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

Disclosures
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Research Grants:

Boehringer Ingelheim, AstraZeneca, MSD,
The Medicines Company, Novartis, Roche, Sanofi-Aventis

Consulting Fees:

Boehringer Ingelheim, AstraZeneca, MSD,
The Medicines Company, Roche, Sanofi-Aventis, Eli Lilly

Speaker's Bureau:

Boehringer Ingelheim, AstraZeneca, MSD, Sanofi-Aventis,
Eli Lilly, The Medicines Company

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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)

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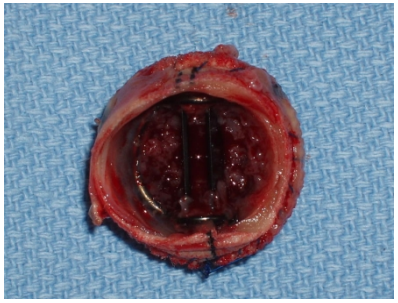
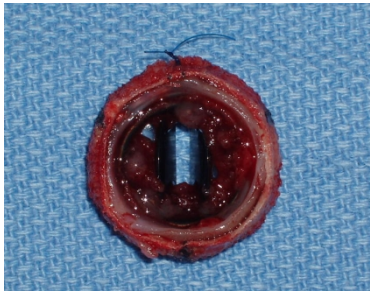
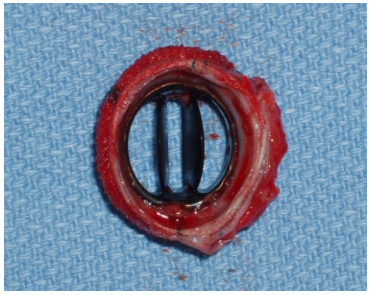
Dabigatran effective in animal models

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







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

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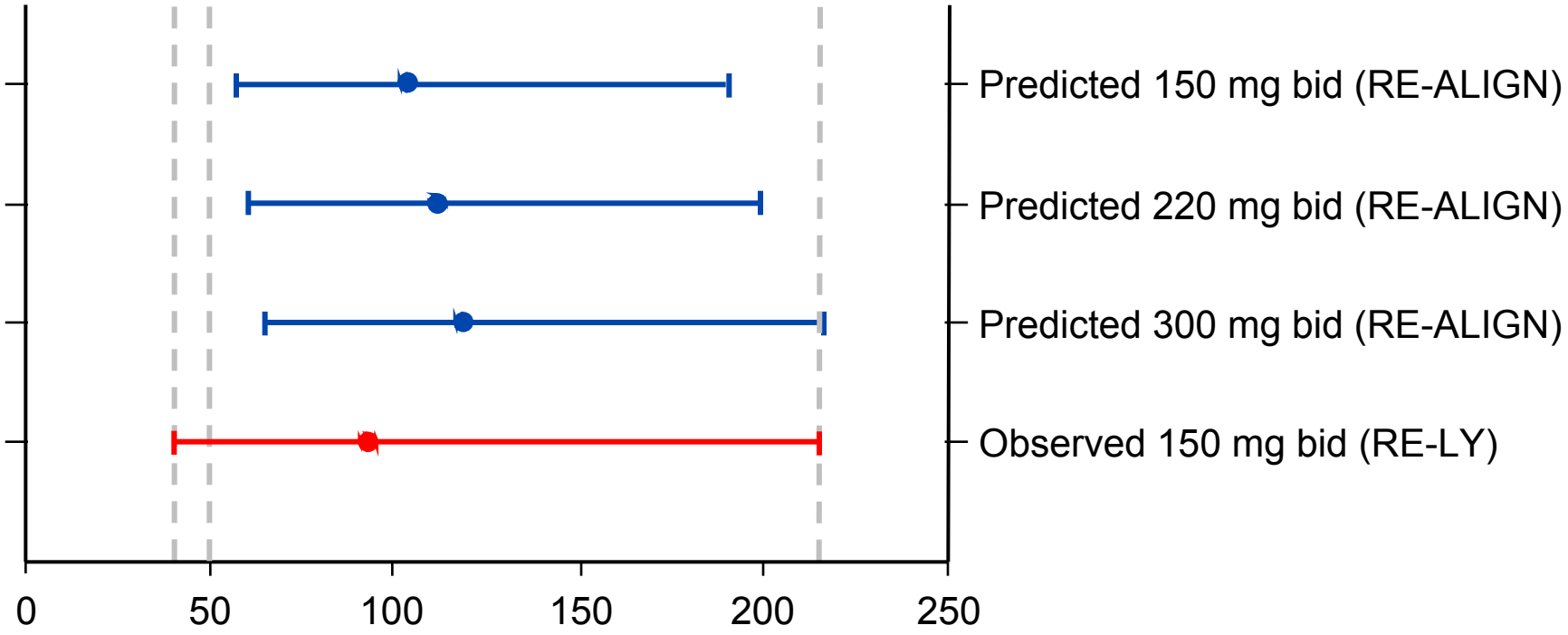
Study objective

