ECOCARDIOGRAFIA 2015
XVII Congresso Nazionale SIEC

Dabigatran: la sicurezza per le diverse tipologie di pazienti

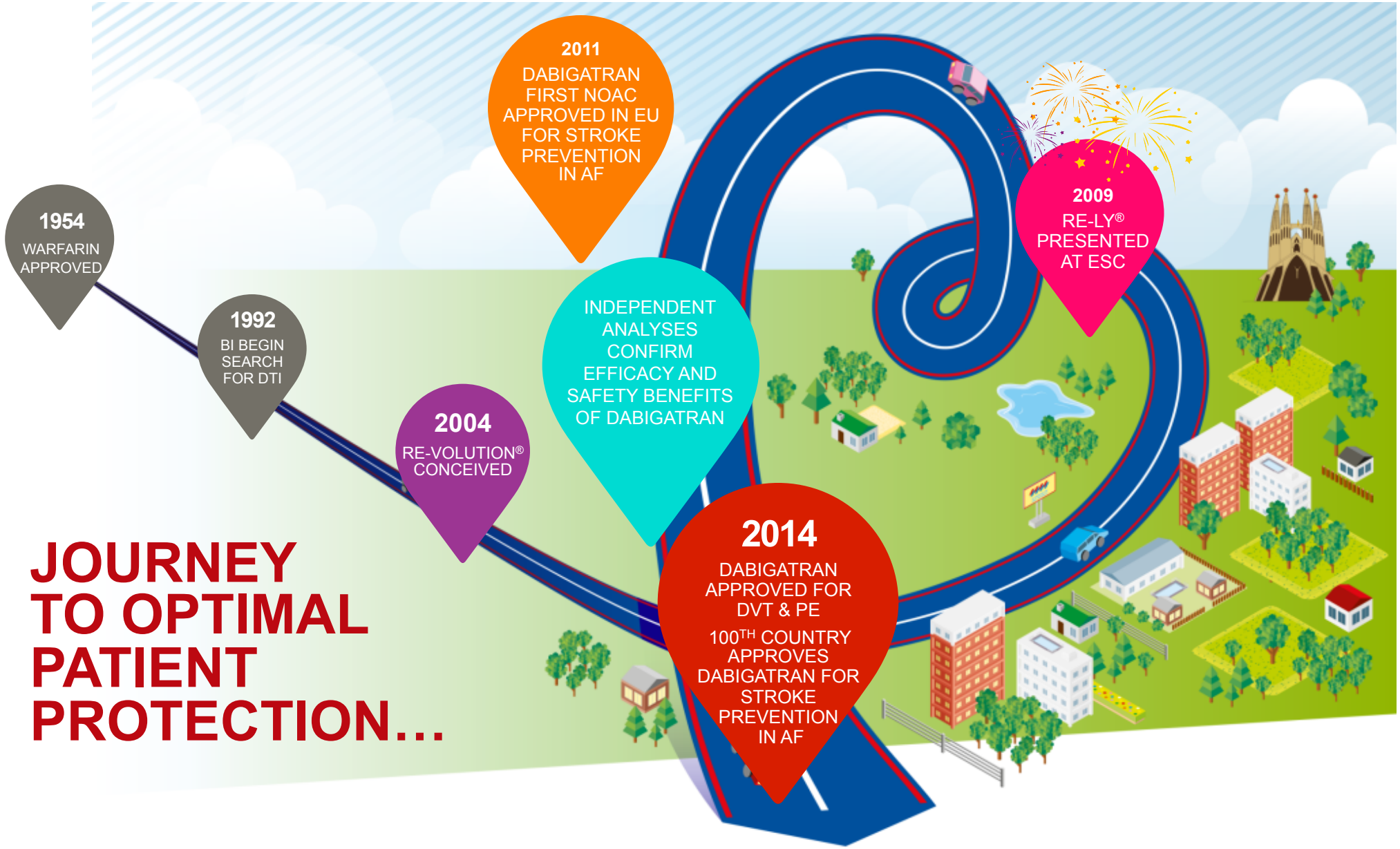
Risultati dai trials

Serenella Conti

Cardiologia P.O. Spoleto

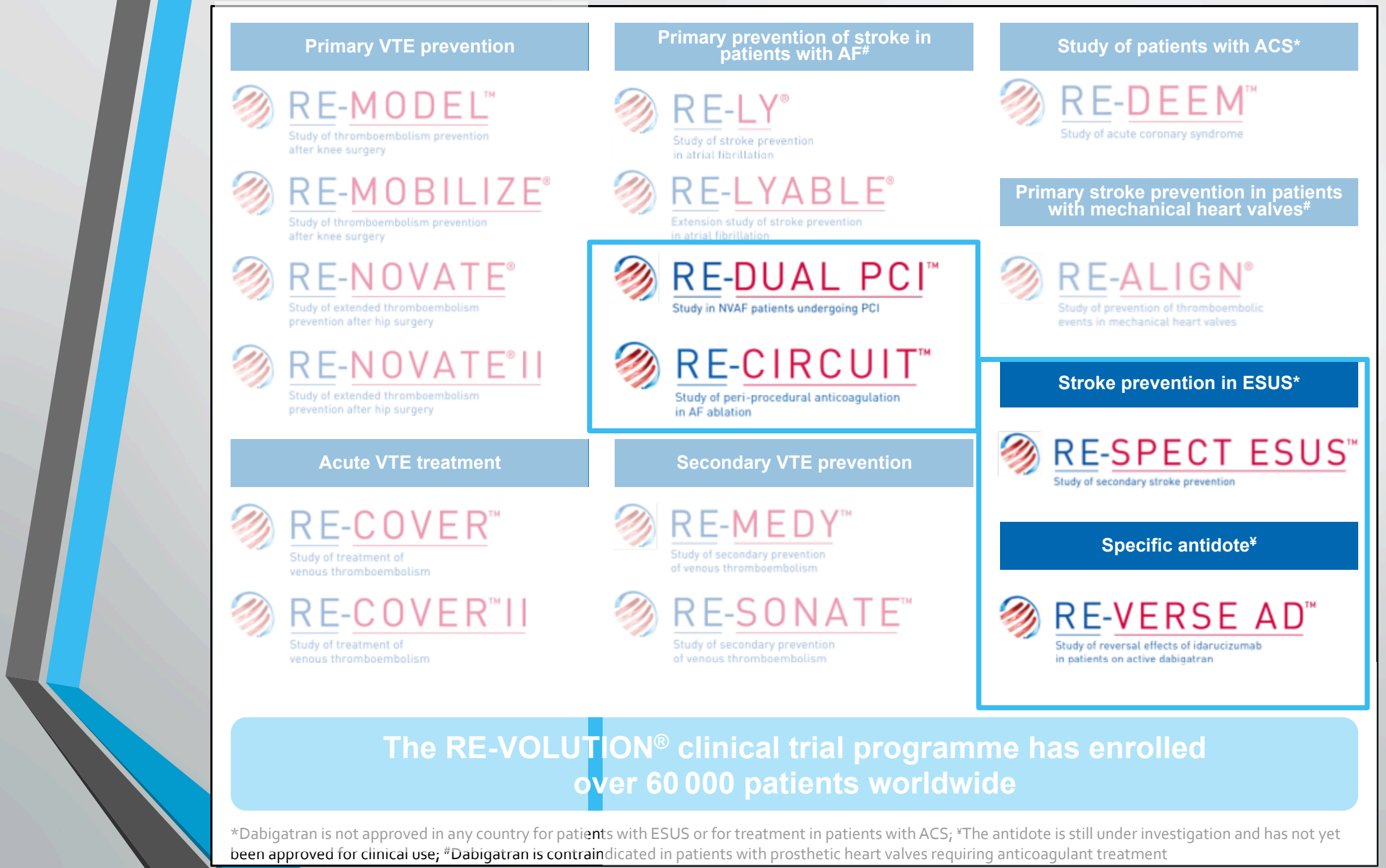
USL Umbria 2

JOURNEY TO OPTIMAL PATIENT PROTECTION…



[redacted]

Dabigatran is not approved in any country for patients with ESUS
The antidote is still under investigation and has not yet been approved for clinical use


