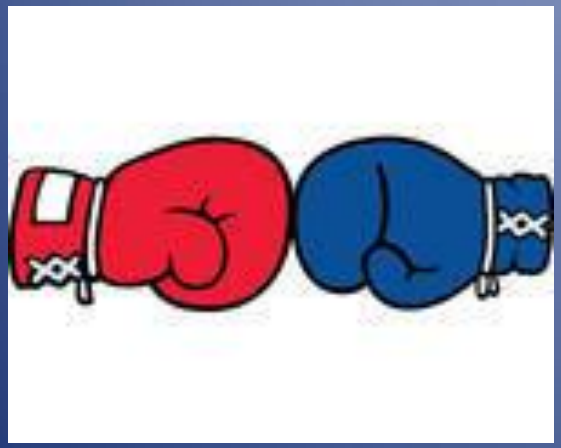
CONTROVERSIE SULL'USO DEI FARMACI ANTITROMBOTICI
7-8 ottobre 2016 Hotel Lloyd's Baia
Vietri sul Mare

Terapia anticoagulante nel trattamento e nella prevenzione del Tromboembolismo Venoso

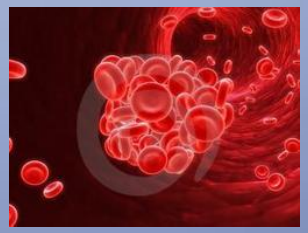


NOA … meglio di AVK

Dott.ssa Simona Pezzella
Battipaglia

Epidemiologia della TEV

Il TEV costituisce la terza causa di morte cardiovascolare dopo l'infarto e l'ictus



Incidenza annuale 100-200 casi/100.000 abitanti

il 70% delle EP fatali viene scoperto postmortem

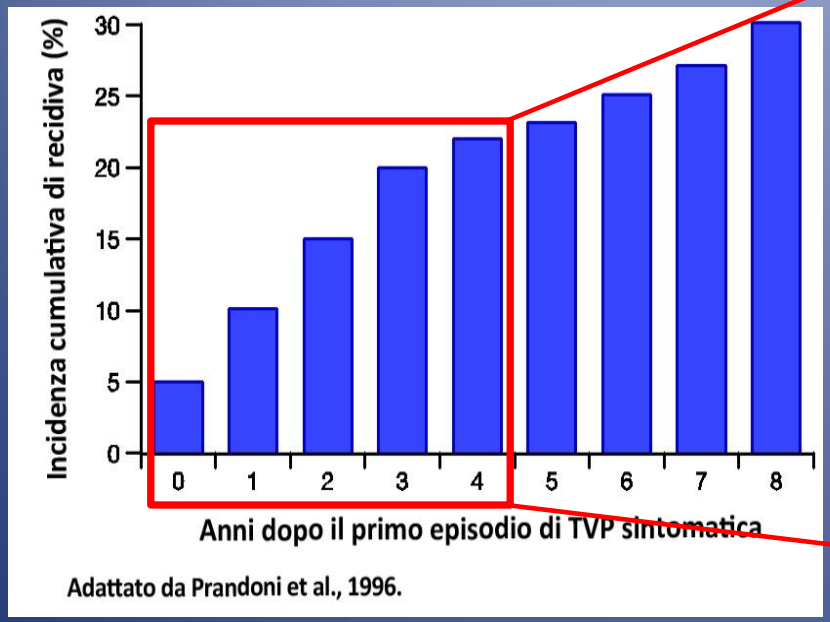
Circa l'80% delle TVP è clinicamente silente

Il 10% dei pazienti con EP muore nella prima ora di inizio dei sintomi

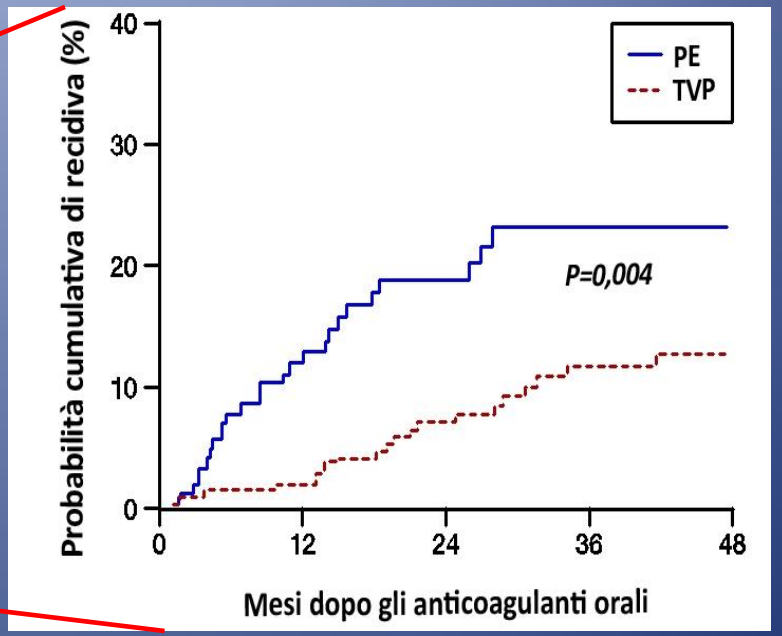
Barcellona, ESC 2014

Rischio di recidiva

Circa il 30% dei pazienti con un primo episodio di TEV avrà una recidiva nei 10 anni successivi.



Adattato da Prandoni et al., 1996.



Adattato da Eichinger et al., 2004.

Prandoni P et al. *Ann Intern Med.* 1996; 125(1): 1-7.
Eichinger S et al. *Arch Intern Med.* 2004; 164(1): 92-96.

TVP ed EP: una malattia frequente

Incidenza TEV stimata 1-2/1000 persone/anno, in progressivo incremento per aumento età media popolazione (il rischio aumenta con l'età)

- 1/10000/anno prima dei 40 anni
- 1/1000/anno tra 40 e 65 anni
- 1/100/anno oltre i 75 anni

Hirsh J Blood 2002; 99: 3102
Rosendaal FR Thromb Haemost 1999; 82: 610
White RL Circulation 2003; 107: I-4

Target della terapia del TEV

- Prevenire la morte per EP
- Lisare il materiale trombotico in casi selezionati
- Arrestare la crescita del trombo riducendo la morbilità
- Prevenire le recidive tromboemboliche
- Prevenire le sequele a lungo termine (sindrome post-trombotica, ipertensione polmonare cronica)

QUALE TRATTAMENTO

Caratteristiche importanti per un anticoagulante 'ideale'

- Orale
- Ampia finestra terapeutica
- Dosaggio fisso
- Poche interazioni con farmaci e alimenti
- Rapida inizio (e fine) dell'azione
- Farmacocinetica e farmacodinamica prevedibili
- Effetto rapidamente reversibile (+/-antidoti)
- Non necessità di stretto monitoraggio laboratoristico
- Test affidabile informativo di attività/concentrazione

Eparine non Frazionate (UFH)

Eparine a Basso Peso Molecolare (LMWH)

Fondaparinux

AVK

- Risposta non prevedibile
- Stretta finestra Terapeutica (INR range 2-3)
- Monitoraggio periodico frequente
- Frequenti aggiustamenti terapeutici
- Lento onset/offset
- Numerose interazioni alimentari
- Numerose interazioni farmacologiche
- Rischio di complicanze emorragiche


Pradaxa


Xarelto
rivaroxaban tablets

NOA


Eliquis


once-daily
Lixiana®
edoxaban

I NOA hanno molte caratteristiche "ideali"

- Orali
- Ampia finestra terapeutica
- Dosaggio fisso
- Poche interazioni con farmaci e alimenti
- Rapido inizio (e fine) dell'azione
- Farmacocinetica e farmacodinamica prevedibile
- Non necessità di monitoraggio laboratoristico