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



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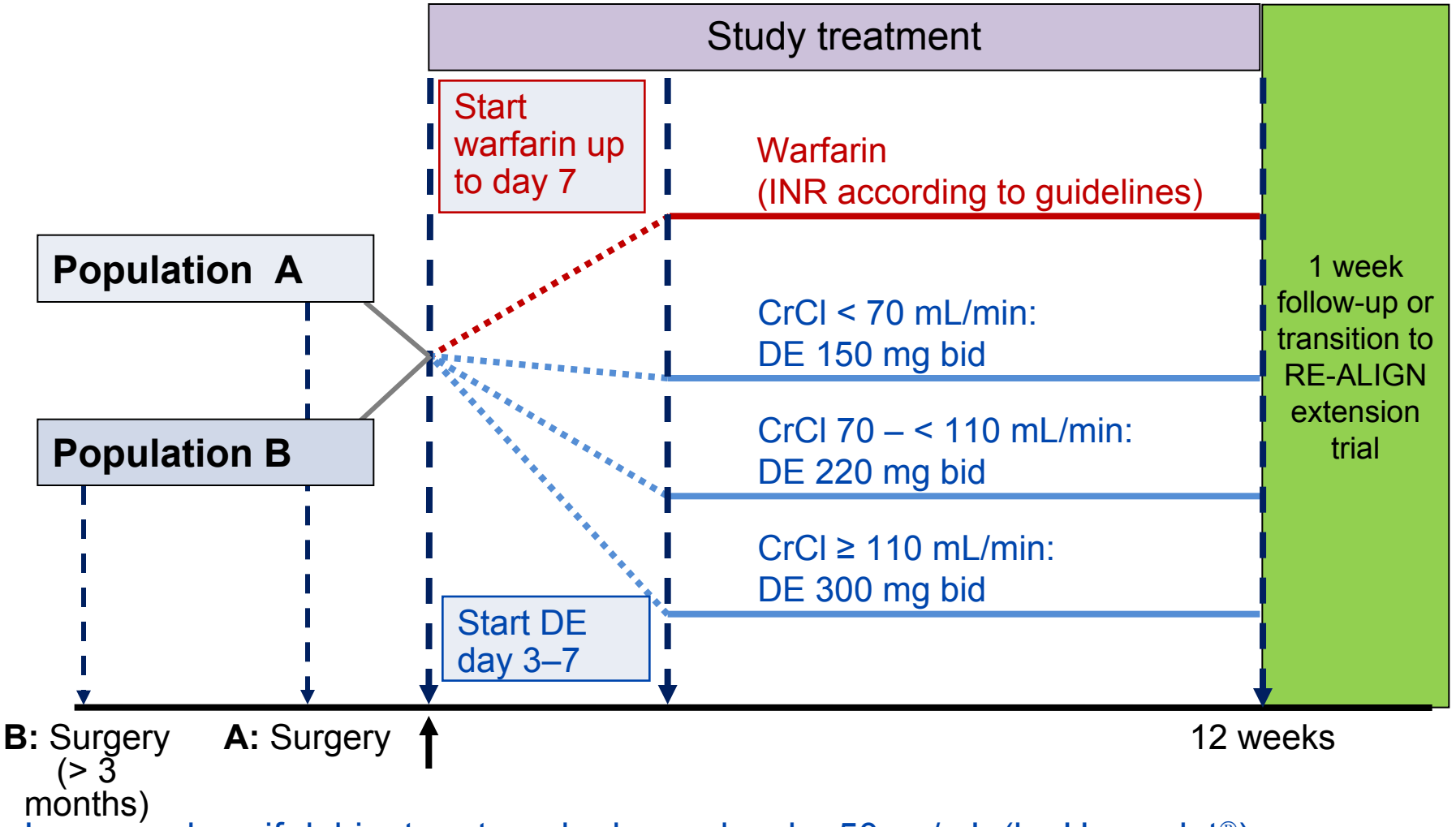
Study design of RE-ALIGN



