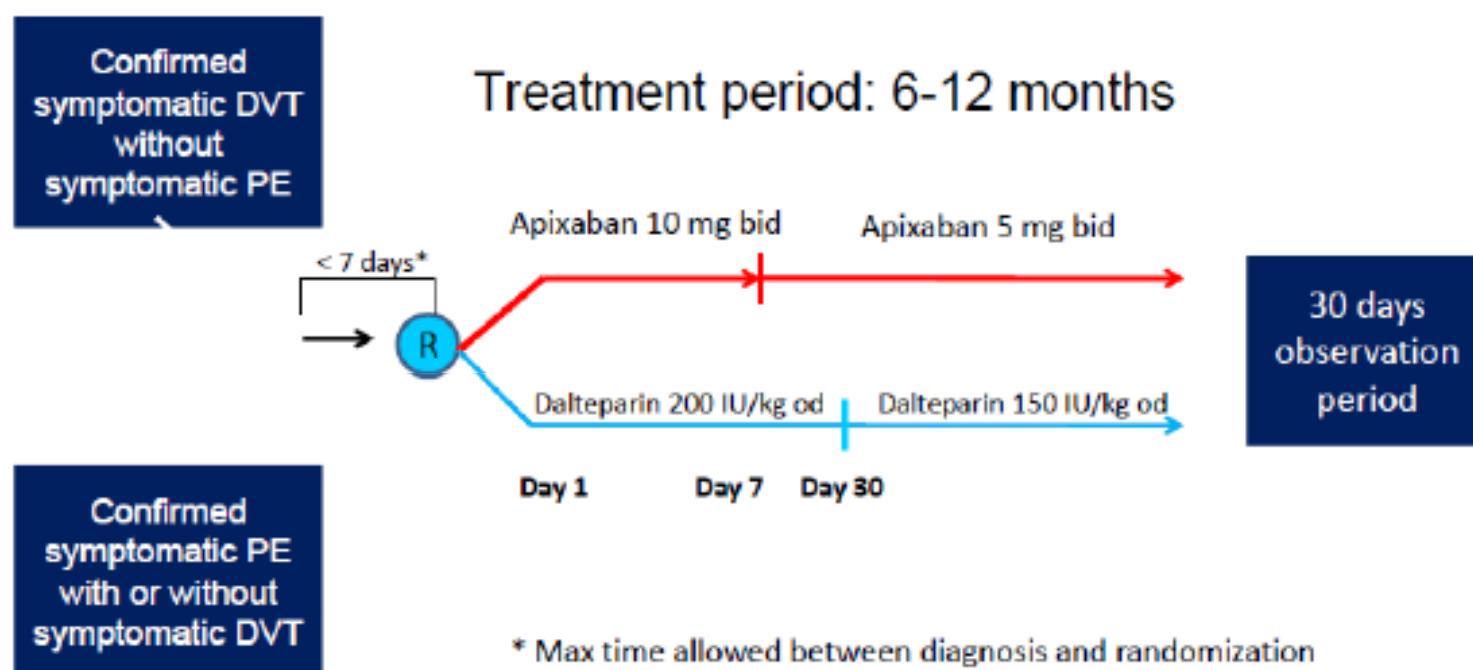
IIR, Investigator Initiated Research; FU, follow-up; R, randomization; RVT, residual vein thrombosis

<http://www2.warwick.ac.uk/fac/med/research/hsscience/clu/trials/cancer/select-d/>; EudraCT number: 2012-005589-37



