I nuovi anticoagulanti orali (NAO). Cosa cambia?

t.lenzi imola

Limiti della terapia con antagonisti della Vitamina K

La terapia con antagonisti della vitamina K presenta diversi limiti che ne rendono difficoltoso l'impiego nella pratica clinica

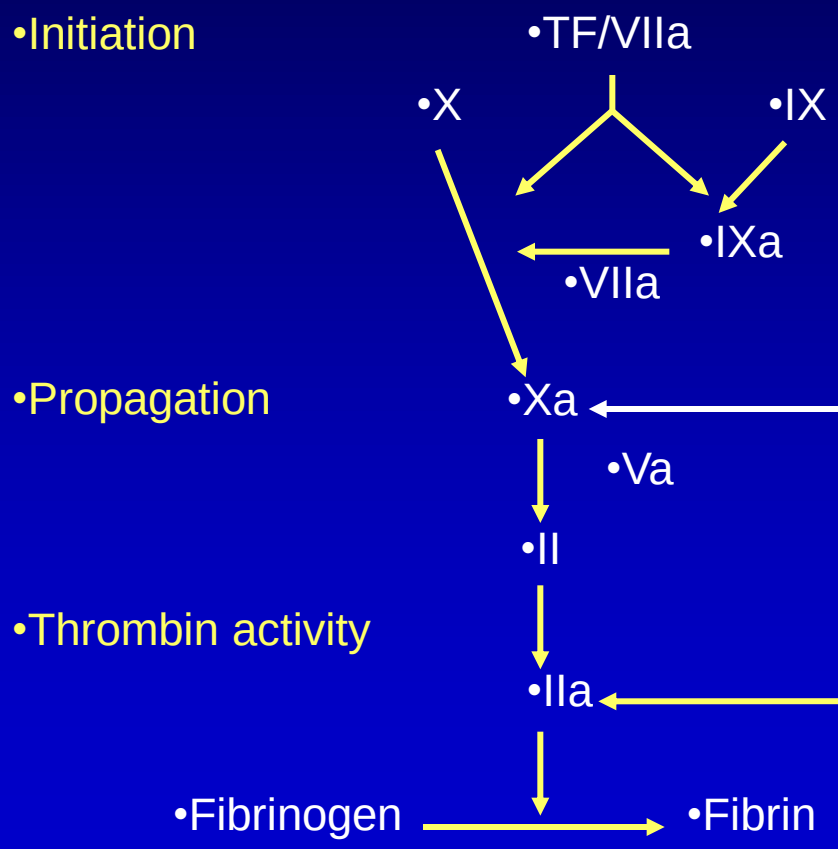
- Risposta non prevedibile
- Finestra di trattamento stretta (INR range 2-3)
- Monitoraggio routinario dei fattori della coagulazione
- Lenta insorgenza/termine d'azione
- Necessità di aggiustamenti della dose
- Interazioni alimentari
- Interazioni con altri farmaci
- Resistenza al Warfarin

1. Ansell J, et al. *Chest* 2008;133;160S-198S; 2. Umer Ushman MH, et al. *J Interv Card Electrophysiol* 2008; 22:129-137; Nutescu EA, et al. *Cardiol Clin* 2008; 26:169-187.

NAO

•Coagulation cascade

• Drug



Direct Oral: rivaroxaban, apixaban, edoxaban

Direct Oral: dabigatran, AZD0837

New Oral Direct IIa Inhibitors for Stroke Prevention in Atrial Fibrillation

		ESC GL 2012
Dabigatran	Boehringer Ingelheim	Classe Ia
AZD0837	Astra Zeneca	
(Ximelagatran)		

New Oral Direct FXa Inhibitors for Stroke Prevention in Atrial Fibrillation

Rivaroxaban	Bayer	Classe IA
Apixaban	BMS / Pfizer	Classe IA
Edoxaban	Daiichi Sankyo	Phase III
Betrixaban	Portola / Merck	
Darexaban	Astellas Pharma	
LY 517717	Lilly	
TAK – 442	Takeda	

Farmacologia clinica: rivaroxaban, apixaban, and dabigatran

	Apixaban[1]	Rivaroxaban[2]	Dabigatran[3]
Mechanism of action	Direct FXa inhibitor	Direct FXa inhibitor	Direct thrombin inhibitor
Absolute availability	~50%	80–100%	6.5%
Route of administration	Oral	Oral	Oral
Dosing	BID in all indications (VTEp, VTEt, AF, ACS)	OD (VTEp, VTEt, AF) BID (ACS)	OD (VTEp) BID (VTEt, AF)
Prodrug	No	No	Yes
Food effect	No	No	No
Renal clearance	~27%	~ 33%	85%
Mean half-life (T½)	~12 h	7–11 h	12–14 h
T_{max}	3–4 h	2–4 h	0.5–2 h
Drug interactions	Strong CYP3A4 and P-gp inhibitors and inducers	Strong CYP3A4 and P-gp inhibitors Strong CYP3A4 inducers	P-gp inhibitors P-gp inducers Amiodarone and verapamil

