Novel Anticoagulants for Mechanical Valve Patients ?

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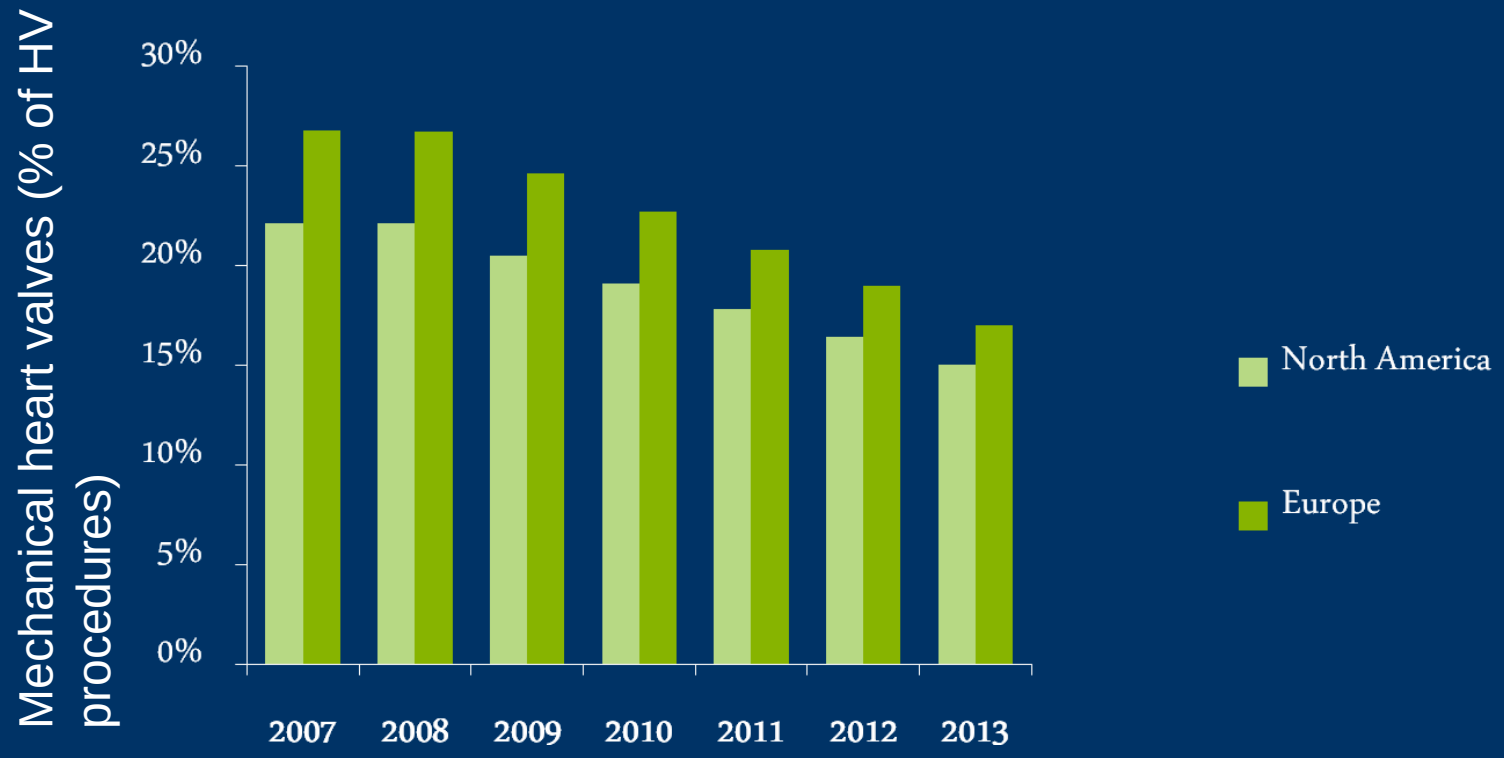
Mechanical heart valves (% of HV procedures)

Mechanical HVR expected to decrease

- Increasing use of biovalves
- Valve repair procedures rising



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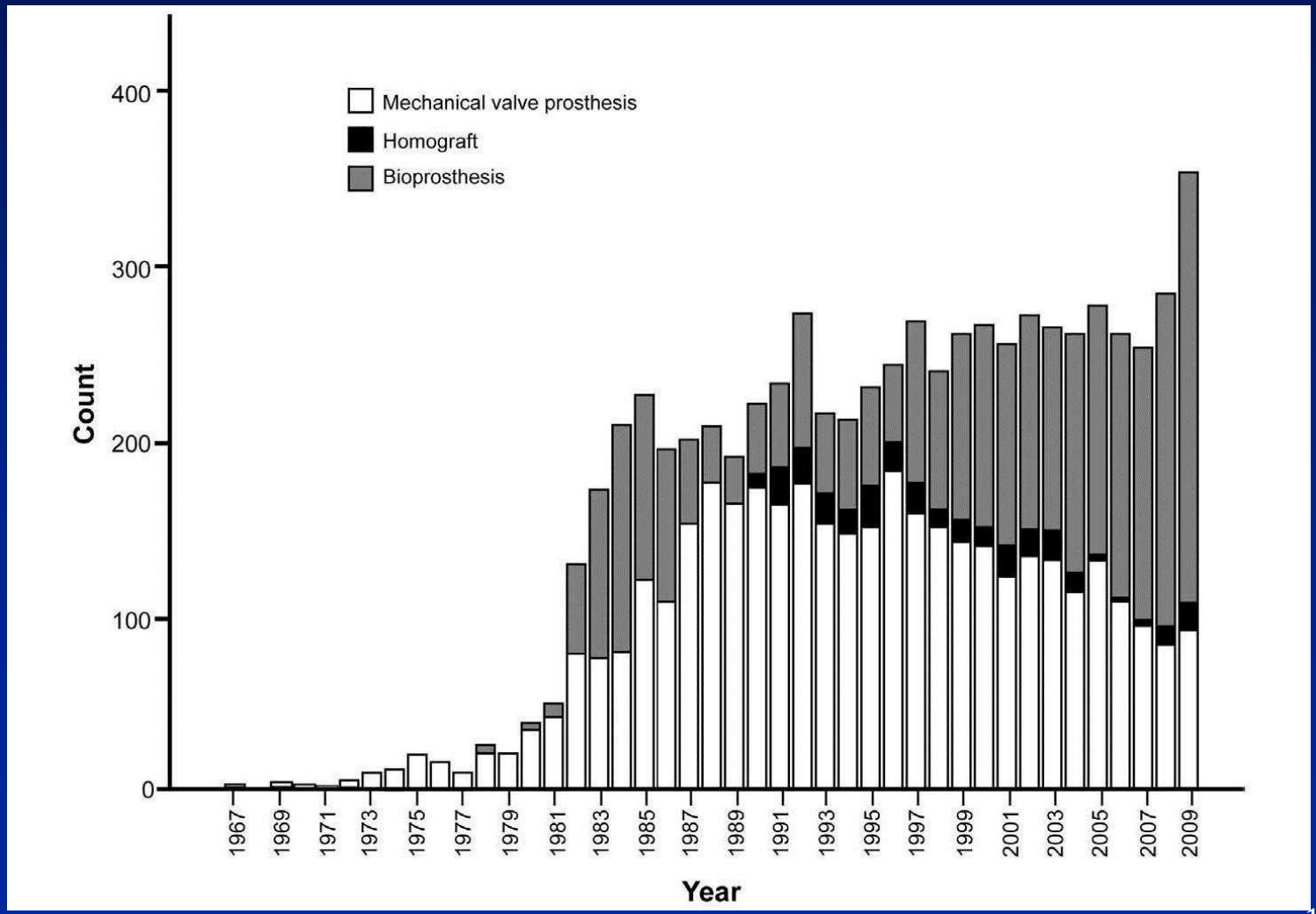