Protocollo TEV per NAO

SINGLE-DRUG approach

Xarelto rivaroxaban tablets

15 mg x 2 die → 20 mg/die*

21 gg

Eliquis

10 mg x 2 die → 5 mg* x2/die

7 gg

Prevenzione recidive : 2,5 mg x 2/die

* Da aggiustare secondo la funzionalità renale del paziente

Protocollo TEV per NAO

TRADITIONAL approach

Pradaxa

UHF o EBPM → 150 mg X 2/die*

5 gg

once-daily Lixiana® edoxaban

UHF o EBPM → 60 mg/die*

5 gg

* Da aggiustare secondo la funzionalità renale del paziente

	DABIGATRAN	RIVAROXABAN	APIXABAN	EDOXABAN
TEV **Profilassi in ortopedia**	•RE-MOBILIZE •RE-NOVATE I-II •RE-MODEL	•RECORD I-IV	•ADVANCE I-III	
Trattamento	•RE-COVER I-II •RE-MEDY •RE-SONATE	•EINSTEIN DVT •EINSTEIN PE •EINSTEIN EXSTENSION	•AMPLIFY •AMPLIFY EXSTENSION	•HOKUSAI
Profilassi paziente medico		•MAGELLAN	•ADOPT	
FA	•RE-LY	•ROCKET-AF	•ARISTOTLE •AVERROES	•ENGAGE-AF
SCA		•ATLAS ACS 2-TIMI 51	•APPRAISE II (fase III)	

Table 1. Study details and baseline patient characteristics

	Hokusai-VTE		RE-COVER		RE-COVER II		AMPLIFY		EINSTEIN-DVT		EINSTEIN-PE		Combined	
	Edoxaban (n = 4118)	VKA (n = 4122)	Dabigatran (n = 1273)	VKA (n = 1266)	Dabigatran (n = 1280)	VKA (n = 1288)	Apixaban (n = 2691)	VKA (n = 2704)	Rivaroxaban (n = 1731)	VKA (n = 1718)	Rivaroxaban (n = 2419)	VKA (n = 2413)	DOAC (n = 13512)	VKA (n = 13511)
Treatment duration	3, 6, or 12 mo*		6 mo		6 mo		6 mo		3, 6 or 12 mo*		3, 6 or 12 mo*		—	—
Design	Double-blinded		Double-blinded		Double-blinded		Double-blinded		Open-label		Open-label		—	—
Treatment regimen													—	—
Initial treatment	LWMH or UFH for ≥5 d		LWMH or UFH for ≥5 d		LWMH or UFH for ≥5 d		Apixaban 10 mg bid for 7 d	LMWH† or UFH for ≥5 d	Rivaroxaban 15 mg bid for 3 wk	LMWH† for ≥5 d	Rivaroxaban 15 mg bid for 3 wk	LMWH† for ≥5 d	—	—
Long-term treatment	Edoxaban 60 mg od‡	Warfarin (INR 2-3)	Dabigatran 150 mg bid	Warfarin (INR 2-3)	Dabigatran 150 mg bid	Warfarin (INR 2-3)	Apixaban 5 mg bid	Warfarin (INR 2-3)	Rivaroxaban 20 mg od	Any VKA (INR 2-3)	Rivaroxaban 20 mg od	Any VKA (INR 2-3)	—	—
Mean age (y)	55.7	55.9	55.0	54.4	54.7	55.1	57.2	56.7	55.8	56.4	57.9	57.5	56.2	56.2
Men	57%	57%	58%	59%	61%	60%	58%	59%	57%	56%	54%	52%	7750 (57%)	7690 (57%)
Index event														
DVT only	60%	60%	69%	69%	69%	68%	65%	66%	99%	99%	0%	0%	7682 (57%)	7675 (57%)
PE ± DVT	40%	40%	31%	31%	31%	32%	35%	34%	0%	0%	100%	100%	5792 (43%)	5797 (43%)
Risk factors														
Unprovoked	66%	65%	NR	NR	NR	NR	90%	90%	61%	63%	65%	64%	7750 (71%)	7760 (71%)
Malignancy (at baseline)	9%	10%	5%	5%	4%	4%	2%	3%	7%	5%	5%	5%	790 (6%)	775 (6%)
Previous VTE	19%	18%	26%	25%	19%	16%	17%	15%	19%	19%	19%	20%	2612 (19%)	2489 (18%)
TTR in VKA group	—	64%	—	60%	—	57%	—	60%	—	58%	—	63%	—	—
Intended treatment duration														
3 mo	12%	13%	0%	0%	0%	0%	0%	0%	12%	12%	5%	5%	820 (6%)	853 (9%)
6 mo	48%	47%	100%	100%	100%	100%	100%	100%	63%	63%	57%	57%	9686 (72%)	9663 (72%)
12 mo	40%	40%	0%	0%	0%	0%	0%	0%	25%	25%	37%	37%	3006 (22%)	2995 (22%)

bid, twice daily; d, day; mo, month(s); od, once daily, UFH, unfractionated heparin; y, year(s).

*Treatment duration was left to the discretion of the physician.

†Enoxaparin 1 mg/kg twice daily.

‡An edoxaban dose of 30 mg once daily was administered to patients with a creatinine clearance of 30 to 50 mL per minute, a body weight <60 kg, and in those receiving concomitant treatment with potent P-glycoprotein inhibitors.

RISULTATI STUDI

THROMBOSIS AND HEMOSTASIS

Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials

Nick van Es,[1] Michiel Coppens,[1] Sam Schulman,[2] Saskia Middeldorp,[1] and Harry R. Büller[1]

[1]Department of Vascular Medicine, Academic Medical Center, Amsterdam, The Netherlands; and [2]Department of Medicine, McMaster University and Thrombosis and Atherosclerosis Research Institute, Hamilton, ON, Canada

Key Points

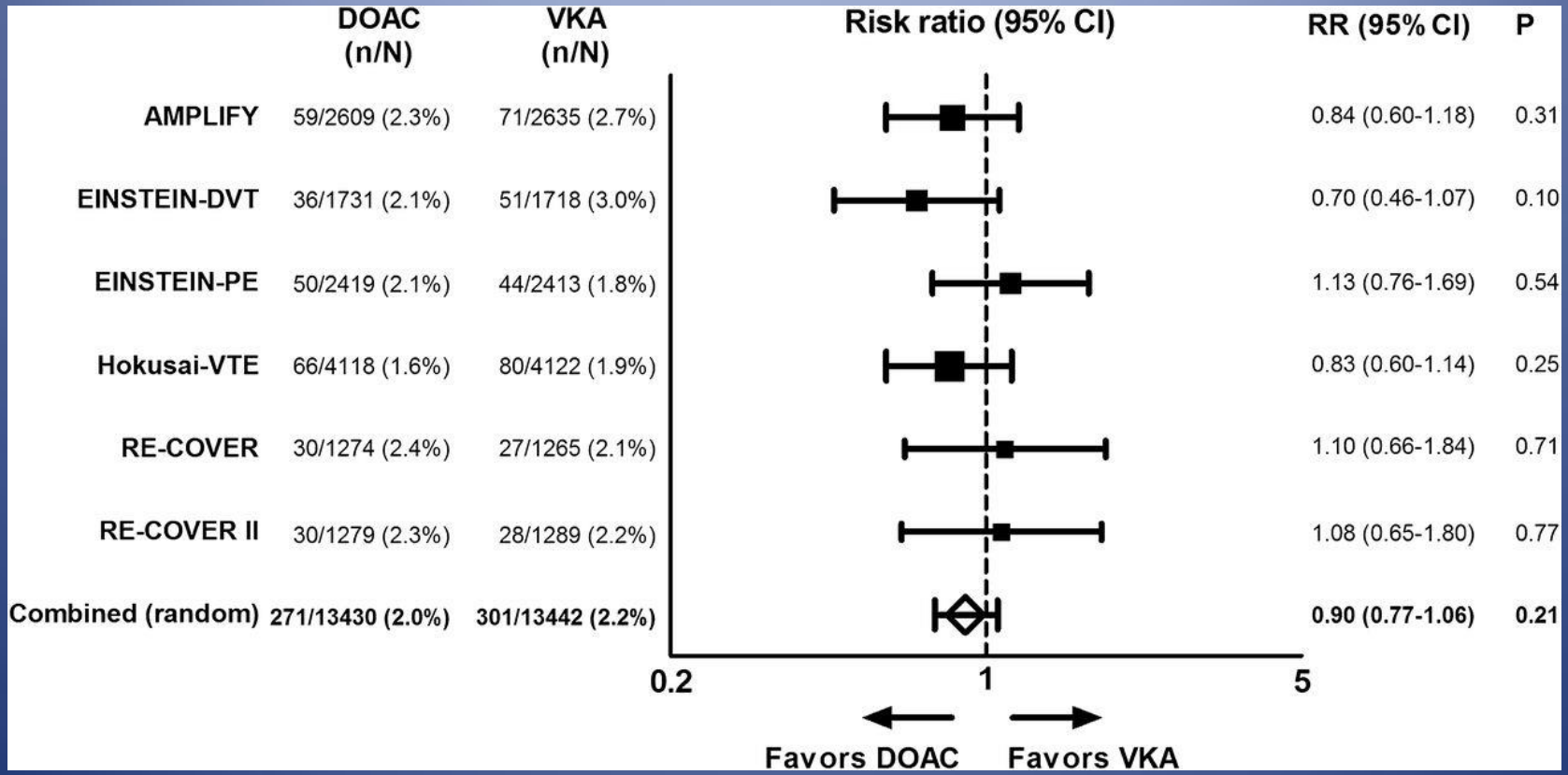
- DOACs have similar efficacy as VKAs in the treatment of acute symptomatic VTE, but significantly reduce the risk of major bleeding.
- The efficacy and safety of DOACs in the treatment of acute VTE are consistent in clinically important subgroups.