Primary VTE prevention
RE-MODEL™
Study of thromboembolism prevention after knee surgery
RE-MOBILIZE®
Study of thromboembolism prevention after knee surgery
RE-NOVATE®
Study of extended thromboembolism prevention after hip surgery
RE-NOVATE® II
Study of extended thromboembolism prevention after hip surgery
Primary prevention of stroke in patients with AF#
RE-LY®
Study of stroke prevention in atrial fibrillation
RE-LYABLE®
Extension study of stroke prevention in atrial fibrillation
RE-DUAL PCI™
Study in NVAF patients undergoing PCI
RE-CIRCUIT™
Study of peri-procedural anticoagulation in AF ablation
Study of patients with ACS*
RE-DEEM™
Study of acute coronary syndrome
Primary stroke prevention in patients with mechanical heart valves#
RE-ALIGN®
Study of prevention of thromboembolic events in mechanical heart valves
Stroke prevention in ESUS*
RE-SPECT ESUS™
Study of secondary stroke prevention
Specific antidote¥
RE-VERSE AD™
Study of reversal effects of idarucizumab in patients on active dabigatran
Acute VTE treatment
RE-COVER™
Study of treatment of venous thromboembolism
RE-COVER™ II
Study of treatment of venous thromboembolism
Secondary VTE prevention
RE-MEDY™
Study of secondary prevention of venous thromboembolism
RE-SONATE™
Study of secondary prevention of venous thromboembolism
The RE-VOLUTION® clinical trial programme has enrolled over 60 000 patients worldwide
*Dabigatran is not approved in any country for patients with ESUS or for treatment in patients with ACS; ¥The antidote is still under investigation and has not yet been approved for clinical use; #Dabigatran is contraindicated in patients with prosthetic heart valves requiring anticoagulant treatment

RE-LY® – Participating Countries

RE-LY® was an international, multicentre study and enrolled patients from Europe, North and South America, Asia, Africa and Australasia

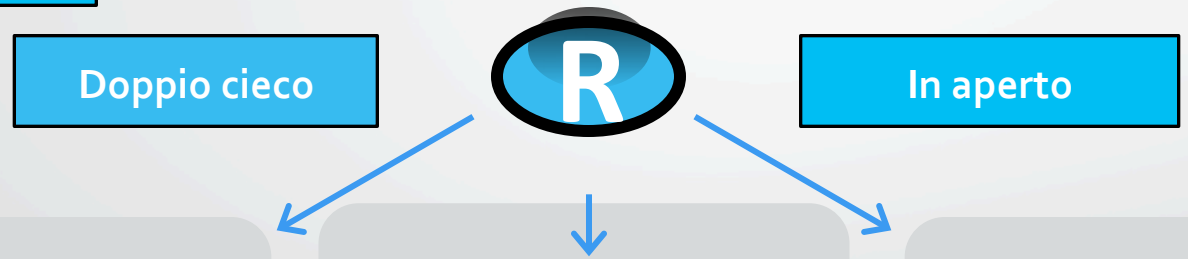
(N=18113 PZ, 44 COUNTRIES, 951 SITES)

Connolly SJ, et al. *N Engl J Med* 2009; 361:1139-1151

RE-LY® – trial design

Prospective Randomised Open trial with Blinded Evaluation of outcomes (PROBE) design

Fibrillazione atriale non valvolare
con ≥1 fattore di rischio
Assenza di controindicazioni



Dabigatran etexilato
150 mg bid
N=6.000

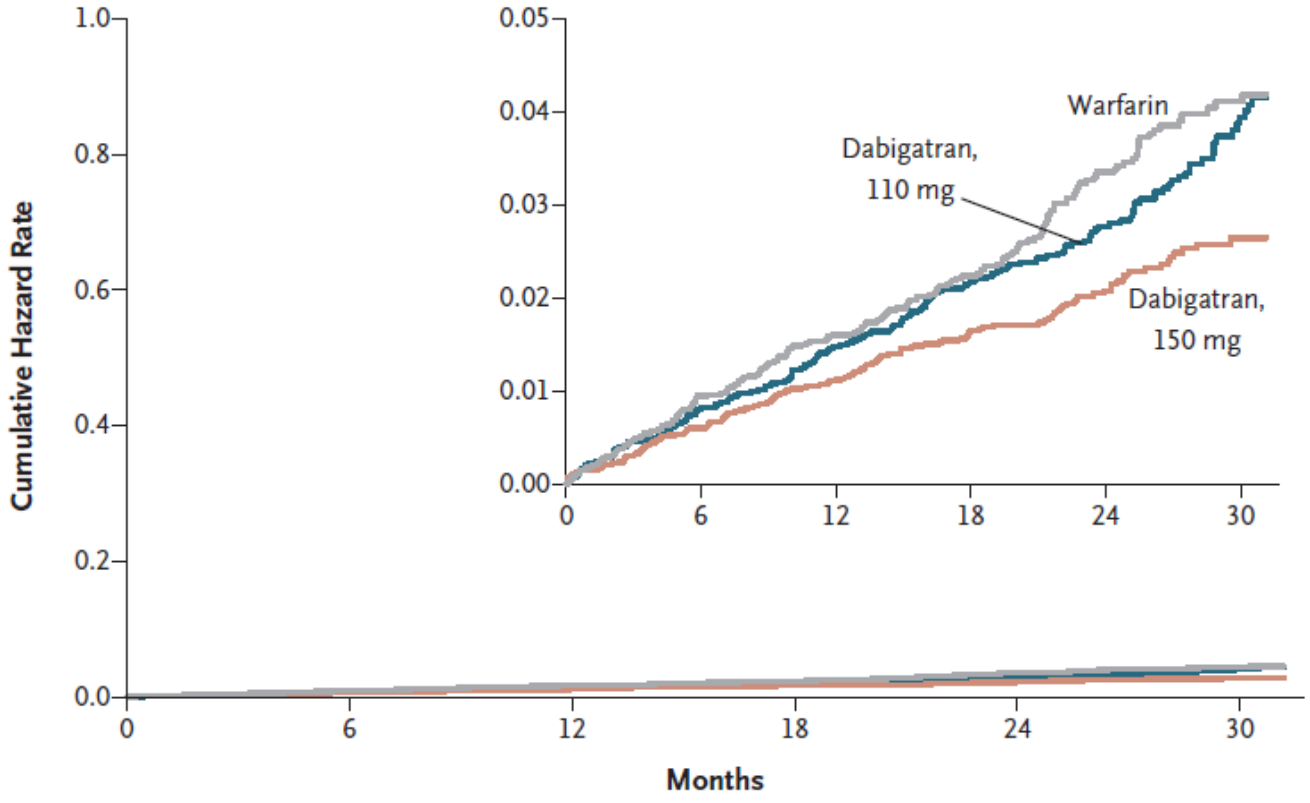
Dabigatran etexilato
110 mg bid
N=6.000

Warfarin
1 mg, 3 mg, 5 mg
(INR 2,0-3,0) N=6000

Obiettivo primario: stabilire la non-inferiorità di dabigatran etexilato vs warfarin;
Minimo 1 anno di follow-up, massimo 3 anni e in media 2 anni di follow-up