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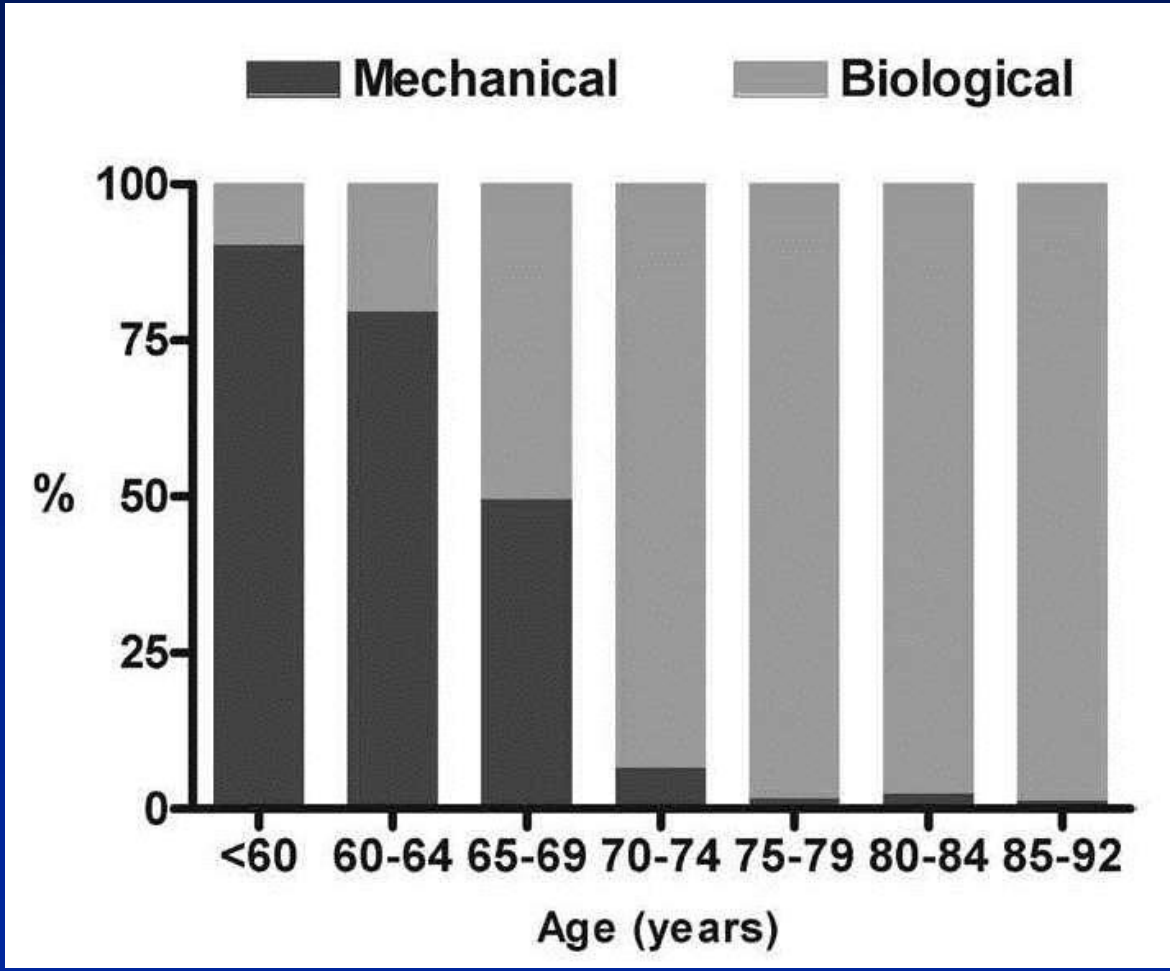


Indications for antithrombotic therapy after valvular surgery

	Class	Level
Oral anticoagulation is recommended lifelong for all patients with a mechanical prosthesis.	I	B
Oral anticoagulation is recommended lifelong for patients with bioprostheses who have other indications for anticoagulation.	I	C
The addition of low-dose aspirin should be considered in patients with a mechanical prosthesis and concomitant atherosclerotic disease.	IIa	C
The addition of low-dose aspirin should be considered in patients with a mechanical prosthesis after thromboembolism despite adequate INR.	IIa	C
Oral anticoagulation should be considered for the first 3 months after implantation of a mitral or tricuspid bioprosthesis.	IIa	C
Oral anticoagulation should be considered for the first 3 months after mitral valve repair.	IIa	C
Low-dose aspirin should be considered for the first 3 months after implantation of an aortic bioprosthesis.	IIa	C
Oral anticoagulation may be considered for the first 3 months after implantation of an aortic bioprosthesis.	IIb	C

European Heart Journal 2012 - doi:10.1093/eurheartj/ehs109 & European Journal of Cardio-Thoracic Surgery 2012 - doi:10.1093/ejcts/ezs455).

Risk factors for thromboembolism

- **Prosthesis thrombogenicity**
  - Low
    - Carbomedics (aortic position), Medtronic Hall, St.Jude Medical, ON-X.
  - Medium
    - Other bileaflet valves.
  - High
    - Lillehei-Kaster, Omniscience, Starr-Edwards, Bjork-Shiley, other tilting-disc valves.
- **Patient-related risk factors**
  - Mitral, tricuspid, or pulmonary valve replacement.
  - Previous thromboembolism.
  - Atrial fibrillation.
  - Mitral stenosis of any degree.
  - Left ventricular ejection fraction < 35%.