- 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*

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*

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:

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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.

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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.

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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

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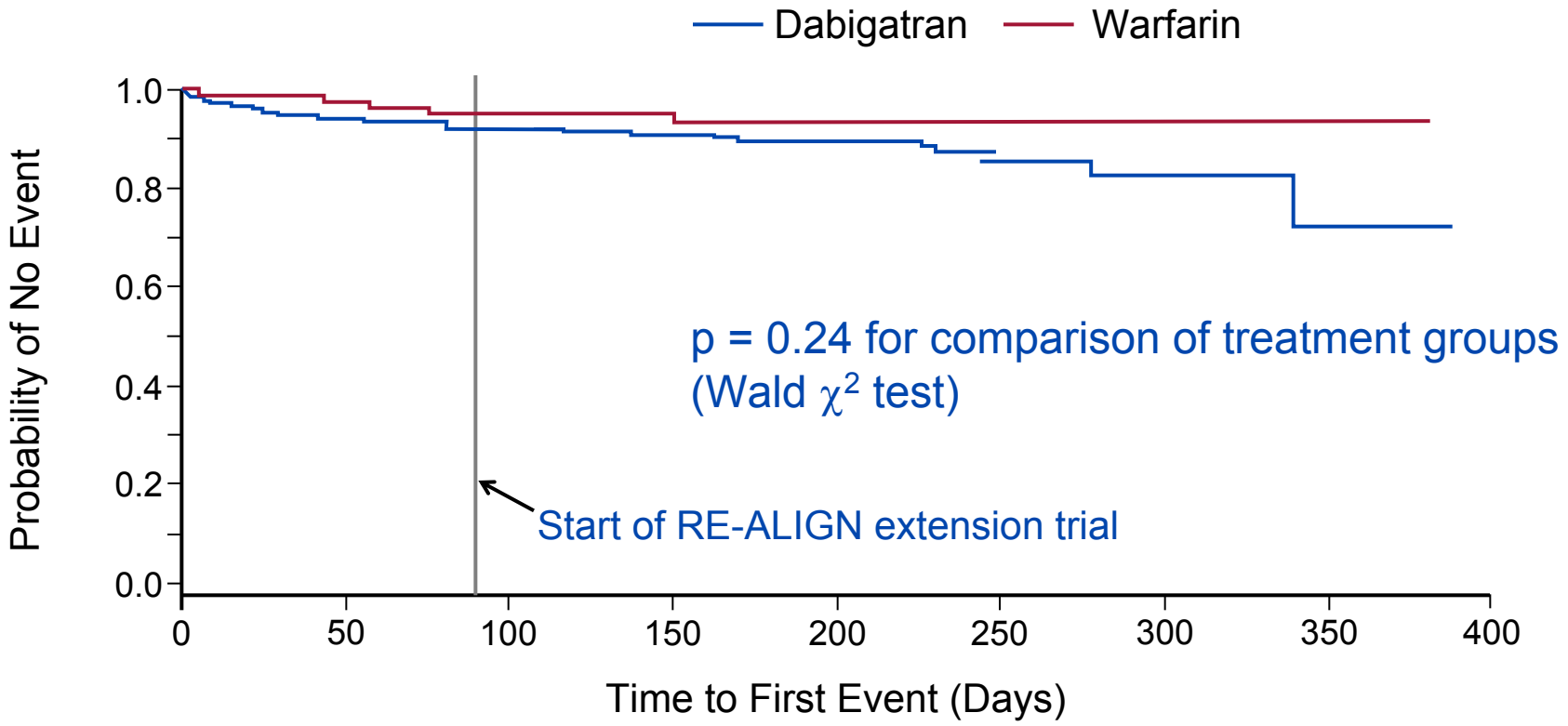
KM curves for the composite of a first thromboembolic event or death



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.