RE-LY®

Dabigatran efficacy

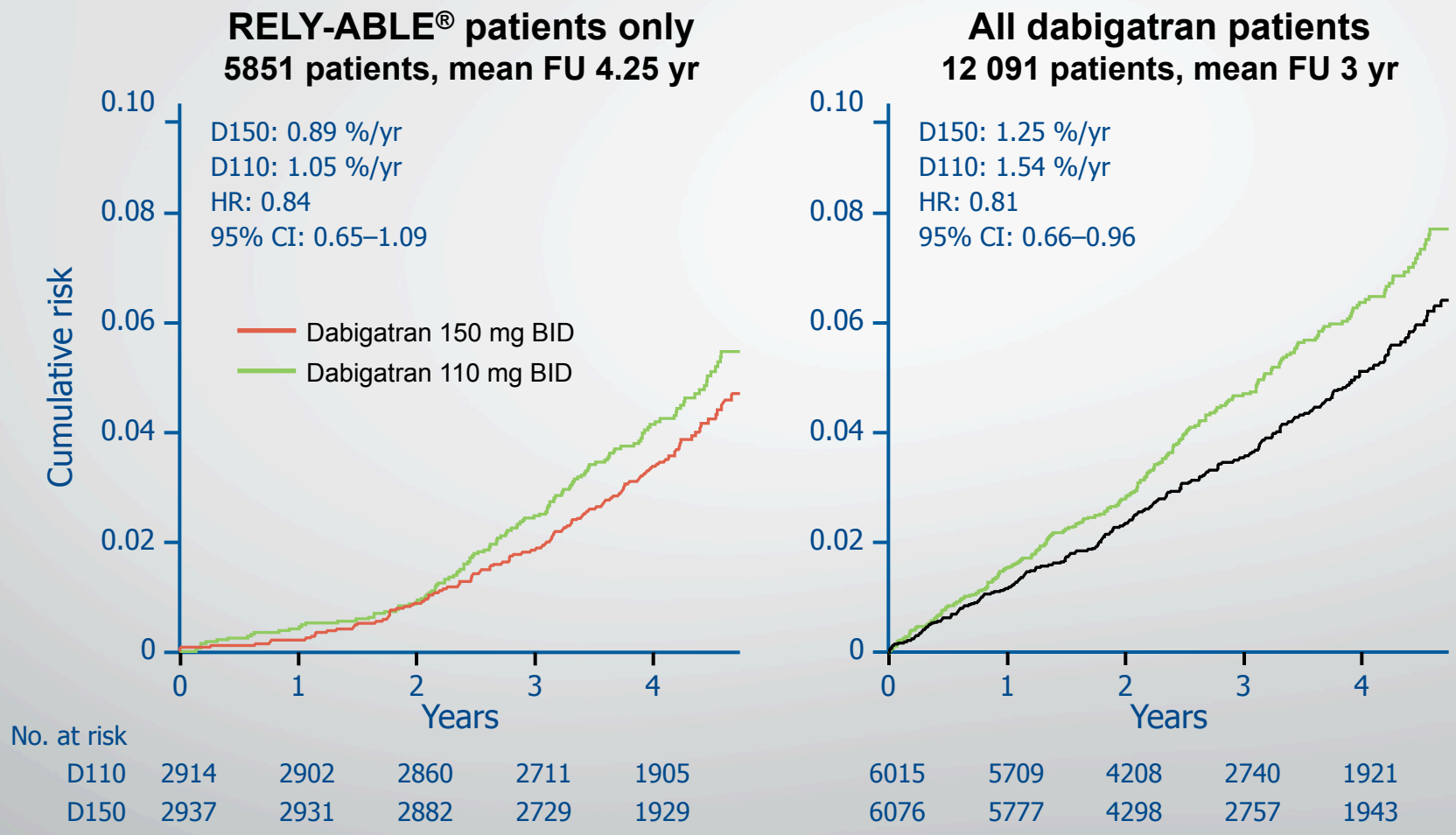


No. at Risk

Warfarin	6022	5862	5718	4593	2890	1322
Dabigatran, 110 mg	6015	5862	5710	4593	2945	1385
Dabigatran, 150 mg	6076	5939	5779	4682	3044	1429

Figure 1. Cumulative Hazard Rates for the Primary Outcome of Stroke or Systemic Embolism, According to Treatment Group.

Long-term Dabigatran: RE-LY® + RELY-ABLE®
Stroke / systemic embolism



No. at risk

D110	2914	2902	2860	2711	1905
D150	2937	2931	2882	2729	1929

6015	5709	4208	2740	1921
6076	5777	4298	2757	1943

In the secondary analysis of RE-LY® and RELYABLE®, dabigatran 150 mg BID was associated with a lower rate of stroke/SE than the 110 mg BID dose

RE-LY® Dabigatran Safety

Significantly lower risk of intracranial bleeding with both doses and of major bleeding with 110 mg BID vs warfarin

	Annual rate (%)			D110 vs warfarin		D150 vs warfarin	
	D110	D150	Warfarin	RR (95% CI)	P value	RR (95% CI)	P value
Major bleeding	2.87	3.31	3.57	0.80 (0.70–0.93)	**0.002**	0.93 (0.81–1.07)	0.32
Intracranial	0.23	0.32	0.76	0.30 (0.19–0.45)	**<0.001**	0.42 (0.29–0.62)	**<0.001**
Intracerebral	0.13	0.13	0.41	0.31 (0.17–0.55)	**<0.001**	0.33 (0.19–0.57)	**<0.001**
Subdural	0.10	0.19	0.34	0.30 (0.16–0.57)	**<0.001**	0.56 (0.34–0.94)	0.028
Extracranial	2.66	3.02	2.84	0.94 (0.81–1.09)	0.42	1.07 (0.92–1.24)	0.36
Gastrointestinal	1.36	1.85	1.25	1.09 (0.87–1.36)	0.44	1.49 (1.21–1.84)	<0.001
Non-gastrointestinal	1.41	1.38	1.71	0.82 (0.67–1.01)	0.06	0.80 (0.65–0.99)	0.038

RE-LY® Dabigatran Safety

Significantly lower risks of life-threatening and minor bleeding with both doses vs warfarin

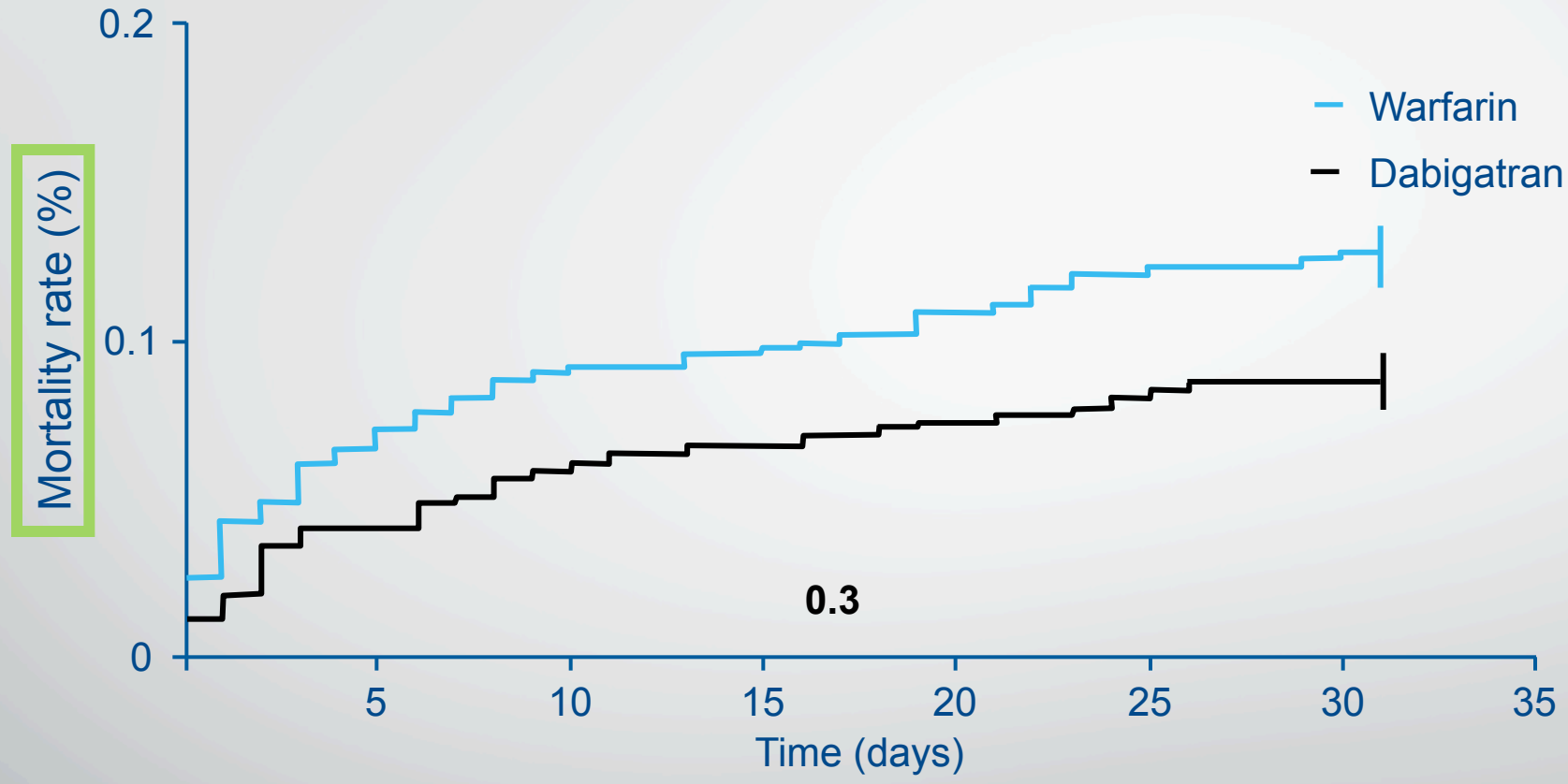
	Annual rate (%)			D110 vs warfarin		D150 vs warfarin	
	D110	**D150**	**Warfarin**	**RR (95% CI)**	**P value**	**RR (95% CI)**	**P value**
Life-threatening bleeding	1.24	1.49	1.85	0.67 (0.54–0.82)	**<0.001**	0.80 (0.66–0.98)	**0.030**
Fatal bleeding	0.19	0.23	0.33	0.58 (0.35–0.97)	0.039	0.70 (0.43–1.14)	0.15
Minor bleeding	13.16	14.84	16.37	0.79 (0.74–0.84)	**<0.001**	0.91 (0.85–0.97)	**0.005**
Total bleeding*	14.66	16.45	18.23	0.78 (0.73–0.83)	**<0.001**	0.91 (0.85–0.96)	**0.002**
Red cell transfusion	1.74	2.10	1.93	0.90 (0.75–1.09)	0.29	1.10 (0.92–1.31)	0.30