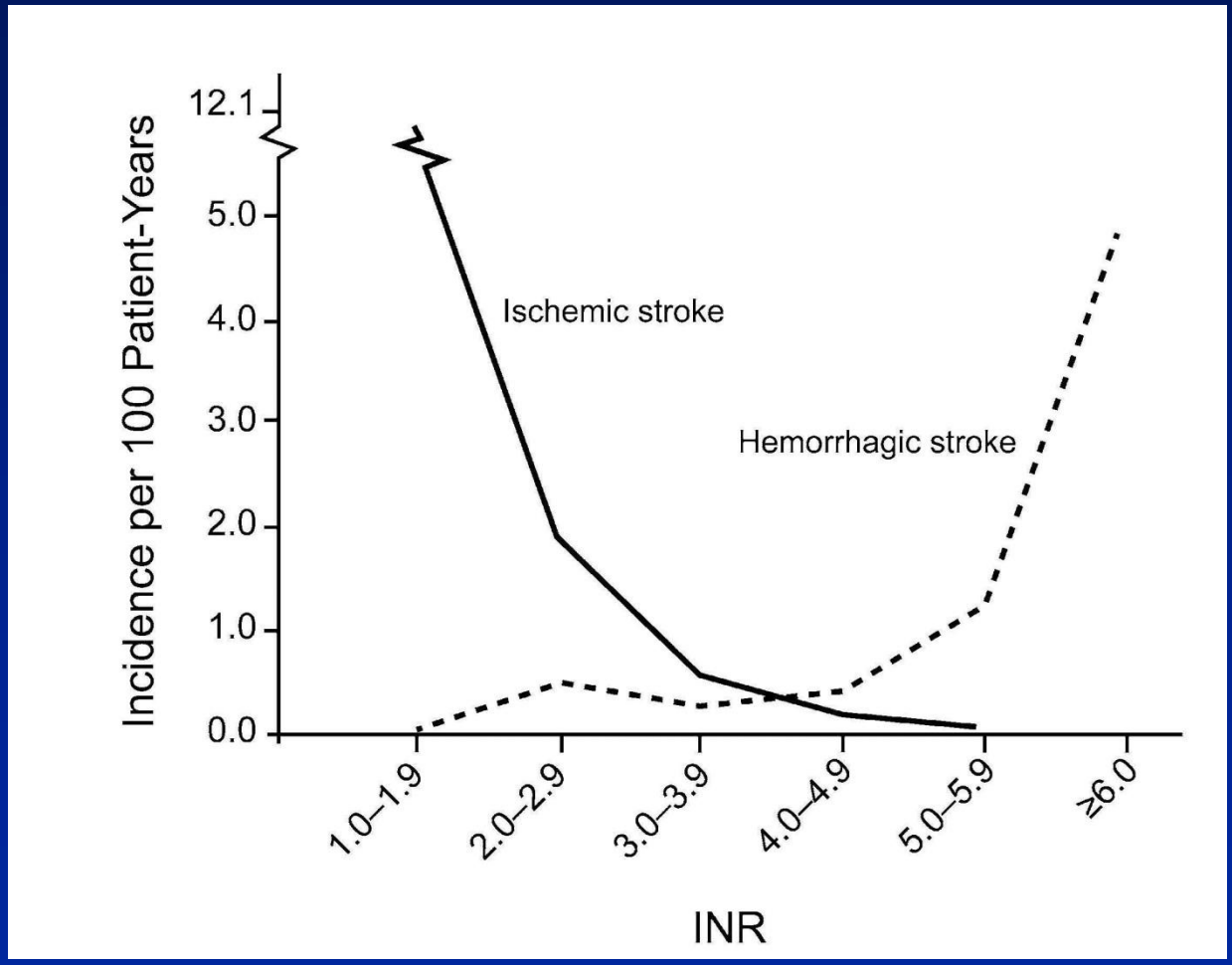
European Heart Journal 2012 - doi:10.1093/eurheartj/ehs109 & European Journal of Cardio-Thoracic Surgery 2012 - doi:10.1093/ejcts/ezs455).

Target international normalized ratio (INR) for mechanical prostheses

Prosthesis thrombogenicity	Patient-related risk factors	
	No risk factor	≥ 1 risk factor
Low	2.5	3.0
Medium	3.0	3.5
High	3.5	4.0

European Heart Journal 2012 - doi:10.1093/eurheartj/ehs109 & European Journal of Cardio-Thoracic Surgery 2012 - doi:10.1093/ejcts/ezs455).

The narrow therapeutic INR



RE-ALIGN: Dabigatran in Patients With a Mechanical Heart Valve

Randomized, phase II study to Evaluate the sAfety and pharmacokinetics of oraL dabIGatran etexilate in patients after heart valve replacemeNt

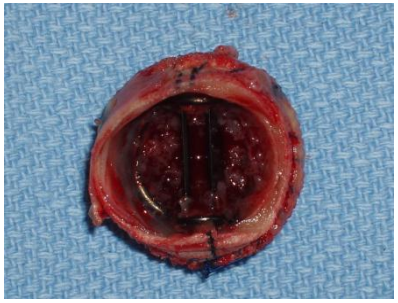
Background

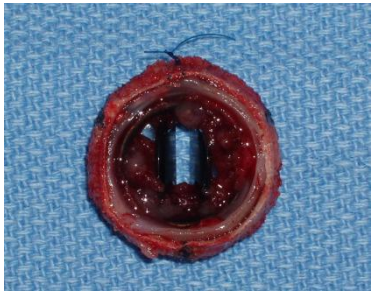
- Vitamin K antagonists provide effective protection against thrombosis in patients with a mechanical valve but require food, alcohol and drug restrictions and coagulation monitoring
- Dabigatran 150 mg bid is superior to warfarin in non-valvular atrial fibrillation (RELY study)
- Encouraging preclinical data with dabigatran in porcine mechanical valve models

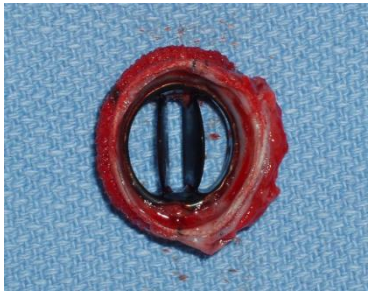
Dabigatran effective in animal models

Aortic valves (high flow, high pressure, shear stress conditions)

- Thrombus deposition was adequately controlled with dabigatran 20 mg/kg bid over 30 days in the pig model







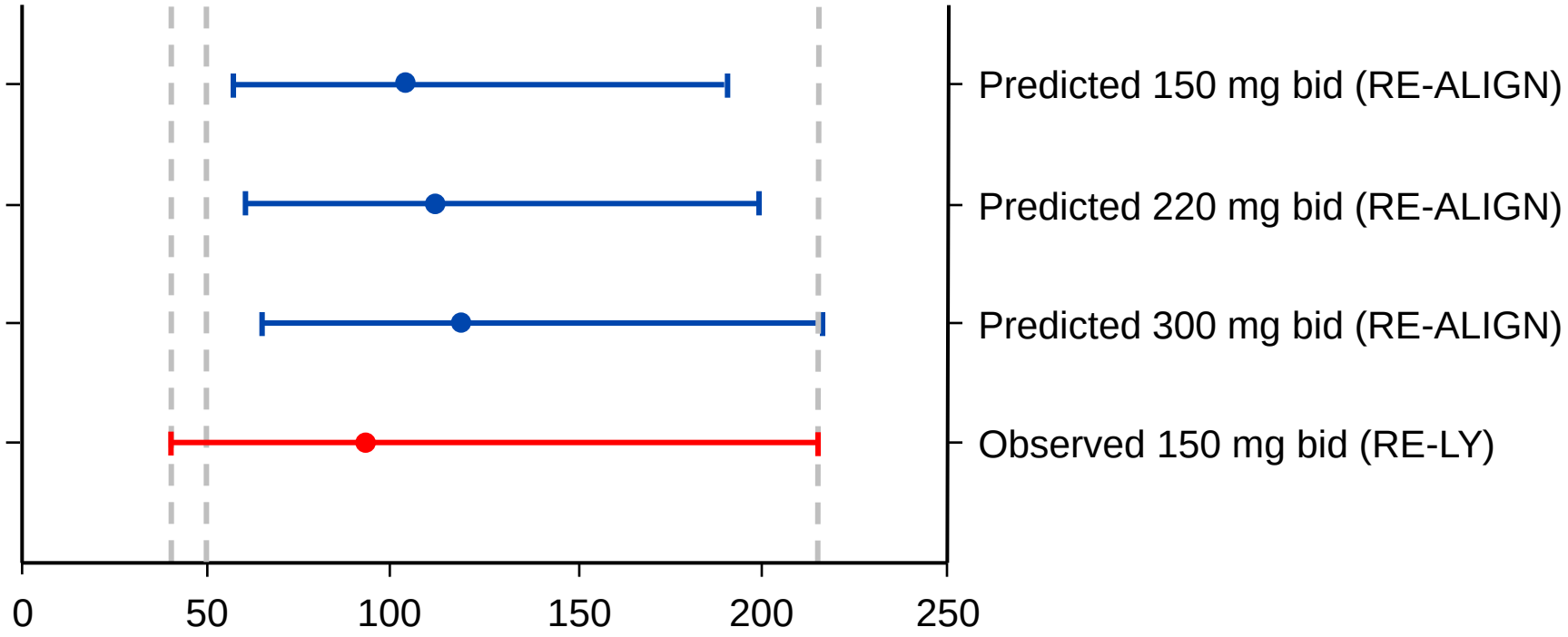
Aortic valve: **No anticoagulant** **LMWH** **Dabigatran**