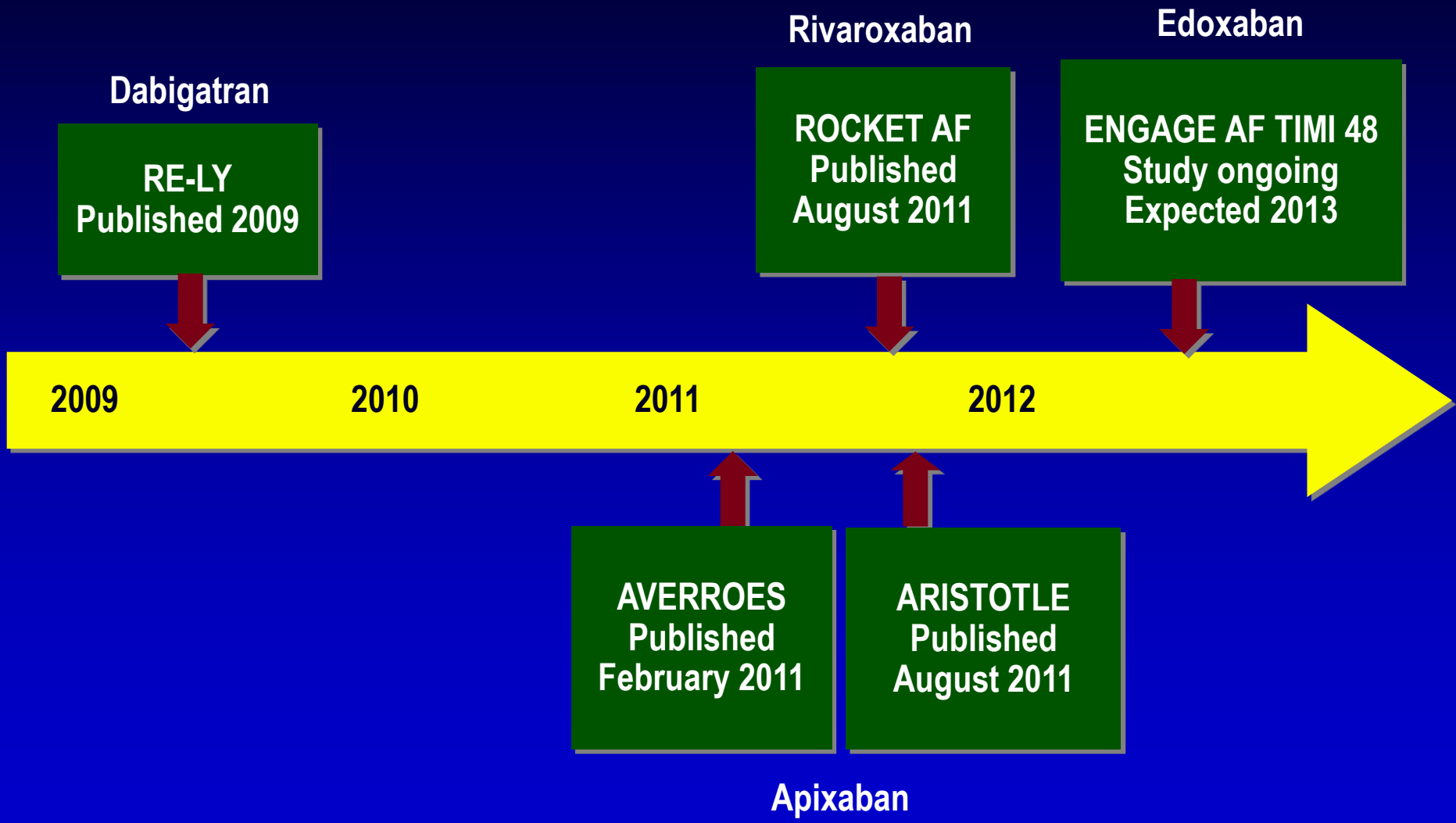
ACS = acute coronary syndrome; AF = atrial fibrillation; BID = twice daily; OD = once daily; VTEp = venous thromboembolism prevention; VTEt = venous thromboembolism treatment

1. Eliquis. SmPC, May 2011; 2. Xarelto. SmPC, December 2011; 3. Pradaxa. SmPC, April 2012

Indicazioni cliniche

- **Profilassi del TEV nella chirurgia ortopedica maggiore (Anca e ginocchio)**
- **Terapia del Trombo Embolismo Venoso (TVP e EP)**
- **Terapia antitrombotica nella FA non valvolare**

