SOCIETÀ ITALIANA
DI GERONTOLOGIA
E GERIATRIA

I nuovi anticoagulanti orali nella **trombosi venosa profonda**

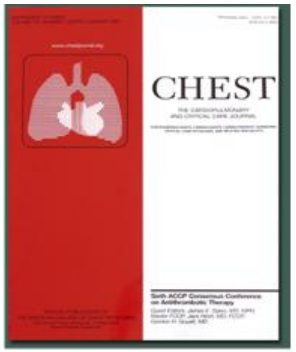
Terapia della TVP

Fulvio POMERO

Medicina Interna
S. Croce e Carle
Cuneo

Antithrombotic Therapy for VTE Disease

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines



Clive Kearon, Elie A. Akl, Anthony J. Comerota, Paolo Prandoni, Henri Bounameaux, Samuel Z. Goldhaber, Michael E. Nelson, Philip S. Wells, Michael K. Gould, Francesco Dentali, Mark Crowther and Susan R. Kahn

- **UHF**
- **LMWH**
- **Fondaparinux**

Vitamin K antagonists

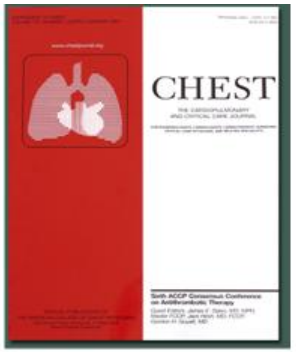
Initial treatment	INR 2.0-3.0	2.0-3.0 or 1.5-1.9
Long term-treatment		
Extended* treatment		
≥ 5 days	**at least 3 months**	**indefinite***

* With re-assessment of the individual risk-benefit at periodic interval

Kearon C et al. Chest 2012; 141: 419-494

Antithrombotic Therapy for VTE Disease

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines



Clive Kearon, Elie A. Akl, Anthony J. Comerota, Paolo Prandoni, Henri Bounameaux, Samuel Z. Goldhaber, Michael E. Nelson, Philip S. Wells, Michael K. Gould, Francesco Dentali, Mark Crowther and Susan R. Kahn

- UHF
- LMWH
- Fondaparinux

1

Initial treatment

Vitamin K antagonists

INR 2.0-3.0 2.0-3.0 or 1.5-1.9

Long term-treatment

2

Extended* treatment

≥ 5 days at least 3 months indefinite*

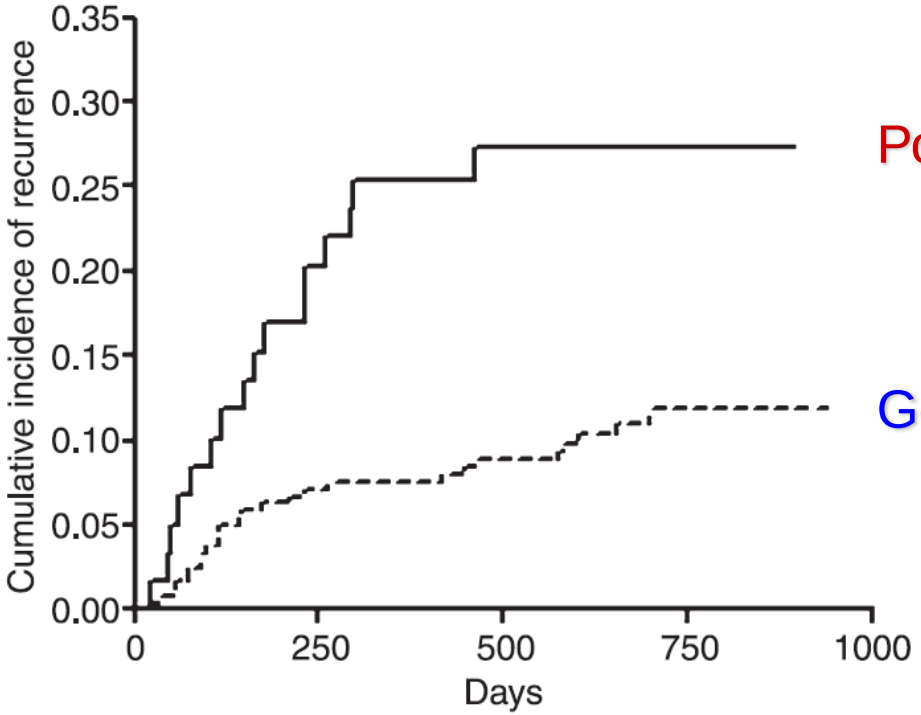
3

* With re-assessment of the individual risk-benefit at periodic interv

Kearon C et al. Chest 2012; 141: 419-494

Poor anticoagulation quality in the first 3 months after unprovoked venous thromboembolism is a risk factor for long-term recurrence

VTE recurrence



Poor VKA control (first 90 days)

Good VKA control (first 90 days)

*Cumulative incidence of recurrence after oral anticoagulation interruption in subjects with a previous **unprovoked venous thromboembolic***

Palareti G et al. JTH 2005; 3: 955-61

Bleeding complications of oral anticoagulant treatment: an inception-cohort, prospective collaborative study (ISCOAT)

BLEEDING

All	153 (7·6)*
Fatal (all cerebral, 4 women)	5 (0·25)
Major	23 (1·1)
Minor	125 (6·2)

	Relative risk (95% CI)
Sex (women *vs* men)	1·21 (0·86–1·70)
Age (⩾70 *vs* <70 years)	1·69 (1·21–2·37, p<0·001)
Target INR (⩽2·8 *vs* >2·8)	0·83 (0·56–1·22)
Indication (arterial disease *vs* others)	1·72 (1·17–2·54, p<0·001)
Actual INR (⩾4·5 *vs* <4·5)	5·96 (3·68–9·67, p<0·0001)
Coumarin type (acenocoumarol *vs* warfarin)	1·20 (0·85–1·69)
Timing of events (⩽90 *vs* >90 days)	2·5 (1·4–3·3, p<0·001)

Palareti G et al. Lancet 1996; 348: 423-428

Use of Vitamin K Antagonist Therapy in Geriatrics: A French National Survey from the French Society of Geriatrics and Gerontology (SFGG).

National cross-sectional survey	Mean **age** was 87.2 ± 4.4 years
2,633 patients were included	Mean (±SD) **TTR** was 57.9 ± 40.4 %.

Poor VKA control (**TTR < 50% vs > 50%**) was associated with:

	OR	**95 % CI**
History of INR > 4.5	1.50	1.21-1.84
Recent VKA prescription (<1 vs. >12 months)	1.70	1.08-2.67
Hospitalization vs. nursing home	1.41	1.11-1.80
History of major bleeding	1.88	1.00-3.53
Falls (≥2 falls during the past year vs. <2)	1.26	1.01-1.56
Antibiotic use	1.83	1.24-2.70

Plichart M et al. Drugs Aging 2013; Oct 30. [*Epub ahead of print*]

Old and new oral anticoagulants for venous thromboembolism and atrial fibrillation: A review of the literature

ACUTE	LONG TERM	EXTENDED
X	Dabigatran (RECOVER) Edoxaban (HOKUSAI)	Dabigatran (REMEDY) Dabigatran (RESONATE) Rivaroxaban (EINSTEIN Extension) Apixaban (AMPLIFY Extension)
Rivaroxaban (EINSTEIN DVT) Rivaroxaban (EINSTEIN PE) Apixaban (AMPLIFY)		

Beccattini C et al. Thromb Res 2012; 129: 392-400

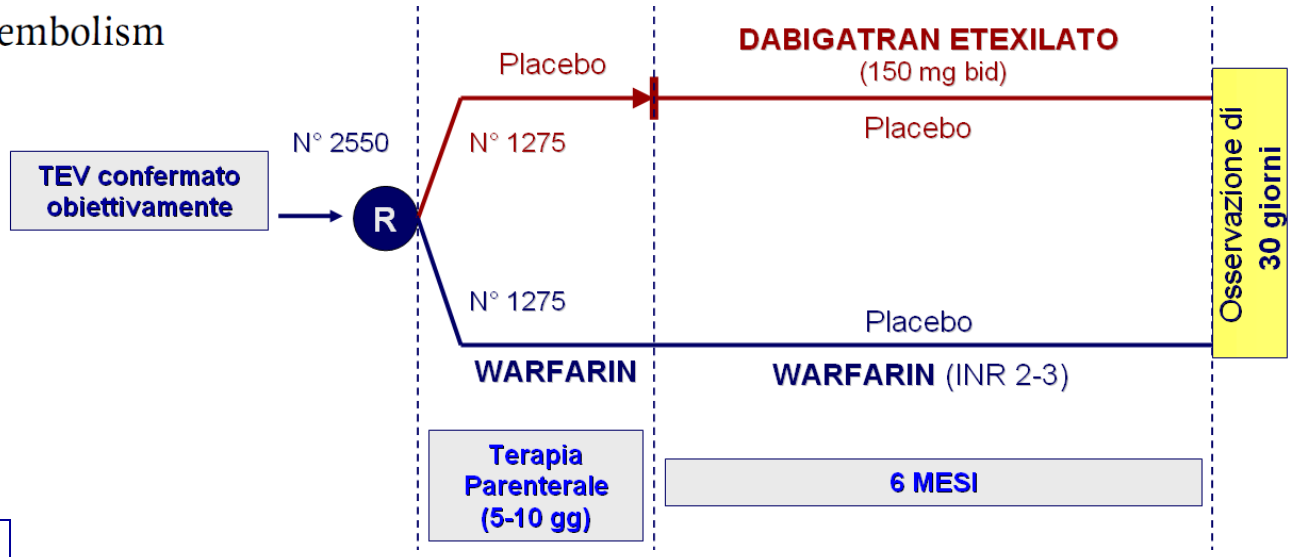
Old and new oral anticoagulants for venous thromboembolism and atrial fibrillation: A review of the literature

ACUTE	LONG TERM
	Dabigatran (RECOVER) Edoxaban (HOKUSAI)