## Caravaggio

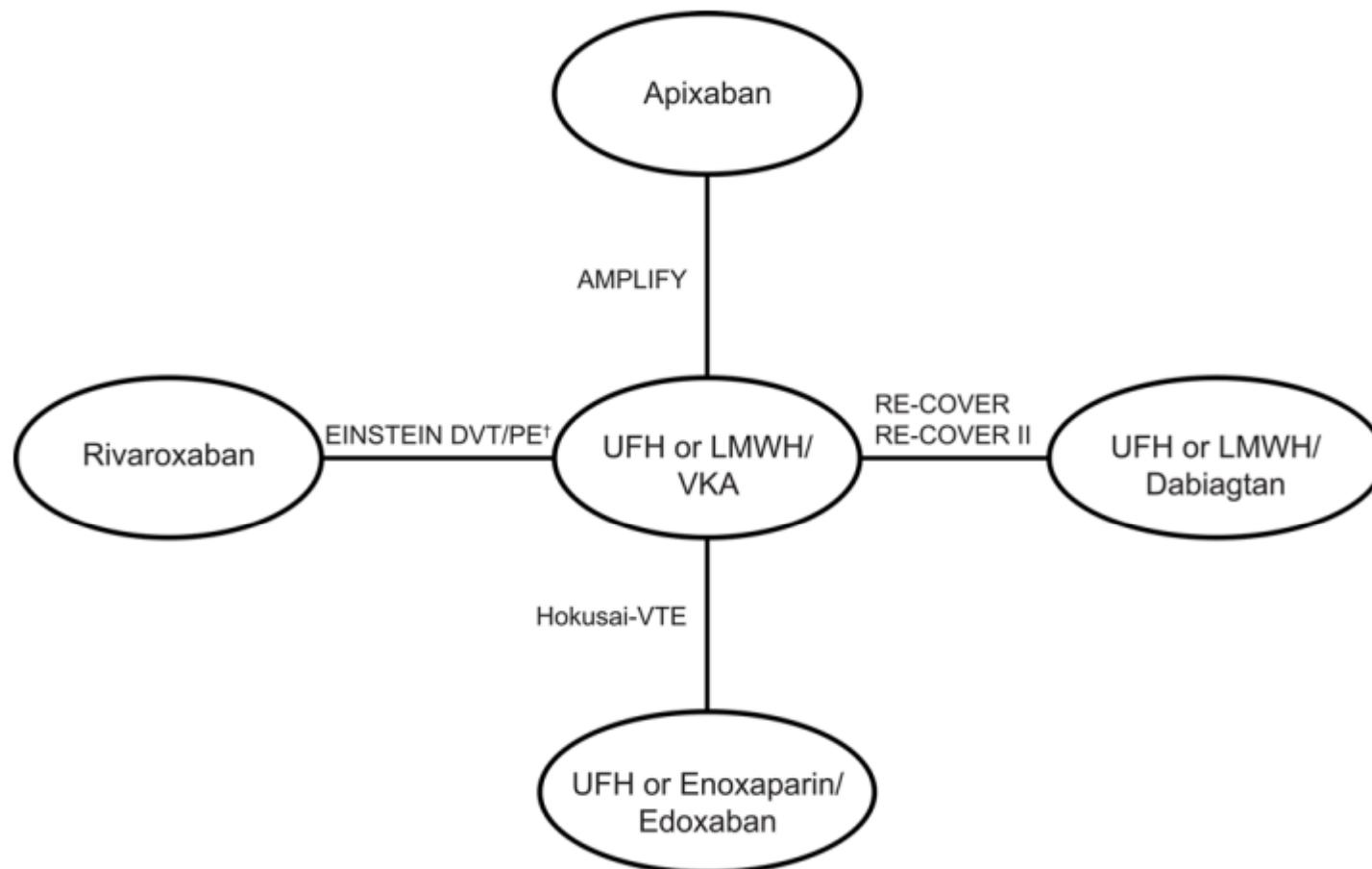
Randomized, open-label, PROBE, non inferiority study



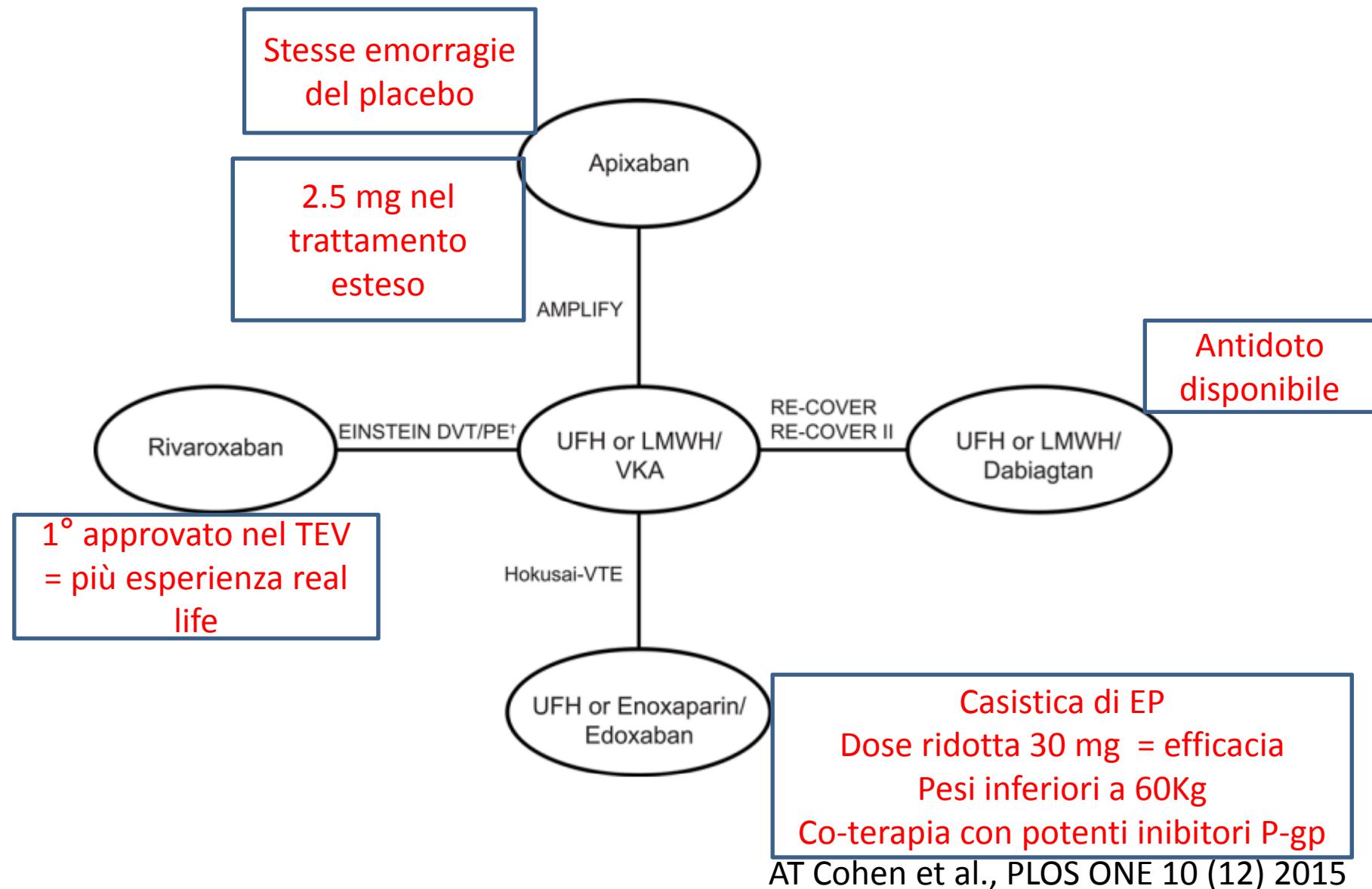
# I DOACs vanno bene per tutti?