Atrial Fibrillation
Phase 3 Study Timelines



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 17, 2009 VOL. 361 NO. 12

Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., Michael D. Ezekowitz, M.B., Ch.B., D.Phil., Salim Yusuf, F.R.C.P.C., D.Phil., John Eikelboom, M.D., Jonas Oldgren, M.D., Ph.D., Amit Parekh, M.D., Janice Pogue, M.Sc., Paul A. Reilly, Ph.D., Ellison Themeles, B.A., Jeanne Varrone, M.D., Susan Wang, Ph.D., Marco Alings, M.D., Ph.D., Denis Xavier, M.D., Jun Zhu, M.D., Rafael Diaz, M.D., Basil S. Lewis, M.D., Harald Darius, M.D., Hans-Christoph Diener, M.D., Ph.D., Campbell D. Joyner, M.D., Lars Wallentin, M.D., Ph.D., and the RE-LY Steering Committee and Investigators*

N Engl J Med 2009;361(12):1139-51

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

Manesh R. Patel, M.D., Kenneth W. Mahaffey, M.D., Jyotsna Garg, M.S., Guohua Pan, Ph.D., Daniel E. Singer, M.D., Werner Hacke, M.D., Ph.D., Günter Breithardt, M.D., Jonathan L. Halperin, M.D., Graeme J. Hankey, M.D., Jonathan P. Piccini, M.D., Richard C. Becker, M.D., Christopher C. Nessel, M.D., John F. Paolini, M.D., Ph.D., Scott D. Berkowitz, M.D., Keith A.A. Fox, M.B., Ch.B., Robert M. Califf, M.D., and the ROCKET AF Steering Committee, for the ROCKET AF Investigators*

N Engl J Med August 10, 2011

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

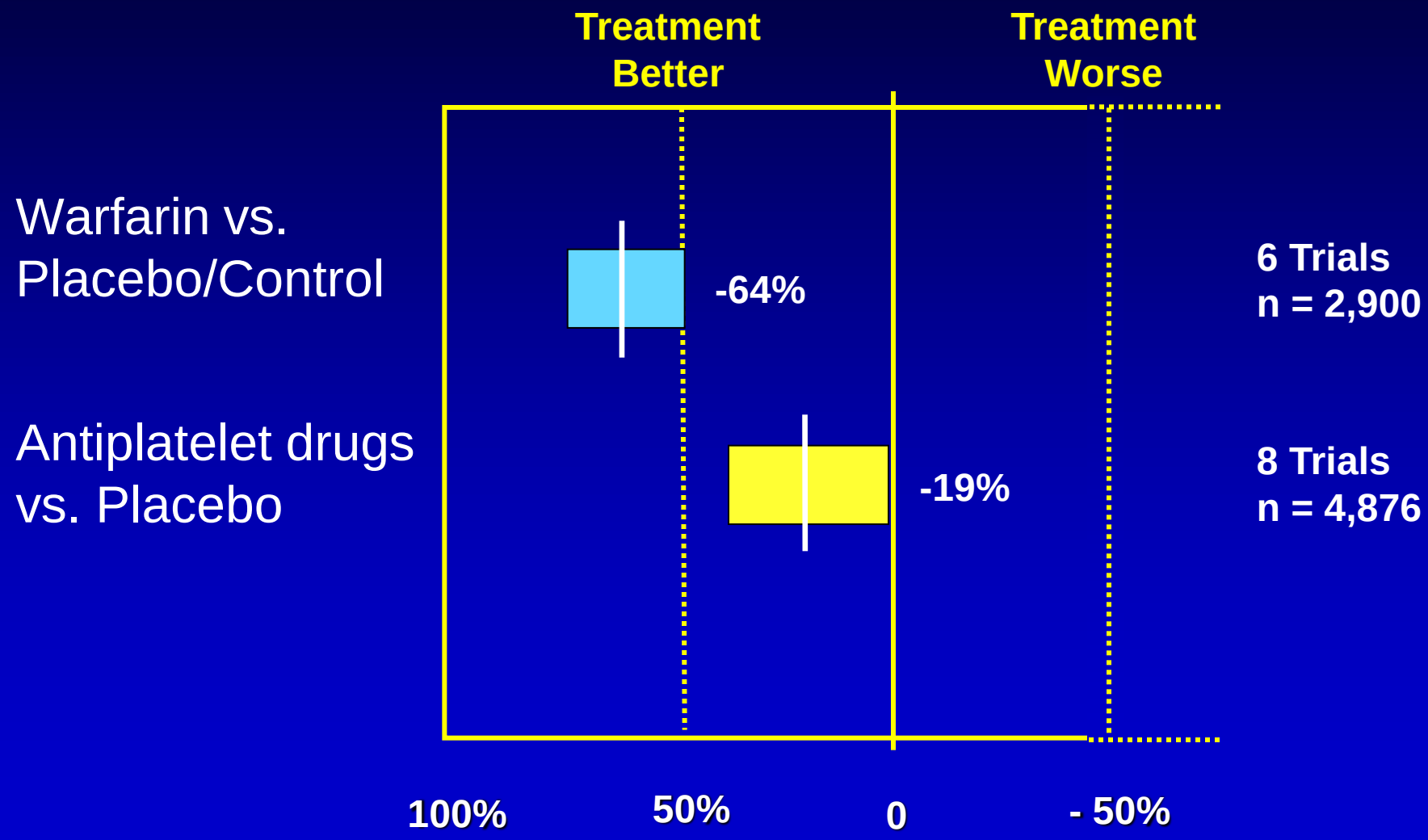
Apixaban versus Warfarin in Patients with Atrial Fibrillation