Beccattini C et al. Thromb Res 2012; 129: 392-400

Dabigatran versus Warfarin in the Treatment of Acute Venous Thromboembolism

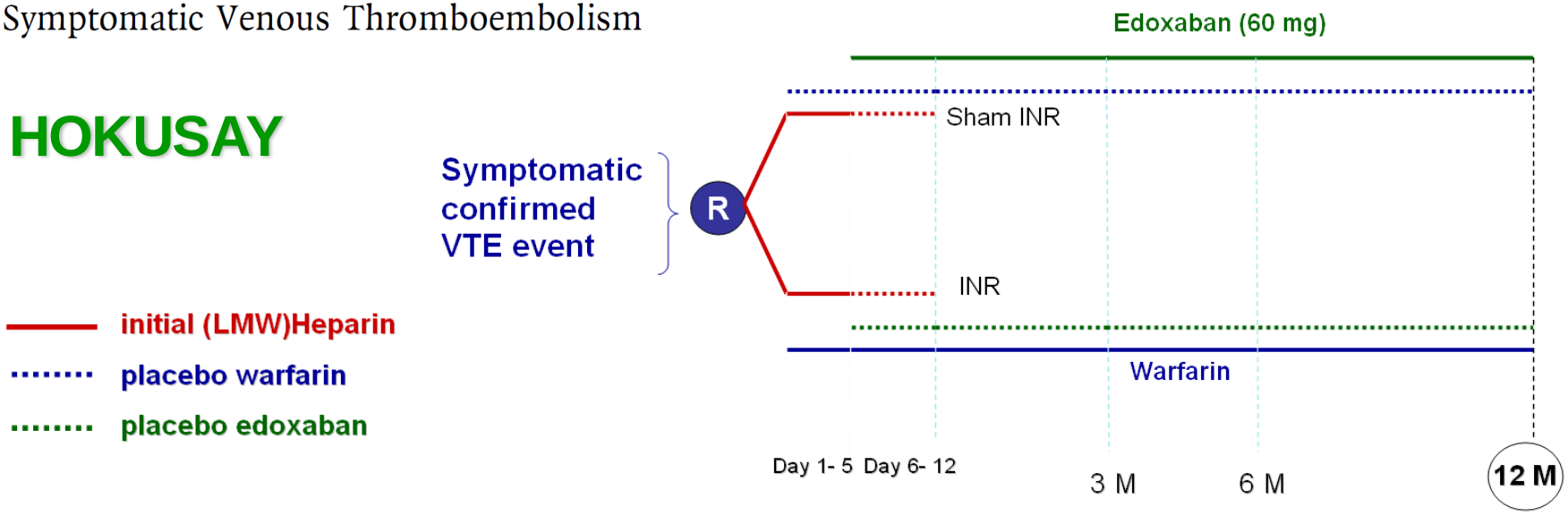
RECOVER



NEJM 2009; 361: 2342-52

Edoxaban versus Warfarin for the Treatment of Symptomatic Venous Thromboembolism

HOKUSAY



NEJM 2013; 369: 1406-15

Dabigatran versus Warfarin in the Treatment of Acute Venous Thromboembolism

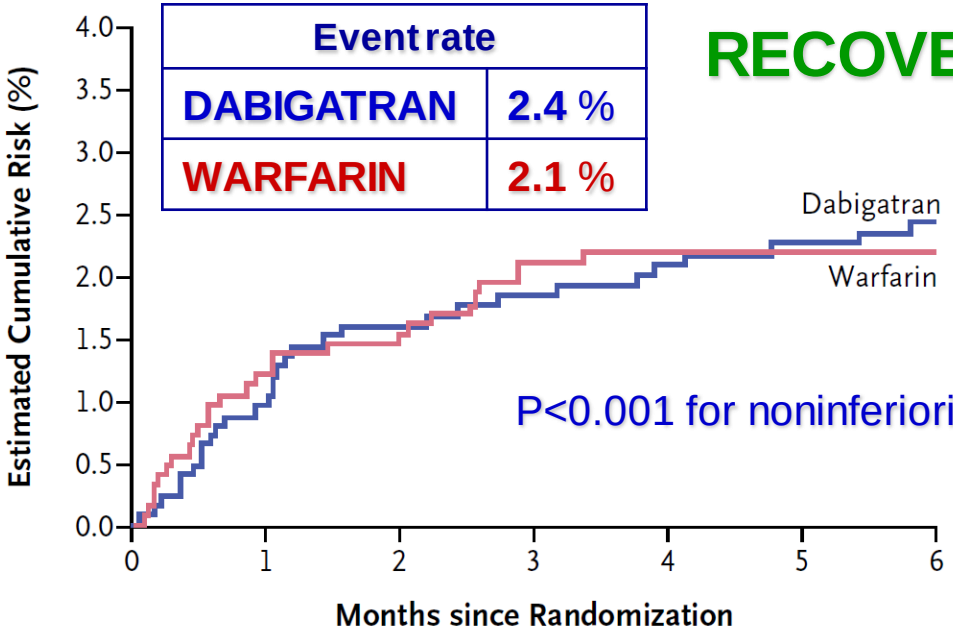
Efficacy outcome
Recurrent VTE

HR= 1.10 (95% CI= 0.65-1.84)

NEJM 2009; 361: 2342-52

Event rate	
DABIGATRAN	2.4 %
WARFARIN	2.1 %

RECOVER



Edoxaban versus Warfarin for the Treatment of Symptomatic Venous Thromboembolism

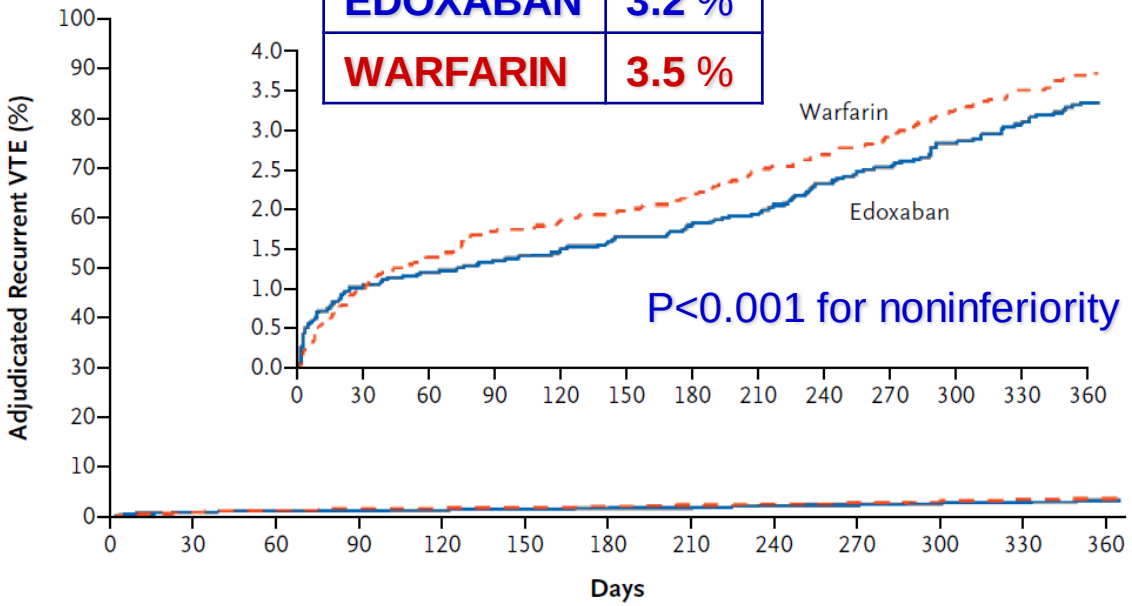
Efficacy outcome
Recurrent VTE

HR= 0.89 (95% CI= 0.7-1.13)

NEJM 2013; 369: 1406-15

Event rate	
EDOXABAN	3.2 %
WARFARIN	3.5 %

HOKUSAY



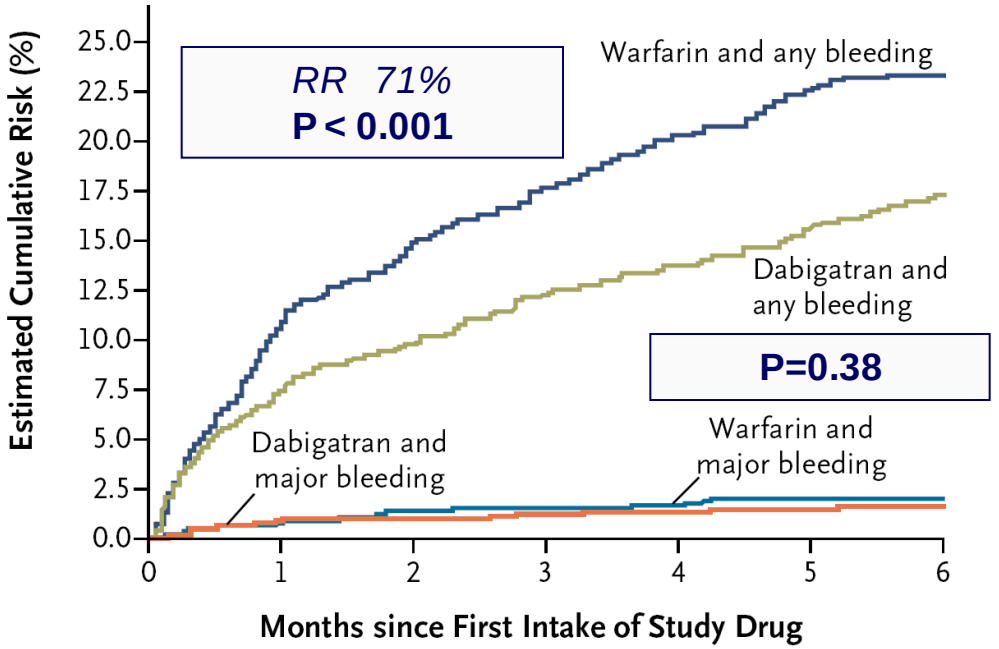
Dabigatran versus Warfarin in the Treatment of Acute Venous Thromboembolism

RECOVER

Safety outcome

Major bleeding / any bleeding

NEJM 2009; 361: 2342-52



Edoxaban versus Warfarin for the Treatment of Symptomatic Venous Thromboembolism

HOKUSAY

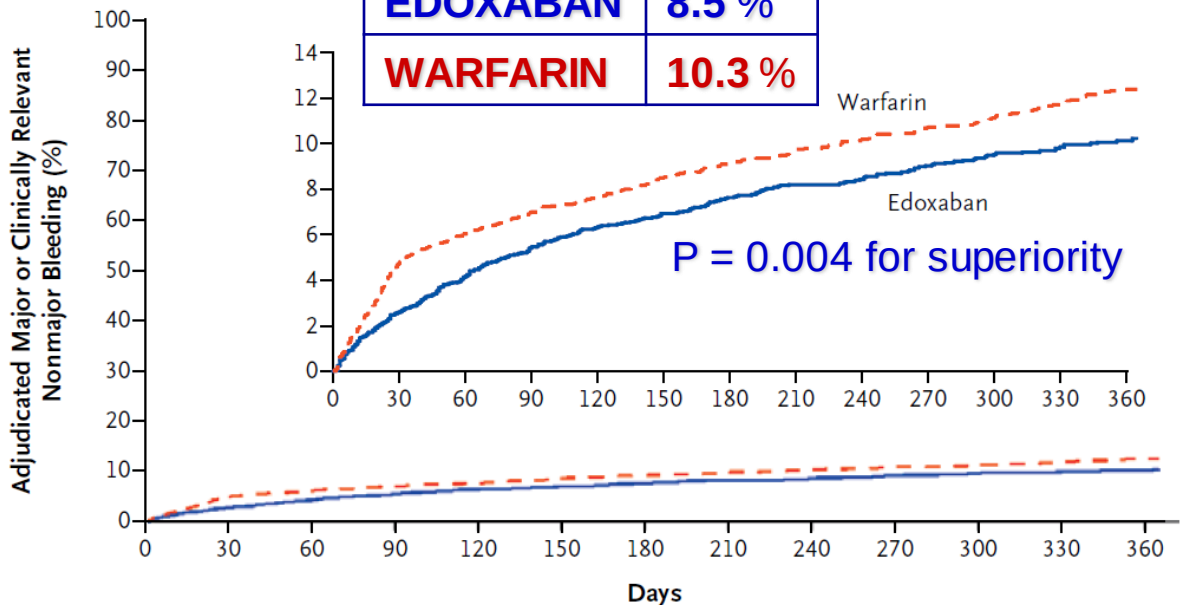
Safety outcome

Major + Clinically Relevant non Major Bleeding

HR= 0.81 (95% CI= 0.71-0.94)

NEJM 2013; 369: 1406-15

Event rate	
EDOXABAN	8.5 %
WARFARIN	10.3 %

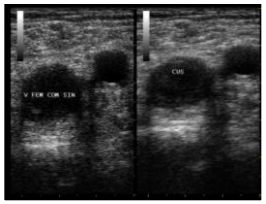


Old and new oral anticoagulants for venous thromboembolism and atrial fibrillation: A review of the literature

<table>
<tr><th>ACUTE</th><th>LONG TERM</th><th>EXTENDED</th></tr>
<tr><td></td><td>Dabigatran (RECOVER)
Edoxaban (HOKUSAI)</td><td rowspan="2">Dabigatran (REMEDY)
Dabigatran (RESONATE)
Rivaroxaban (EINSTEIN Extension)
Apixaban (AMPLIFY Extension)</td></tr>
<tr><td colspan="2">Rivaroxaban (EINSTEIN DVT)
Rivaroxaban (EINSTEIN PE)
Apixaban (AMPLIFY)</td></tr>
</table>

