Would the new oral thrombin inhibitors replace vitamin K antagonists in atrial fibrillation?

A. Pipilis, FESC, FACC

Metsovo, January 27-29, 2012

υγεία
ΜΕΛΟΣ ΤΟΥ ΟΜΙΛΟΥ ΥΓΕΙΑ

ALPIC2012
Advanced Learning on Platelets & Thrombosis International Course

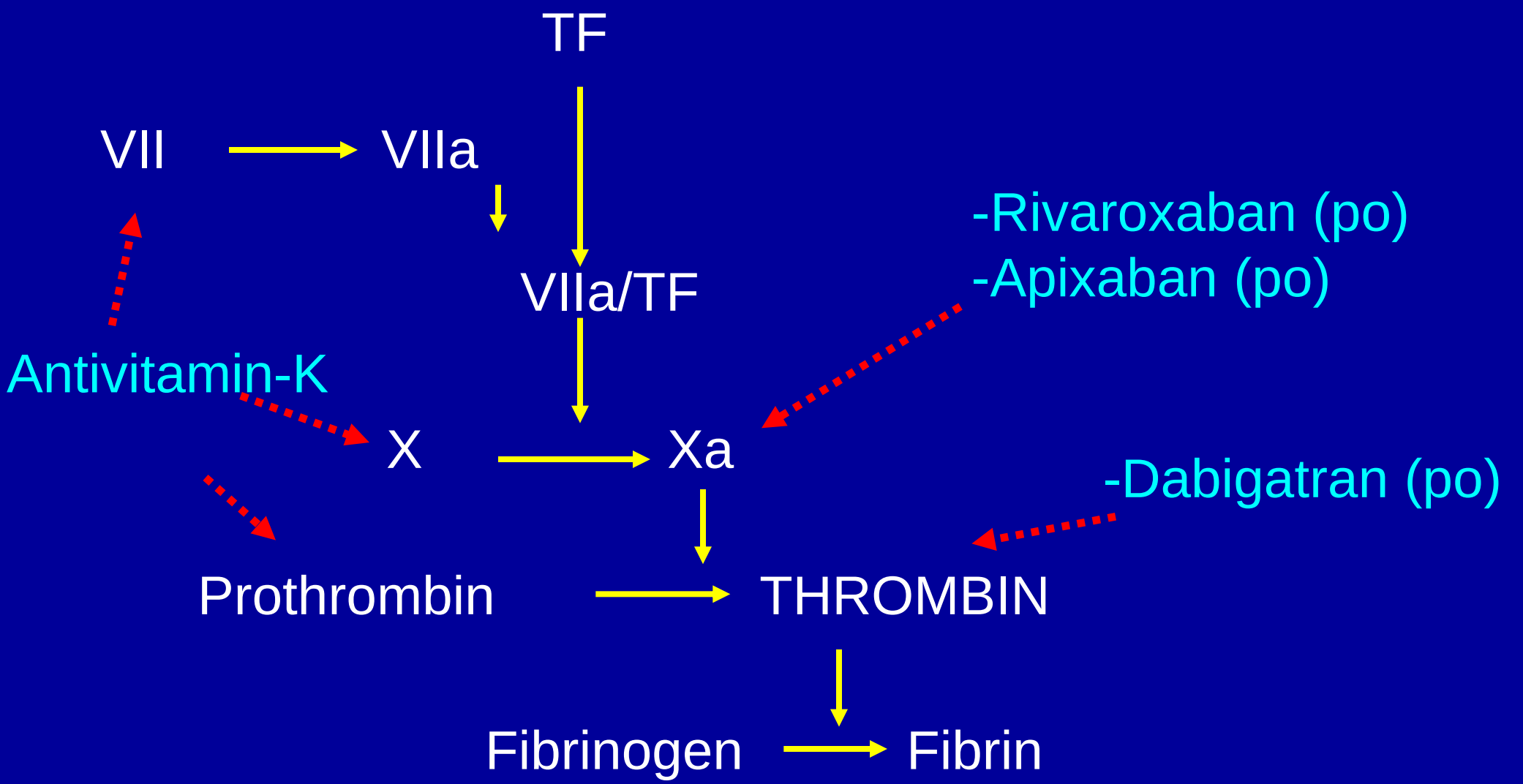
What the clinician needs to know

- Evidence from trials (RE-LY)
- Guidelines
- Practical issues from use in real world

in order to make a decision

- In which patient to prescribe dabigatran instead of VKA

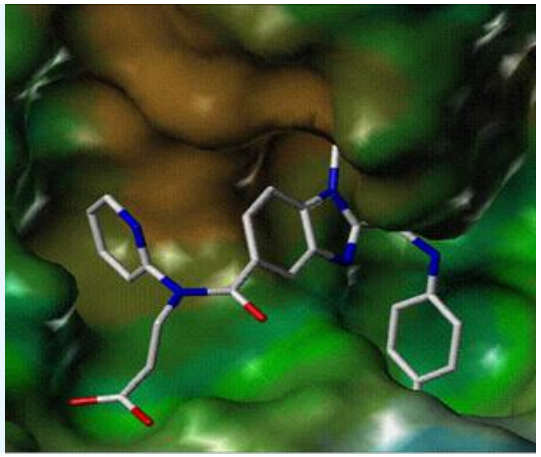
Coagulation cascade: NOVEL ANTICOAGULANT DRUGS



Dabigatran
oral reversible direct thrombin inhibitor

- Stable and predictable anticoagulant effect
- No interactions with food
- Fast onset of action
- 80% renal elimination
- No significant metabolism via cytochrome P450