RE-LY® Short-term consequences of major bleeding

	Dabigatran *	Warfarin	P value
Patients with major bleeds, n (%)	741 (100)	421 (100)	
Patients with hospitalization,† n (%)	456 (61.5)	254 (60.3)	0.68
Length of stay, days, mean (SD)	8.4 (9.1)	8.9 (9.8)	0.48
Nights in ICU/CCU, mean (SD)	1.6 (4.3)	2.7 (6.6)	0.01
Nights in step-down unit, mean (SD)	1.0 (2.5)	1.0 (2.7)	0.84
Patients with major bleed requiring surgery, n (%)	90 (12.1)	63 (15.0)	0.17

Length of stay in ICU is shorter with dabigatran treatment than with comparator

RE-LY® Mortality after a major bleed



The Kaplan–Meier analysis indicated a reduced risk for death with dabigatran* vs warfarin during 30 days from the bleeding (P=0.052)

*Data combined from dabigatran 150 mg and 110 mg BID treatment groups. Only first major bleed included. Analysis not adjusted for covariates

RE-LY® Prognosis of intracranial haemorrhage

Data on the initial and final Rankin score evaluations were available for 78 (55%) patients with ICH

Treatment comparison	P value for comparison of change in modified Rankin score
Dabigatran* vs warfarin	0.97
Dabigatran 150 mg BID vs warfarin	0.81
Dabigatran 110 mg BID vs warfarin	0.80
Dabigatran 150 mg BID vs 110 mg BID	0.78

No significant difference between treatments in modified Rankin scale score for ICH since admission

RE-LY® Dabigatran Safety and Patients Age

Lower risks of major bleeding with both doses vs warfarin in patients **aged <75 years** and similar or higher risks for those **aged ≥75 years**

	Annual rate (%)			D110 vs warfarin		D150 vs warfarin	
	D110	D150	Warfarin	RR (95% CI)	P value*	RR (95% CI)	P value*
<75 yrs	1.89	2.12	3.04	0.62 (0.50–0.77)	<0.001	0.70 (0.57–0.86)	<0.001
≥75 yrs	4.43	5.10	4.37	1.01 (0.83–1.23)		1.18 (0.98–1.42)	

RE-LY® Dabigatran and CKD

- About one-third of outpatients with atrial fibrillation have CKD
- Stage 3 CKD is an independent risk factor for stroke in patients with atrial
- Excretion dabigatran 80% renal

Stage	Description	GFR ml/min/1.73m²
1(p)	Kidney damage with normal or raised eGFR	≥90
2(p)	Kidney damage with mild decreased eGFR	60–89
3A(p)	Moderate decreased eGFR	45–59
3B(p)	Moderate decreased eGFR	30–44
4(p)	Severe decreased eGFR	15–29
5(p)	Kidney failure	<15 or dialysis

Hart, R. G. *et al. Nat. Rev. Nephrol.* advance online publication 24 July 2012;

RE-LY® Dabigatran e CKD

Estimated GFR (eGFR) <30 mL/min according to Cockcroft-Gault was an exclusion criteria in the RE-LY trial.

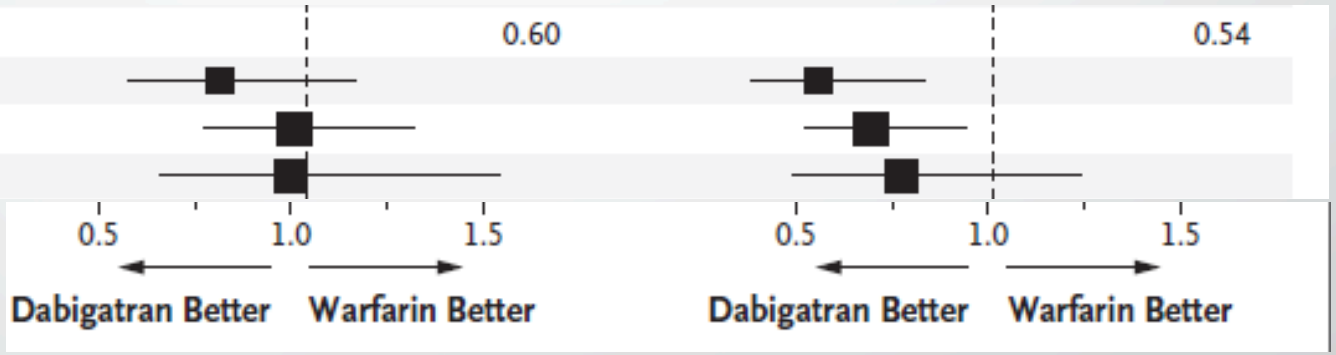
The trial design randomly tested both dabigatran doses and warfarin in all predefined renal function subgroups without a predefined dose adjustment in any subgroups.

In RE-LY® A glomerular filtration rate(Cockcroft_Gault)
≥80 mL/min 32,6%
50 to <80 mL/min 47,6% and
<50 mL/min 19.8%

(*Circulation*. 2014;129:961-970.)

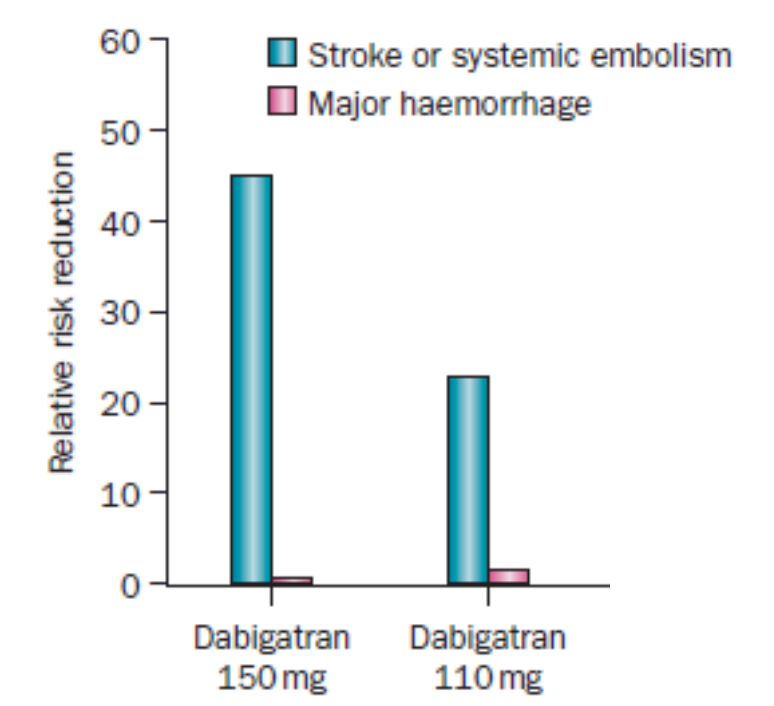
RE-LY® Safety of Dabigatran and renal function

Subgroup	Patients total no.	Dabigatran 110 mg % per yr	Dabigatran 150 mg % per yr	Warfarin	Hazard Ratio with Dabigatran, 110 mg (95% CI)	P Value for Interaction	Hazard Ratio with Dabigatran, 150 mg (95% CI)	P Value for Interaction
Creatinine clearance						0.60		0.54
<50 ml/min	3,505	2.15	1.52	2.78				
50–79 ml/min	8,766	1.70	1.20	1.76				
≥80 ml/min	5,826	0.94	0.75	0.98				



The efficacy of both dosages of dabigatran was consistent with the overall trial irrespective of renal function.