In the last 4 years, 6 phase 3 trials including a total of 27 023 patients with venous thromboembolism (VTE) compared a direct oral anticoagulant (DOAC) with vitamin K antagonists (VKAs). To aid the clinician in assessing the amount of information, we address frequently raised clinical questions in a review of combined trial results. We included the phase 3 trials that compared dabigatran etexilate, rivaroxaban, apixaban, or edoxaban with VKA therapy in patients with acute symptomatic VTE. Recurrent VTE occurred in 2.0% of DOAC recipients compared with 2.2% in VKA recipients (relative risk [RR] 0.90, 95% confidence interval [CI] 0.77-1.06). Treatment with a DOAC significantly reduced the risk of major bleeding (RR 0.61, 95% CI 0.45-0.83). In parallel, intracranial bleeding, fatal bleeding, and clinically relevant nonmajor bleeding occurred significantly less in DOAC recipients. The efficacy and safety of DOACs were consistent in patients with pulmonary embolism, deep venous thrombosis, a body weight ≥100 kg, moderate renal insufficiency, an age ≥75 years, and cancer. In conclusion, DOACs and VKAs have similar efficacy in the treatment of acute symptomatic VTE, a finding that is consistent in key clinical subgroups. Treatment with a DOAC significantly reduces the risks of major bleeding. (*Blood*. 2014;124(12):1968-1975)

RISULTATI STUDI -1-

	RE-COVER	RE-COVER II *	EINSTEIN DVT	EINSTEIN PE	AMPLIFY
Drug	Dabigratan vs. warfarin		Rivaroxaban vs. VKA	Rivaroxaban vs. VKA	Apixaban vs. VKA
Study Design	Double blind		Open label	Open label	Double blind
Dosing schedule	Parenteral anticoagulation followed by Dabigatran 150 mg bid		Rivaroxaban 15 mg bid for 3 weeks followed by 20 mg od	Rivaroxaban 15 mg bid for 3 weeks followed by 20 mg od	Apixaban 10 mg bid for 7 days followed by 5 mg bid
Treatment Period	6 months		3-6 -12 months	3-6 -12 months	6 months
Patient Number	2564	2559	3449	4832	5395
Recurrent VTE	2.4% vs. 2.1% P<0.001 (non-inferiority)	2.4% vs. 2.1% P<0.001 (non-inferiority)	2.1% vs. 3.0% P<0.0001 (non-inferiority)	2.1% vs. 1.8% P<0.003 (non-inferiority)	2.3% vs. 2.7% P<0.001 (non-inferiority)
Major Bleeding	1.6% vs. 1.9%	1.1% vs. 1.7%	0.8% vs 1.2%	1.1% vs. 2.2% (P=0.003)	0.6% vs. 1.8% (P<0.001)

RISULTATI STUDI -2-



First recurrent VTE or VTE-related death. For Hokusai-VTE, we used event data for the on-treatment period. Heterogeneity: $I^2 = 0\%$; $P = .53$.

RISULTATI STUDI-3-

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oral Rivaroxaban for Symptomatic Venous Thromboembolism

The EINSTEIN Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Extended Use of Dabigatran, Warfarin, or Placebo in Venous Thromboembolism

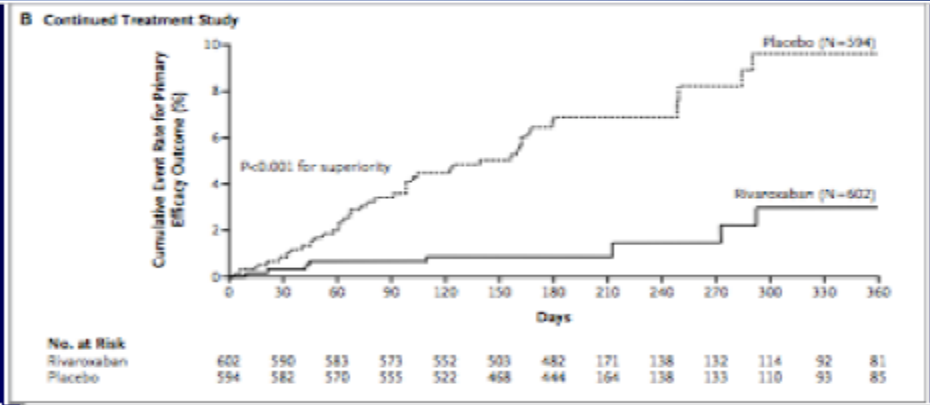
Sam Schulman, M.D., Ph.D., Clive Kearon, M.D., Ajay K. Kakkar, M.B., B.S., Ph.D., Sebastian Schellong, M.D., Henry Eriksson, M.D., Ph.D., David Baanstra, M.Sc., Anne Mathilde Kvamme, M.Sc.Pharm., Jeffrey Friedman, M.D., Patrick Mismetti, M.D., and Samuel Z. Goldhaber, M.D., for the RE-MEDY and the RE-SONATE Trials Investigators*