Dabigatran etexilate

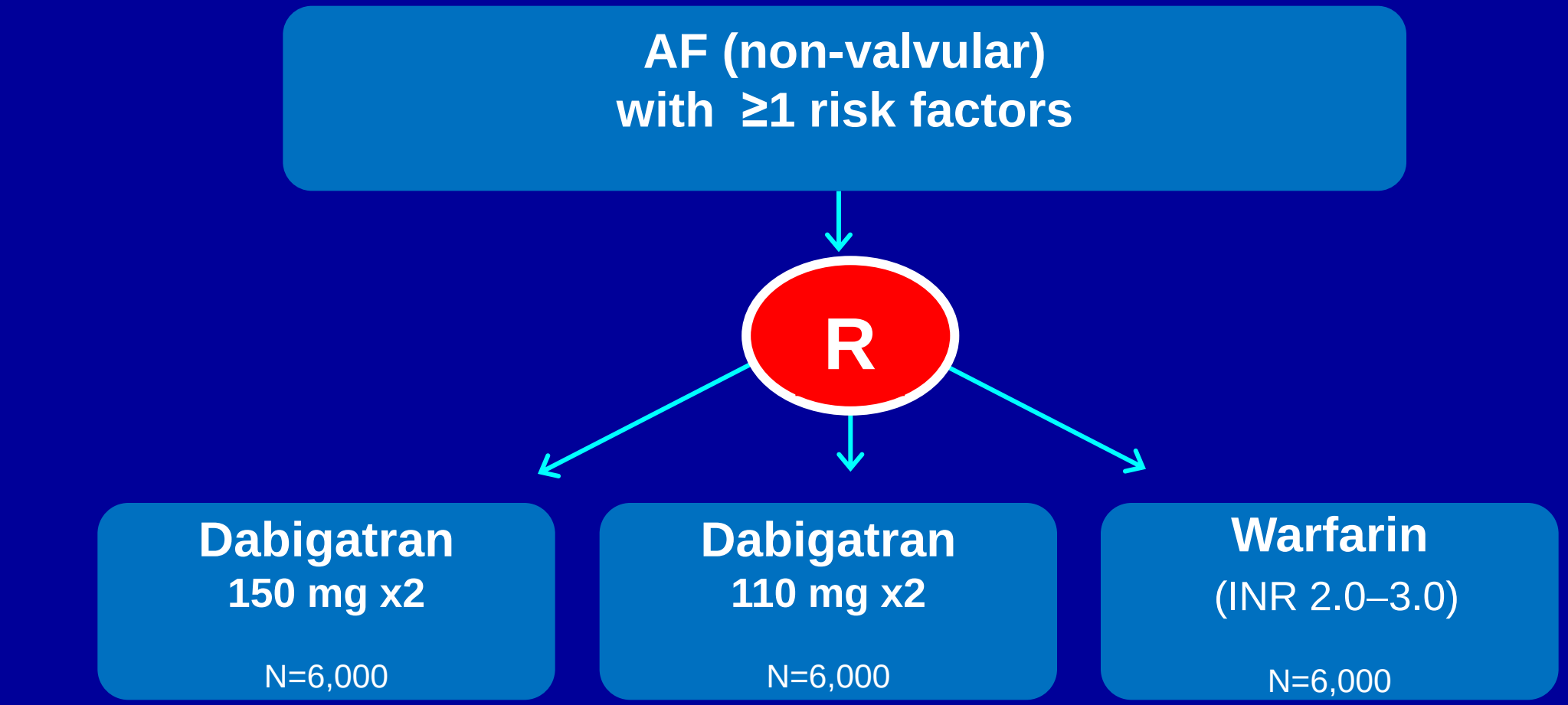


Properties of dabigatran vs VKA

	Dabigatran (Pradaxa)	VKA
Target	Thrombin	IX, VII, X, II
Dose	110 or 150 mg x2	per INR
Onset of action	1.5 hrs	2-4 days
Interactions	few	many
Renal impairment	no if CrCl <30	yes
Laboratory monitoring	no	yes
Antidote	no	yes
Cost	expensive	cheap

RELY®

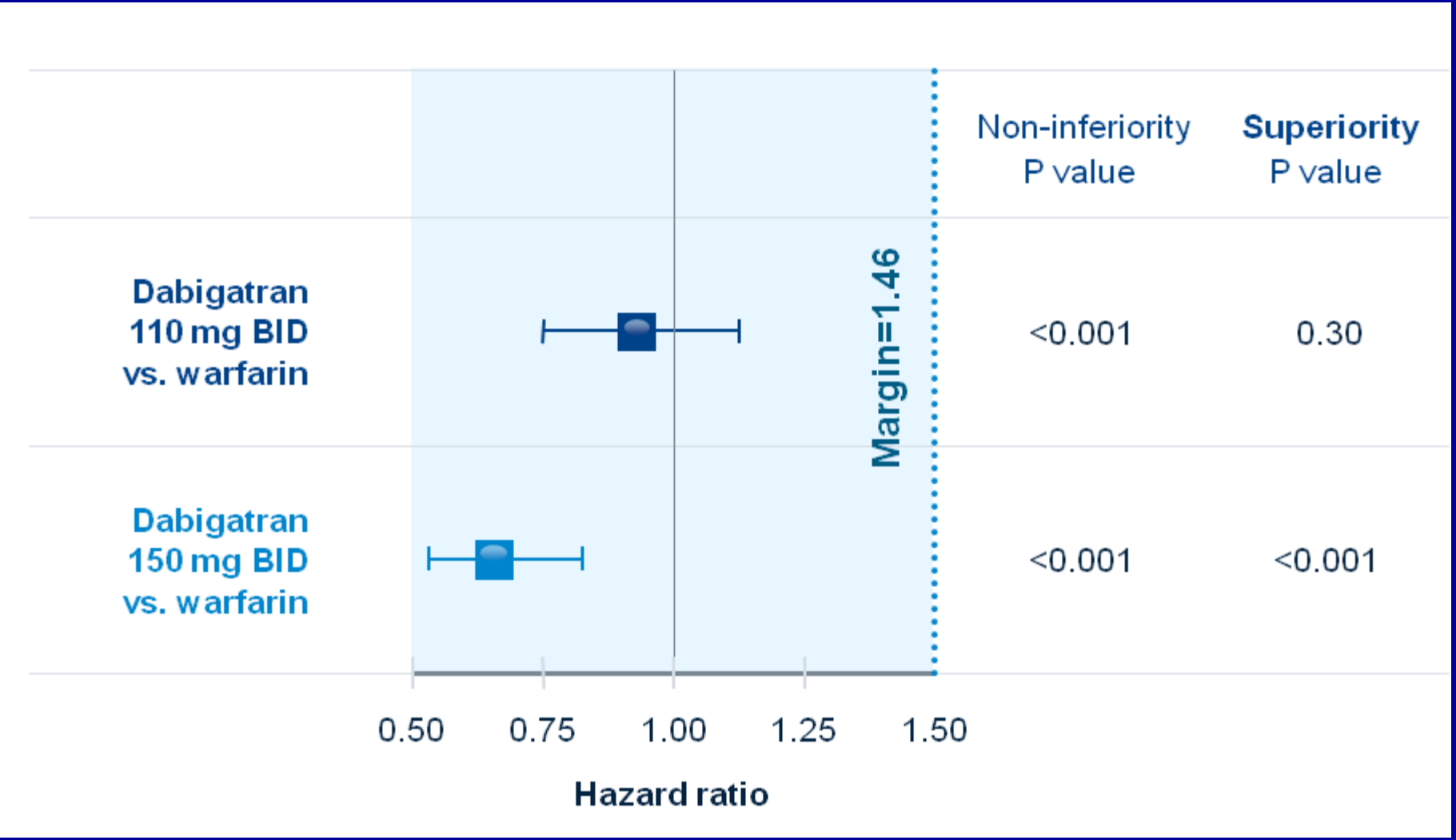
Study of stroke prevention in atrial fibrillation



Non inferiority trial, open label of dabigatran vs warfarin
End point: Stroke and other embolic events; 2 year follow-up