RE-LY® Stage 3 CKD and Stroke



Agency	Dabigatran
FDA[42,43]	Stage 3 CKD: 150 mg twice daily Stage 4 CKD: 75 mg twice daily‡
European Medicines Agency[46,47]	Stage 3 CKD: 110 mg twice daily if aged >80 years or at high risk of bleeding Stage 4 CKD: not approved
Health Canada[44,45]	CrCl 30–50 ml/min: either 110 mg or 150 mg twice daily except 110 mg twice daily for those aged >75 years and CrCl <50 ml/min Stage 4 CKD: not approved

Hart, R. G. *et al. Nat. Rev. Nephrol.* advance online publication 24 July 2012; doi:10.1038/nrneph.2012.160

RE-LY® Cardioversion subgroup analysis

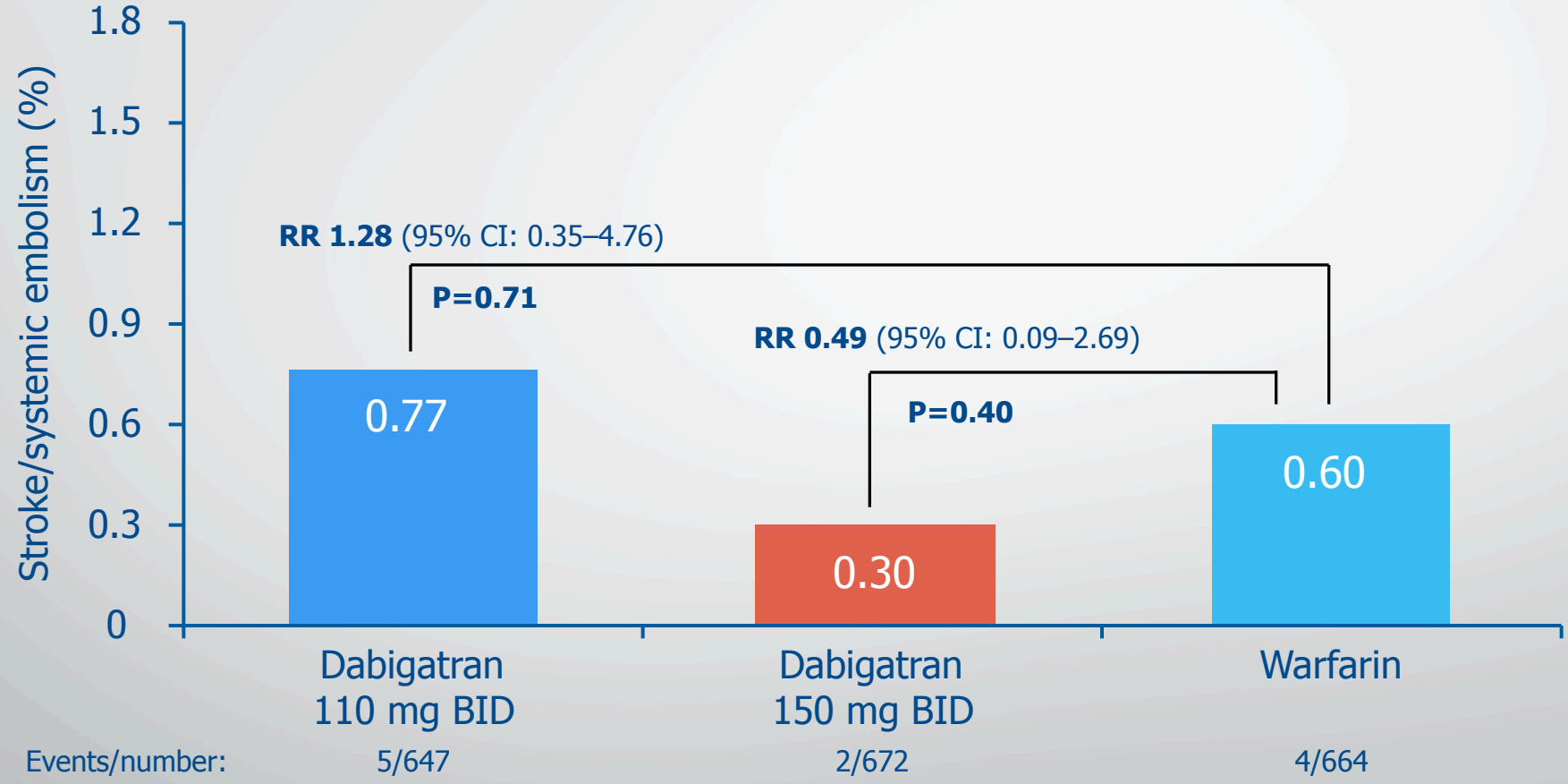
- 1983 cardioversions performed in 1270 patients
- >80% of cardioversions were electric
- TEE performed before conversion in more dabigatran patients (P<0.0001 for each dose vs warfarin)
- For patients undergoing TEE, no difference between treatment groups in incidences of left atrial spontaneous echo contrast or LAA thrombus

	Dabigatran 110 mg BID		Dabigatran 150 mg BID		Warfarin	
	n	%	n	%	n	%
Total randomized	6015		6076		6022	
Cardioversions performed						
Electrical	554	85.6	550	81.9	553	83.3
Pharmacological	91	14.1	122	18.2	111	16.7
TEE	165	25.5	162	24.1	88	13.3
Normal sinus rhythm at discharge	566	87.5	596	88.7	595	89.6

RE-LY® Cardioversion subgroup analysis: antithrombotic therapy

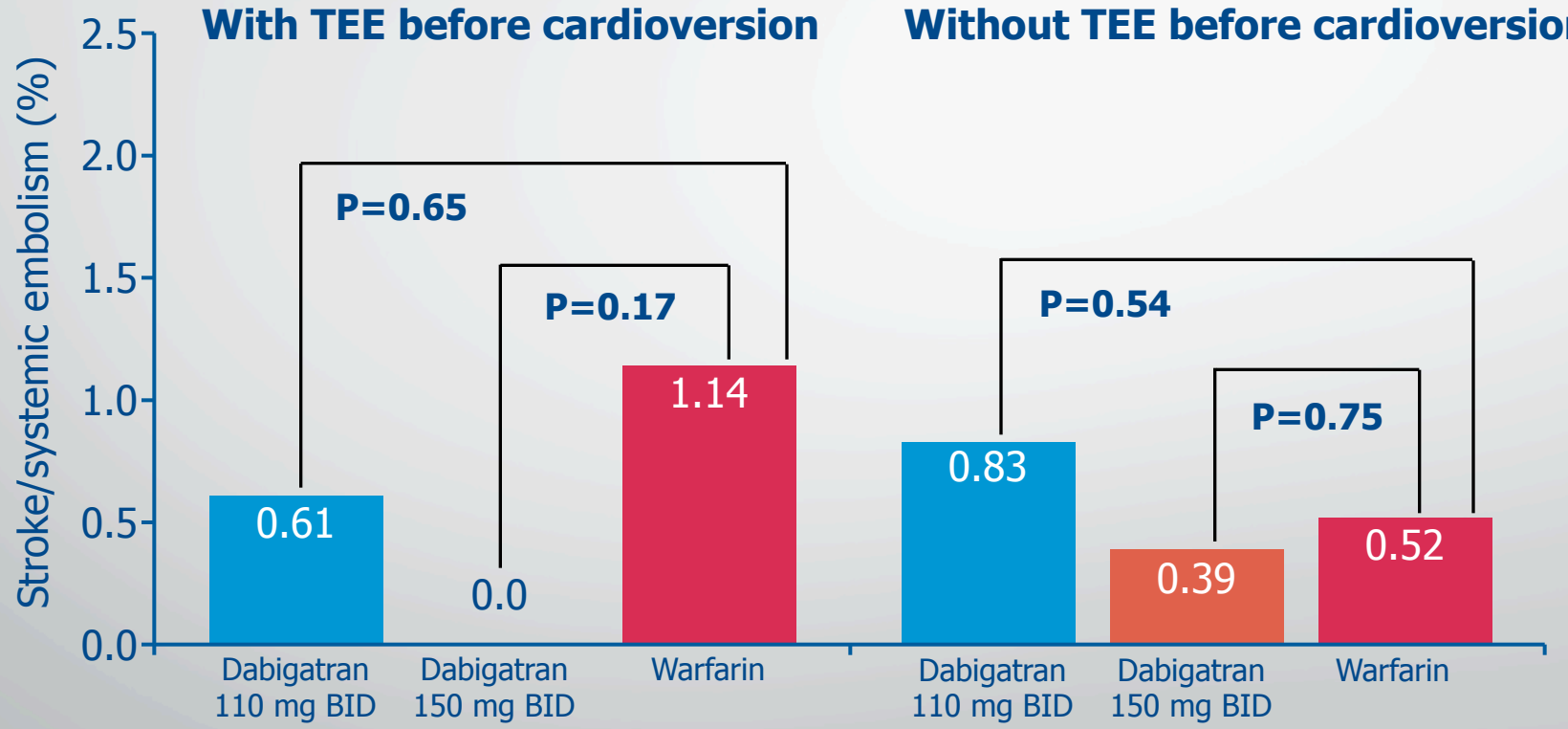
- Most patients received study drug for ≥3 weeks before conversion
  - D110 76.4%; D150 79.2%; warfarin 85.5%
  - D110 vs warfarin P<0.0001; D150 vs warfarin P=0.002
- Some patients were switched to a non-study oral anticoagulant
  - Proportion was higher for both dabigatran doses vs warfarin
  - D110 9.7%; D150 8.6%; warfarin 5.4%
  - D110 vs warfarin P=0.003; D150 vs warfarin P=0.02
- Most patients continued on randomized treatment within 30 days after cardioversion
  - D110 85.8%; D150 88.7%; warfarin 94.3%
  - D110 vs warfarin P<0.0001; D150 vs warfarin P=0.0003