Christopher B. Granger, M.D., John H. Alexander, M.D., M.H.S., John J.V. McMurray, M.D., Renato D. Lopes, M.D., Ph.D., Elaine M. Hylek, M.D., M.P.H., Michael Hanna, M.D., Hussein R. Al-Khalidi, Ph.D., Jack Ansell, M.D., Dan Atar, M.D., Alvaro Avezum, M.D., Ph.D., M. Cecilia Bahit, M.D., Rafael Diaz, M.D., J. Donald Easton, M.D., Justin A. Ezekowitz, M.B., B.Ch., Greg Flaker, M.D., David Garcia, M.D., Margarida Geraldes, Ph.D., Bernard J. Gersh, M.D., Sergey Golitsyn, M.D., Ph.D., Shinya Goto, M.D., Antonio G. Hermosillo, M.D., Stefan H. Hohnloser, M.D., John Horowitz, M.D., Puneet Mohan, M.D., Ph.D., Petr Jansky, M.D., Basil S. Lewis, M.D., Jose Luis Lopez-Sendon, M.D., Prem Pais, M.D., Alexander Parkhomenko, M.D., Freek W.A. Verheugt, M.D., Ph.D., Jun Zhu, M.D., and Lars Wallentin, M.D., Ph.D., for the ARISTOTLE Committees and Investigators*

N Engl J Med August 28, 2011

Antithrombotic Therapy for AFib

Stroke Risk Reduction

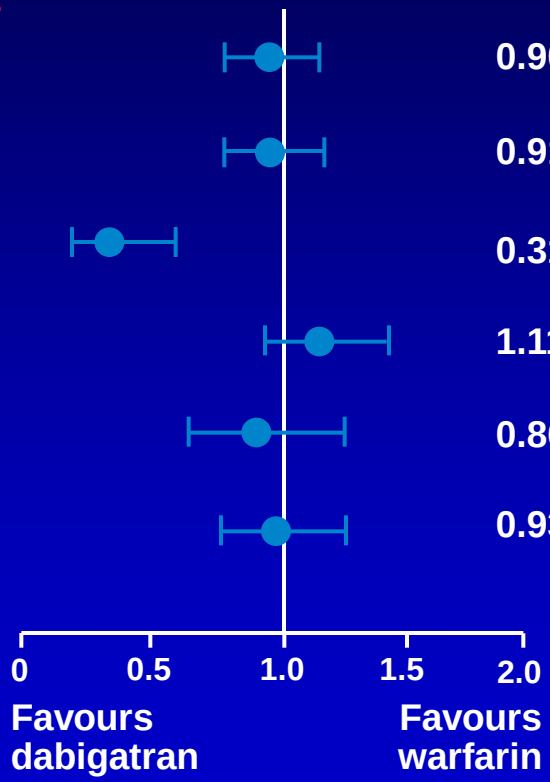


Hart RG et al. Ann Intern Med 2007; 146: 857

Dabigatran

RE-LY: dabigatran etexilate 110 mg BID was found to be non-inferior to warfarin for stroke or systemic embolism

	Rate (%/yr)		Dabigatran 110 mg BID vs warfarin	RR (95% CI); P value
	Dabigatran	Warfarin		
Stroke or systemic embolism	1.54	1.71		0.90 (0.74, 1.10); P<0.001
Stroke	1.44	1.58		0.91 (0.74, 1.12); P=0.38
Haemorrhagic stroke	0.12	0.38		0.31 (0.17, 0.56); P<0.001
Ischaemic or unspecified stroke	1.34	1.21		1.11 (0.88, 1.39); P=0.35
Non-disabling stroke	0.50	0.58		0.86 (0.61, 1.22); P=0.40
Disabling or fatal stroke	0.94	1.01		0.93 (0.72, 1.21); P=0.61