Beccattini C et al. Thromb Res 2012; 129: 392-400

Oral Rivaroxaban for Symptomatic Venous Thromboembolism



TVP confermata senza EP sintomatica

N° 3449

EP confermata con o senza TVP sintomatica

N° 4832

R

RIVAROXABAN 15 mg bid

gg 21

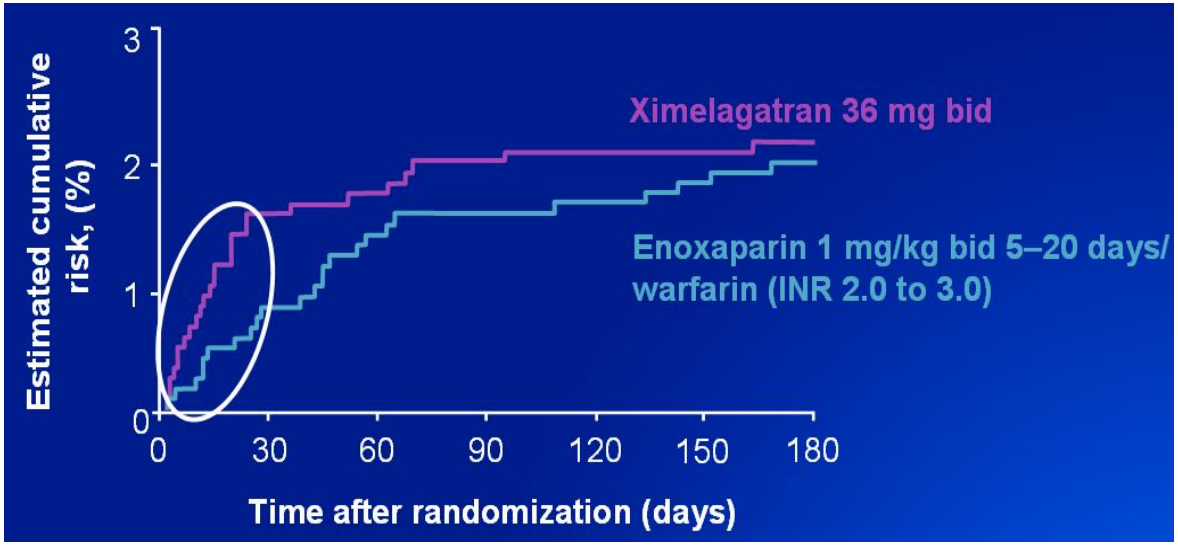
RIVAROXABAN 20 mg od

Periodo di trattamento predefinito (3-6-12 mesi)

Enoxaparina 1 mg/Kg bid per almeno 5 gg
+
VKA (INR 2-3)

Osservazione di 30 giorni

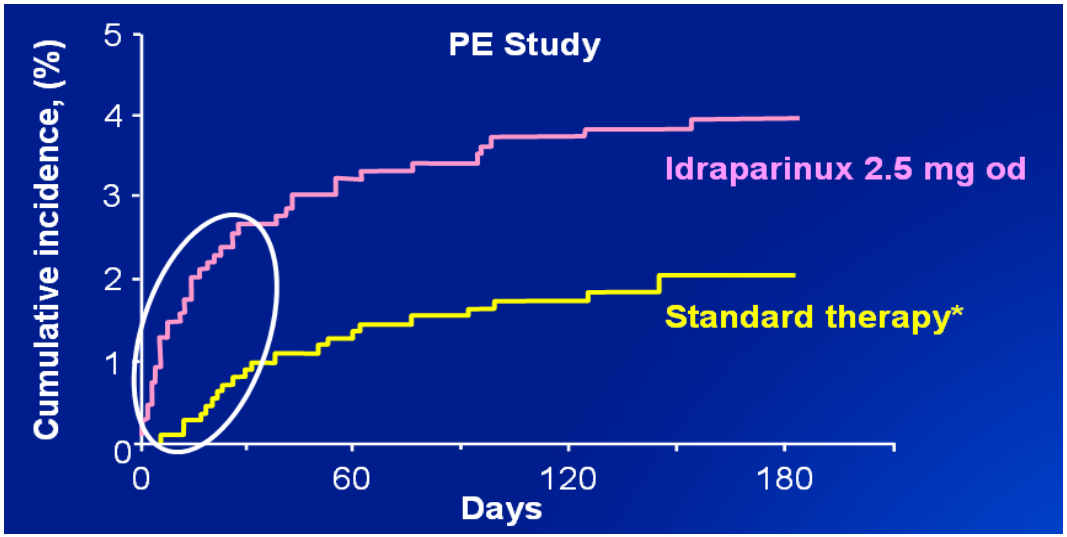
EINSTEIN investigators NEJM 2010; 363: 2499-2510



THRIVE study
(Ximelagatran)

Efficacy outcome
Recurrent VTE

Fiessinger J-N *et al. JAMA* 2005;293:681–689



van Gogh PE study
(Idraparinux)

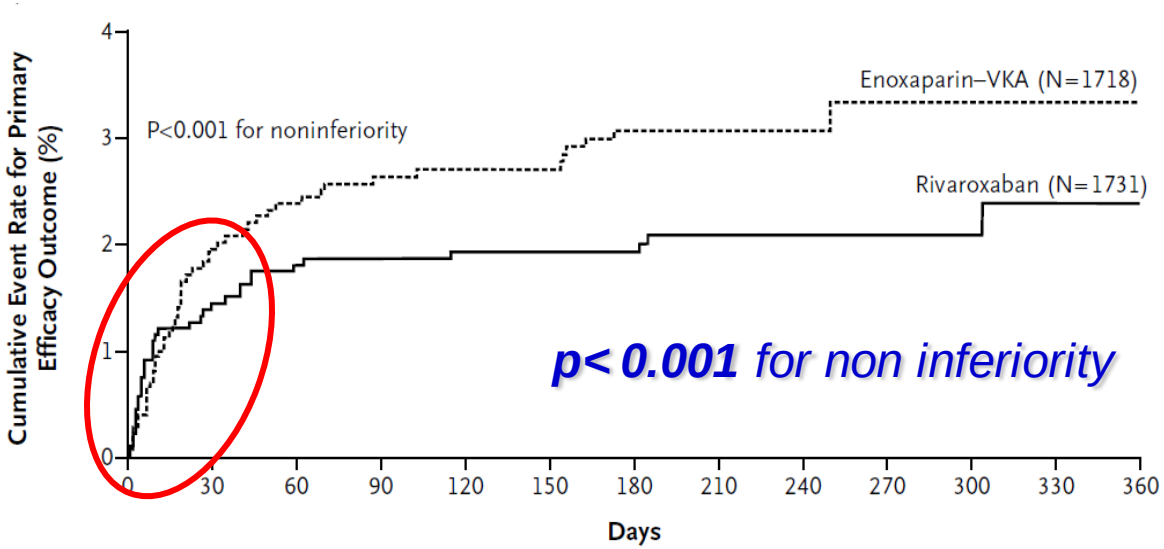
Efficacy outcome
Recurrent VTE

The van Gogh Investigators. *N Engl J Med* 2007;357:1094–1104

Oral Rivaroxaban for Symptomatic Venous Thromboembolism

Efficacy outcome

Recurrent venous thromboembolism



p< 0.001 *for non inferiority*

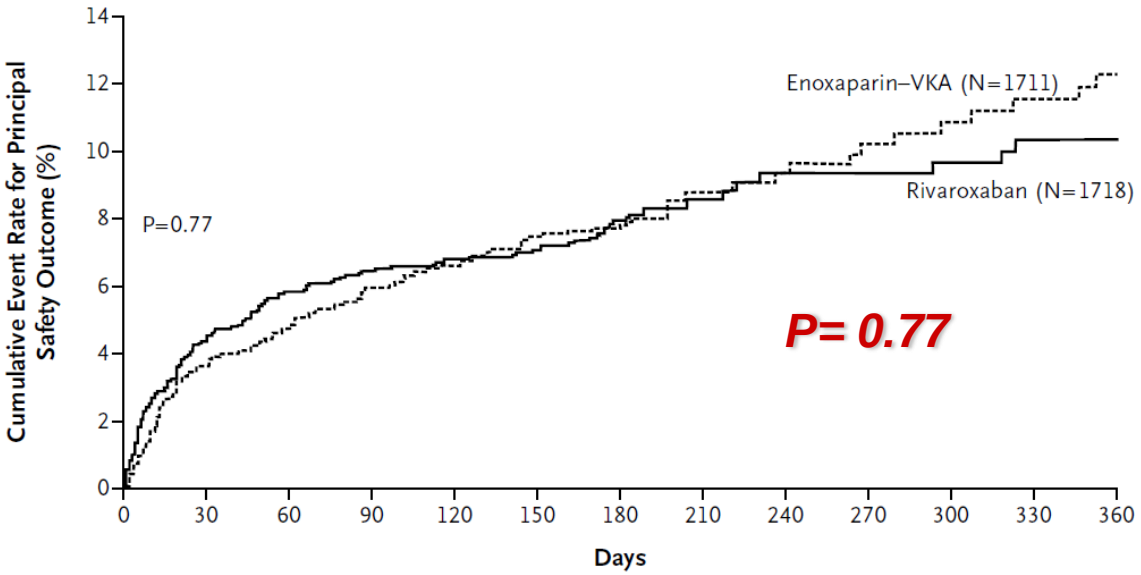
Event rate	
RIVAROXABAN	**2.1 %**
Enox- WARFARIN	**3.0 %**

HR= 0.68 (95% CI= 0.44-1.04)

EINSTEIN investigators NEJM 2010; 363: 2499-2510

Oral Rivaroxaban for Symptomatic Venous Thromboembolism

Safety outcome



Major bleeding or clinically relevant nonmajor bleeding

P= 0.77

Event rate	
RIVAROXABAN	**8.1 %**
Enox- WARFARIN	**8.1 %**

Major bleeding

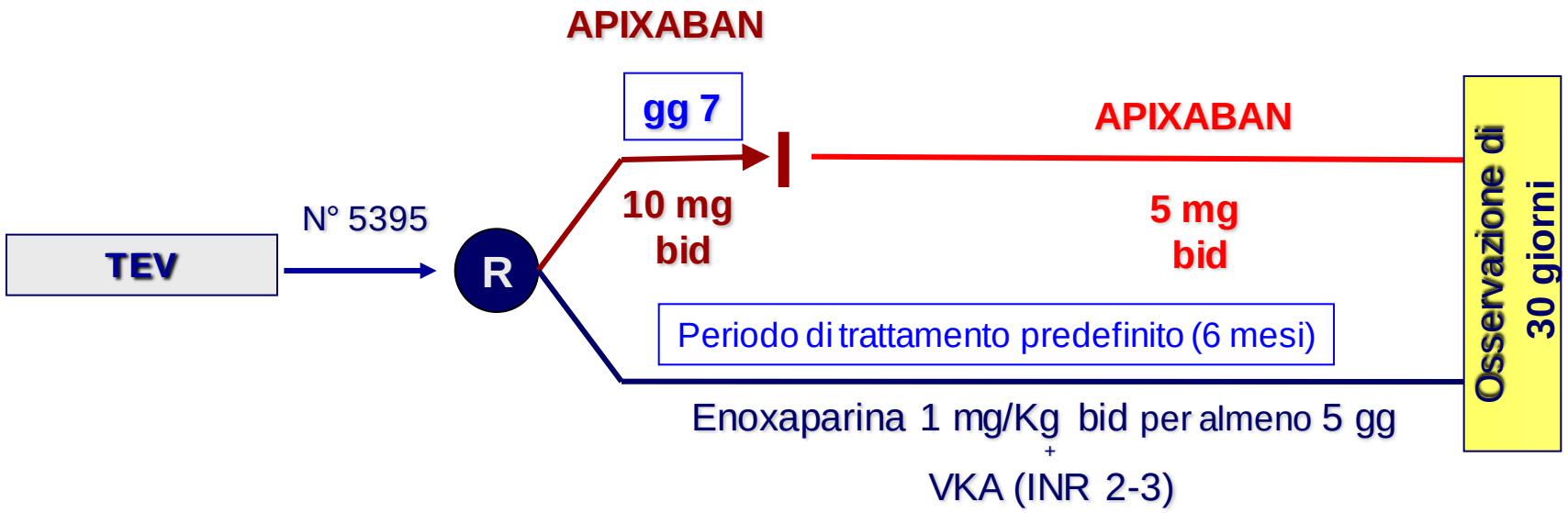
Event rate	
RIVAROXABAN	**0.8 %**
Enox-WARFARIN	**1.2 %**

HR= 0.65 (95% CI= 0.33-1.30)