RE-LY® Rates of stroke/SE within 30 days of cardioversion were similarly low for both dabigatran and warfarin



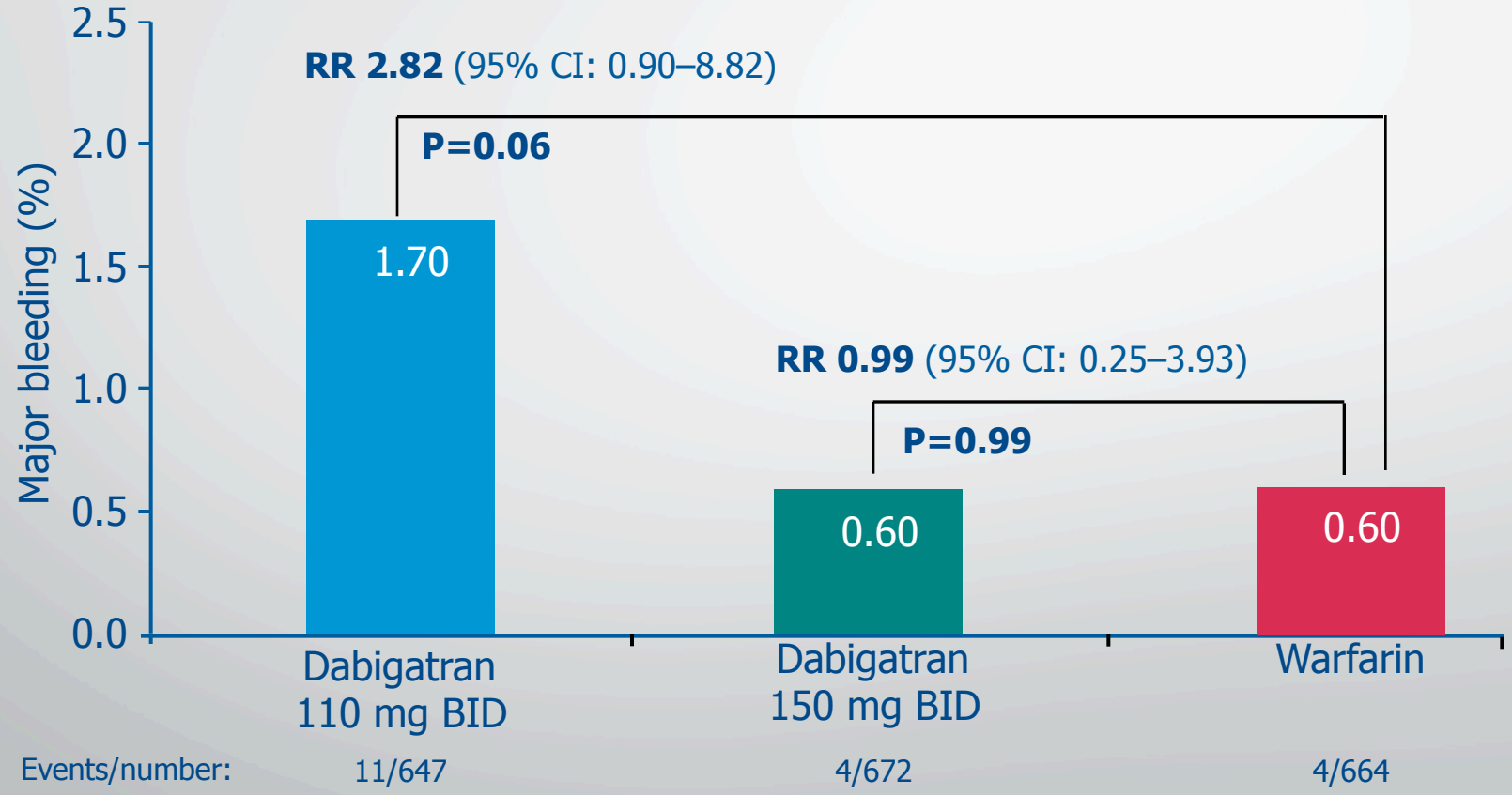
RE-LY® Similar rates of stroke/SE with and without TEE before cardioversion

Similar rates of stroke or systemic embolism with/without TEE before cardioversion



RE-LY® Cardioversion subgroup analysis: major bleeding

Major bleeding <30 days after cardioversion was infrequent in all groups



RE-LY®

Dabigatran and Cardioversion

Recommendations for prevention of thromboembolism in non-valvular AF—peri-cardioversion		
For patients with AF of ≥48 h duration, or when the duration of AF is unknown, OAC therapy (e.g. VKA with INR 2-3 or dabigatran) is recommended for ≥3 weeks prior to and for ≥4 weeks after cardioversion, regardless of the method (electrical or oral/i.v. pharmacological).	I	B
In patients with risk factors for stroke or AF recurrence, OAC therapy, whether with dose-adjusted VKA (INR 2-3) or a NOAC, should be continued lifelong irrespective of the apparent maintenance of sinus rhythm following cardioversion.	I	B

Table 11. Summary of Recommendations for Electrical and Pharmacological Cardioversion of AF and Atrial Flutter

With AF or atrial flutter <48 h and high stroke risk, IV heparin or LMWH, or factor Xa or direct thrombin inhibitor, is recommended before or immediately after cardioversion, followed by long-term anticoagulation	I	C
With AF or atrial flutter <48 h and low thromboembolic risk, IV heparin, LMWH, a new oral anticoagulant, or no antithrombotic may be considered for cardioversion	IIb	C
With AF or atrial flutter ≥48 h, or unknown duration, anticoagulation with dabigatran, rivaroxaban, or apixaban is reasonable for ≥3 wk prior to and 4 wk after cardioversion	IIa	C

LINEE GUIDA AIAC PER LA GESTIONE E IL TRATTAMENTO DELLA FA - AGGIORNAMENTO 2013

Tabella 23. Raccomandazioni per la terapia antitrombotica in corso di cardioversione elettrica.