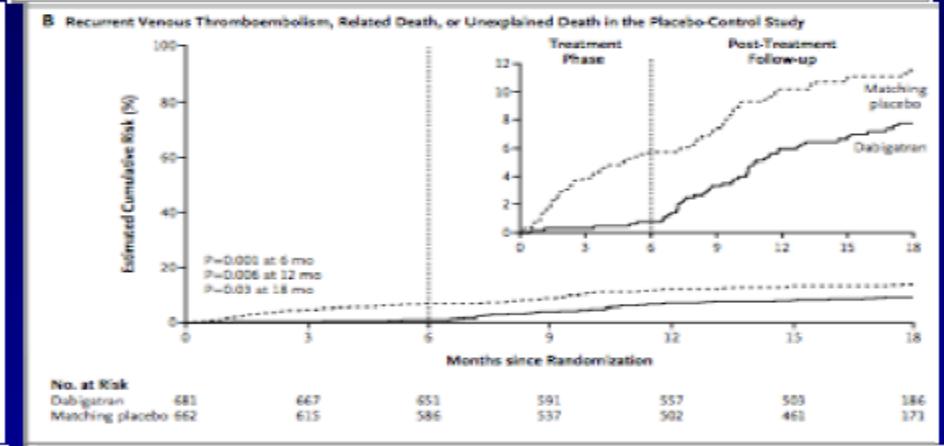
The NEW ENGLAND JOURNAL of MEDICINE

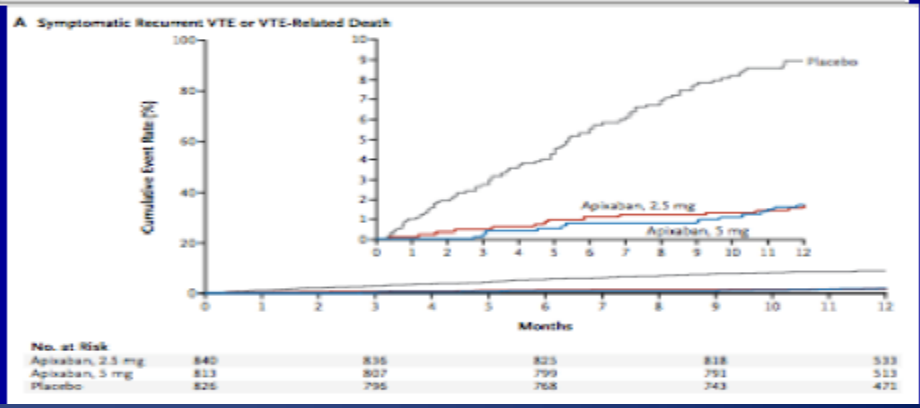
ORIGINAL ARTICLE

Apixaban for Extended Treatment of Venous Thromboembolism

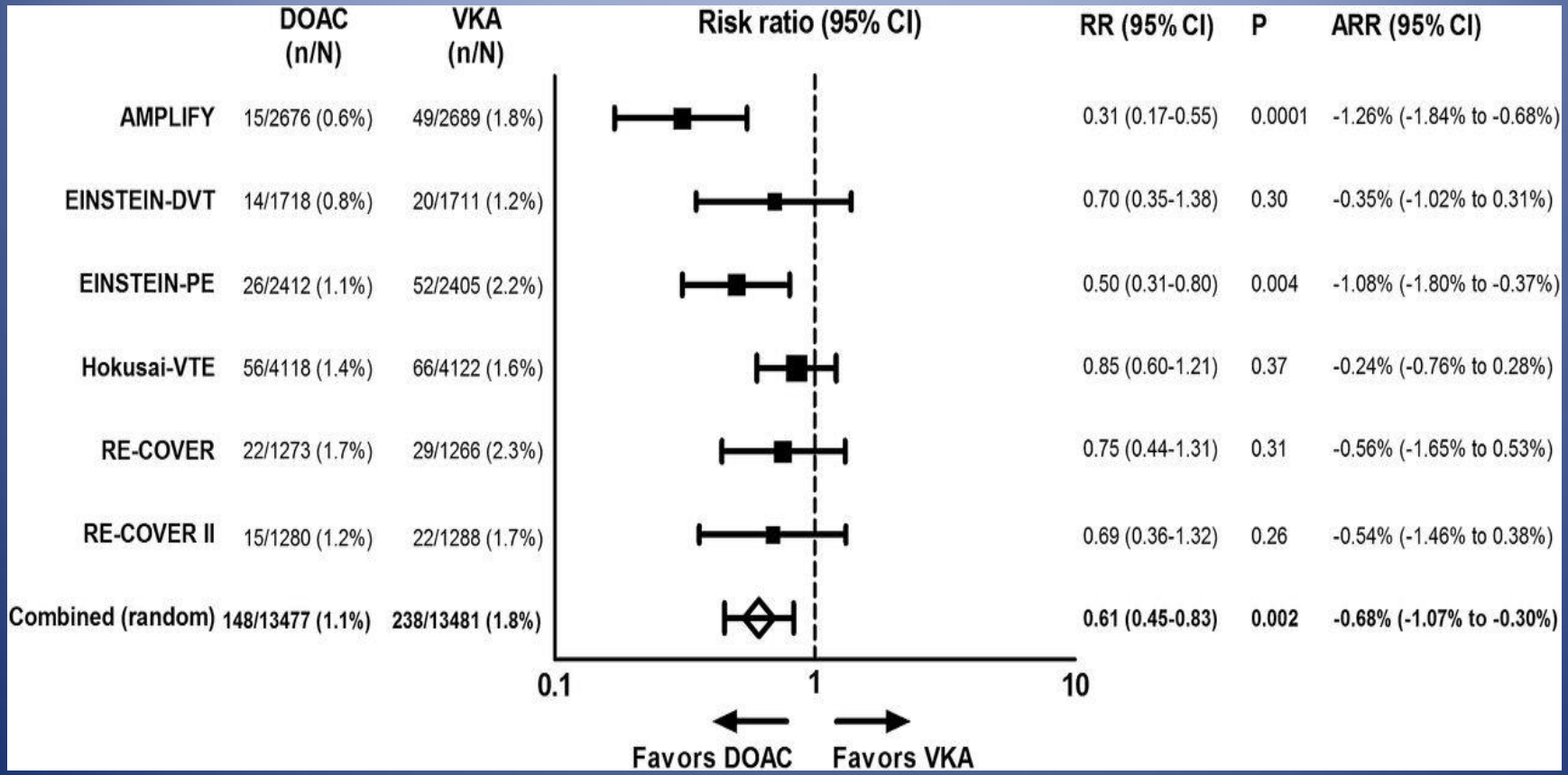
Giancarlo Agnelli, M.D., Harry R. Buller, M.D., Ph.D., Alexander Cohen, M.D., Madelyn Curto, D.V.M., Alexander S. Gallus, M.D., Margot Johnson, M.D., Anthony Porcari, Ph.D., Pharm.D., Gary E. Raskob, Ph.D., and Jeffrey I. Weitz, M.D., for the AMPLIFY-EXT Investigators*





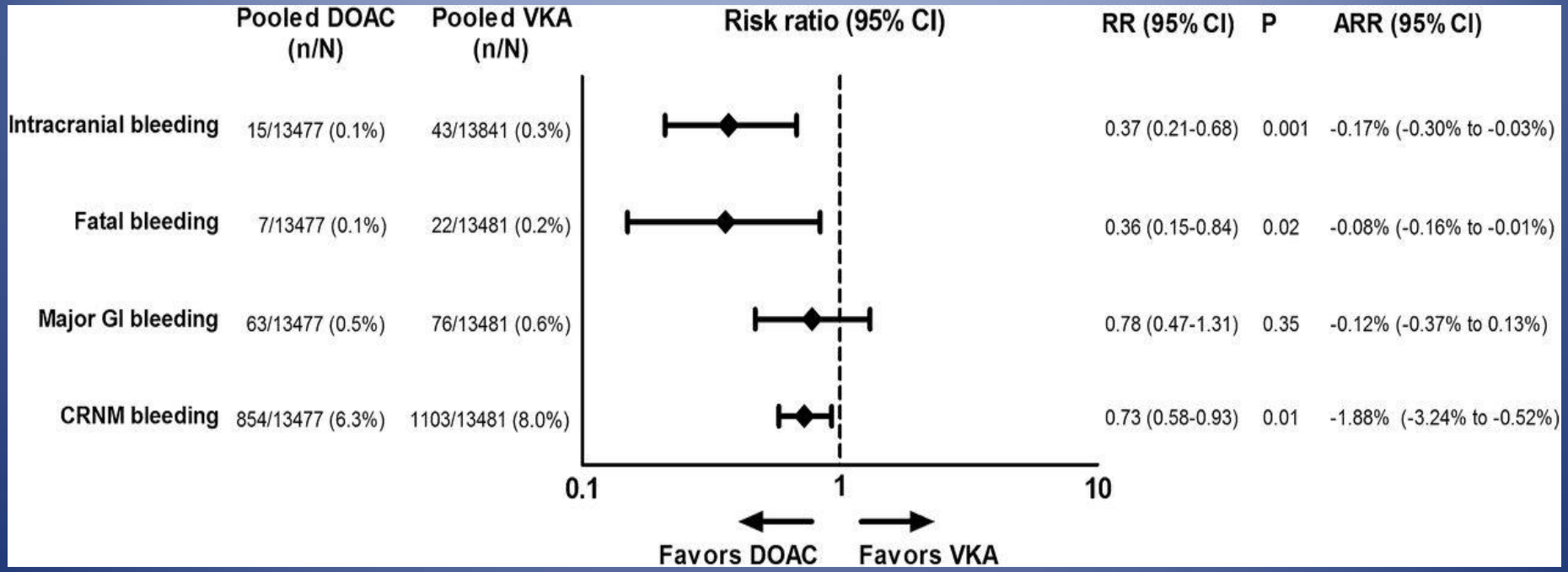


RISULTATI STUDI-4-



Major bleeding. The sums of numbers of events from RE-COVER and RE-COVER II with respect to major bleeding slightly differ from those in the pooled analysis. We used data from the pooled analysis because these were most accurate. Heterogeneity: $I^2 = 51\%$, $P = .07$. ARR, absolute risk reduction.