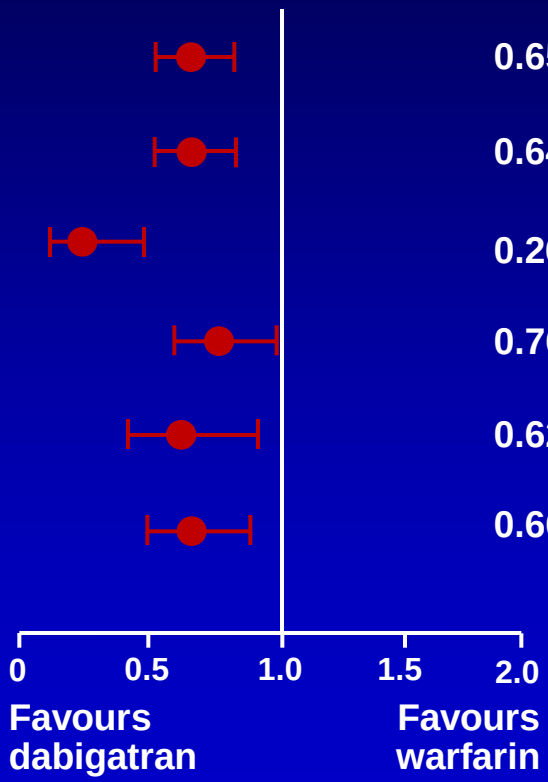


Error bars = 95% confidence intervals; BID = twice daily; RR = relative risk

Connolly SJ et al. N Engl J Med 2009;361:1139–51; Connolly SJ et al. N Engl J Med 2010;363:1875–6

RE-LY: dabigatran etexilate 150 mg BID was found to be superior to warfarin for stroke or systemic embolism

	Rate (%/yr)		Dabigatran 150 mg BID vs warfarin	RR (95% CI); P value
	Dabigatran	Warfarin		
Stroke or systemic embolism	1.11	1.71		0.65 (0.52, 0.81); P<0.001
Stroke	1.01	1.58		0.64 (0.51, 0.81); P<0.001
Haemorrhagic stroke	0.10	0.38		0.26 (0.14, 0.49); P<0.001
Ischaemic or unspecified stroke	0.92	1.21		0.76 (0.59, 0.97); P=0.03
Non-disabling stroke	0.37	0.58		0.62 (0.43, 0.91); P=0.01
Disabling or fatal stroke	0.66	1.01		0.66 (0.50, 0.87); P=0.004



Error bars = 95% confidence intervals; BID = twice daily; RR = relative risk

Connolly SJ et al. N Engl J Med 2009;361:1139–51; Connolly SJ et al. N Engl J Med 2010;363:1875–6