	Terapia antitrombotica raccomandata	Classe[a]	Livello
FA insorta <48h	Cardioversione senza anticoagulazione	IIa	C
FA insorta ≥48h o non databile per insorgenza	– Warfarin (INR 2.0-3.0)	I	B
	– Dabigatran per 3 settimane pre-cardioversione e per 4 settimane post-cardioversione (indefinitamente in caso di CHA_2DS_2-VASc score ≥2)	IIa	B
FA insorta ≥48h o non databile per insorgenza	Strategia eco-guidata – Warfarin (INR 2.0-3.0) per 4 settimane post-cardioversione	I	B

RE-LY® Concomitant use of antipleteled therapy

Table 1. Prevalence of Antiplatelet Use at Baseline and at 4 Landmark Periods Throughout the Study

Landmark Period	DE110, n/N (%)	DE150, n/N (%)	Warfarin, n/N (%)
Day 180	1626/5901 (27.6)	1569/5966 (26.3)	1592/5909 (26.9)
Day 360	1605/5778 (27.8)	1521/5833 (26.1)	1561/5784 (27.0)
Day 540	1301/4693 (27.7)	1269/4759 (26.7)	1262/4685 (26.9)
Day 720	876/3204 (27.3)	886/3285 (27.0)	849/3164 (26.8)

34.8% antipletelet therapy

32% on ASA

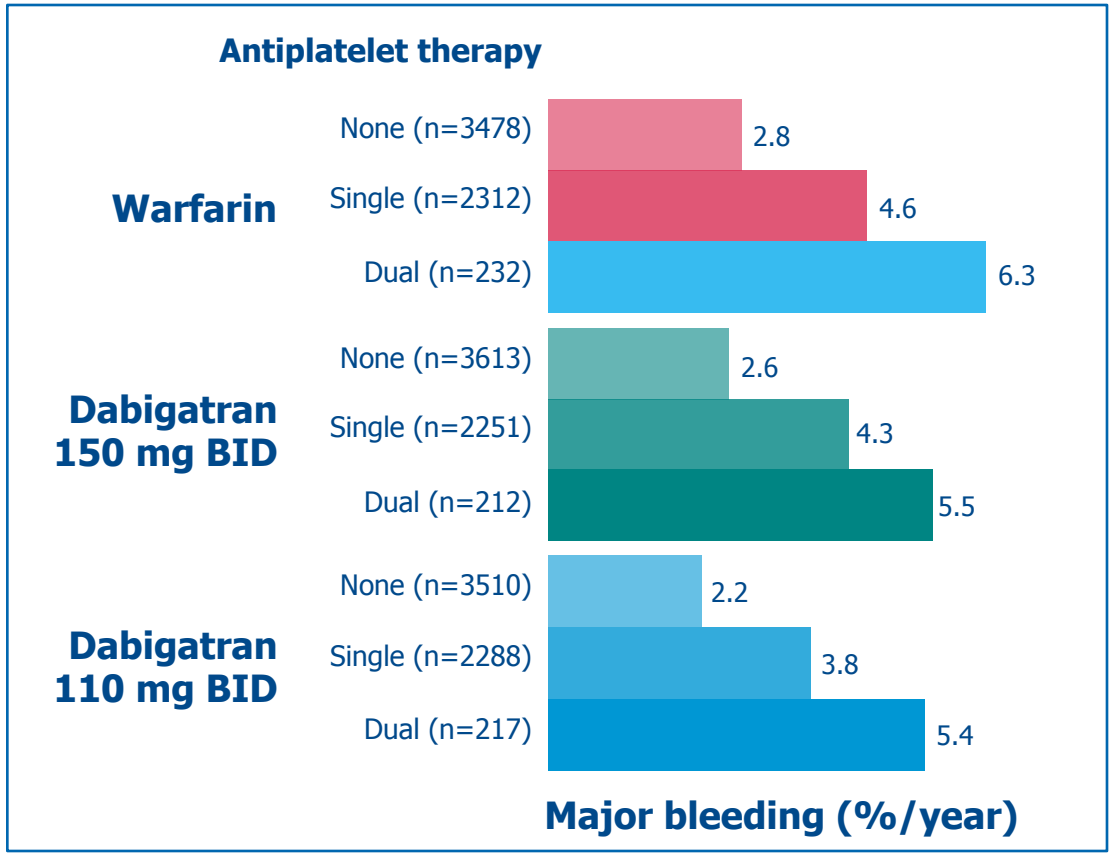
1.9% on Clopidogrel

4.5% both ASA+Clopidogrel

Circulation. 2013;127:634-640; originally published online December 27, 2012;

RE-LY® Addition of antiplatelet agents to anticoagulant therapy increases the risk of bleeding with all OACs

Outcomes from RE-LY®:[1]



RE-LY was the only Phase III trial of a NOAC vs VKA to allow concomitant treatment with both ASA and clopidogrel

Triple therapy is associated with the greatest increase in bleeding risk with **all** OAC/ antiplatelet combinations[1–5]

1. Dans AL et al. Circulation 2013;127:634–40; **2.** Dewilde WJ et al. Lancet 2013;381:1107–15;
3. Lip GY et al. Thromb Haemost 2010;103:13–28; **4.** Nikolsky E et al. Am J Cardiol 2012;109:831–8;
5. Lamberts M et al. Circulation 2014;129:1577–85

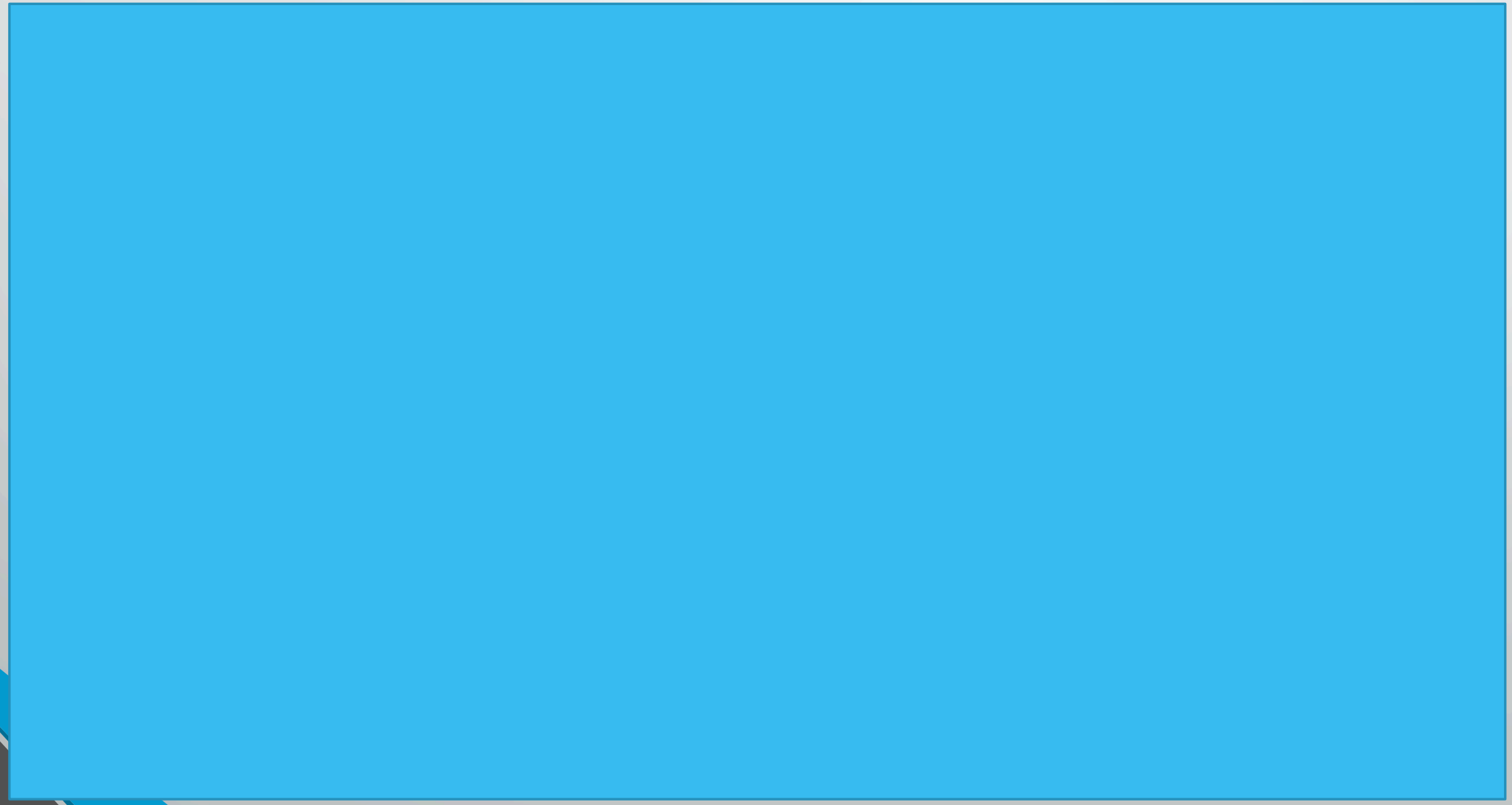
Latest guidance for combination therapy in patients with NVAF and ACS/PCI