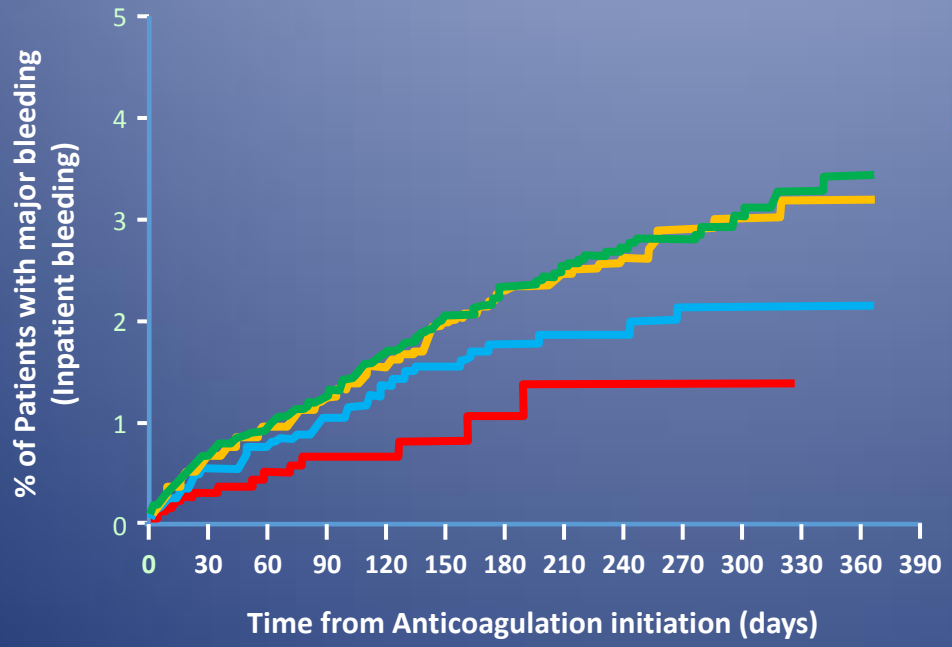
RISULTATI STUDI-5-



Intracranial, major gastrointestinal, fatal, and clinically relevant non major bleeding. Intracranial bleeding numbers comprise fatal and nonfatal events. Because CRNM bleeding was not a predefined outcome on its own in both RE-COVER studies, we obtained these numbers by subtracting major bleeding numbers from the composite of major and CRNM bleeding. Heterogeneity: intracranial bleeding $I^2 = 0\%$, $P = .66$; major GI bleeding $I^2 = 51\%$, $P = .07$; fatal bleeding $I^2 = 0\%$, $P = .86$; CRNM bleeding $I^2 = 85\%$, $P < .00001$. GI, gastrointestinal.

Real Life

US comparative real world research on major bleeding



Apixaban (N=2,402)

Dabigatran (N=4,173)

150 mg	NR
N=3,768	N=405

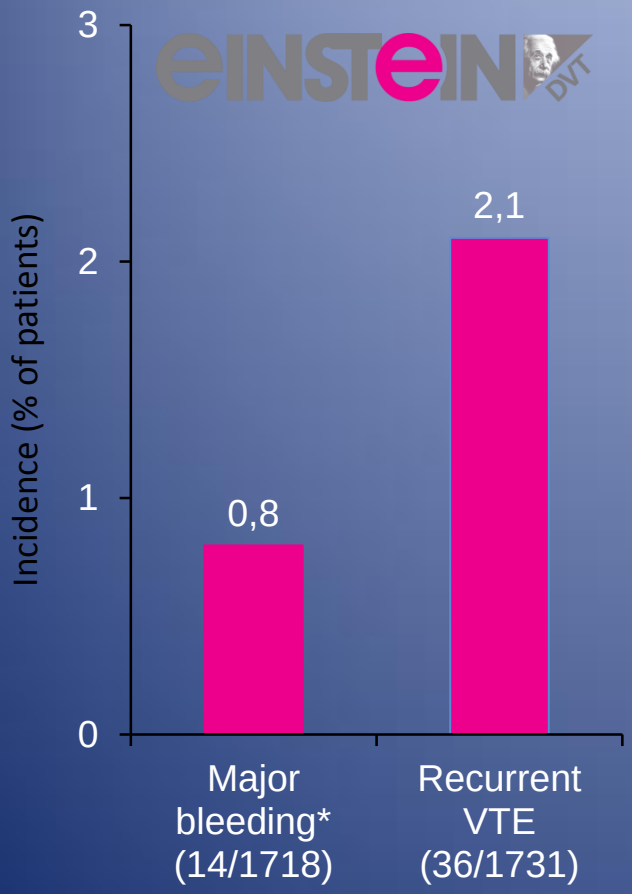
Rivaroxaban (N=10,050)

Warfarin (N=12,713)

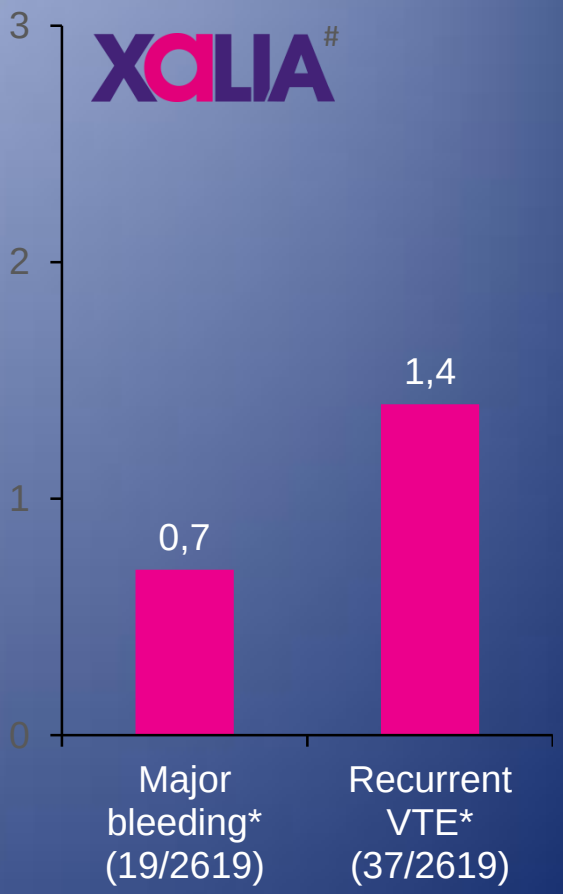
Lip et al. Poster presentation at ESC Aug/Sept 2015; London, UK Poster/oral poster no.P6217

CI, confidence interval;
HR, hazard ratio

RIVAROXABAN: trial clinico vs real life



Characteristic		
55.8	Età (media)	57.3
57.4%	Sesso maschile	55%
19.4%	Precedente VTE	24.%
6.8%	Cancro attivo	6%
6.2%	trombofilia	6.0%