Mitral valves (low flow, low pressure conditions)

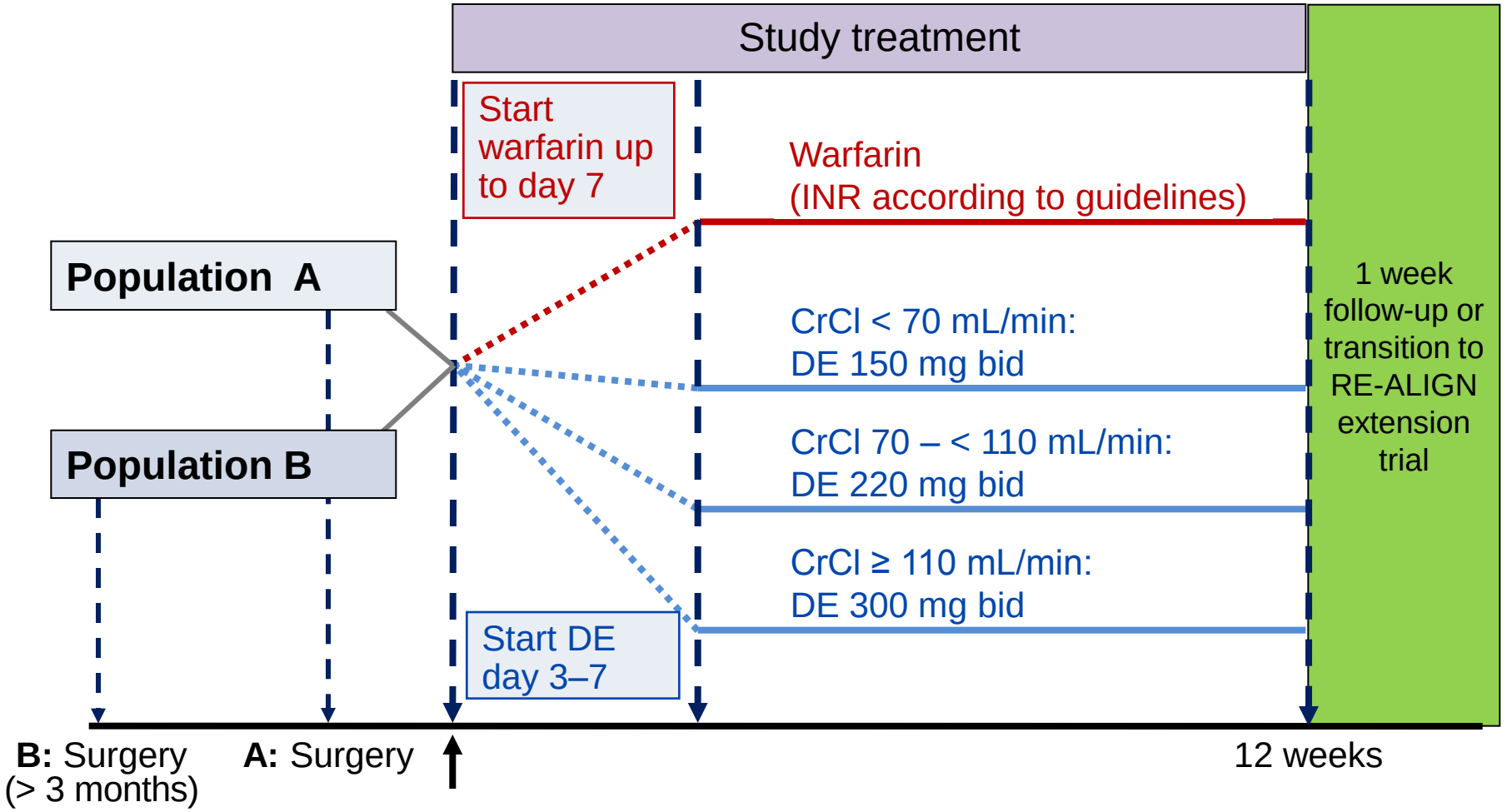
- Although thrombus deposition was not fully prevented with dabigatran 20 mg/kg bid over 90 days, survival overall was prolonged with dabigatran

Study objective

- To test a dosing algorithm of dabigatran based on the RE-LY study in patients with a bi-leaflet mechanical heart valve replacement



Study design of RE-ALIGN



- Increase dose if dabigatran trough plasma level < 50 ng/mL (by Hemoclot®)
- Discontinue dabigatran (switch to nonstudy VKA) if < 50 ng/mL with 300 mg bid after 2 measurements

Analysis and statistical methods

- **Primary outcome**: Trough plasma concentrations of dabigatran
  - Determined by high-performance liquid chromatography/tandem mass spectrometry (HPLC-MS/MS)

- **Clinical outcomes**: Stroke, systemic embolism, transient ischaemic attack, valve thrombosis, bleeding, venous thromboembolism, myocardial infarction and death
  - Clinical events were analysed descriptively (study not powered for clinical outcome events)

Sample Size

- The sample size was based on the validation of the dosing regimen: with 405 patients and a 2:1 randomization less than 10% of the patients would have a trough level of dabigatran of < 50ng/ml

- The study was prematurely stopped because of an excess of thromboembolic and bleeding events in the dabigatran arm after recruiting 252 patients

Patients studied

- Patients aged 18–75 years, with or without additional thromboembolic risk factors:
  - **Population A** (n=199, 67%): Aortic and/or mitral valve implantation during current hospital stay
  - **Population B** (n=53, 33%): Mitral valve implantation > 3 months before randomzation

Baseline characteristics – I

	Dabigatran (n = 168)	Warfarin (n = 84)
Male, n (%)	107 (64)	56 (67)
Age, mean (SD), years	56.0 (9.4)	55.7 (10.4)
CrCl, mean (SD), mL/min	107.8 (39.9)	106.4 (34.4)
Type of valve replacement (n, %)		
Aortic	113 (67)	59 (70)
Mitral	49 (29)	22 (26)
Aortic and mitral	6 (4)	3 (4)
Thromboembolic risk, n (%)		
Low (aortic valve, no additional risk factors)	51 (30)	23 (27)
Intermediate or high (aortic valve with additional risk factors, or mitral valve)	117 (70)	61 (73)
Population A or B (n, %)		
A (current surgery)	133 (79)	66 (79)
B (surgery ≥ 3 months before)	35 (21)	18 (21)

SD, standard deviation.