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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)

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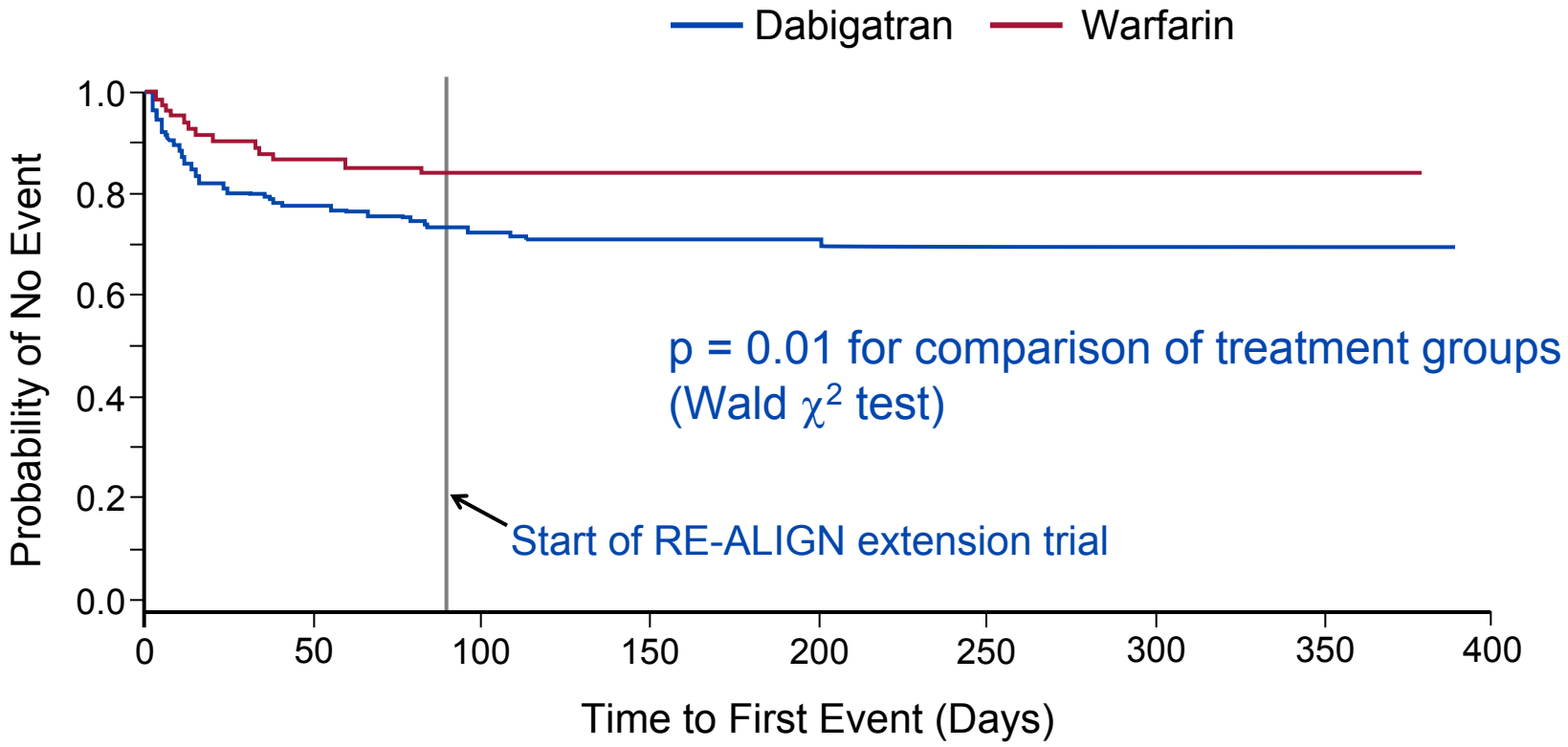
KM curves for a first bleeding event (any bleeding)