❑ **CONSISTENZA CON I RISULTATI DEL TRIAL CLINICO**

safety analisi

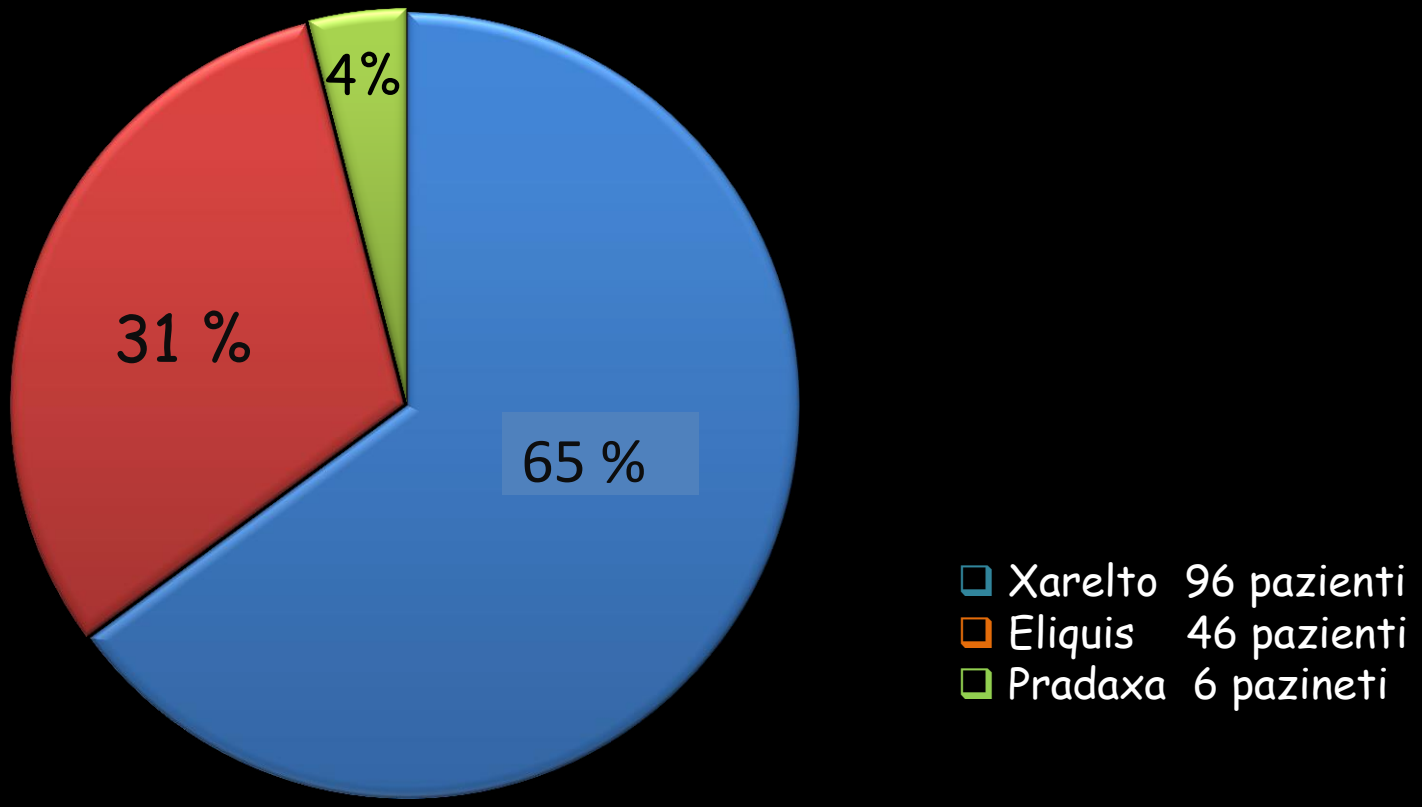
The EINSTEIN Investigators, *N Engl J Med* 2010;363:2499–2510

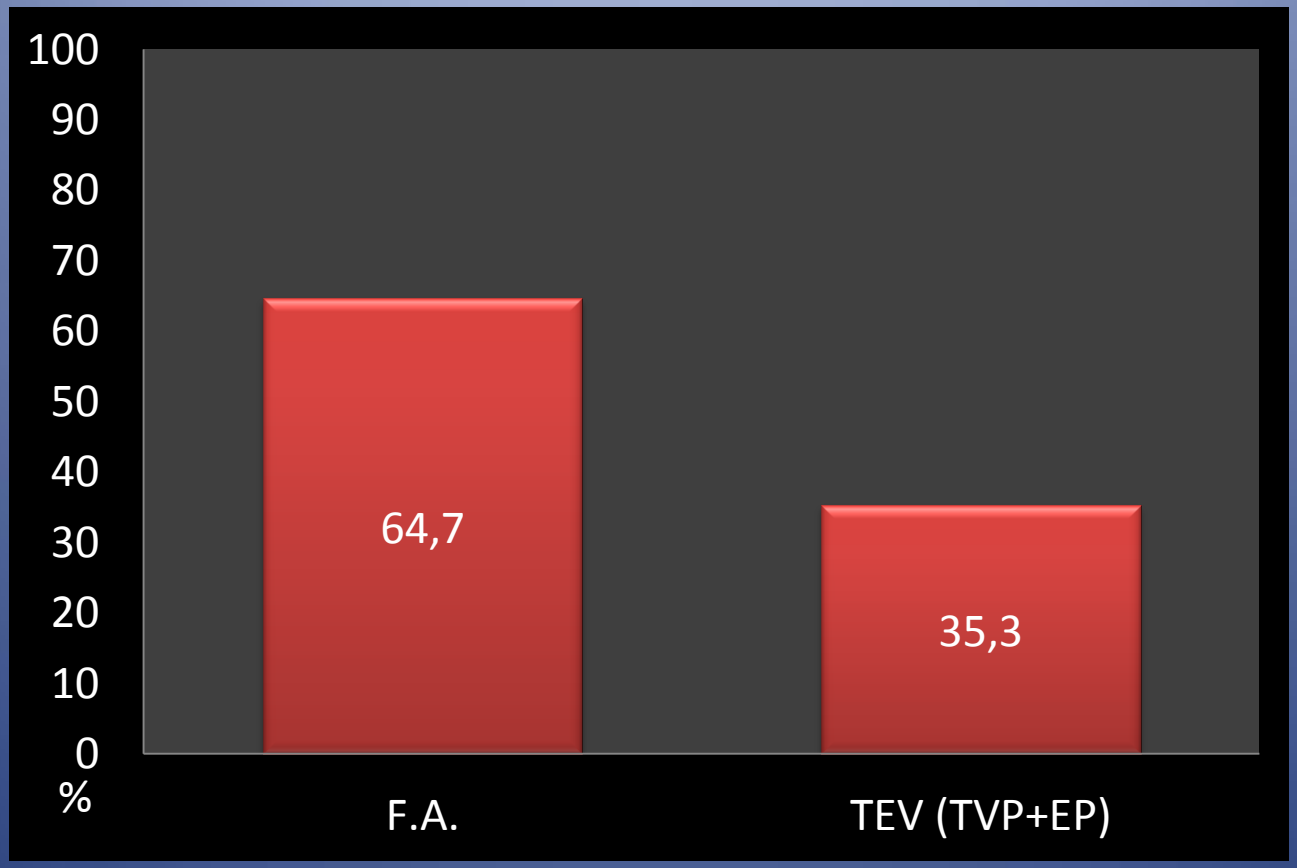
The real-world data to be presented at ACC.16 are part of ACROPOLIS™ (**A**pixaban Experien**C**e Through **R**eal-W**O**rld **PO**pu**L**at**I**on **S**tudies), a global real-world data research program designed to further evaluate the effectiveness and safety of *Eliquis* in routine clinical practice.