EINSTEIN investigators NEJM 2010; 363: 2499-2510

Oral Apixaban for the Treatment of Acute Venous Thromboembolism

AMPLIFY



Agnelli G et al. NEJM 2013; 369: 799-808

Oral Apixaban for the Treatment of Acute Venous Thromboembolism

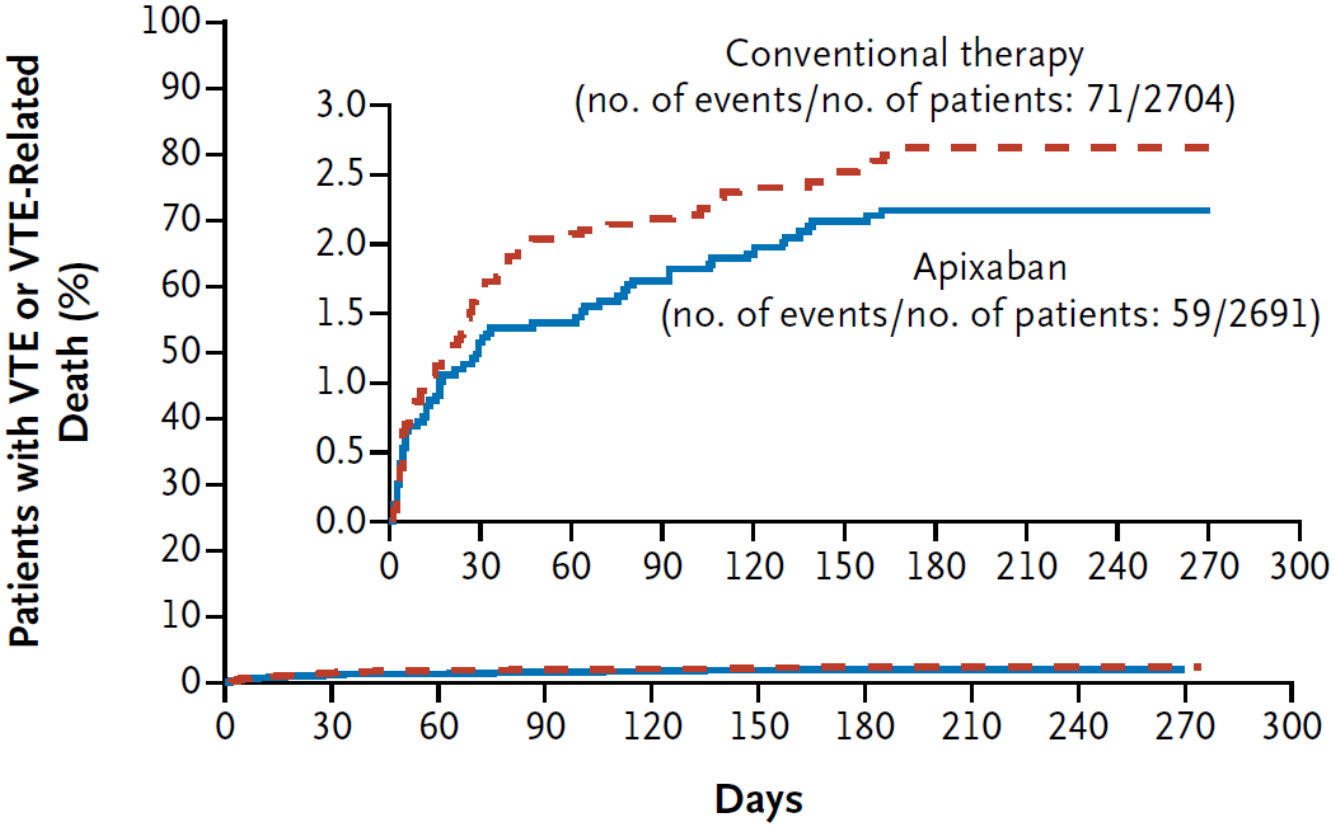
AMPLIFY

Event rate	
APIXABAN	2.3 %
Enox- WARFARIN	2.7 %

Efficacy outcome

Recurrent venous thromboembolism

HR= 0.84 (95% CI= 0.60-1.18)



Agnelli G et al. NEJM 2013; 369: 799-808

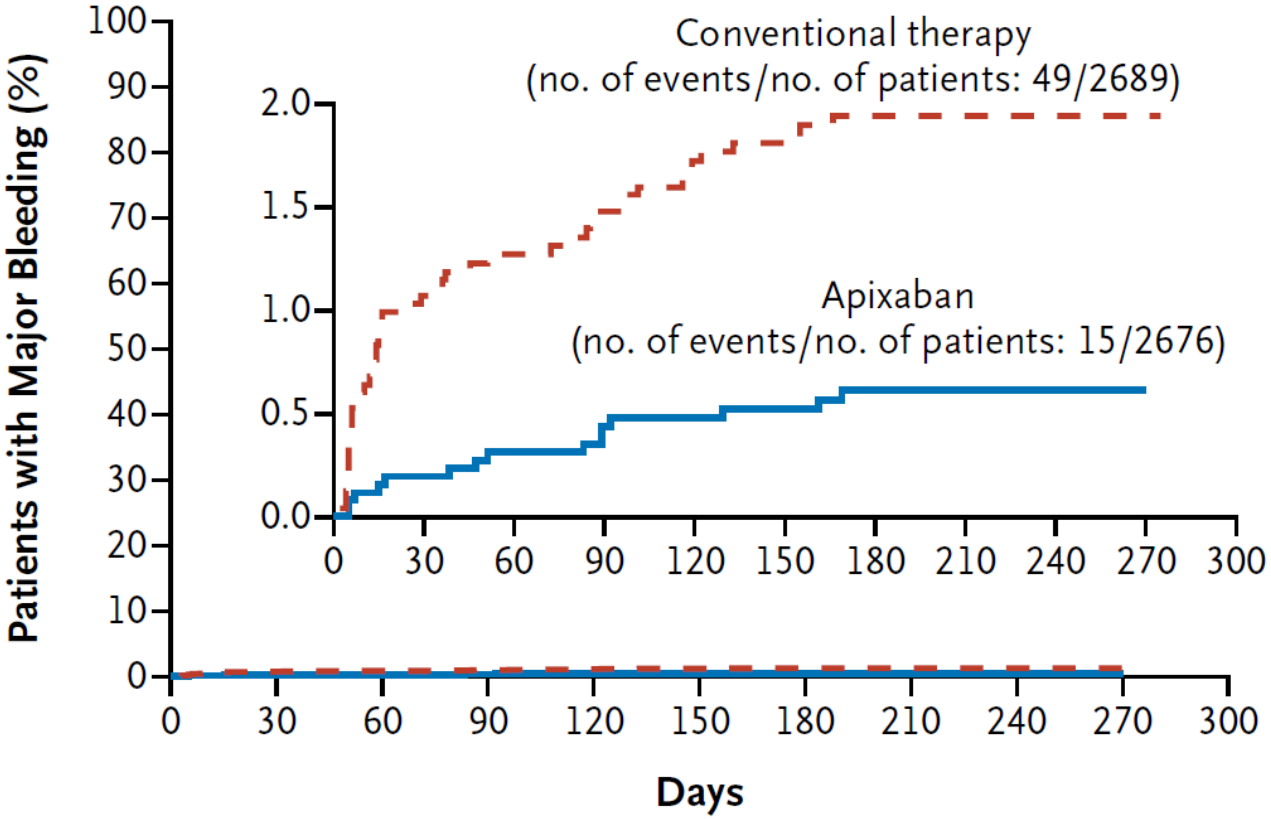
Oral Apixaban for the Treatment of Acute Venous Thromboembolism

AMPLIFY

Major Bleeding

HR= 0.31 (95% CI= 0.17-0.55)

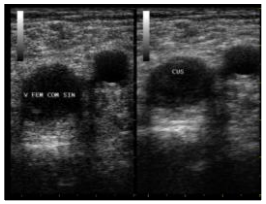
Event rate	
APIXABAN	0.6 %
Enox- WARFARIN	1.8 %



Agnelli G et al. NEJM 2013; 369: 799-808

Oral Rivaroxaban for Symptomatic Venous Thromboembolism

POOLED ANALYSIS



TVP confermata senza EP sintomatica

N° 3449

RIVAROXABAN 15 mg bid → **gg 21** → **RIVAROXABAN** 20 mg od

R

Periodo di trattamento predefinito (3-6-12 mesi)

Enoxaparina 1 mg/Kg bid per almeno 5 gg
+
VKA (INR 2-3)

Osservazione di 30 giorni

EP confermata con o senza TVP sintomatica

N° 4832

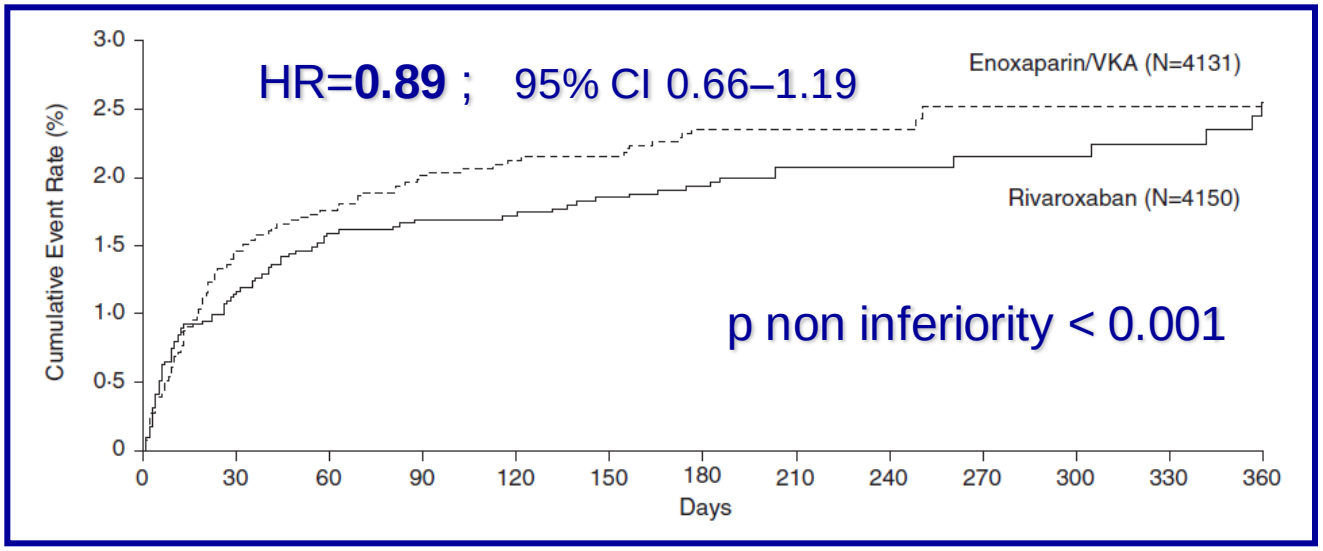
EINSTEIN investigators NEJM 2010; 363: 2499-2510

Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies

ORIGINAL CLINICAL INVESTIGATION Open Access

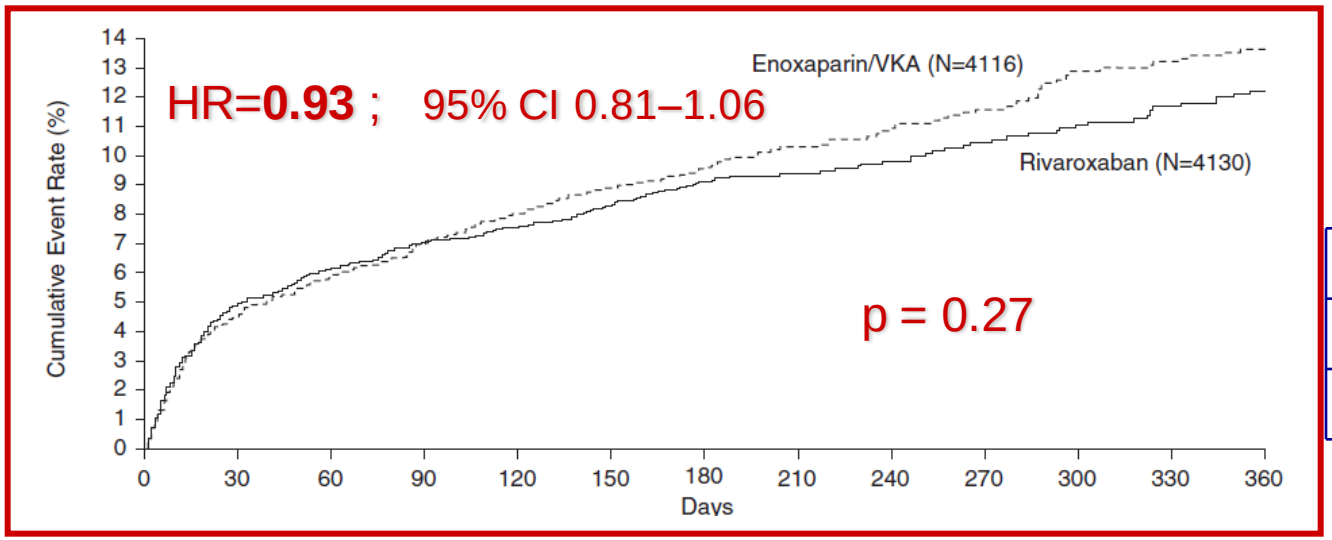
EINSTEIN

8282 patients



Primary efficacy outcome

Event rate	
RIVAROXABAN	2.1 %
Enox- WARFARIN	2.3 %



Principal safety outcome

Event rate	
RIVAROXABAN	9.4 %
Enox- WARFARIN	10 %

Prins MH et al. Thrombosis Journal 2013; 11: 21-31

ORIGINAL CLINICAL INVESTIGATION Open Access

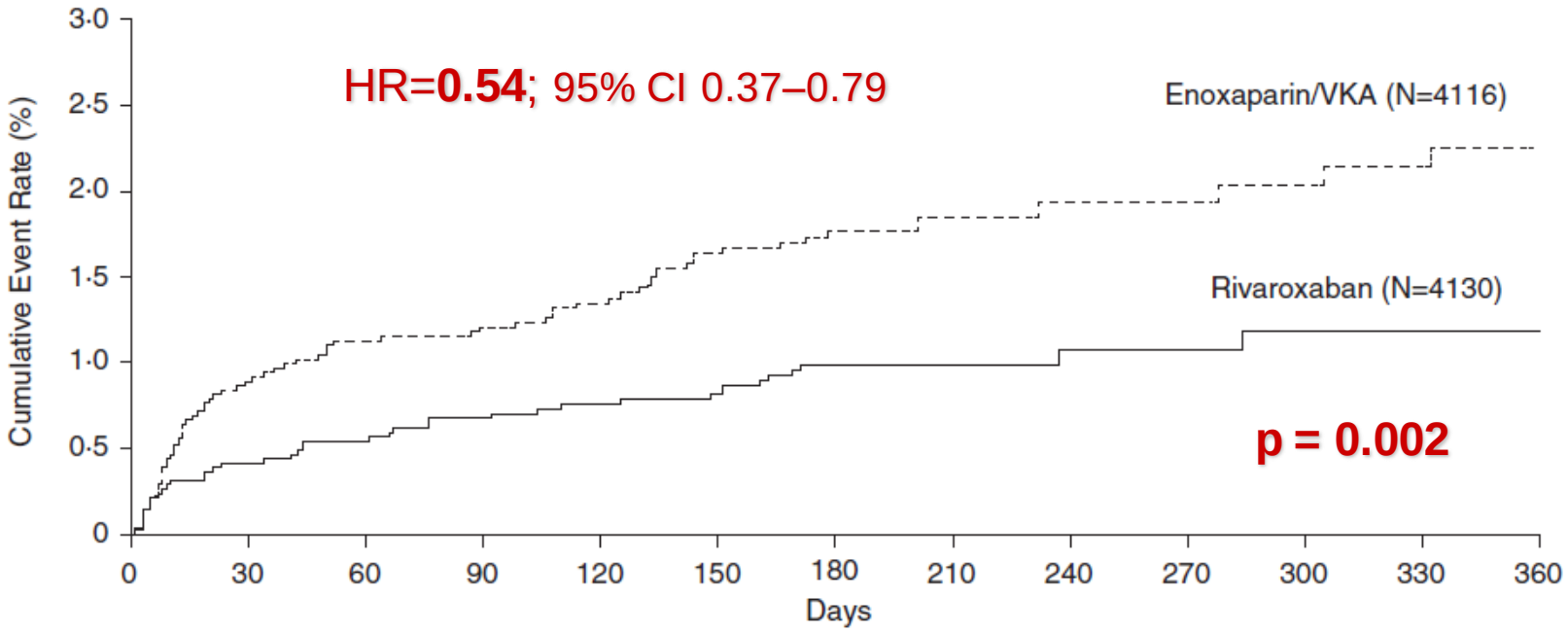
Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies

EINSTEIN

8282 patients

Major bleeding

Event rate	
RIVAROXABAN	**1.0 %**
Enox- WARFARIN	**1.7 %**



Prins MH et al. Thrombosis Journal 2013; 11: 21-31

ORIGINAL CLINICAL INVESTIGATION Open Access

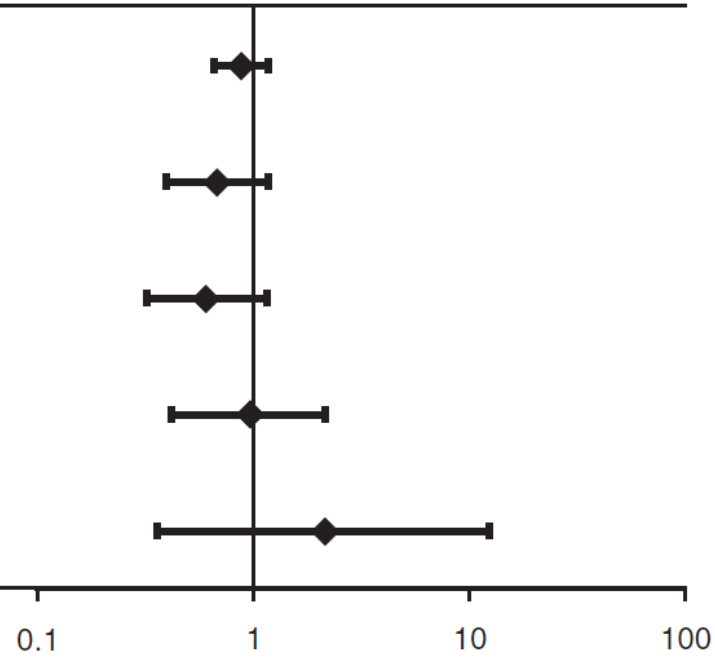
Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies

8282 patients

EINSTEIN

Efficacy outcomes in fragile patients and subgroups

	Rivaroxaban		Enoxaparin/VKA		HR (95% CI)
	n/N	%	n/N	%	Favors Rivaroxaban / Favors Enoxaparin/VKA
Nonfragile	65/3359	1.9	65/3349	1.9	
Fragile	21/791	2.7	30/782	3.8	
Age >75 years	15/656	2.3	23/627	3.7	
Creatinine clearance <50 ml/min	11/332	3.3	11/322	3.4	
Body weight <50 kg	3/42	7.1	2/66	3.0	



Prins MH et al. Thrombosis Journal 2013; 11: 21-31

ORIGINAL CLINICAL INVESTIGATION Open Access

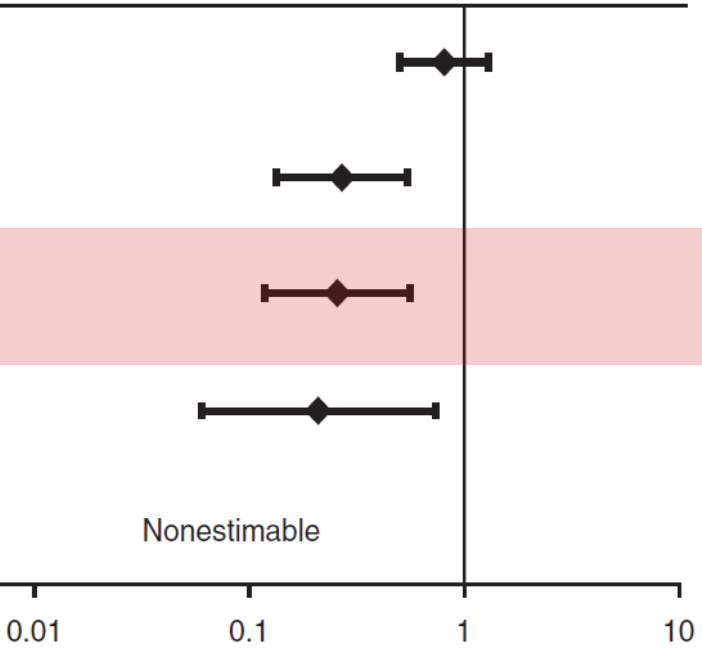
Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies

8282 patients

EINSTEIN

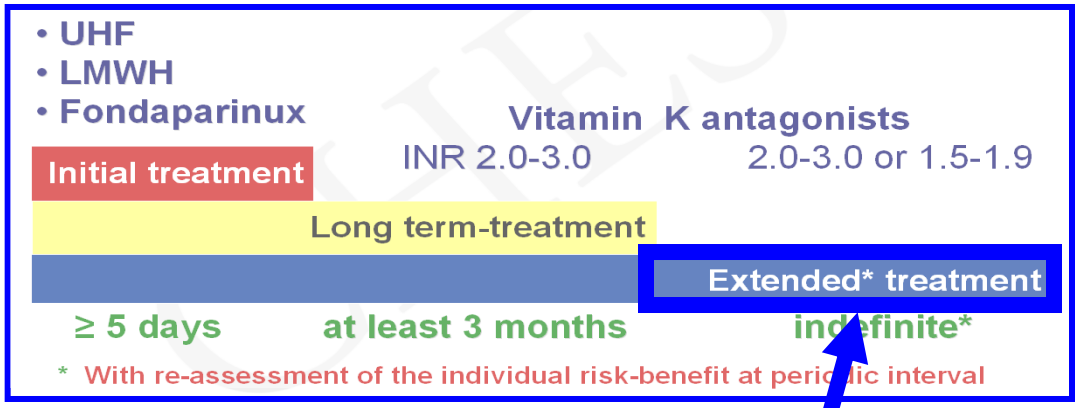
Safety outcomes in fragile patients and subgroups

	Rivaroxaban		Enoxaparin/VKA		HR (95% CI)
	n/N	%	n/N	%	Favors Rivaroxaban / Favors Enoxaparin /VKA
Nonfragile	30/3342	0.9	37/3337	1.1	
Fragile	10/788	1.3	35/779	4.5	
Age >75 years	8/655	1.2	28/624	4.5	
Creatinine clearance <50 ml/min	3/329	0.9	13/320	4.1	
Body weight <50 kg	0/42	0.0	3/65	4.6	Nonestimable



Prins MH et al. Thrombosis Journal 2013; 11: 21-31

Old and new oral anticoagulants for venous thromboembolism and atrial fibrillation: A review of the literature