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

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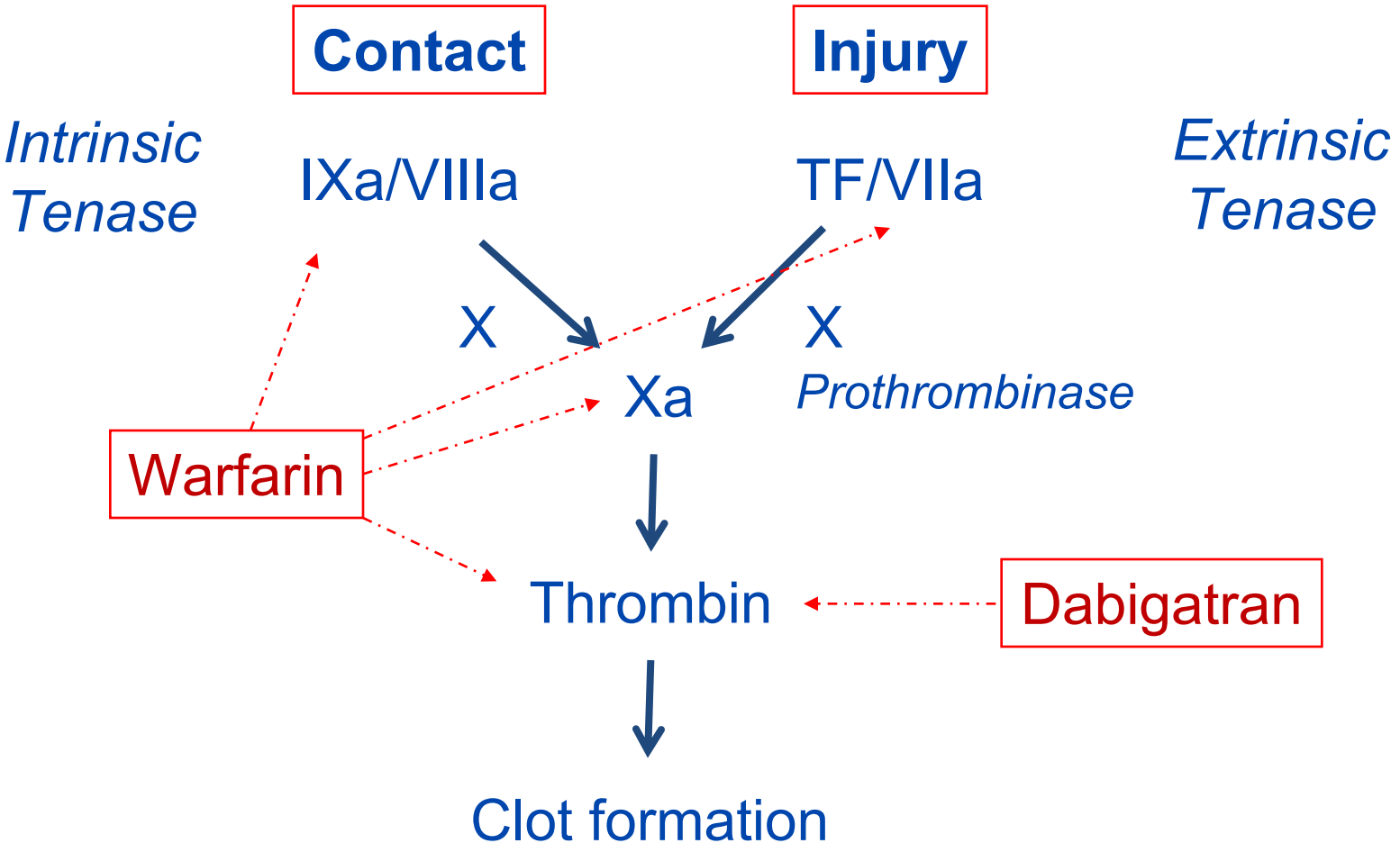
Possible explanations for negative study results

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 *

Mechanism of Action
Dabigatran vs. Warfarin



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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