RELY®
Study of stroke prevention in atrial fibrillation

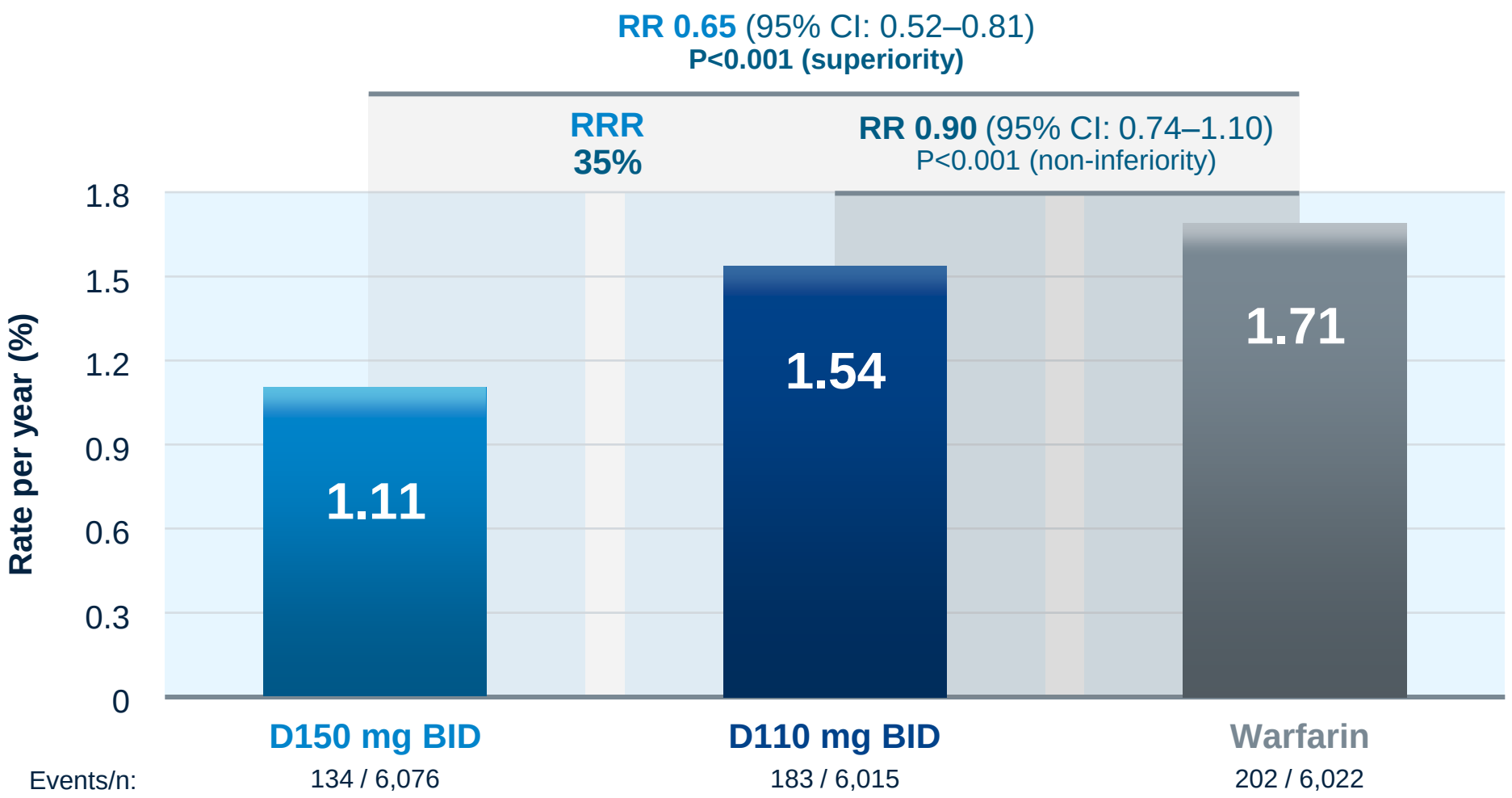
Stroke and systemic embolism



NEJM 2009

RELY®
Study of stroke prevention in atrial fibrillation

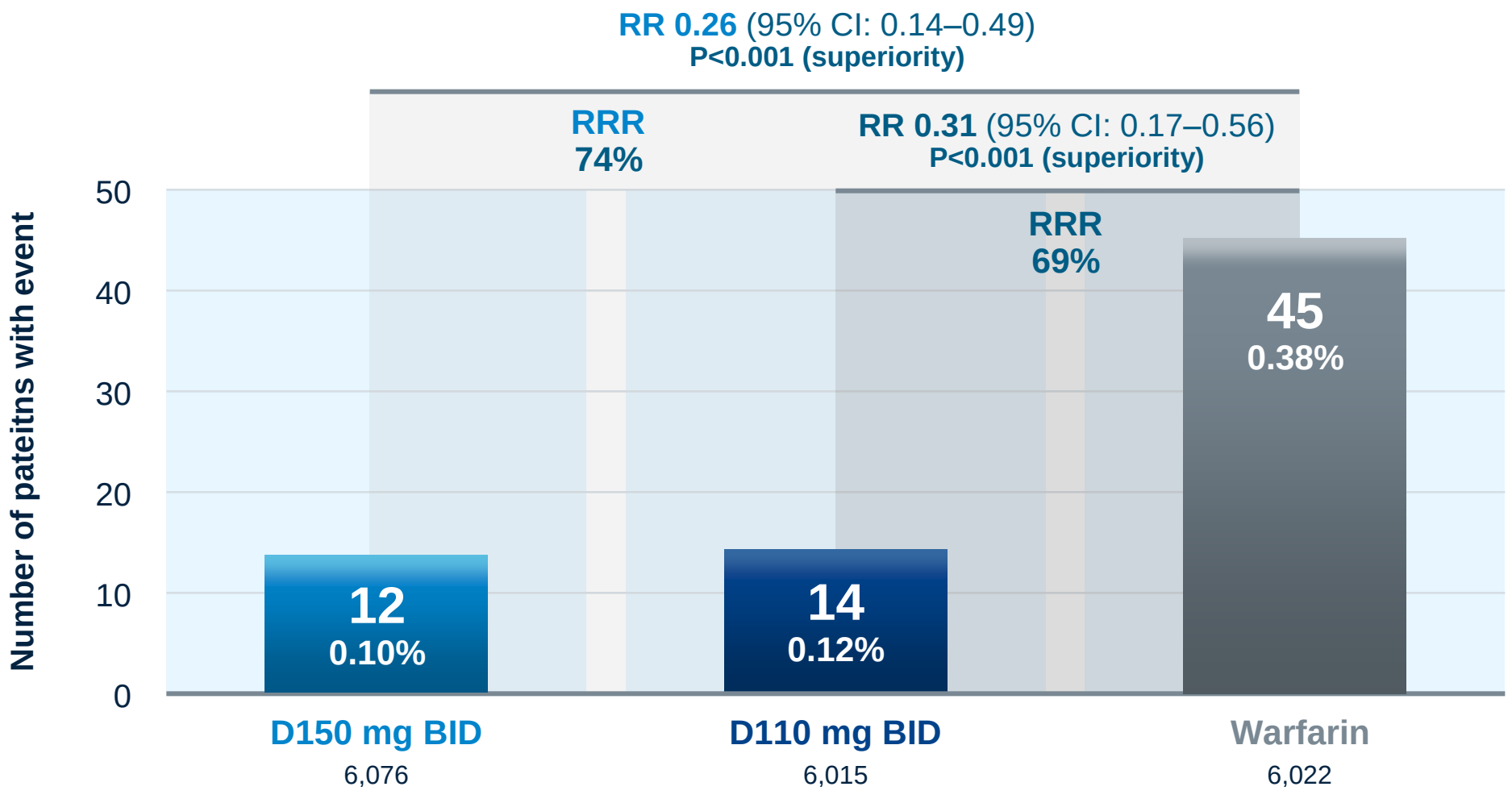
Stroke and systemic embolism



NEJM 2009

RELY®
Study of stroke prevention in atrial fibrillation

Haemorrhagic stroke



NEJM 2009

RELY®
Study of stroke prevention in atrial fibrillation

Major bleeding

Characteristic	Dabigatran 150 mg	Dabigatran 110 mg	Warfarin	P value D150 vs. W	P value D110 vs. W
Number of patients	6,076	6,015	6,022		
Major bleeding rate (% per year)	3.32	2.87	3.57	0.32	0.003
• **Life threatening**	1.49	1.24	1.85	0.03	<0.001
• **Non-life threatening**	2.06	1.83	1.92	0.39	0.65
• **Gastro-intestinal**	1.56	1.15	1.07	0.001	0.52

RELY®
Study of stroke prevention in atrial fibrillation

Other side effects

	Dabigatran 150 mg %	Dabigatran 110 mg %	Warfarin %
Dyspepsia*	11.3	11.8	5.8
Dyspnoea	9.5	9.3	9.7
Dizziness	8.3	8.1	9.4
Peripheral oedema	7.9	7.9	7.8
Fatigue	6.6	6.6	6.2
Cough	5.7	5.7	6.0
Chest pain	6.2	5.2	5.9
Arthralgia	5.5	4.5	5.7
Back pain	5.2	5.3	5.6
Nasopharyngitis	5.4	5.6	5.6
Diarrhoea	6.5	6.3	5.7
Urinary tract infection	4.8	4.5	5.6
Upper respiratory tract infection	4.7	4.8	5.2