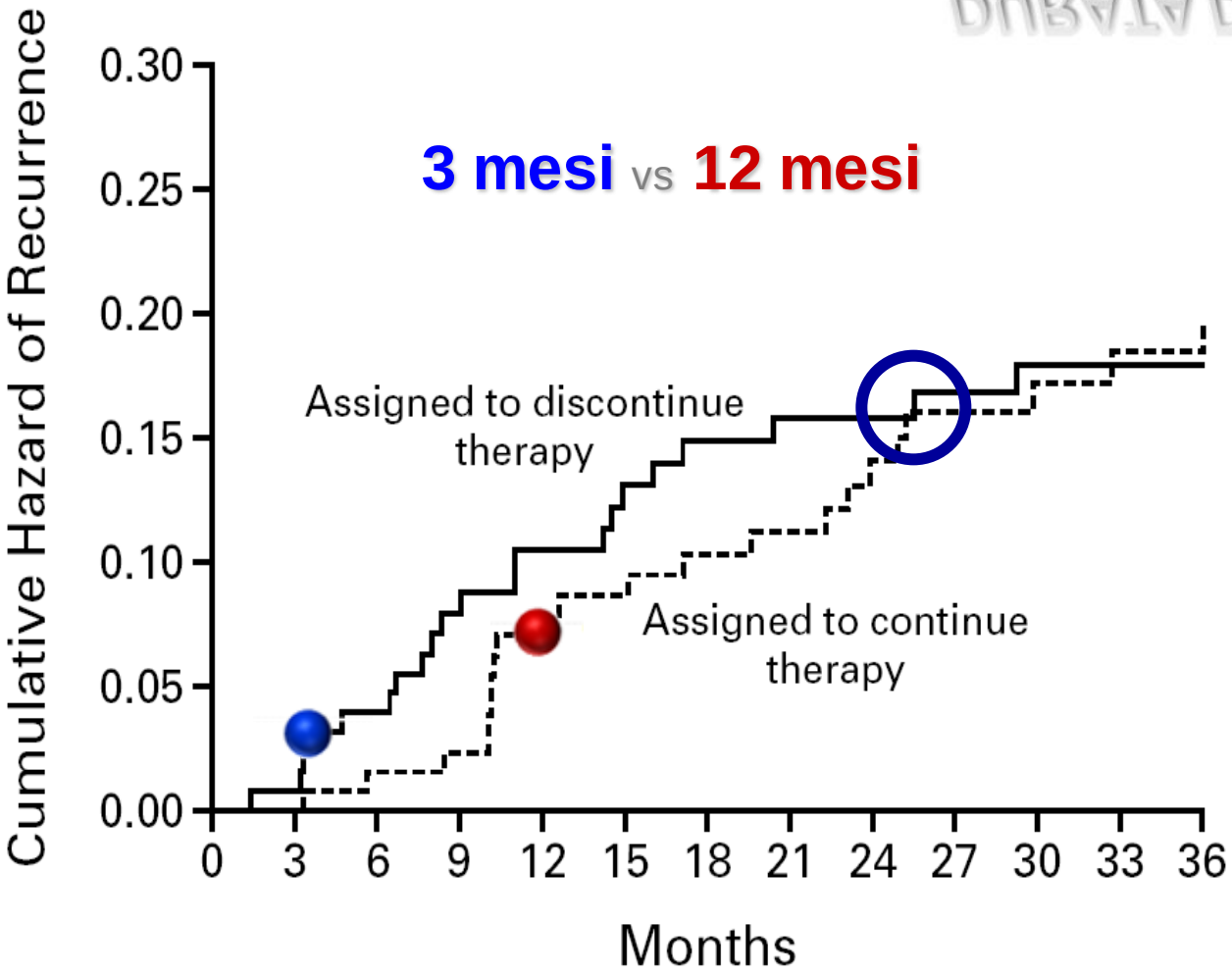
ACUTE	LONG TERM	EXTENDED
	Dabigatran (RECOVER) Edoxaban (HOKUSAI)	Dabigatran (REMEDY) Dabigatran (RESONATE) Rivaroxaban (EINSTEIN Extension) Apixaban (AMPLIFY Extension)
Rivaroxaban (EINSTEIN DVT) Rivaroxaban (EINSTEIN PE) Apixaban (AMPLIFY)		

Beccattini C et al. Thromb Res 2012; 129: 392-400

THREE MONTHS VERSUS ONE YEAR OF ORAL ANTICOAGULANT THERAPY FOR IDIOPATHIC DEEP VENOUS THROMBOSIS

DURATA DELLA TAO

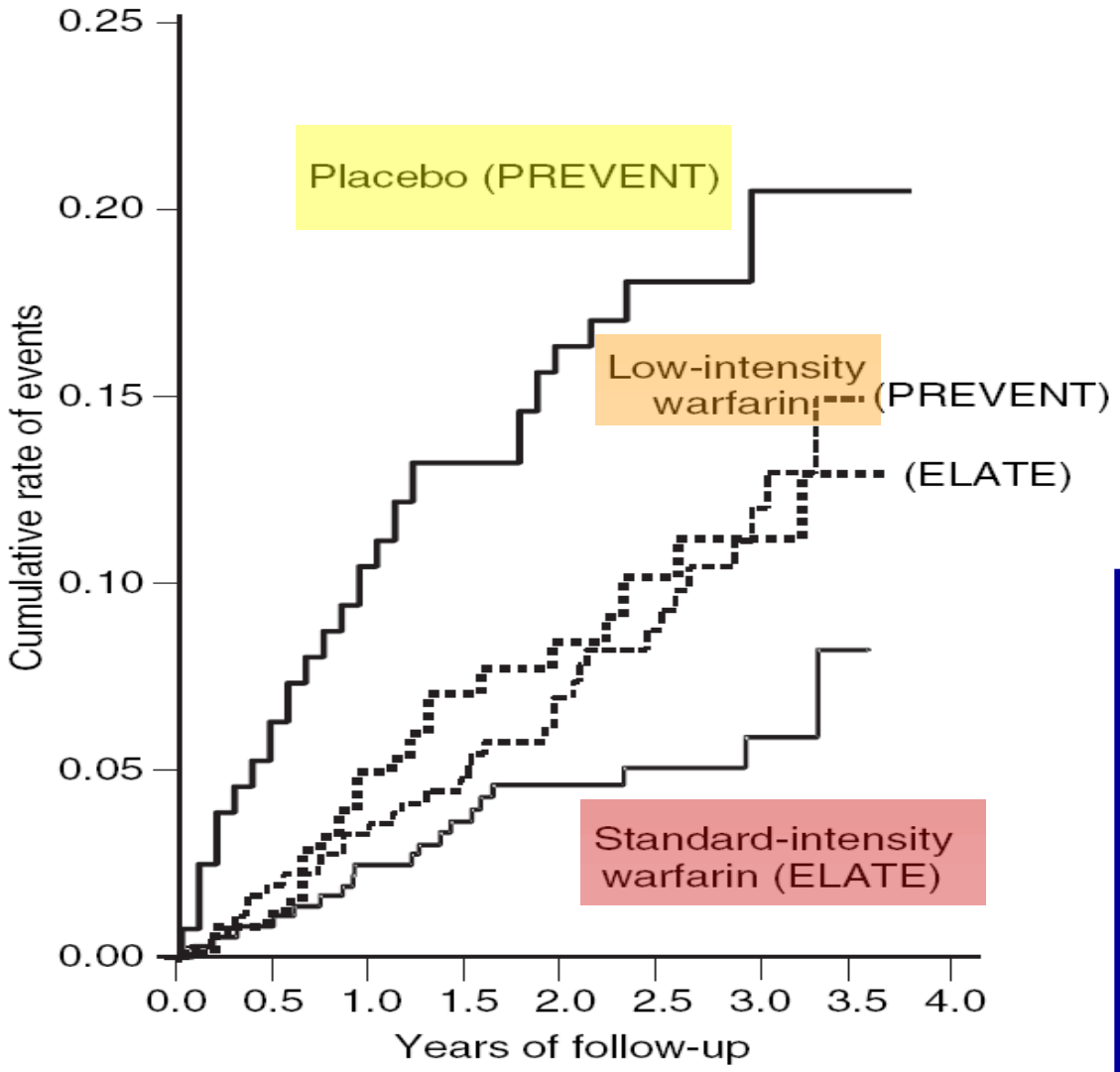
3 mesi vs **12 mesi**



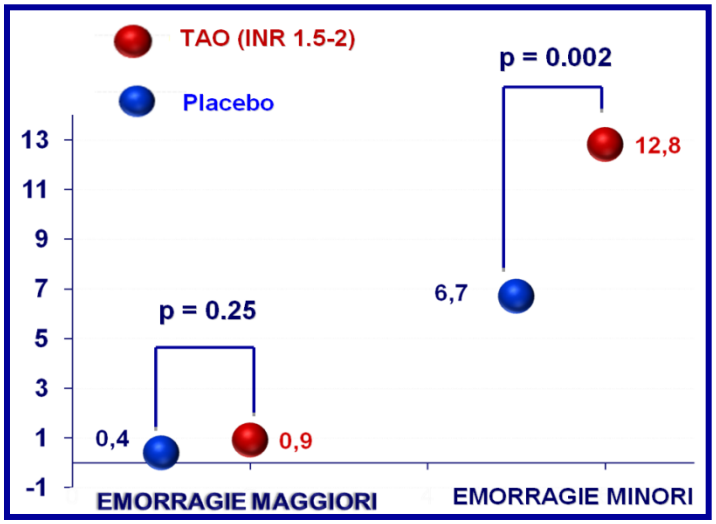
Agnelli G et al. NEJM 2001; 345: 165-9

DEBATE

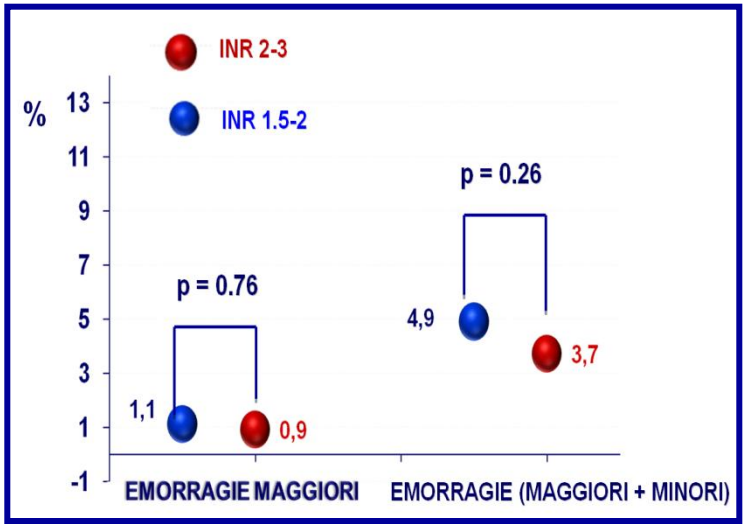
Indefinite anticoagulation after a first episode of unprovoked venous thromboembolism: yes



PREVENT study



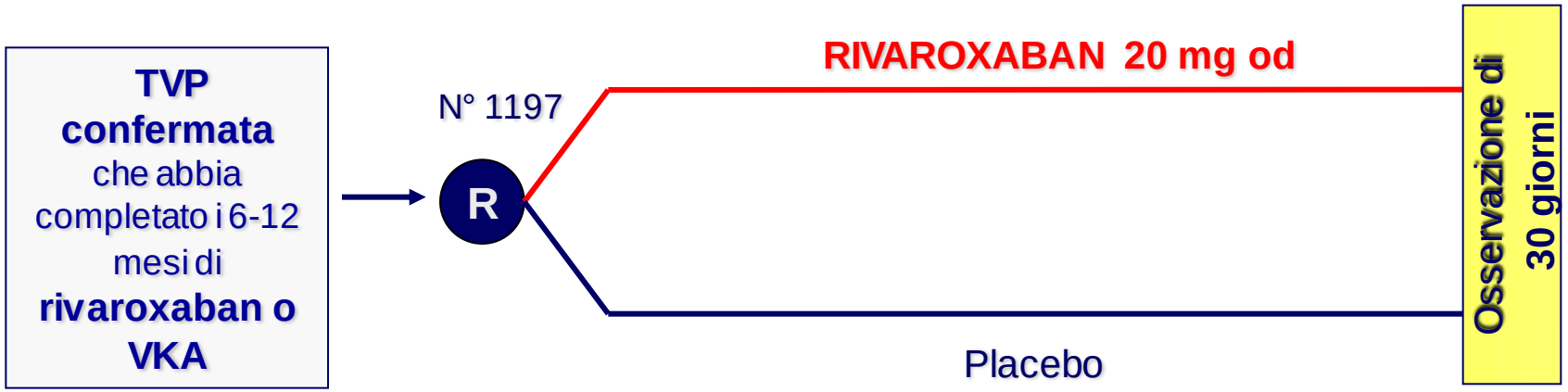
ELATE study



Kearon K et al. JTH 2007; 5: 2330-2335

Oral Rivaroxaban for Symptomatic Venous Thromboembolism

Periodo di trattamento predefinito (12 mesi)