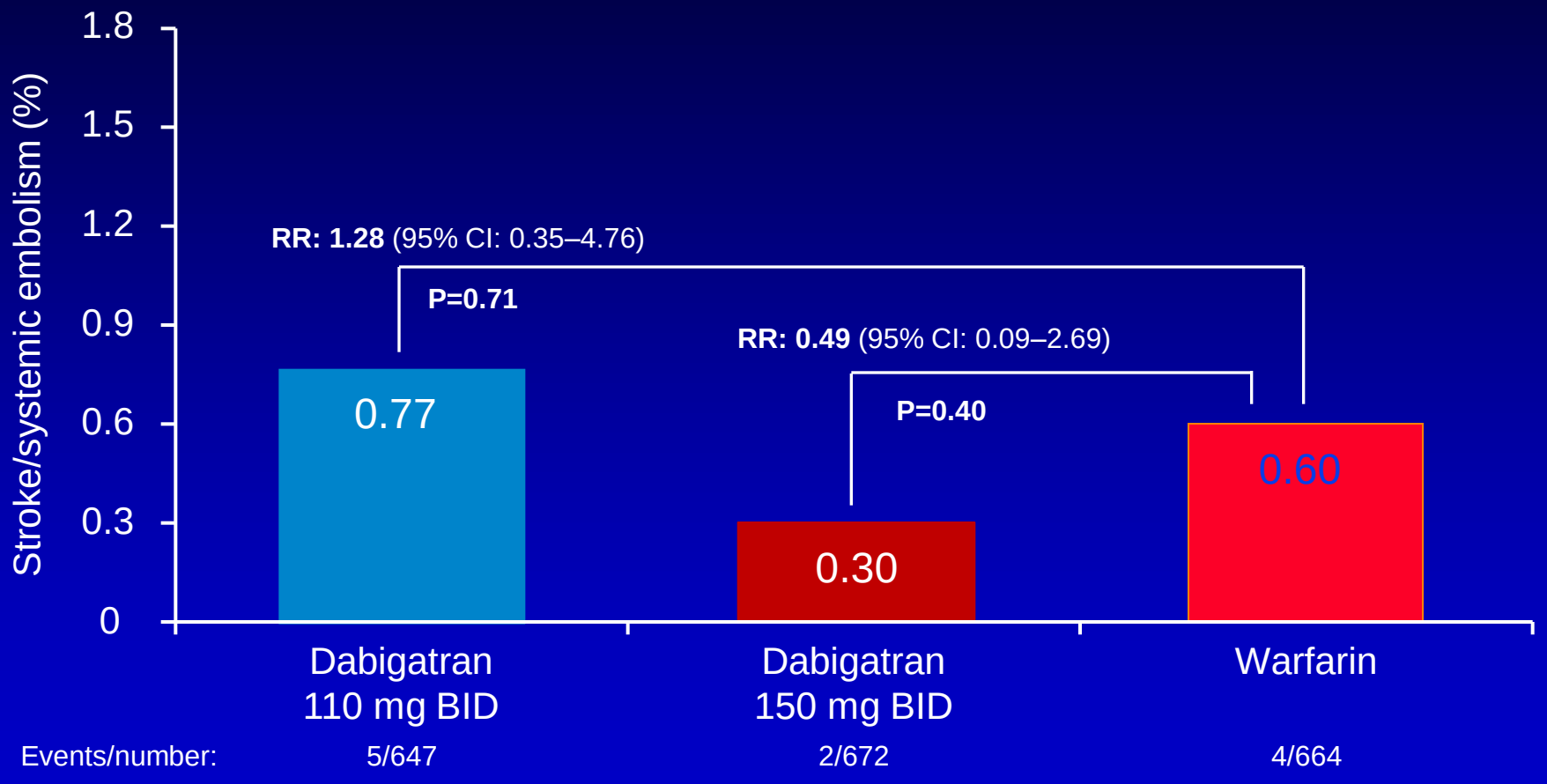
RE-LY: bleeding outcomes

Outcome	D110 BID n = 6015	D150 BID n = 6076	Warfarin n=6022	D110 vs W RR (95% CI)	P value D110 vs W	D150 vs W RR (95% CI)	P value D150 vs W
Major bleeding	2.87	3.32	3.57	0.80 (0.7–0.93)	0.003	0.93 (0.81–1.07)	0.31
Life-threatening	1.24	1.49	1.85	0.67 (0.54–0.82)	<0.001	0.80 (0.66–0.98)	0.03
Non-life-threatening	1.83	2.06	1.92	0.96 (0.80–1.15)	0.65	1.08 (0.90–1.30)	0.39
GI	1.15	1.56	1.07	1.08 (0.85–1.38)	0.52	1.48 (1.18–1.85)	0.001
Intracranial bleeding	0.23	0.32	0.76	0.30 (0.19–0.45)	<0.001	0.41 (0.28–0.60)	<0.001

Data represent %/year; BID = twice daily; D = dabigatran; W = warfarin; RR = relative risk

Connolly SJ et al. N Engl J Med 2010;363:1875–6

Cardioversion subgroup analysis: stroke or systemic embolism



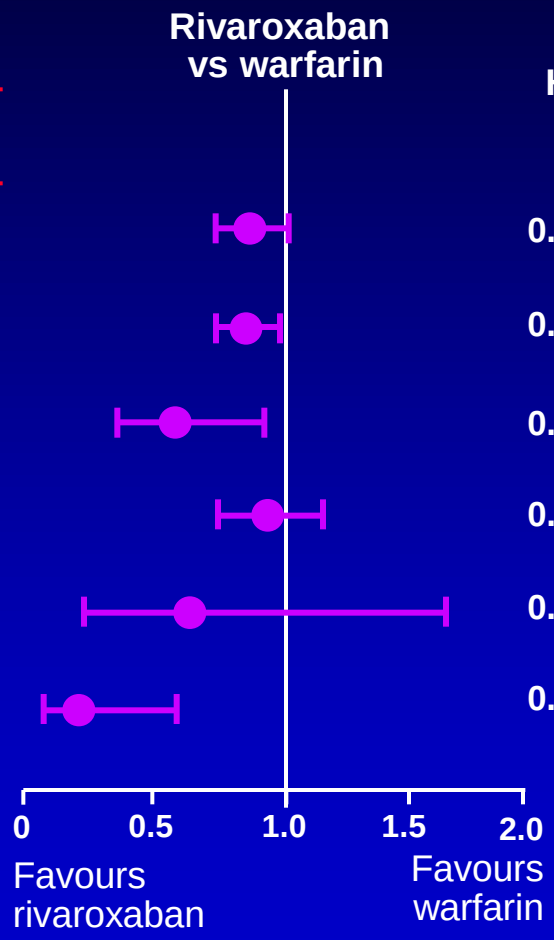
BID = twice daily; RR = relative risk

Nagarakanti R et al. Circulation 2011;123:131–6

Rivaroxaban

ROCKET-AF: rivaroxaban was non-inferior to warfarin for the primary outcome of stroke and systemic embolism