Baseline characteristics – II

	Dabigatran (n = 168)	Warfarin (n = 84)
Previous myocardial infarction, n (%)	9 (5)	7 (8)
Previous CABG, n (%)	5 (3)	4 (5)
Atrial fibrillation, n (%)	37 (22)	22 (26)
Atrial flutter, n (%)	7 (4)	5 (6)
NYHA class ≥ II, n (%)	62 (37)	29 (35)
Left ventricular ejection fraction ≤ 40%, n (%)	11 (7)	4 (5)
Hypertension, n (%)	101 (60)	53 (63)
Diabetes mellitus, n (%)	27 (16)	13 (15)
History of stroke, n (%)	5 (3)	5 (6)
History of transient ischaemic attack, n (%)	4 (2)	3 (4)
EuroSCORE, mean (SD)	2.3 ±1.9	2.3 ±1.8
STS risk score, mean (SD)	2.0 ±2.3	1.8 ±1.7

CABG, coronary artery bypass graft; NYHA, New York Heart Association; STS, Society of Thoracic Surgeons.

Patients requiring dabigatran dose up-titration or discontinuation

Dabigatran dose	Population A receiving dabigatran (n = 127)		Population B receiving dabigatran (n = 35)		Total receiving dabigatran (n = 162)	
	Required up-titration/Stop, n/N[a] (%)	% of time ≥ 50 ng/mL[b]	Required up-titration/Stop, n/N[a] (%)	% of time ≥ 50 ng/mL[b]	Required up-titration/Stop n/N[a] (%)	% of time ≥ 50 ng/mL[b]
150 mg bid	4/11 (36)	99	2/13 (15)	98	6/24 (25)	98
220 mg bid	32/71 (45)	84	1/16 (6)	100	33/87 (38)	87
300 mg bid	11/45 (24)	79	2/6 (33)	83	13/51 (25)	79
Total	47/127 (37)	84	5/35 (14)	96	52/162 (32)	86

[a]N includes all patients who received at least one dose of dabigatran.

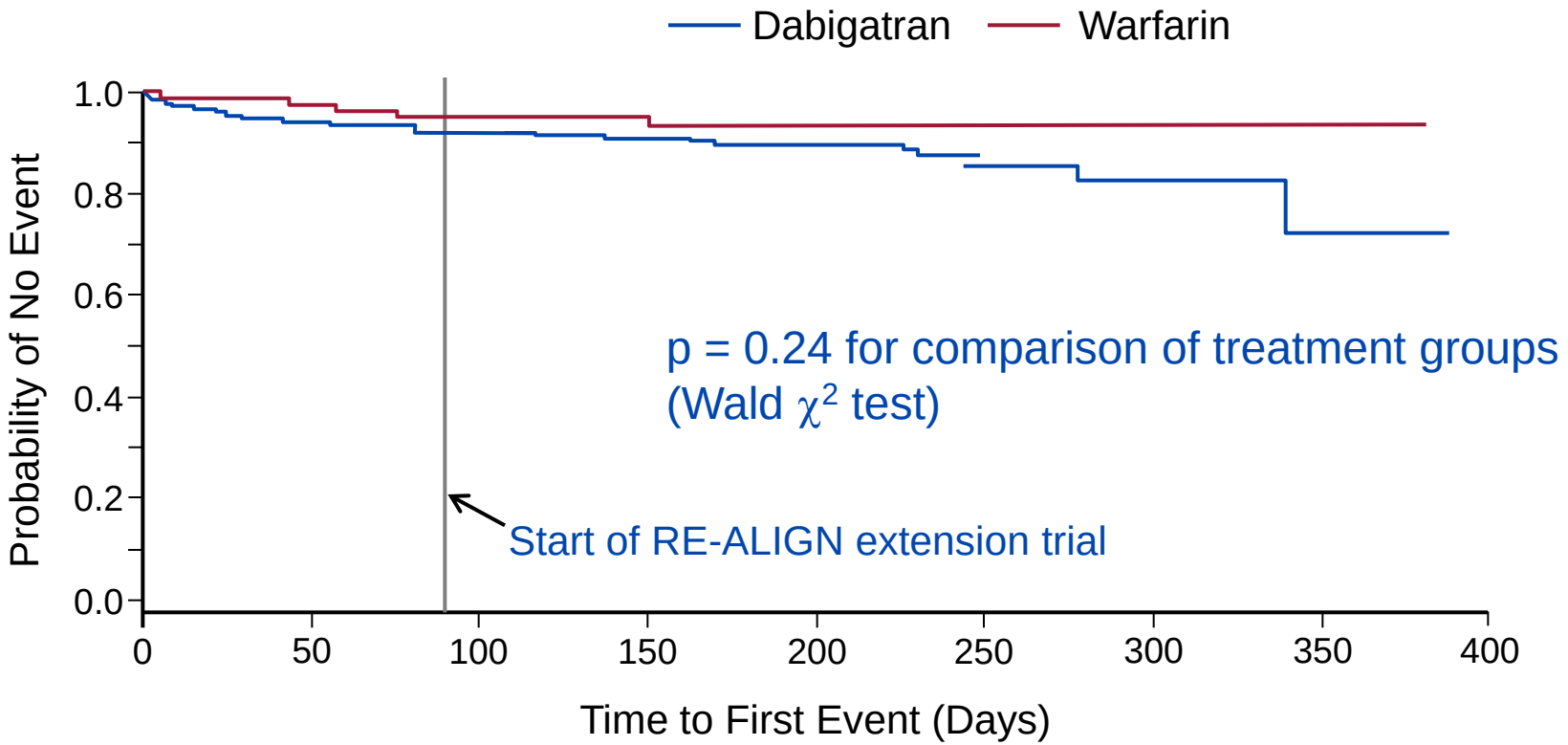
[b]Calculated using Rosendaal method based on dabigatran trough concentrations measured by HPLC-MS/MS.