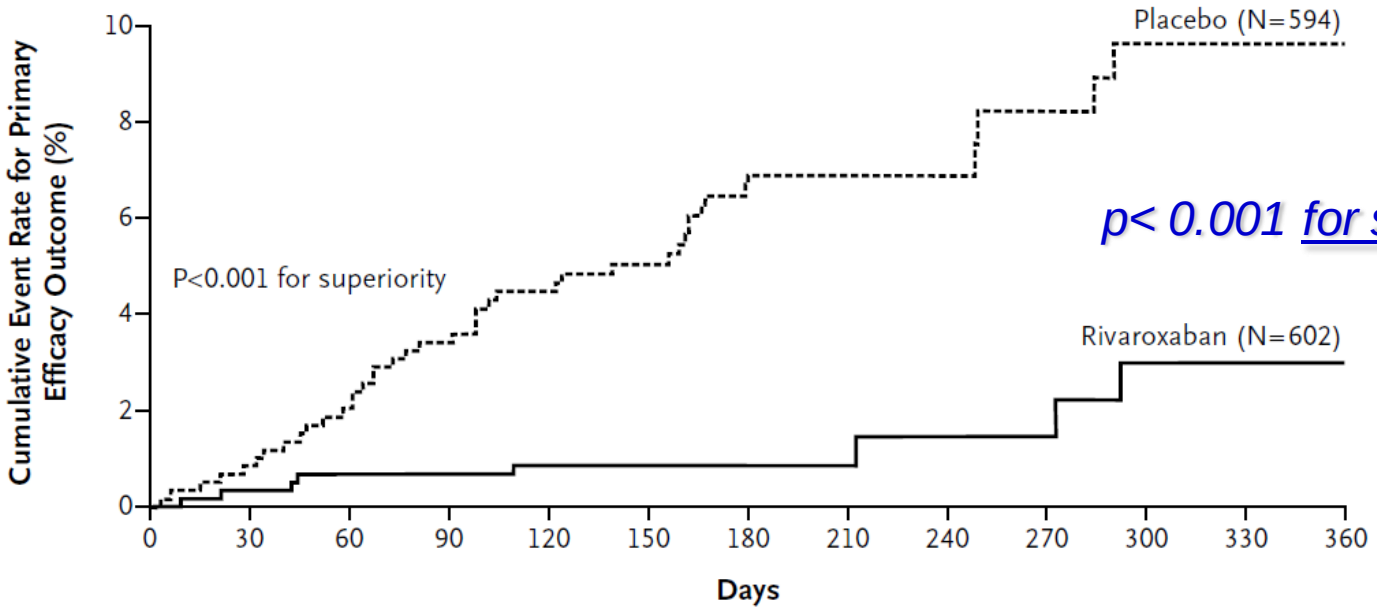
EINSTEIN investigators NEJM 2010; 363: 2499-2510

Oral Rivaroxaban for Symptomatic Venous Thromboembolism

Symptomatic Recurrent VTE

Event rate	
RIVAROXABAN	**1.3 %**
PLACEBO	**7.1 %**

HR= 0.18 (95% CI= 0.09-0.39)



p< 0.001 for superiority

EINSTEIN investigators NEJM 2010; 363: 2499-2510

Oral Rivaroxaban for Symptomatic Venous Thromboembolism

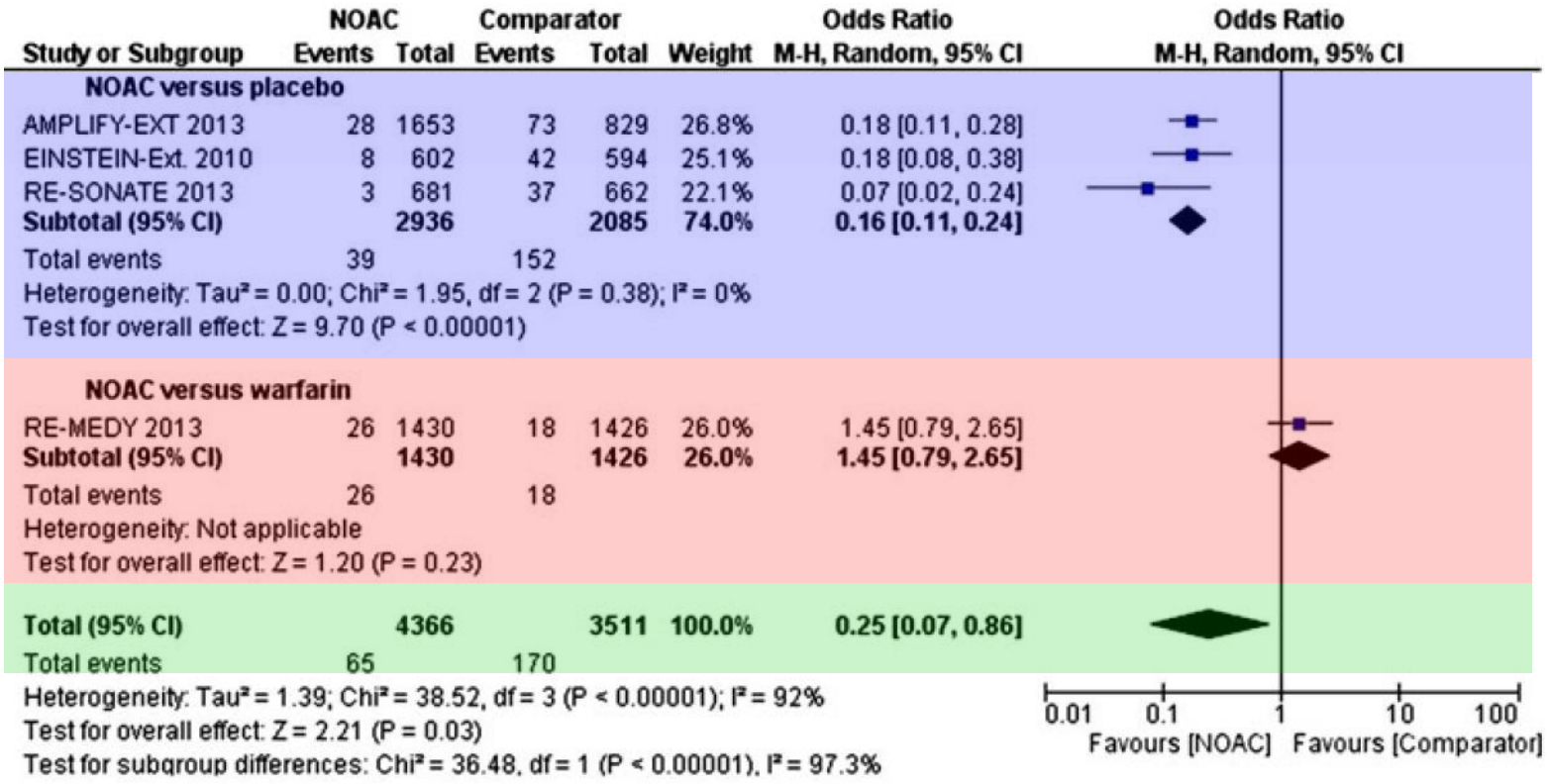
Safety outcome

Event rate				
	Major or clinically relevant non major		Major bleeding	
RIVAROXABAN	**6.0** %	**p < 0.001**	0.7	**p = 0.11**
Placebo	**1.2** %		0	

EINSTEIN investigators NEJM 2010; 363: 2499-2510

Efficacy and Safety of New Oral Anticoagulants for Extended Treatment of Venous Thromboembolism: Systematic Review and Meta-Analyses of Randomized Controlled Trials

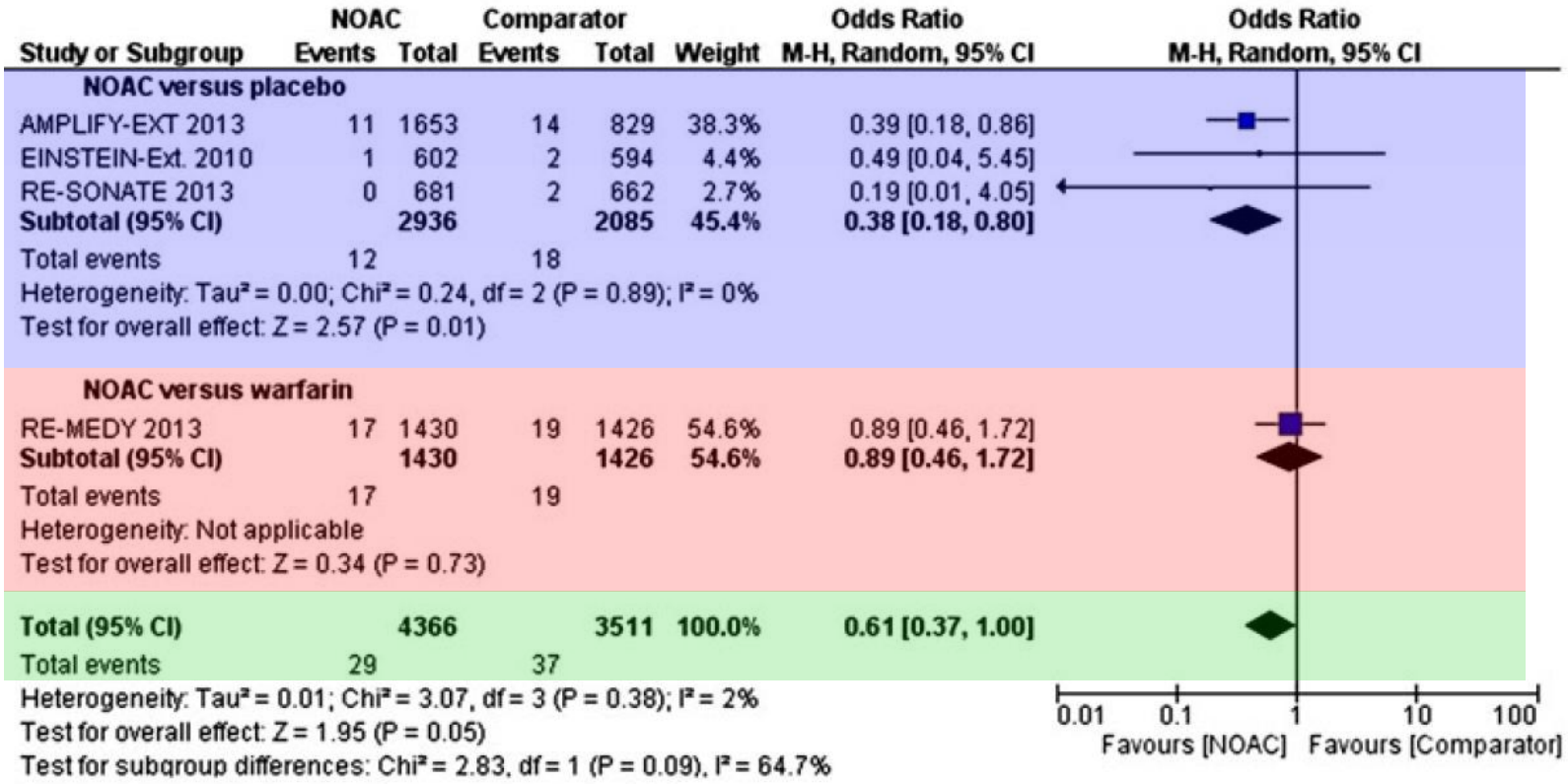
Recurrent symptomatic VTE and VTE-related deaths



Sardar P et al. Drugs 2013; 73: 1171-82

Efficacy and Safety of New Oral Anticoagulants for Extended Treatment of Venous Thromboembolism: Systematic Review and Meta-Analyses of Randomized Controlled Trials