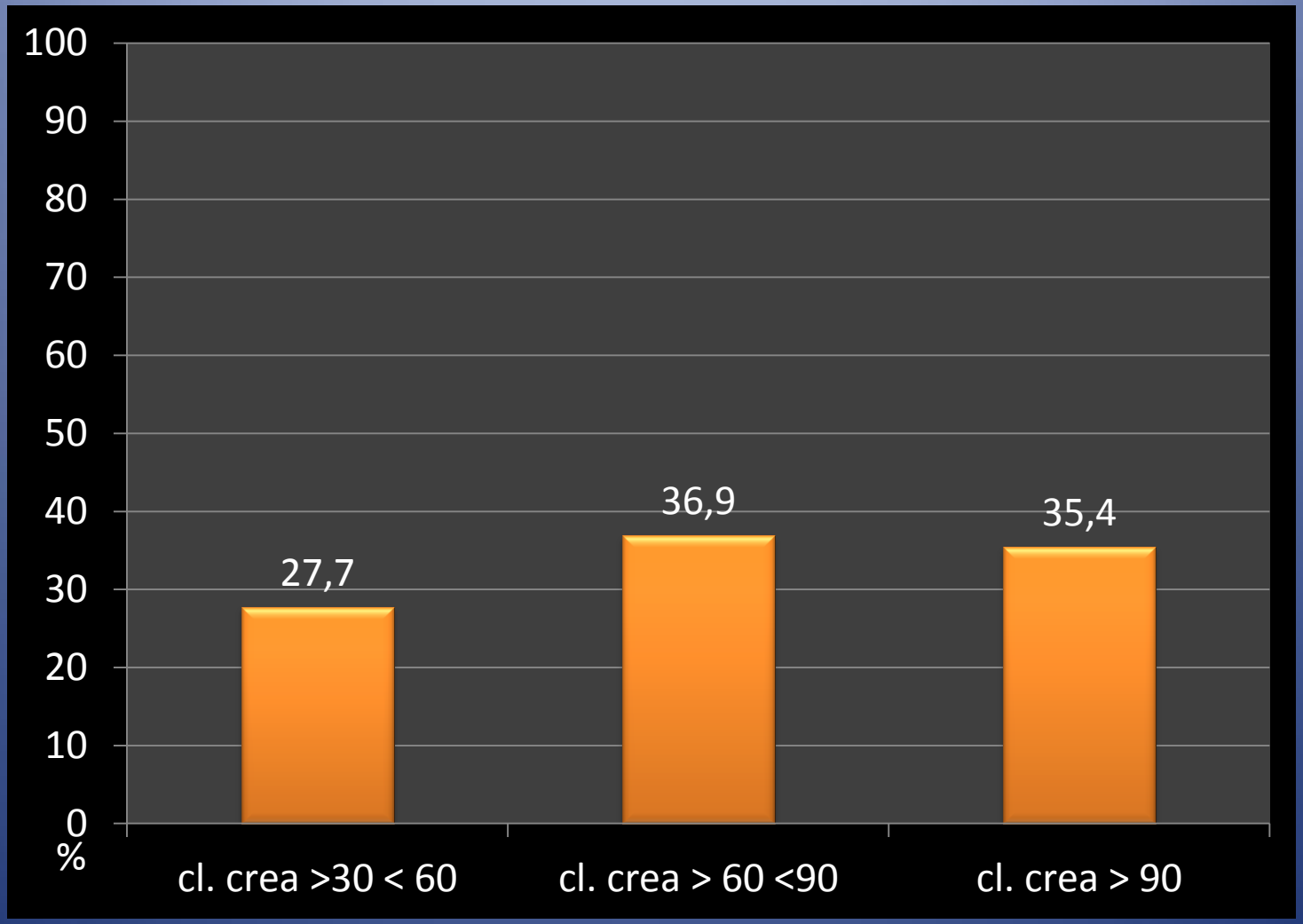
Abstracts include new analyses from Phase 3 ARISTOTLE and AMPLIFY clinical studies, as well as a number of retrospective analyses of real-world data

La nostra piccola esperienza

Distribuzione NOA
Centro FCSA 126
148 pazienti




100
90
80
70
60
50
40
30
20
10
0
%
64,7
35,3
F.A.
TEV (TVP+EP)


100
90
80
70
60
50
40
30
20
10
0
%
27,7
36,9
35,4
cl. crea >30 < 60
cl. crea > 60 <90
cl. crea > 90

Eventi avversi

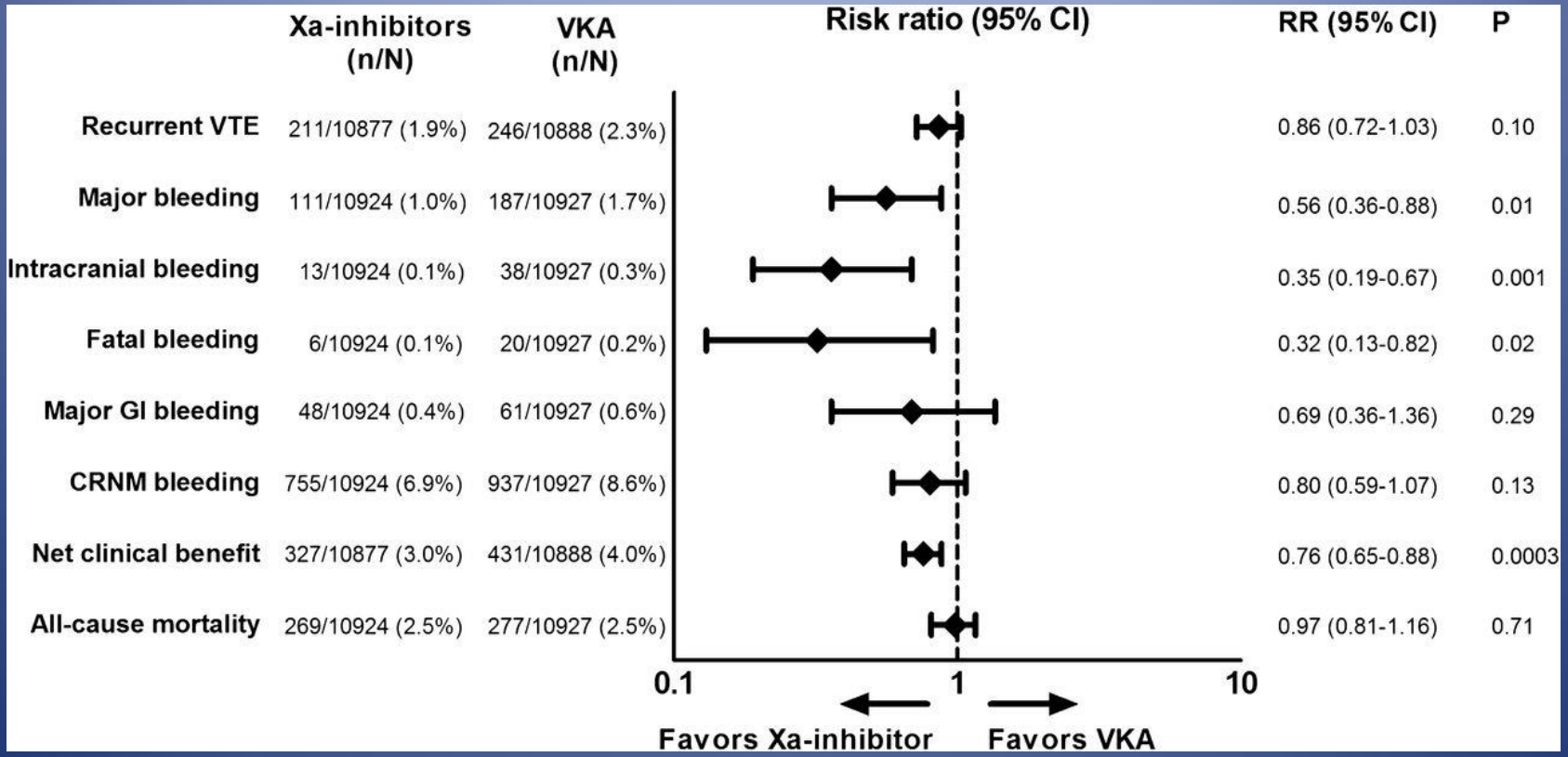
1 Emorragia gastrointestinale (0.6 %)

2 ematuria (1.35%)
1 metrorragie (0.6%)

Conclusioni

I NOA hanno dimostrato di essere una efficace e sicura alternativa alla terapia tradizionale del TEV, mantenendo un elevato profilo di efficacia e sicurezza e migliorando notevolmente la qualità di vita del paziente

Grazie per l'attenzione



Efficacy and safety of factor Xa inhibitors. Heterogeneity overall I^2 = 0%, *P* = .43; major bleeding I^2 = 69%, *P* = .02; intracranial bleeding I^2 = 0%, *P* = .60; major gastrointestinal bleeding I^2 = 62%, *P* = .05; fatal bleeding I^2 = 0%, *P* = .72; CRNM bleeding I^2 = 89%, *P* = .13; net clinical benefit I^2 = 11%, *P* = .34; all-cause mortality I^2 = 10%, *P* = .34. Xa-inhibitor, oral direct factor Xa inhibitor

A pharmacoeconomic study of traditional anticoagulation versus direct oral anticoagulation for the treatment of venous thromboembolism in the emergency department.

Law S[1], Ghag D[1], Grafstein E[2], Stenstrom R[2], Harris D[3].

OBJECTIVES:
Patients with venous thromboembolism (VTE) (deep vein thrombosis [DVT] and pulmonary embolism [PE]) are commonly treated as outpatients. Traditionally, patients are anticoagulated with low-molecular-weight heparin (LMWH) and warfarin, resulting in return visits to the ED. The direct oral anticoagulant (DOAC) medications do not require therapeutic monitoring or repeat visits; however, they are more expensive. This study compared health costs, from the hospital and patient perspectives, between traditional versus DOAC therapy.