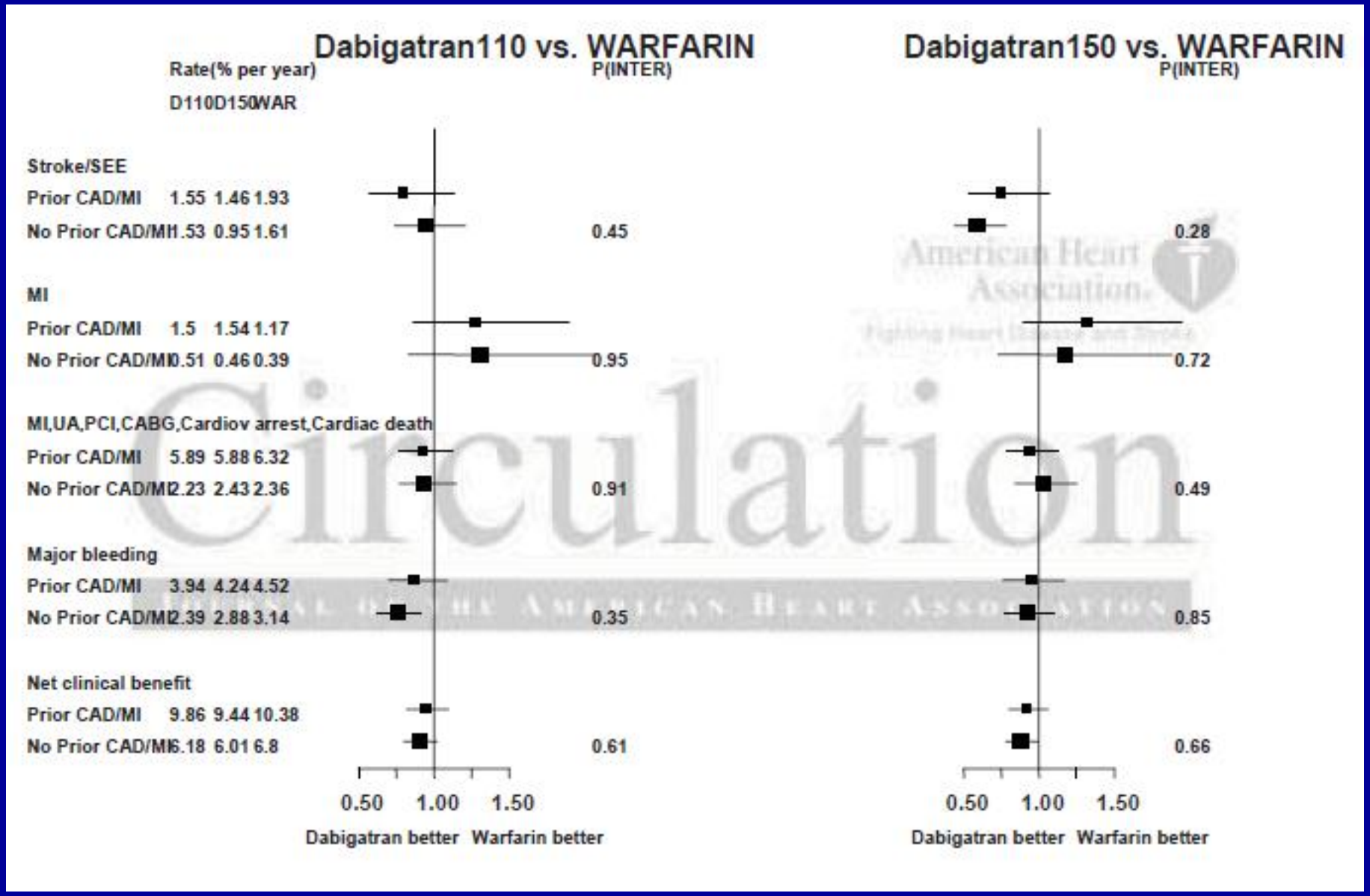
RELY®
Study of stroke prevention in atrial fibrillation

Myocardial infarction

Table 2. Efficacy Outcomes, According to Treatment Group.

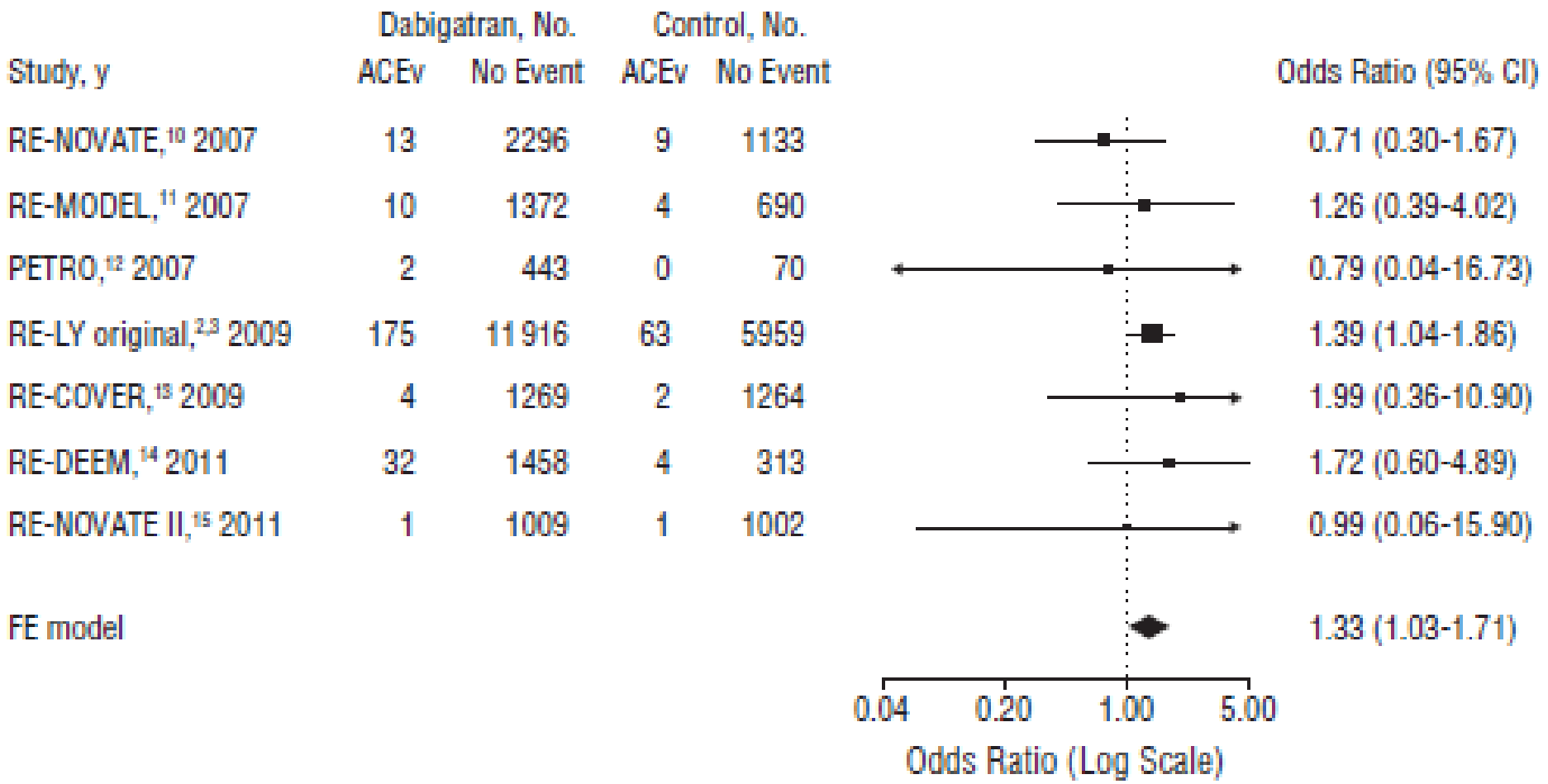
Event	Dabigatran, 110 mg (N=6015)		Dabigatran, 150 mg (N=6076)		Warfarin (N=6022)		Dabigatran, 110 mg, vs. Warfarin		Dabigatran, 150 mg, vs. Warfarin		Dabigatran, 150 mg vs. 110 mg	
							Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
	no. of patients	%/yr	*no. of patients*	%/yr	*no. of patients*	%/yr						
Stroke or systemic embolism*	182	1.53	134	1.11	199	1.69	0.91 (0.74–1.11)	<0.001 for noninferiority, 0.34	0.66 (0.53–0.82)	<0.001 for noninferiority, <0.001	0.73 (0.58–0.91)	0.005
Stroke	171	1.44	122	1.01	185	1.57	0.92 (0.74–1.13)	0.41	0.64 (0.51–0.81)	<0.001	0.70 (0.56–0.89)	0.003
Hemorrhagic	14	0.12	12	0.10	45	0.38	0.31 (0.17–0.56)	<0.001	0.26 (0.14–0.49)	<0.001	0.85 (0.39–1.83)	0.67
Ischemic or unspecified	159	1.34	111	0.92	142	1.20	1.11 (0.89–1.40)	0.35	0.76 (0.60–0.98)	0.03	0.69 (0.54–0.88)	0.002
Nondisabling stroke	60	0.50	44	0.37	69	0.58	0.86 (0.61–1.22)	0.40	0.62 (0.43–0.91)	0.01	0.72 (0.49–1.07)	0.10
Disabling or fatal stroke	112	0.94	80	0.66	118	1.00	0.94 (0.73–1.22)	0.65	0.66 (0.50–0.88)	0.005	0.70 (0.53–0.94)	0.02
Myocardial infarction	86	0.72	89	0.74	63	0.53	1.35 (0.98–1.87)	0.07	1.38 (1.00–1.91)	0.048	1.02 (0.76–1.38)	0.88
Pulmonary embolism	14	0.12	18	0.15	11	0.09	1.26 (0.57–2.78)	0.56	1.61 (0.76–3.42)	0.21	1.27 (0.63–2.56)	0.50
Hospitalization	2311	19.4	2430	20.2	2458	20.8	0.92 (0.87–0.97)	0.003	0.97 (0.92–1.03)	0.34	1.06 (1.00–1.12)	0.04
Death from vascular causes	289	2.43	274	2.28	317	2.69	0.90 (0.77–1.06)	0.21	0.85 (0.72–0.99)	0.04	0.94 (0.79–1.11)	0.44
Death from any cause	446	3.75	438	3.64	487	4.13	0.91 (0.80–1.03)	0.13	0.88 (0.77–1.00)	0.051	0.97 (0.85–1.11)	0.66