	Rate (%/yr)	
	Rivaroxaban	Warfarin
Stroke or systemic embolism	2.1	2.4
Vascular death, stroke, embolism	3.11	3.63
Haemorrhagic stroke	0.26	0.44
Ischaemic stroke	1.34	1.42
Unspecified stroke	0.06	0.10
Non-CNS embolism	0.04	0.19



*P value for non-inferiority, intention-to-treat population, all other results based on safety on-treatment population

Error bars = 95% confidence intervals; BID = twice daily; CNS = central nervous system; HR = hazard ratio

Patel MR et al. N Engl J Med 2011;365:883–91

ROCKET-AF: bleeding outcomes

Outcome	Event rate/100 patient-yrs		HR (95% CI)	P value
	Rivaroxaban	Warfarin		
Major and non-major clinically relevant bleeding	14.9	14.5	1.03 (0.96–1.11)	0.44
Major bleeding	3.6	3.4	1.04 (0.90–1.20)	0.58
≥2 g/dL Hgb drop	2.8	2.3	1.22 (1.03–1.44)	0.02
Transfusion	1.6	1.3	1.25 (1.01–1.55)	0.04
Critical bleeding	0.8	1.2	0.69 (0.53–0.91)	0.007
Fatal bleeding	0.2	0.5	0.50 (0.31–0.79)	0.003
Intracranial haemorrhage	0.5	0.7	0.67 (0.47–0.93)	0.02
Gastrointestinal bleeding (upper, lower, and rectal)	3.15	2.16	Data not provided	<0.001
Non-major clinically relevant bleeding	11.8	11.4	1.04 (0.96–1.13)	0.35

Based on safety on-treatment population

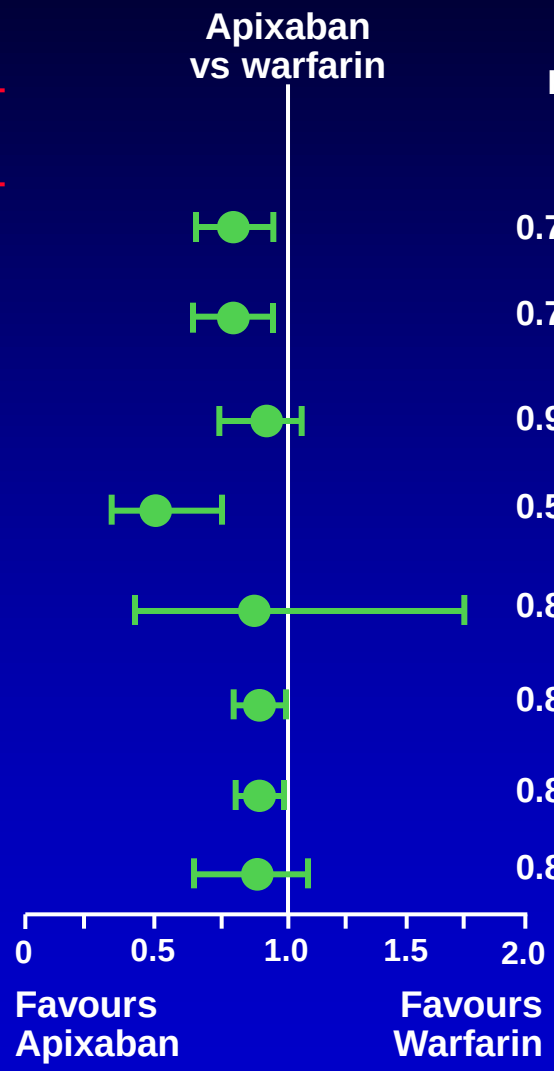
CI = confidence interval; Hgb = haemoglobin; HR = hazard ratio

Patel MR et al. N Engl J Med 2011;365:883–91

Apixaban

ARISTOTLE: apixaban was found to be superior to warfarin for the primary outcome of stroke or systemic embolism

	Rate (%/yr)	
	Apixaban	Warfarin
Stroke or systemic embolism*	1.27	1.60
Stroke	1.19	1.51
Ischaemic or uncertain	0.97	1.05
Haemorrhagic	0.24	0.47
Systemic embolism (SE)	0.09	0.10
All cause death*	3.52	3.94
Stroke, SE, or all-cause death	4.49	5.04
Myocardial infarction	0.53	0.61