Adjudicated efficacy outcomes

	Population A		Population B		All patients	
	Dabigatran (n = 133)	Warfarin (n = 66)	Dabigatran (n = 35)	Warfarin (n = 18)	Dabigatran (n = 168)	Warfarin (n = 84)
Death, n (%)	1 (1)	2 (3)	0	0	1 (1)	2 (2)
Stroke, n (%)	9 (7)	0	0	0	9 (5)	0
SE, n (%)	0	0	0	0	0	0
TIA, n (%)	2 (2)	2 (3)	1 (3)	0	3 (2)	2 (2)
MI, n (%)	1 (1)	0	2 (6)	0	3 (2)	0
Valve thrombosis without symptoms	2 (2)	0	3 (9)	0	5 (3)	0
Death/stroke/SE/ MI, n (%)	11 (8)	2 (3)	2 (6)	0	13 (8)	2 (2)
Death/stroke/TIA/ SE/MI, n (%)	12 (9)	4 (6)	3 (9)	0	15 (9)	4 (5)

MI, myocardial infarction; SE, systemic embolism; TIA, transient ischaemic attack

KM curves for the composite of a first thromboembolic event or death



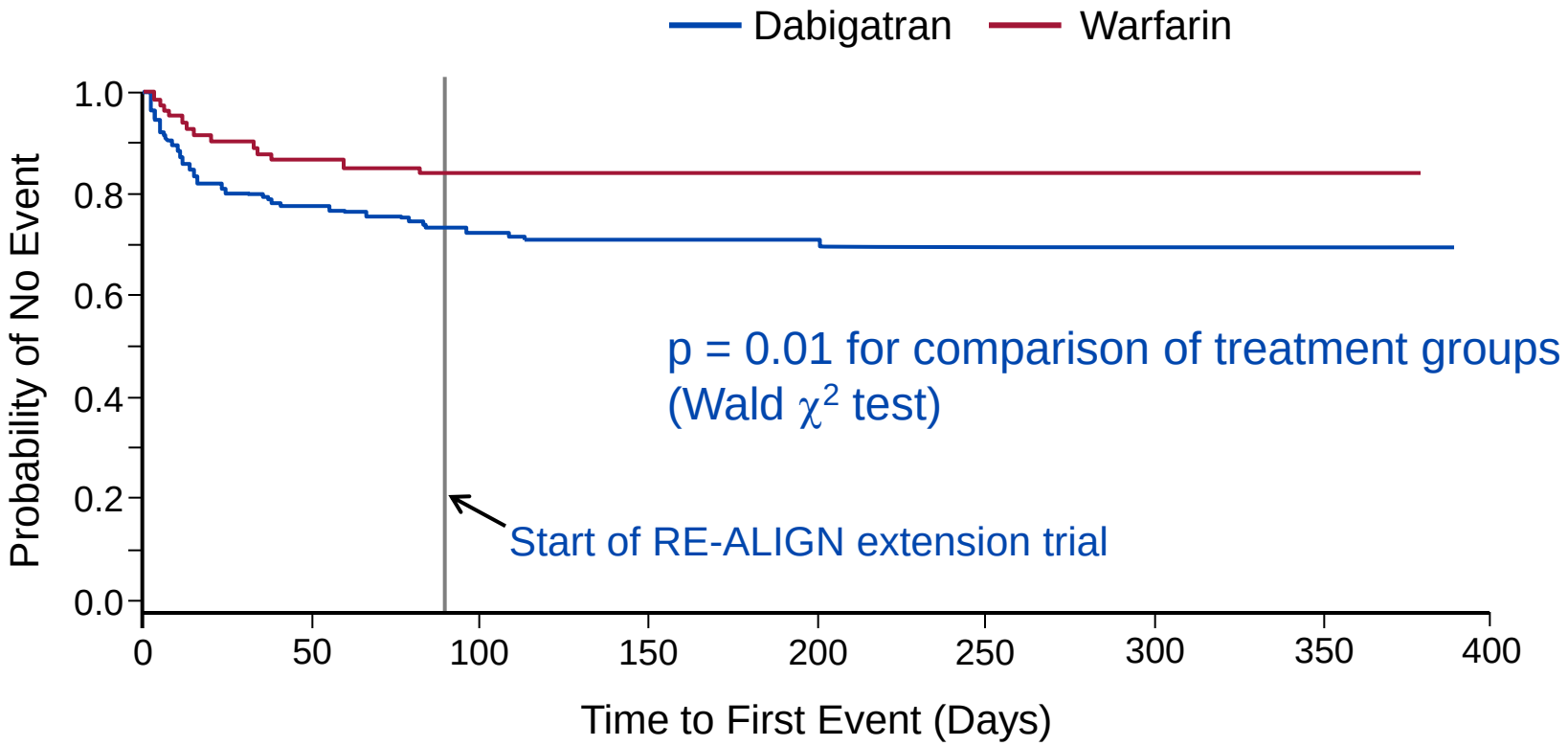
No. at risk								
Dabigatran	168	156	126	108	73	44	15	7
Warfarin	84	82	66	55	40	22	9	4

First thromboembolic event includes stroke, systemic embolism,TIA, myocardial infarction.

Adjudicated safety outcomes

	Population A		Population B		All patients	
	Dabigatran (n = 133)	Warfarin (n = 66)	Dabigatran (n = 35)	Warfarin (n = 18)	Dabigatran (n = 168)	Warfarin (n = 84)
Major bleeding, n (%)	7 (5)	2 (3)	0	0	7 (4)	2 (2)
Major bleeding with pericardial location, n (%)	7 (5)	2 (3)	0	0	7 (4)	2 (2)
Any bleeding, n (%)	35 (26)	8 (12)	10 (29)	2 (11)	45 (27)	10 (12)

KM curves for a first bleeding event (any bleeding)