RE-LY: MI data



Hohnloser, Circulation 2012

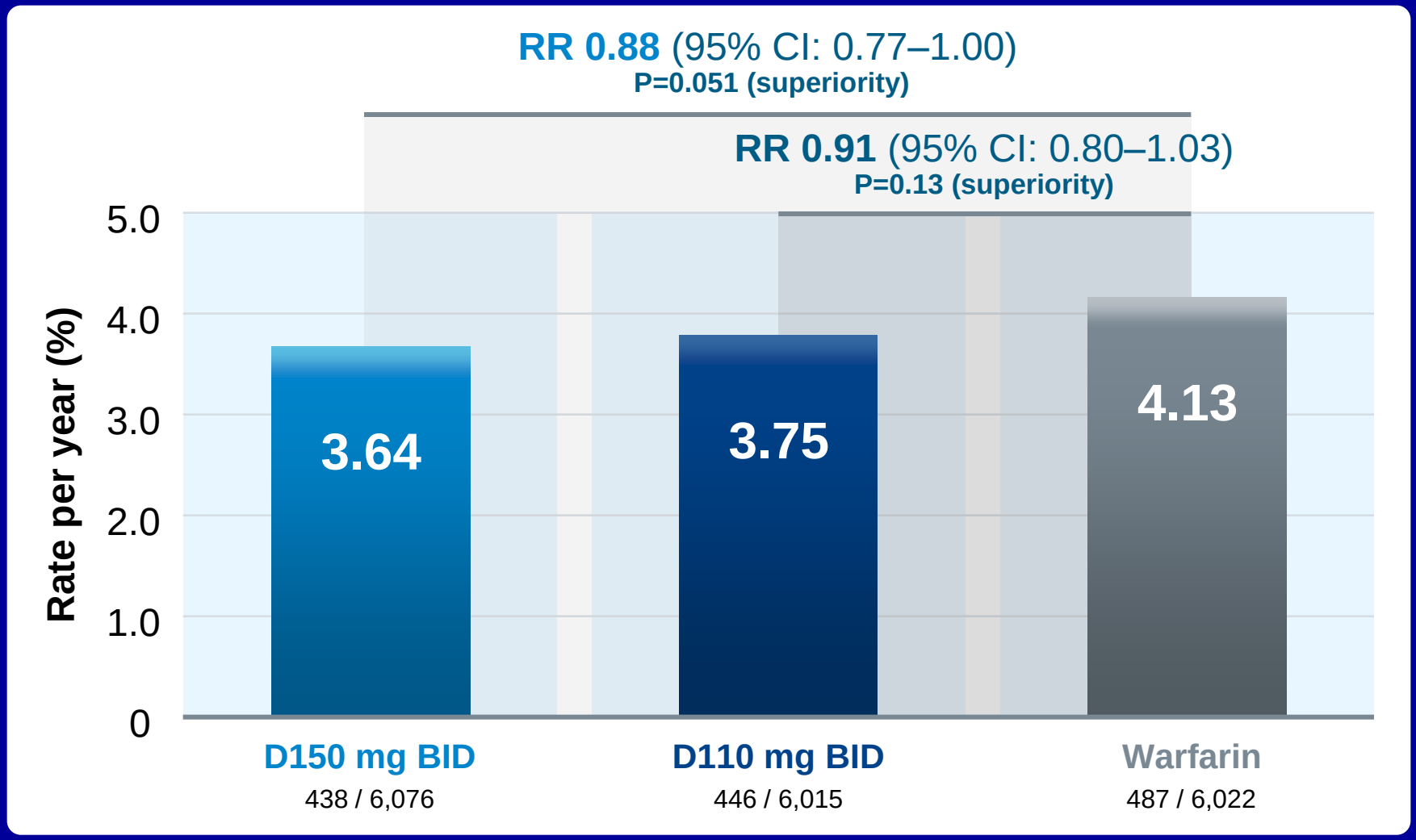
Dabigatran and MI



Uchino, Arch Intern Med 2012

RELY®
Study of stroke prevention in atrial fibrillation

All cause mortality



NEJM 2009

Comparison of dabigatran with Warfarin

In comparison with warfarin	Dabigatran 150 mg x2	Dabigatran 110 mg x2
Ischaemic stroke	less	similar
Haemorrhagic stroke	less	less
Major bleeding	similar	less
GI bleeding	more	similar
Myocardial infarction	more (ns)	similar
CV mortality	reduced	similar

Guidelines

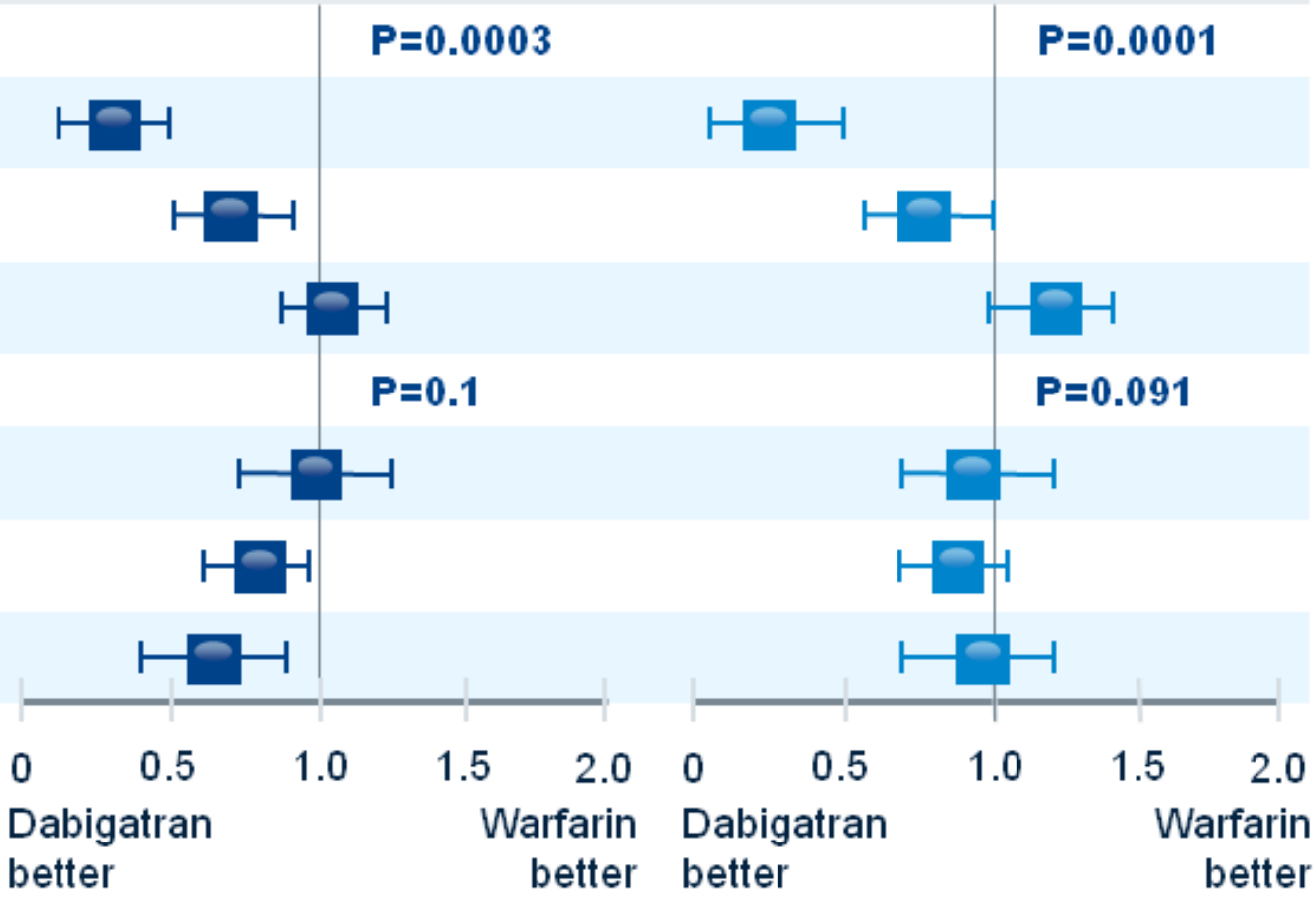
- European Society of Cardiology (Aug 2010)
  - Dabigatran may be considered as an alternative to adjusted dose VKA
- Canadian Cardiovascular Society (Sept 2010)
  - Dabigatran alternative (preferable) to Warfarin
- ACC/AHA/HRS guideline update (Feb 2011)
  - Dabigatran alternative to Warfarin (Class I-B)

Dabigatran in daily practice
Is it an easy drug to use?