METHODS:
A chart review of VTE cases at two tertiary, urban hospitals from January 1, 2010 to December 31, 2012 was performed to capture historical practice in VTE management, using LMWH/warfarin. This historical data were compared against data derived from clinical trials, where a DOAC was used. Cost minimization analyses comparing the two modes of anticoagulation were completed from hospital and patient perspectives.

RESULTS:
Of the 207 cases in the cohort, only 130 (63.2%) were therapeutically anticoagulated (international normalized ratio 2.0-3.0) at emergency department (ED) discharge; patients returned for a mean of 7.18 (range: 1-21) visits. Twenty-one (10%) were admitted to the hospital; 4 (1.9%) were related to VTE or anticoagulation complications. From a hospital perspective, a DOAC (in this case, rivaroxaban) had a total cost avoidance of $1,488.04 per VTE event, per patient. From a patient perspective, it would cost an additional $204.10 to $349.04 over 6 months, assuming no reimbursement.

CONCLUSIONS:
VTE management in the ED has opportunities for improvement. A DOAC is a viable and cost-effective strategy for VTE treatment from a hospital perspective and, depending on patient characteristics and values, may also be an appropriate and cost-effective option from a patient perspective.

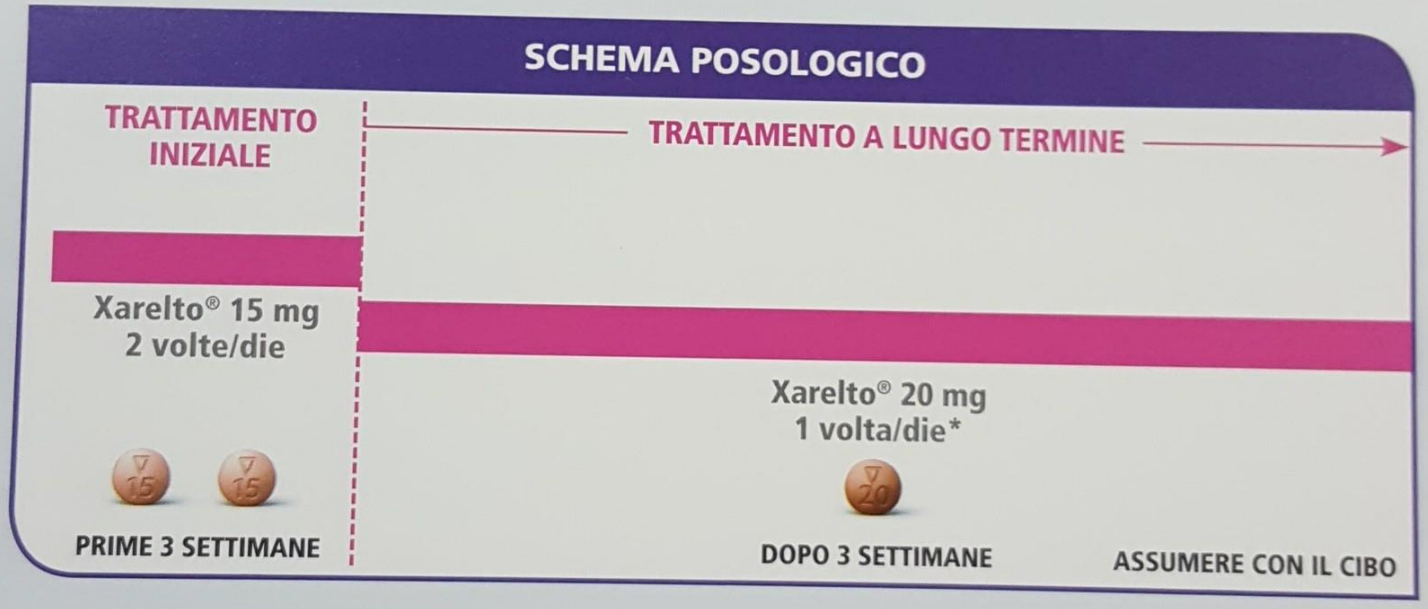
Clinical presentation and course of bleeding events in patients with venous thromboembolism, treated with apixaban or enoxaparin and warfarin. Results from the AMPLIFY trial.

Bleker SM[1], Cohen AT, Büller HR, Agnelli G, Gallus AS, Raskob GE, Weitz JI, Curto M, Sisson M, Middeldorp S.

Apixaban, a direct acting oral anticoagulant (DOAC), was found to be non-inferior to and safer as enoxaparin followed by warfarin for treatment of venous thromboembolism (VTE) in the AMPLIFY trial. Information is needed on how bleeding events with DOACs present and develop. In this post-hoc analysis, the clinical presentation and course of all major and clinically relevant non major (CRNM) bleeding events in the AMPLIFY trial were blindly classified by three investigators, using pre-designed classification schemes containing four categories. Odds ratios (OR) for classifying as category three or four (representing a more severe clinical presentation and course) were calculated between apixaban and enoxaparin/warfarin. In total, 63 major and 311 CRNM bleeding events were classified. Of the major bleeds, a more severe clinical presentation occurred in 28.5 % of apixaban versus 44.9 % of enoxaparin/warfarin related recipients (OR 0.49, 95 % confidence interval [CI] 0.14-1.78). A severe clinical course was observed in 14.3 % and in 12.2 %, respectively (OR 1.19, 95 %CI 0.21-6.69). Of the CRNM bleeding events, a more severe clinical presentation and extent of clinical care was found in 25 % of apixaban recipients compared to 22.7 % in the enoxaparin/warfarin group (OR 1.13, 95 %CI 0.65-1.97). There was a trend for a less severe clinical presentation of major bleeding events in apixaban treated patients, compared with enoxaparin/warfarin treated patients. The clinical course of major bleeds was similar. The clinical presentation and subsequent extent of clinical care of CRNM bleeding events associated with apixaban and enoxaparin/warfarin were comparable.

Dosaggio nel trattamento della trombosi venosa profonda (TVP), dell'embolia polmonare (EP) e prevenzione delle recidive della TVP e dell'EP nell'adulto

La dose raccomandata per il trattamento iniziale è 15 mg **due volte al giorno** nelle prime tre settimane.
Il trattamento iniziale è seguito da una dose di 20 mg **una volta al giorno** per la prosecuzione del periodo di trattamento.



TEV: mortalità

- Circa il 6% dei pazienti muore entro 30 giorni dopo un primo evento di TVP, il 12% dopo una EP.
- I pazienti anziani e quelli neoplastici e/o con malattie CV sono particolarmente a rischio di morte dopo TEV
- In molti casi la TEV è clinicamente silente:
  - quasi l'80% delle TVP
  - più del 50% delle TVP prossimali
  - fino al 50% dei pazienti con TVP sintomatiche può avere una EP asintomatica e meno di 1/3 dei pazienti con EP mostra segni o sintomi di TVP
- <u>L'embolia polmonare è la causa preventivabile più comune di morte ospedaliera e la terza causa più comune di mortalità vascolare dopo IM e ictus</u>

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NOAC VTE trials: Treatment duration

	RE-COVER I[1]	EINSTEIN-DVT[2]	EINSTEIN-PE[3]	AMPLIFY[4]	Hokusai-VTE[5-7]
Drug	**Dabigatran**	**Rivaroxaban**	**Rivaroxabn**	**Apixaban**	**Edoxaban**
Treatment duration (%)					
3 months	-	12	5	-	12
6 months*	100	63	58	100	26
6-12 months	-	-	-	-	61
12 months	-	25	37	-	40†
Mean treatment duration, days	<180	NR	215	<180	249
≥1 dose heparin prior to randomization (%)	100	72	92	86	100
Adherence to therapy >80% (%)	98	NR	94	96	99

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3. EINSTEIN–PE Investigators. N Engl J Med 2012;366:1287–1297; 4. Agnelli et al. N Engl J Med 2013. doi:10.1056/NEJMoa.1302507
5. The Hokusai-VTE Investigators. N Engl J Med 2013; 6. Raskob et al. J Thromb Haemost 2013;11:1287-1294; 7. Daiichi Sankyo, data on file.

*For Hokusai-VTE duration was 3 to 6 months
†40% of patients in Hokusai-VTE reaching 12 months is included within 61% of patients reaching 6-12 months
NR= Not Reported