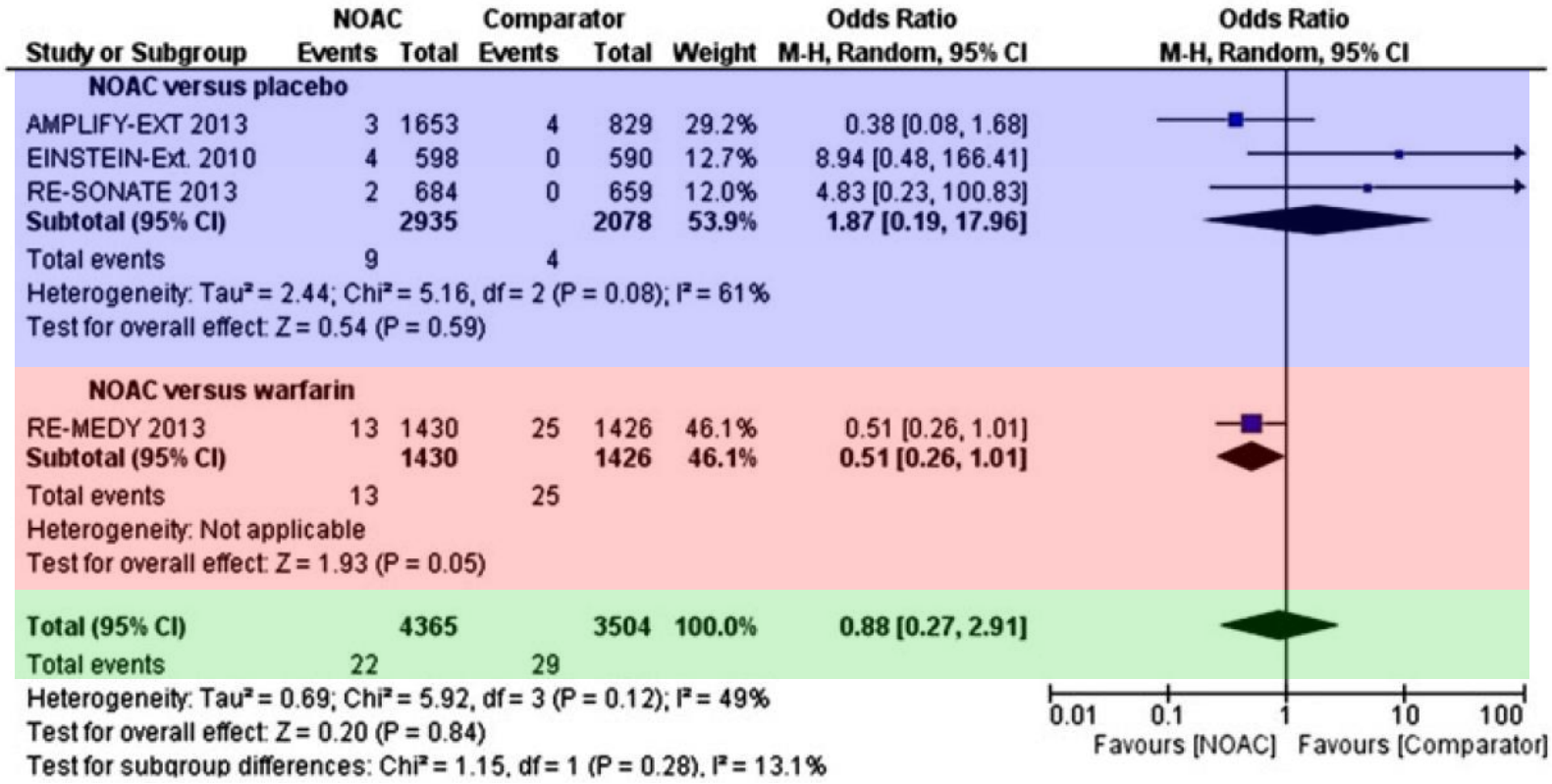
All-cause mortality



Sardar P et al. Drugs 2013; 73: 1171-82

Efficacy and Safety of New Oral Anticoagulants for Extended Treatment of Venous Thromboembolism: Systematic Review and Meta-Analyses of Randomized Controlled Trials

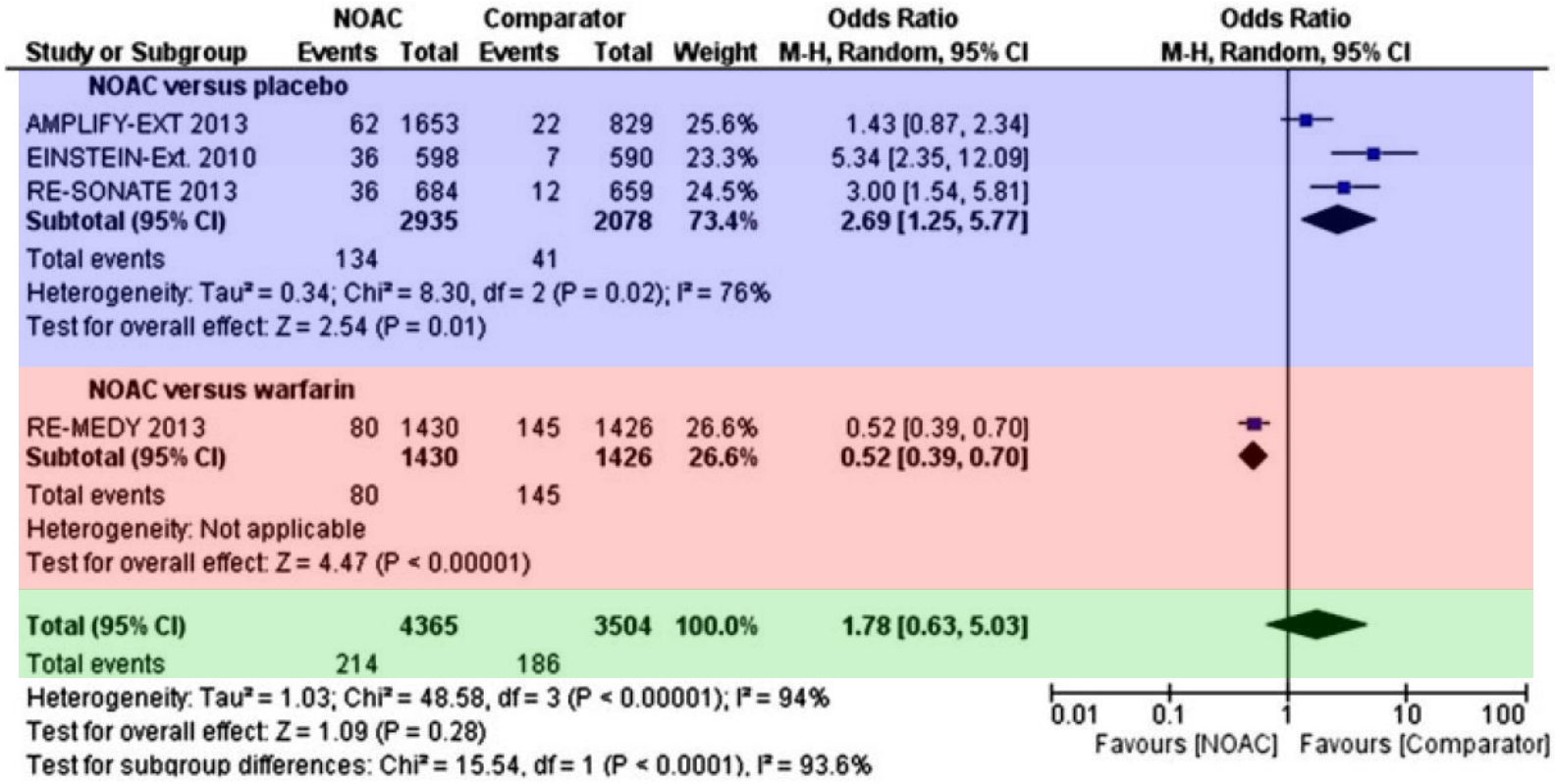
Major bleeding



Sardar P et al. Drugs 2013; 73: 1171-82

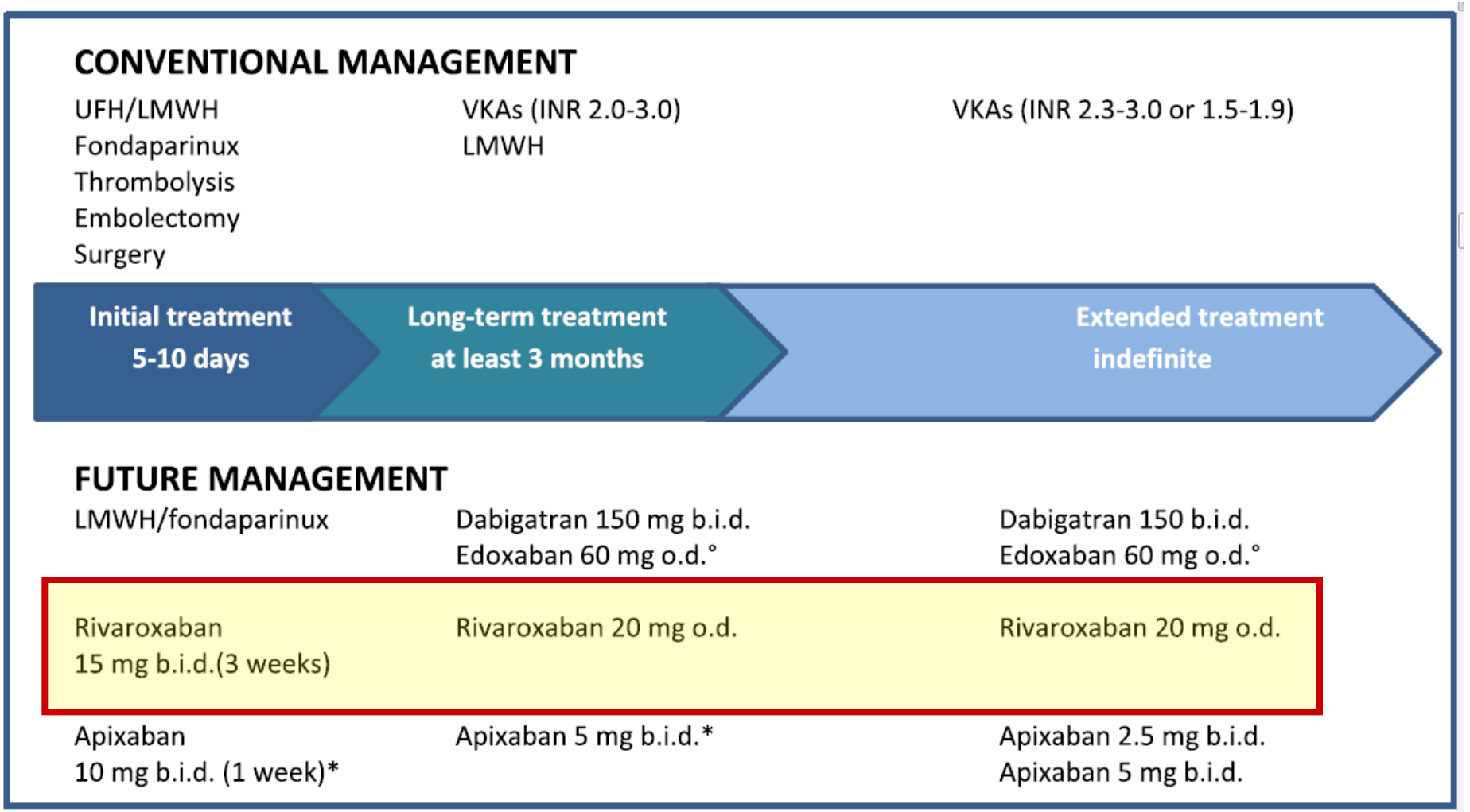
Efficacy and Safety of New Oral Anticoagulants for Extended Treatment of Venous Thromboembolism: Systematic Review and Meta-Analyses of Randomized Controlled Trials

Major or Clinically Relevant Nonmajor Bleeding



Sardar P et al. Drugs 2013; 73: 1171-82

New oral anticoagulants for the treatment of venous thromboembolism



Agnelli G et al. Best Practice & Research Clinical Haematology 2013; 26: 151-61

SOCIETÀ ITALIANA
DI GERONTOLOGIA
E GERIATRIA

I nuovi anticoagulanti orali nella **trombosi venosa profonda**

Grazie

Terapia della TVP

Fulvio POMERO

Medicina Interna
S. Croce e Carle
Cuneo