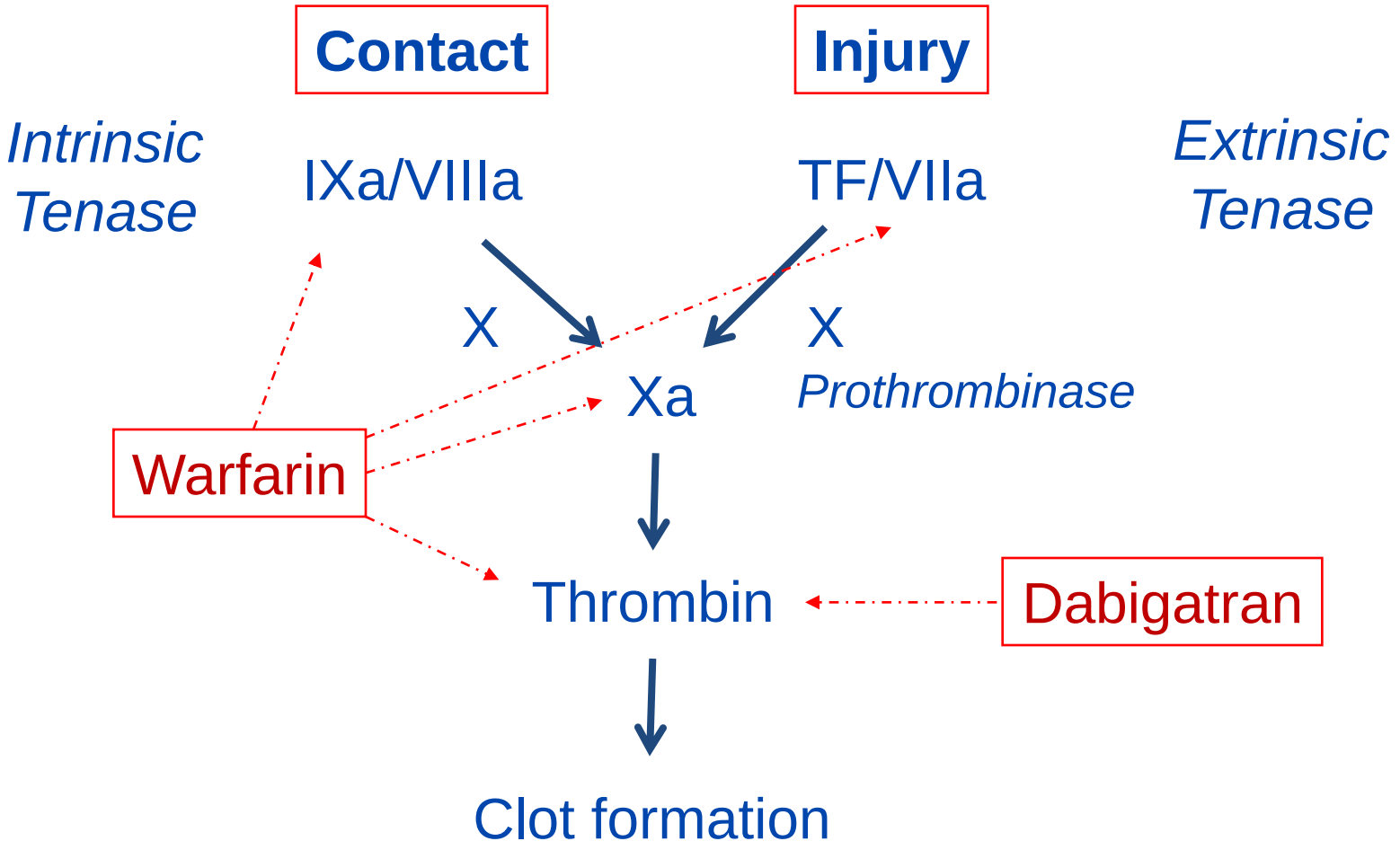


No. at risk								
Dabigatran	168	129	103	86	58	32	11	6
Warfarin	84	73	56	50	38	22	11	4

Possible explanations for negative study results

- Inadequate blood levels of dabigatran
- Play of chance with relatively few events seen in the warfarin arm
- Differences in the mechanism of action of dabigatran compared with warfarin
  - e.g., the inability of dabigatran to suppress activation of coagulation that occurs when blood is exposed to the artificial surface of mechnical valves

Mechanism of Action
Dabigatran vs. Warfarin



Conclusions

- RE-ALIGN is the first randomized study comparing a novel oral anticoagulant with warfarin in patients with a mechanical valve
- Dabigatran is not as effective as warfarin for prevention of thromboembolic complications in patients with mechanical heart valves and is associated with more bleeding
- Dabigatran should not be prescribed in patients with mechanical heart valves

RE-ALIGN INVESTIGATORS

- **Steering Committee:** F. Van de Werf (co-chair), J. Eikelboom (co-chair), S. Connolly, C. Granger, P. Kappetein, M. Brueckmann, M. Mack

- **Data Safety Monitoring Board:** M.L. Simoons , D. Lindblom, M. Prins; J.G.P. Tijssen

- **Echocardiography Core Lab** J-U. Voigt, Dept. of Cardiovasc. Sciences, Leuven, Belgium

- **Data Management and Statistics:** Boehringer Ingelheim, UK

- **Principal Investigators in the RE-ALIGN trial** (at least one patient screened):

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ORIGINAL ARTICLE

Dabigatran versus Warfarin in Patients with Mechanical Heart Valves

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Future

- Anti-XA agents ?
- Other agents ?

Tecarfarin: a new VKA ?

- **Tecarfarin (ATI-5923):**

  A novel oral vitamin K antagonist, metabolized by esterases and escaping metabolism by the cytochrome P450 system, thereby avoiding cytochrome P450-mediated genetic variations and drug-drug or drug-food interactions

- **EmbraceAC Trial:**
  A Head-to-Head Comparison of Warfarin with Tecarfarin

  Randomized, double-blind, multicenter study comparing Warfarin vs. Tecarfarin

Garcia A, ASH, 2009

TABLE 1. ACCP Guidelines on the Use of Antithrombotic Therapy in Patients With a Heart Valve Prosthesis

		Aorta (INR)	Mitral (INR)
ACCP 1995	Mechanical prosthesis		
	Caged-ball, caged-disk	> 3.0	> 3.0
	+ Risk factors	+ ASA	+ ASA
	Bileaflet	3.0	3.0
	+ Risk factors	+ ASA	+ ASA
	Bioprosthesis	2.5 (90 days) then ASA	2.5 (90 days) then ASA
	+ Risk factors	2.5	2.5
ACCP 2004	Mechanical prosthesis		
	Caged-ball, caged-disk	3.0 + ASA	3.0 + ASA
	+ Risk factors	3.0 + ASA	3.0 + ASA
	St. Jude Medical, Medtronic Hall, Carbomedics	2.5	3.0
	+ Risk factors	3.0 + ASA	3.0 + ASA
	Bioprosthesis	ASA or 2.5 (90 days) then ASA	2.5 (90 days) then ASA
	+ Risk factors	2.5 + ASA	2.5 + ASA
	Mitral valve repair		2.5 from 3 weeks pre- to 4 weeks postprocedure
ACCP 2008	Mechanical prosthesis		
	Caged-ball, caged-disk	3.0 + ASA	3.0 + ASA
	+ Risk factors	3.0 + ASA	3.0 + ASA
	St. Jude Medical, Medtronic Hall, Carbomedics	2.5	3.0
	+ Risk factors	3.0 + ASA	3.0 + ASA
	Bioprosthesis	ASA	2.5 (90 days) then ASA
	+ Risk factors	2.5 + ASA	2.5 + ASA
	Mitral valve repair		2.5 from 3 weeks pre to 4 weeks postprocedure
ACCP 2012	Mechanical prosthesis*	2.5	3.0
	+ Low bleeding risk	2.5 + ASA	3.0 + ASA
	Bioprosthesis	ASA (90 days)	2.5 (90 days) then ASA
	Valve repair	ASA	ASA

*The 2012 update only addresses newer generation tilting-disk and bileaflet mechanical valves.
ACCP: American College of Clinical Pharmacology; INR: international normalized ratio; ASA: acetylsalicylic acid.