Recommendation	Class	Level
In general, the period of **triple therapy should be as short as possible**, followed by OAC plus a single antiplatelet therapy (preferably clopidogrel 75 mg/d, or as an alternative, ASA 75–100 mg/d)	General recommendation	
Long-term antithrombotic therapy with OAC (beyond 12 months) is recommended in all patients	I	B
Where a NOAC is used in combination with clopidogrel and/or low-dose ASA, the **lower tested dose for stroke prevention** in AF (dabigatran 110 mg BID, rivaroxaban 15 mg OD, or apixaban 2.5 mg BID) may be considered	IIb	C

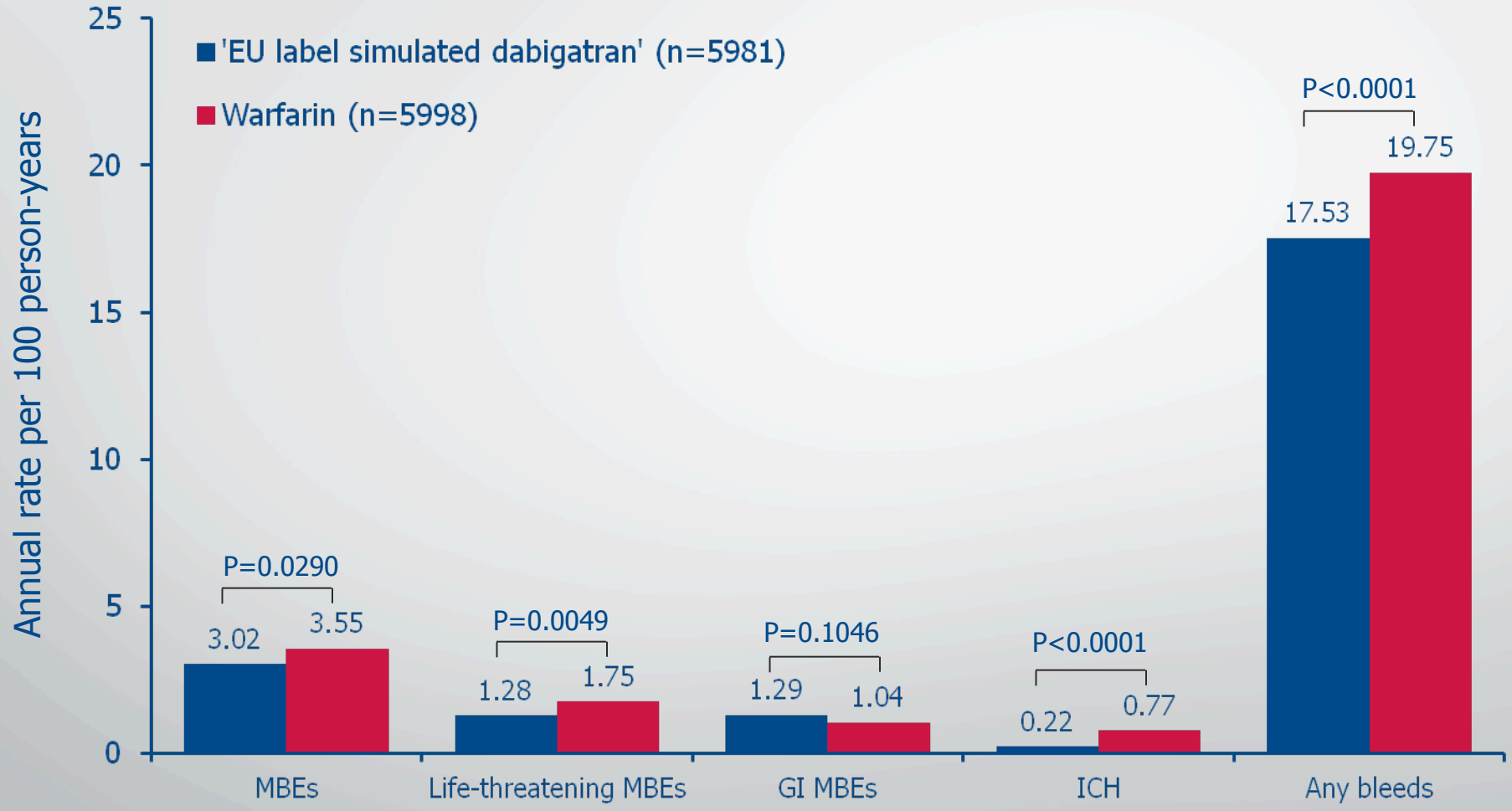
Lip GYH et al. Eur Heart J. 2014;doi:10.1093/eurheartj/ehu298

Clinical flowchart for the use of dabigatran for stroke prevention in AF

(as per European prescribing guidelines)



RE-LY® EU label analysis: bleeding events



GI = gastrointestinal; ICH = intracranial haemorrhage; MBE = major bleeding event

Lip G et al. Presented at ESC Congress 2013, Amsterdam, September 2013

RE-VERSE AD™

Study of reversal effects of idarucizumab in patients on active dabigatran

EVALUATE REVERSAL OF THE ANTICOAGULANT EFFECTS OF DABIGATRAN WITH IDARUCIZUMAB

- **Bleeding patients** – overt bleeding judged by the physician to require a reversal agent

- **Surgical patients** – require an emergency surgery or procedure for a condition other than bleeding

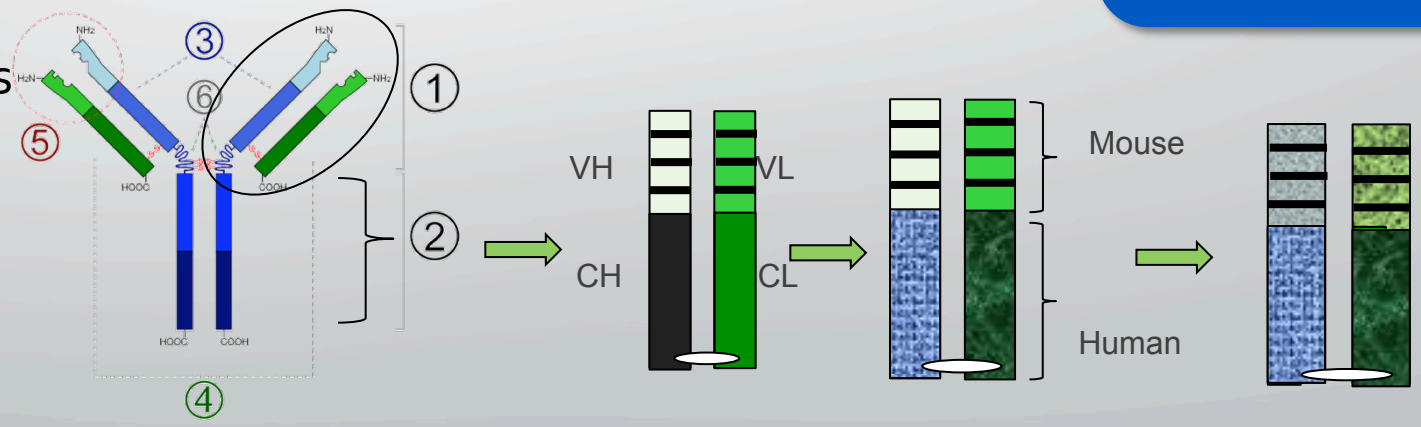
Started in April 2014, currently recruiting in >35 countries worldwide

NCT02104947: Available at http://www.clinicaltrials.gov/ct2/show/NCT02104947;

IDARUCIZUMAB: an antidote specific to dabigatran

- Restoration of coagulation
  - Potent binding affinity ~350 times higher than the binding of dabigatran to thrombin
  - No procoagulant or anticoagulant effects
  - Short half-life
- Easy and rapid administration
  - IV administration, immediate onset of action
- Low risk of adverse reactions
  - No Fc receptor binding
  - No endogenous targets

Fully humanized antibody fragment (Fab)



Glund S et al. AHA 2013; abstract 17765;
van Ryn J. AHA 2012; Presentation 9928; van Ryn J et al. Circulation 2012;126:A9928

IDARUCIZUMAB-NEWS FROM *FDA and EMA*

March 02, 2015 **Boehringer Ingelheim Submits Biologics License Application to FDA and EMA for Idarucizumab*, Investigational Specific Reversal Agent for Pradaxa® (dabigatran etexilate mesylate)**

- *First BLA submission for an investigational reversal agent for a novel oral anticoagulant*
- *Boehringer Ingelheim applying for Accelerated Approval pathway for idarucizumab*

A specific reversal agent may provide an additional option for patient management during emergency situations

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