- Choice of dose: 110 or 150 mg x2 ?
- Management in case of surgery or bleeding
- Management in case of cardioversion
- Laboratory monitoring

Major bleeding by age and renal function

	Annual rate (%)		
	D 110 mg BID	D 150 mg BID	Warfarin
Age (yrs)			
<65	0.76	0.79	2.32
65–74	2.12	2.45	3.08
≥75	4.21	4.81	4.09
Creatinine clearance (mL/min)			
30–50	5.07	4.85	5.17
51–80	2.62	3.04	3.44
>80	1.36	1.88	2.18



Dose of dabigatran

- Generally recommended dose: 150mg x2.
- 110mg x2 :
  - In pts ≥ 80 year old
  - In pts 75–80 year old with low embolic and high bleeding risk (CHA_2DS_2VASC <2, HAS-BLED >3)
  - In pts taking verapamil and in pts with gastritis, oesophagitis or reflux
- 75 mg x2: Only FDA suggests this dose for pts with severe renal dysfunction (CrCl 15-30 ml/min)
- Contraindicated if CrCl < 30 ml/min

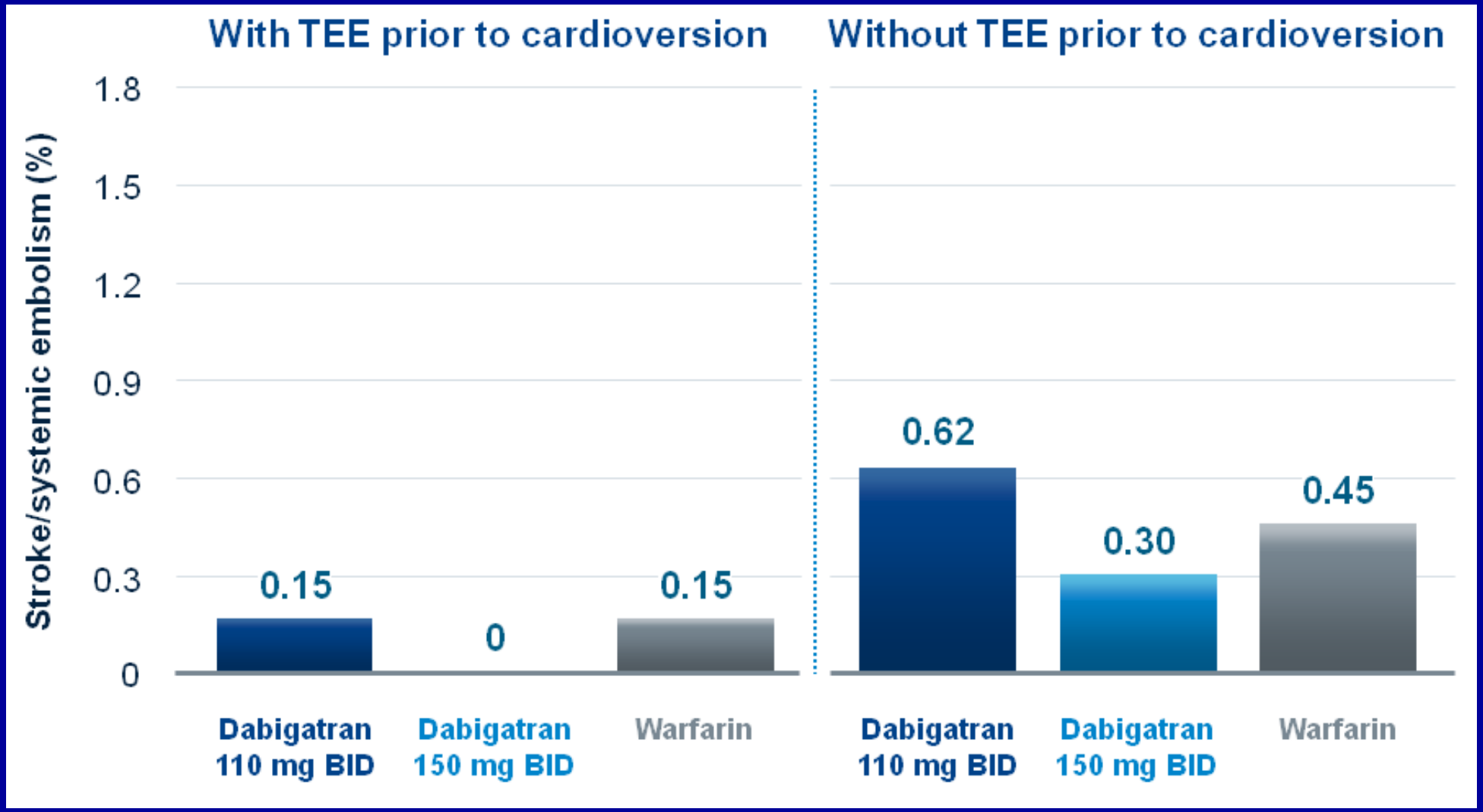
Stopping dabigatran for elective surgery

Renal function (CrCl in ml/min)	T1/2 (hrs)	Stop dabigatran	
		High bleeding risk or major surgery	Usual risk
>80	~ 13	2 days	24 hrs
50-80	~15	2-3 days	1-2 days
30-50	~~18	4 days	2-3 days (>48 hrs)

In case of bleeding

- General measures (like in pts on VKA)
  - FBC, aPTT, X-Match
  - Haemostasis, ensure adequate diuresis, FFP, blood
- Dialysis
- Special haemostatic factors
  - Concentrated prothrombin complex (II, VII, IX, X) dose: 50 IU/kg - “Beriplex” (250 – 500 IU)
  - rFVII (Novoseven) 40-80 µg/kg
  - Monoclonal ab under clinical development

Cardioversion



N=1983 pts

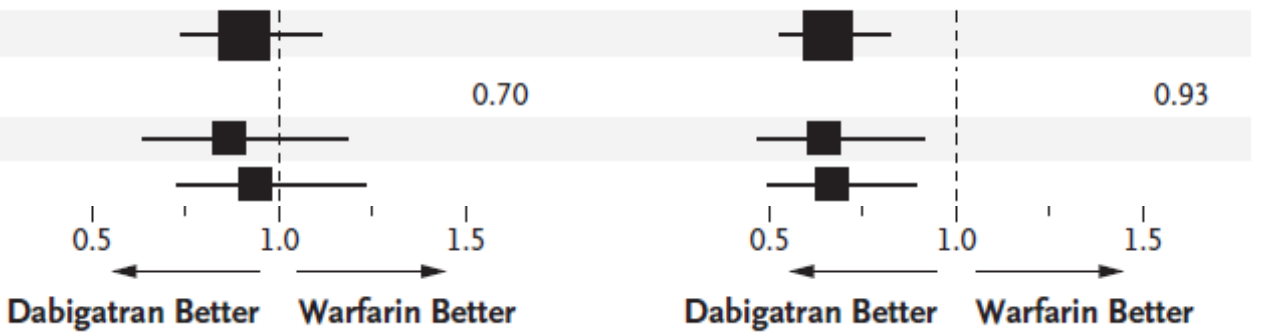
Circulation 2011;123:131–6

Dabigatran and antiplatelet therapy

- Increased haemmorhagic risk
- Few data about DAPT + dabigatran
- In ACS difficult decisions just like in pts on AVK
  - Thrombolysis contraindcated
  - BMS prefferred
  - Low aspirin dose, low INR