TABLE 2. Guidelines of the ESC on the Use of Antithrombotic Therapy in Patients With a Heart Valve Prosthesis

		Aorta (INR)	Mitral (INR)
ESC 1993	Mechanical prosthesis		
	Low thrombogenic risk: Medtronic Hall, bileaflet	2.5 – 3.0	3.0 – 4.5
	+ Risk factors	3.0 – 4.5	3.0 – 4.5
	High thrombogenic risk: Starr-Edwards, BjorkShiley	3.0 – 4.5	3.0 – 4.5
	+ Risk factors	3.0 – 4.5	3.0 – 4.5
	Bioprosthesis	? (90days)	? (90 days)
	+ Risk factors	3.0 – 4.5	3.0 – 4.5
ESC 2007	Mechanical prosthesis		
	Low thrombogenic risk: Medtronic Hall, St. Jude Medical, carbomedics	2.5	3.0
	+ Risk factors	3.0	3.0
	Medium thrombogenic risk: Bjork Shiley, new bileaflet with insufficient data	3.0	3.5
	+ Risk factors	3.5	3.5
	High thrombogenic risk: Starr-Edwards, Lillehei Kaster, Omniscience	3.5 ± dipyr	4.0 ± dipyr
	+ Risk factors	4.0 ± dipyr	4.0 ± dipyr
	Bioprosthesis	2.5 (90 days)	2.5 (90 days)
	+ Risk factors	3.0	3.0
	Mitral valve repair		2.5 (90 days)

ESC, European Society of Cardiology; INR, international normalized ratio; ASA, acetylsalicylic acid, Dipyr, dipyridamole

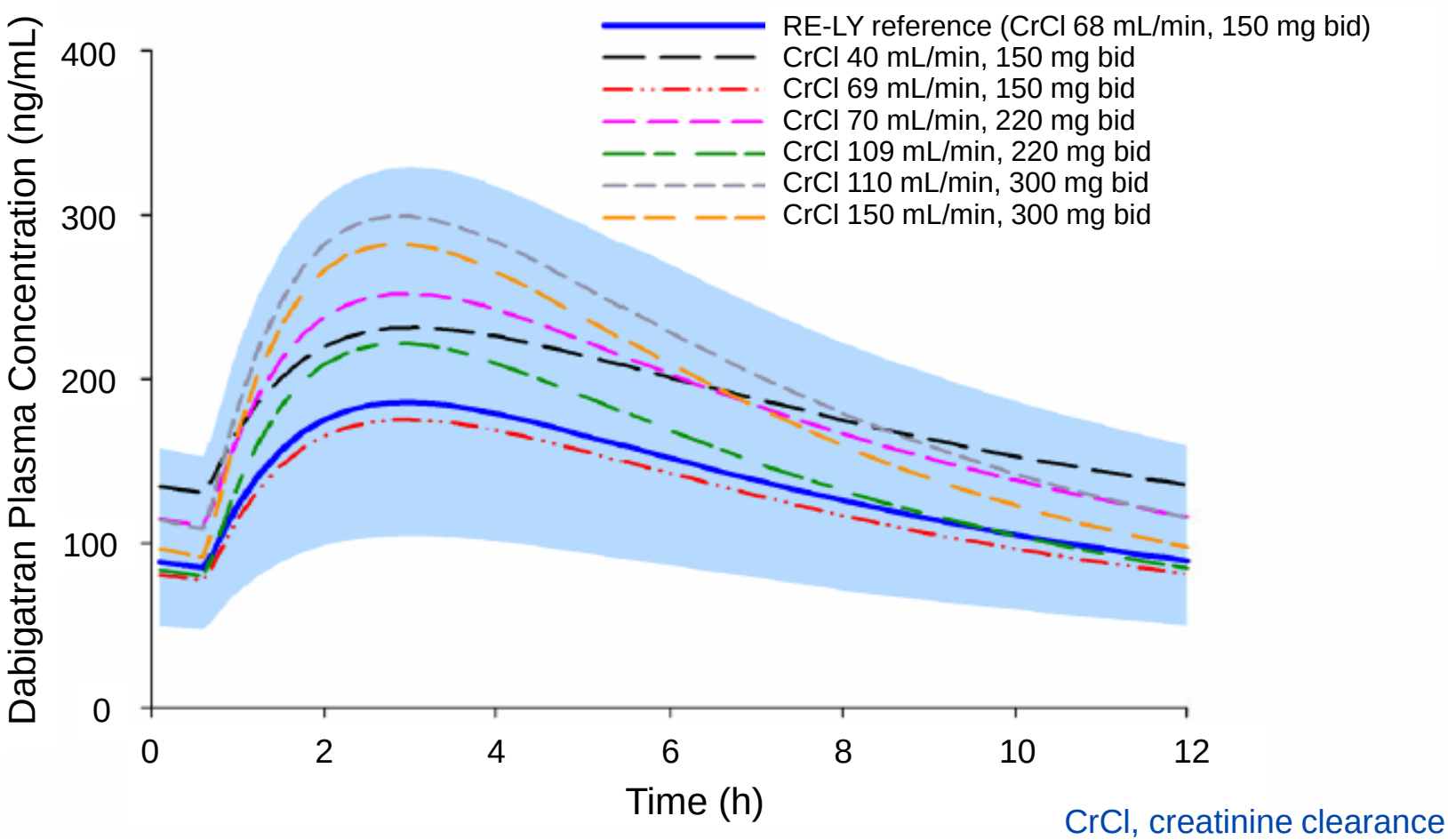
TABLE 3. Guidelines From the ACC/AHA on the Use of Antithrombotic Therapy in Patients With a Heart Valve Prosthesis

		Aorta (INR)	Mitral (INR)
ACC/AHA 1998	Mechanical prosthesis		
	First 3 months after replacement	2.5 – 3.5 + ASA	2.5 – 3.5 + ASA
	After 3 months		
	Medtronic hall, bileaflet	2.0 – 3.0 + ASA	2.5 – 3.5 + ASA
	Starr-Edwards, tilting disk	2.5 – 3.5 + ASA	2.5 – 3.5 + ASA
	+ Risk factors	2.5 – 3.5 + ASA	2.5 – 3.5 + ASA
	Bioprosthesis		
	First 3 months after replacement	2.5 – 3.5 + ASA	2.5 – 3.5 + ASA
	After 3 months	ASA	ASA
	+ Risk Factors	2.0 – 3.0 + ASA	2.5 – 3.5 + ASA
ACC/AHA 2008	Mechanical prosthesis		
	Low thrombogenic risk: Medtronic Hall, bileaflet	2.0 – 3.0 + ASA	2.5 – 3.5 + ASA
	+ Risk factors	2.5 – 3.5 + ASA	2.5 – 3.5 + ASA
	High thrombogenic risk: Starr-Edwards, tilting disk other than medtronic hall	2.5 – 3.5 + ASA	2.5 – 3.5 + ASA
	+ Risk factors	2.5 – 3.5 + ASA	2.5 – 3.5 + ASA
	Bioprosthesis	2.0 – 3.0 (90 days) or ASA	2.0 – 3.0 (90 days) or ASA
	+ Risk factors	2.0 – 3.0 + ASA	2.0 – 3.0 + ASA

ACC/AHA, American College of Cardiology/American Heart Association; INR, international normalized ratio; ASA, acetylsalicylic acid.

Study objective

- To test a dosing algorithm of dabigatran based on the RE-LY study in patients with a bi-leaflet mechanical heart valve replacement



CrCl, creatinine clearance.

Median concentration–time profiles at steady state of virtual patients with their respective target dose. The 80% prediction interval (10–90th percentiles) of a typical RE-LY patient receiving dabigatran 150 mg bid (reference exposure profile) is provided as shaded area.