*Part of sequential testing sequence preserving the overall type I error; CI = confidence interval; HR = hazard ratio

Granger CB et al. N Engl J Med 2011;365:981–92

ARISTOTLE: bleeding outcomes

Outcome	Apixaban (n=9088) event rate (%/yr)	Warfarin (n=9052) event rate (%/yr)	HR (95% CI)	P value
Primary safety outcome: ISTH major bleeding*	2.13	3.09	0.69 (0.60–0.80)	<0.001
Intracranial	0.33	0.80	0.42 (0.30–0.58)	<0.001
Other location	1.79	2.27	0.79 (0.68–0.93	0.004
Gastrointestinal	0.76	0.86	0.89 (0.70–1.15)	0.37
Major or clinically relevant non-major bleeding	4.07	6.01	0.68 (0.61–0.75)	<0.001
Any bleeding	18.1	25.8	0.71 (0.68–0.75)	<0.001

*Part of sequential testing sequence preserving the overall type I error

HR = hazard ratio; ISTH = International Society on Thrombosis and Haemostasis

Granger CB et al. N Engl J Med 2011;365:981–92

Quello che sappiamo

- **Trials ampi hanno mostrato l'efficacia nella prevenzione di stroke e di trombembolsmo sistemico dei 3 farmaci con una più bassa incidenza di emorragie intracraniche rispetto al Warfarin**

- **L'incidenza di emorragie complessivamente è risultata inferiore o simile al warfarin**

Nuovi Anticoagulanti Orali non VKA Antagonisti

Vantaggi

- Dose – risposta prevedibile : **dose fissa giornaliera**
- **Non necessità di monitoraggio dell'anticoagulazione**
- **Elevata efficacia e sicurezza**
- Riduzione del rischio emorragico
- Inizio e termine d'azione rapidi: **non necessità di bridge con eparina**
- Minime interazioni farmacologiche
- Assenza di interazioni alimentari

Di Pasquale G, Riva L, G Ital Cardiol 2011; 12: 556-65

Maggior numero di pazienti che accettano questa terapia

Nuovi Anticoagulanti Oralianti non VKA Antagonisti

Svantaggi

Necessità di nuovi test laboratoristici da eseguire in caso di eventi emorragici o trombotici

- **Difficoltà di valutare l'aderenza del paziente alla terapia**
- **Mancanza di antidoto in caso di sovradosaggio o emorragie**
- Inizio e termine d'azione rapidi: potenziale svantaggio nei pazienti con bassa aderenza terapeutica
- Possibile ridotta consapevolezza della terapia da parte del paziente
- **Costo elevato**

Di Pasquale G, Riva L, G Ital Cardiol 2011; 12: 556-65

Reversal of Rivaroxaban and Dabigatran by Prothrombin Complex Concentrate

A Randomized, Placebo-Controlled, Crossover Study in Healthy Subjects

Elise S. Eerenberg, MD; Pieter W. Kamphuisen, MD; Meertien K. Sijpkens, BSc; Joost C. Meijers, PhD; Harry R. Buller, MD; Marcel Levi, MD

Background—Rivaroxaban and dabigatran are new oral anticoagulants that specifically inhibit factor Xa and thrombin, respectively. Clinical studies on the prevention and treatment of venous and arterial thromboembolism show promising results. A major disadvantage of these anticoagulants is the absence of an antidote in case of serious bleeding or when an emergency intervention needs immediate correction of coagulation. This study evaluated the potential of prothrombin complex concentrate (PCC) to reverse the anticoagulant effect of these drugs.

Methods and Results—In a randomized, double-blind, placebo-controlled study, 12 healthy male volunteers received rivaroxaban 20 mg twice daily (n=6) or dabigatran 150 mg twice daily (n=6) for 2½ days, followed by either a single bolus of 50 IU/kg PCC (Cofact) or a similar volume of saline. After a washout period, this procedure was repeated with the other anticoagulant treatment. Rivaroxaban induced a significant prolongation of the prothrombin time (15.8±1.3 versus 12.3±0.7 seconds at baseline; $P<0.001$) that was immediately and completely reversed by PCC (12.8±1.0; $P<0.001$). The endogenous thrombin potential was inhibited by rivaroxaban (51±22%; baseline, 92±22%; $P=0.002$) and normalized with PCC (114±26%; $P<0.001$), whereas saline had no effect. Dabigatran increased the activated partial thromboplastin time, ecarin clotting time (ECT), and thrombin time. Administration of PCC did not restore these coagulation tests.

Conclusion—Prothrombin complex concentrate immediately and completely reverses the anticoagulant effect of rivaroxaban in healthy subjects but has no influence on the anticoagulant action of dabigatran at the PCC dose used in this study.

Eerenberg ES et al. *Circulation*. 2011; 124:1573-79