- Usare con cautela
- Pesi estremi
- Insufficienza renale
- Insufficienza epatica
- Non usare
  - Insufficienza renale in stadio IV
  - Insufficienza epatica grave Child Plugh C (deficit sintesi fattori coagulativi)
  - Cancro attivo
  - Trombosi vene cerebrali o splanchniche
  - S. ACA o LAC
  - EP emodinamicamente instabili (trombolisi)
  - Gravidanza o allattamento
  - Farmaci fortemente interferenti

# Confronto indiretto fra i DOACs



# Confronto indiretto fra i DOACs



# Analisi di sensibilità per la efficacia e la sicurezza dei DOACs nella TEV

Outcome measure	Apixaban Rivaroxaban vs VKA (RR)		Dabigatran Edoxaban vs VKA (RR)	
DVT	0.67	p 0.02	1.00	p 0.99
MB	0.45	p < 0.0001	0.81	p 0.14
CRNM	0.75	p < 0.00001	0.75	p < 0.00001
Fatal bleeding	0.75	p 0.51	0.28	p < 0.04
Net clinical benefit	0.72	p 0.0002	0.88	p 0.16

# Confronto indiretto su rischio emorragico

Treatment comparison (95% CrI)	RR	MB o CRNM	MB	CRNM
Apixaban vs rivaroxaban	<b>0.47</b>	0.55	<b>0.47</b>	
vs dabigatran	<b>0.69</b>	<b>0.40</b>	0.80	
vs edoxaban	<b>0.54</b>	<b>0.36</b>	<b>0.59</b>	
Rivaroxaban vs dabigatran	<b>1.48</b>	0.73	<b>1.70</b>	
vs edoxaban	1.14	0.65	<b>1.26</b>	
Dabigatran vs edoxaban	<b>0.77</b>	0.89	<b>0.74</b>	