Dabigatran and antiplatelet therapy

Subgroup	Patients *total no.*	Dabigatran 110 mg	Dabigatran 150 mg	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
			% *per yr*					
All patients	18,113	1.53	1.11	1.69				
Aspirin use at baseline						0.70		0.93
Yes	7,198	1.66	1.26	1.92				
No	10,910	1.44	1.03	1.53				



Major bleeding

	Dabigatran 110 mg BID	Dabigatran 150 mg BID	Warfarin
Annual rate, %			
No antiplatelets	2.2	2.6	2.8
Plus antiplatelets	3.9	4.4	4.8
HR (95% CI)	1.5 (1.2–1.9)	1.6 (1.3–2.0)	1.7 (1.3–2.0)

Dabigatran and dual antiplatelet therapy
Major bleeding

Subgroup	D110 mg bid, n/N (%)	D150 mg bid, n/N (%)	Warfarin, n/N (%)	D110 mg bid vs. warfarin, RR (95% CI)	D150 mg bid vs. warfarin, RR (95% CI)
Aspirin + clopidogrel	29/335 (4.72%)	30/328 (4.66%)	33/339 (5.21%)	0.77 (0.50 to 1.21)	0.81 (0.52 to 1.26)
No aspirin + clopidogrel	313/5677 (2.77%)	369/5747 (3.24%)	388/5681 (3.48%)	0.81 (0.61-0.94)	0.95 (0.82 to 1.10)
P interaction				**0.8727**	**0.5167**

D, dabigatran; CI, confidence interval; RR, relative risk

Circulation 2011; 123: 2363-2372

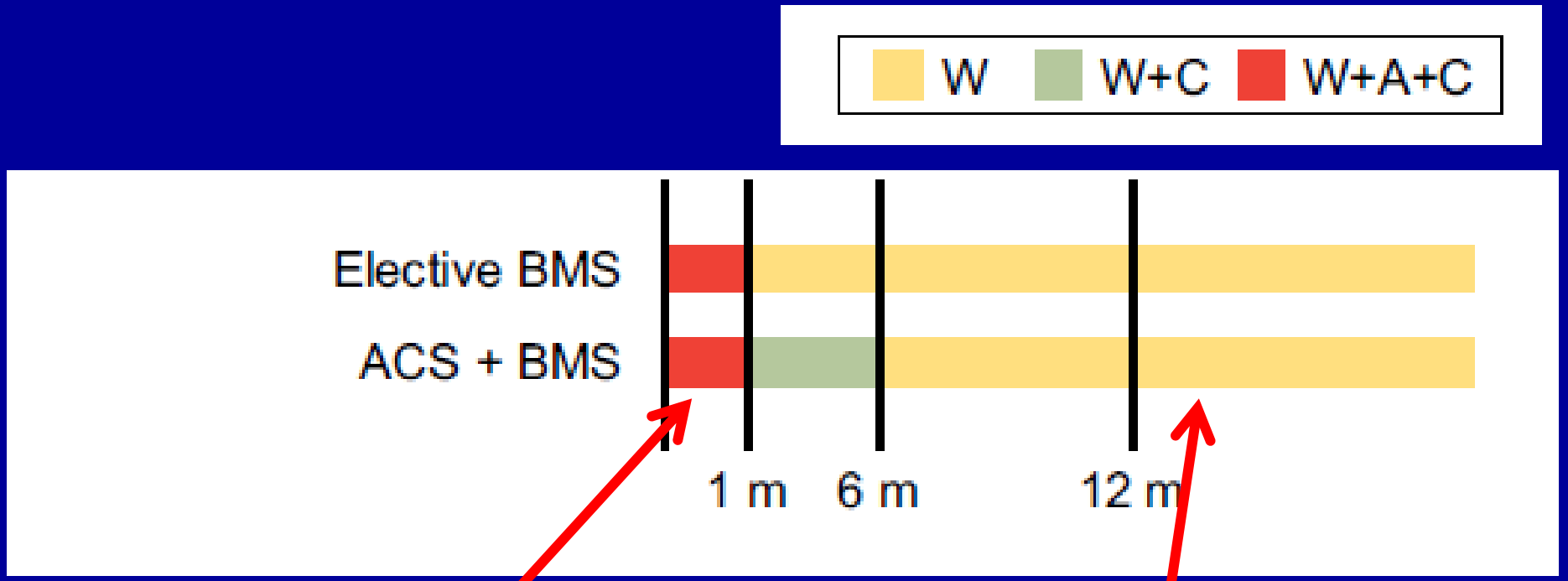
Hellenic J Cardiol 2010; 51: 330-337

Review Article

Triple Antithrombotic Therapy with Aspirin, a Thienopyridine Derivative Plus Oral Anticoagulation in Patients with Atrial Fibrillation Undergoing Coronary Stenting

Athanasios Pipilis[1], George Lazaros[2], Georgios Tsakonas[1], Christodoulos Stefanadis[2]

[1]First Cardiology Department, "Hygeia" Diagnostic and Therapeutic Centre of Athens,
[2]1st Cardiology Department, Athens Medical School, Hippokration Hospital, Athens, Greece