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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

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Data Management and Statistics: Boehringer Ingelheim, UK

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ORIGINAL ARTICLE

Dabigatran versus Warfarin in Patients with Mechanical Heart Valves

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Study objective

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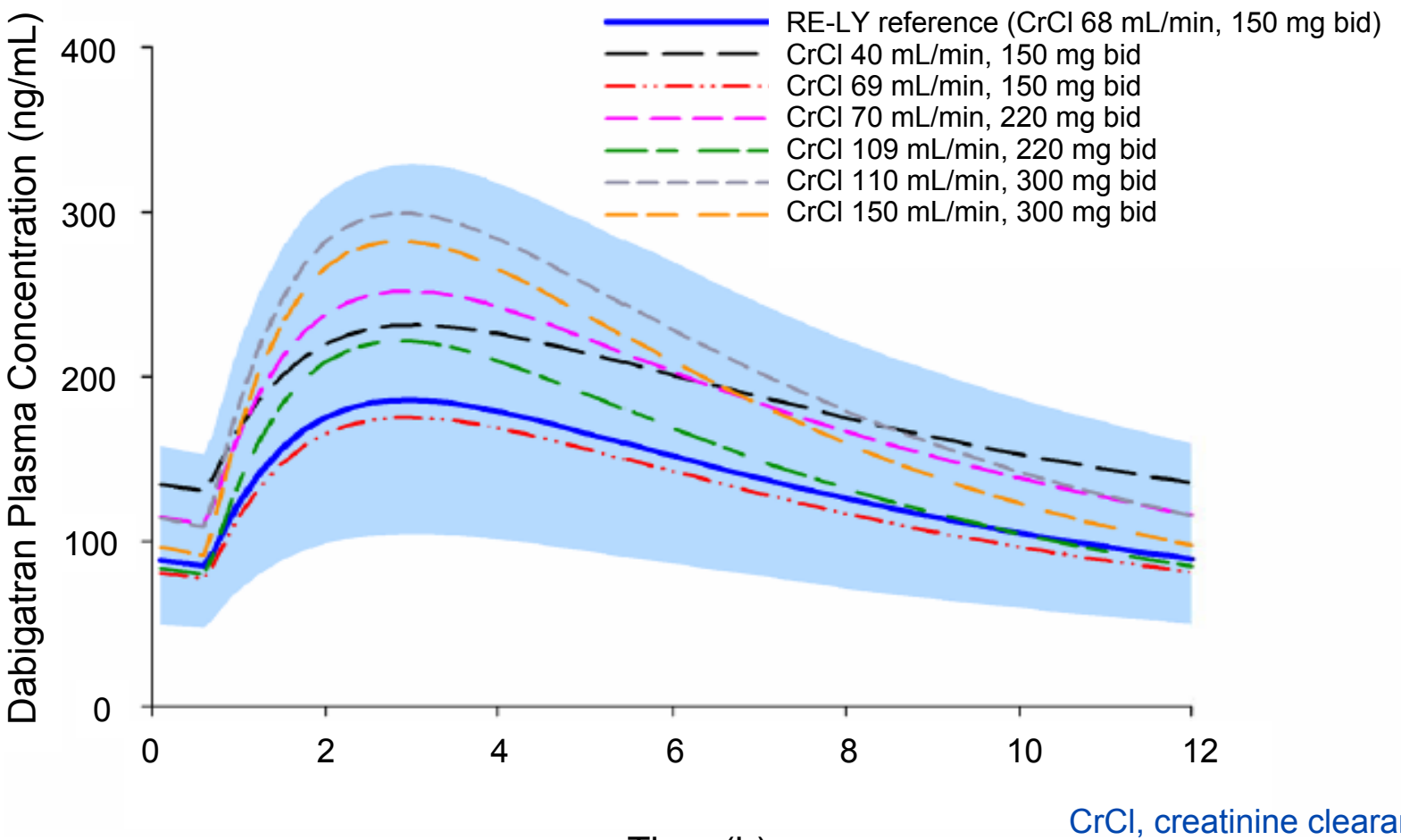

CrCl, creatinine clearance.

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.

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