**APIXABAN: < rischio MB + CRNM vs altri 3 DOACs**

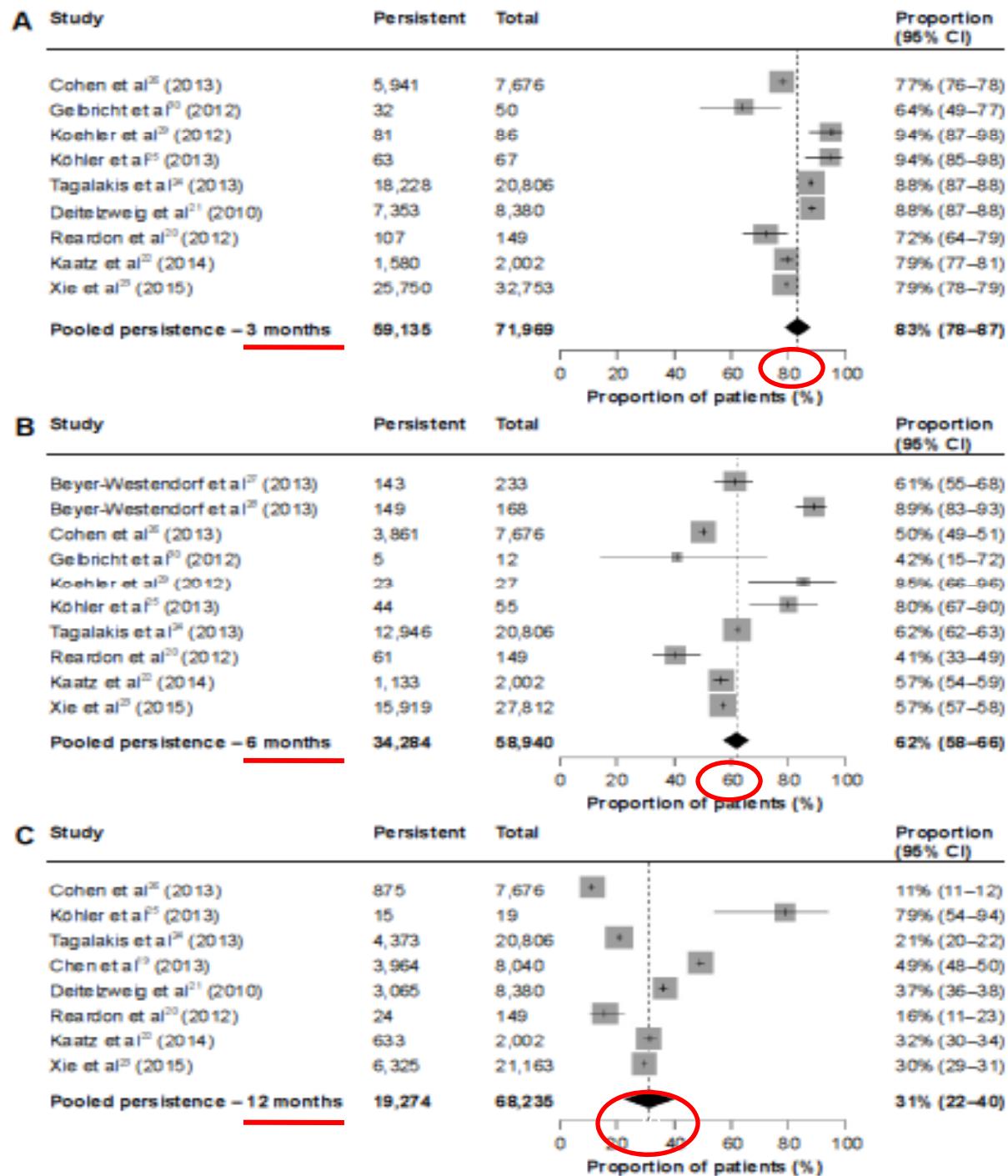
**RIVAROXABAN: > rischio CRNM vs Dabigatran e Edoxaban**  
**> rischio MB o CNM vs Dabigatran**

**DABIGATRAN: < rischio MB o CRNM vs edoxaban**

:

# Come scegliere fra le 4 molecole?

Caratteristica	Farmaco di scelta	razionale
<b>IRC non stadio IV</b>	Apixaban, Edoxaban, Rivaroxaban	Dabigatran metabolismo renale
<b>Solo terapia orale</b>	Apixaban, Rivaroxaban	Dabigatran e Edoxaban necessitano di inizio con eparina
<b>Rischio emorragico GI</b>	Apixaban – (Edoxaban 30 mg)	emorragie GI con Dabigatran, Rivaroxaban e Edoxaban dose alta
<b>Rischio CAD</b>	Apixaban, Edoxaban, Rivaroxaban	Segnalati IM con Dabigatran
<b>Età 75, IRC, donna, basso peso</b>	Apixaban, Rivaroxaban	Trials AMPLIFY e EINSTEIN-DVT



**Limited evidence on persistence with anticoagulants, and its effect on the risk of recurrence of VTE: a systematic review of observational studies**

(P. Vora et al., Patient Preference and Adherence 2016)

12 studi  
VKA e DOACs  
71.969 p. a 3 mesi  
58.940 p. a 6 mesi  
68.325 p. a 12 mesi



# Safe and effective use of rivaroxaban for treatment of cancer-associated VTE: a prospective cohort study

(S. Mantha et al., J. Thromb. Thrombolysis 2017)

200 p. CAT (PE or proximal DVT), whose full course of anticoagulation was with rivaroxaban

Competing risk analysis, primary endpoints at 6 months

Recurrent VTE was 4.4 % ( 1.4–7.4 %)

MB 2.2 % ( 0–4.2 %)

all-cause mortality 17.6 % ( 11.7–23.0 %)

-rates of recurrent TEV and MB were comparable to cancer subgroup of EINSTEIN and similar to LMWH