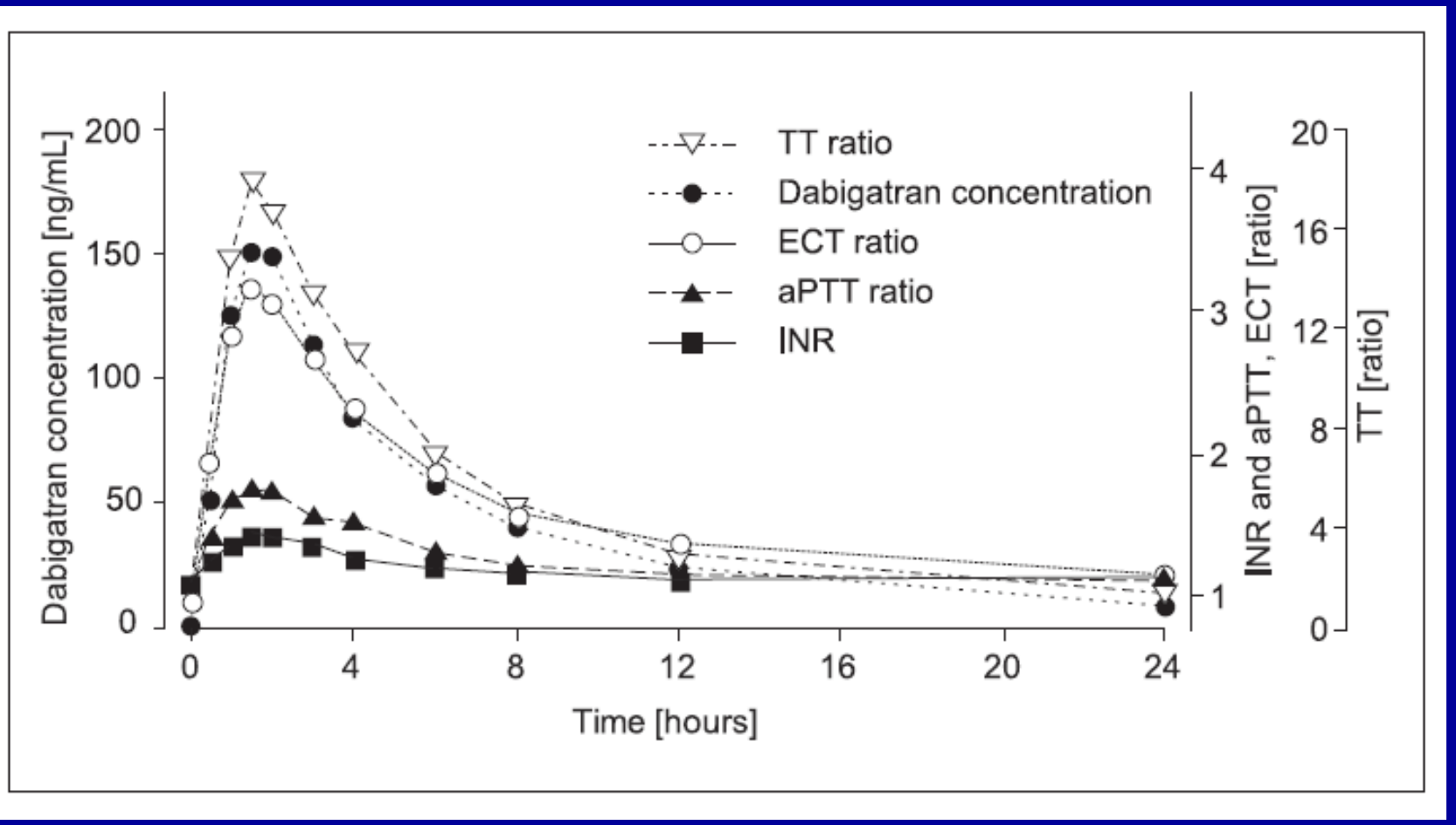


1st month.: DAPT+ AVK or DAPT + dabigatran 110 (?) mg x2

Longterm: Only AVK or (?) dabigatran 110 mg x2 + ASA

Dabigatran coagulation laboratory measurements

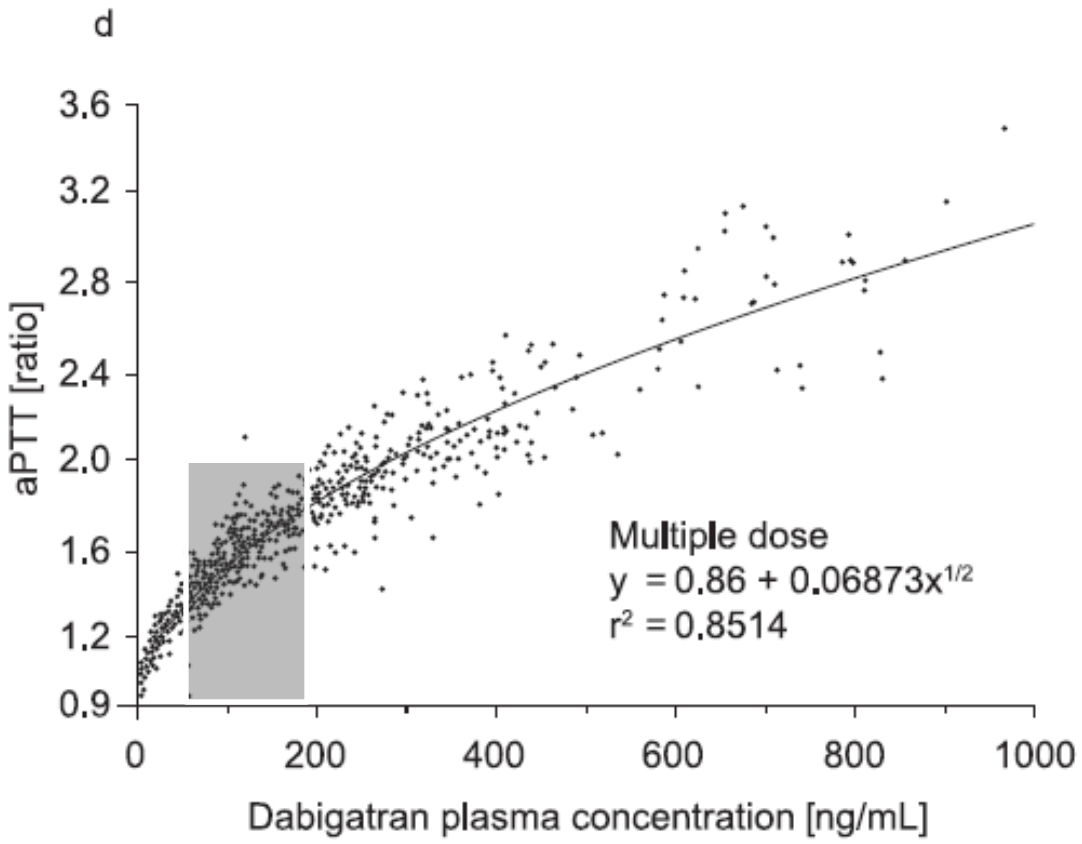
- Not necessary
- May be useful in case of bleeding or surgery

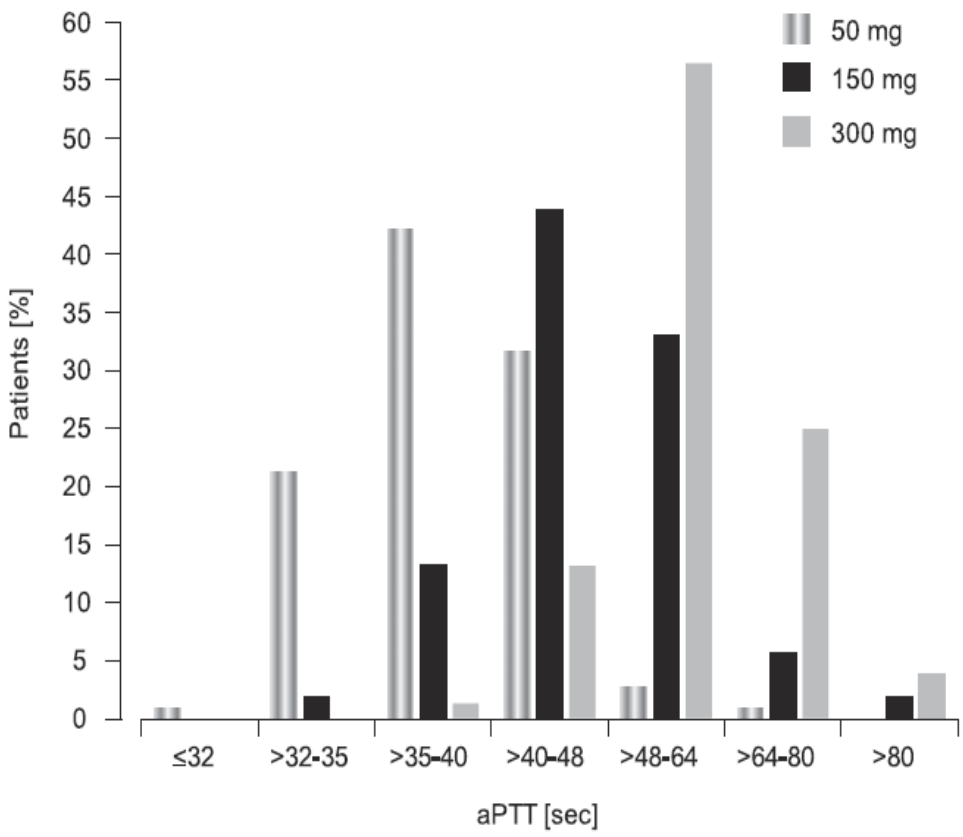


Van Ryn, Thromb Haemost 2010

Dabigatran and aPTT

- Value > 80 sec 12 hr after last dosen (trough level) indicates increased activity and risk of bleeding





Van Ryn, Thromb Haemost 2010

Dabigatran vs AVK

In comparison with warfarin	Dabigatran 150 mg x2	Dabigatran 110 mg x2
Ischaemic stroke	less	similar
Haemorrhagic stroke	less	less
Major bleeding	similar	less
Total events	less	similar

Do pts on AVK with good INR control benefit from switching to dabigatran?

Stroke and embolism according to INR control

	Dabigatran 110 mg	Dabigatran 150 mg	Warfarin	Dabigatran 110 mg vs. warfarin		Dabigatran 150 mg vs. warfarin	
cTTR	Rate per 100-person yrs	Rate per 100-person yrs	Rate per 100-person yrs	HR (95% CI)	P value (interaction)	HR (95% CI)	P value (interaction)
<57.1%	1.91	1.10	1.92	1.00 (0.68–1.45)	-	0.57 (0.37–0.88)	-
57.1–65.5%	1.67	1.04	2.06	0.81 (0.56–1.17)	-	0.50 (0.33-0.77)	-
65.5–72.6%	1.34	1.04	1.51	0.89 (0.58–1.36)	-	0.69 (0.44–1.09)	-
>72.6%	1.23	1.27	1.34	0.92 (0.59–1.45)	0.89	0.95 (0.61–1.48)	0.20

Lancet 2010

Total events* according to INR control

	Dabigatran 110 mg	Dabigatran 150 mg	Warfarin	Dabigatran 110 mg vs. warfarin		Dabigatran 150 mg vs. warfarin	
cTTR	Rate per 100-person yrs	Rate per 100-person yrs	Rate per 100-person yrs	HR (95% CI)	P value (interaction)	HR (95% CI)	P value (interaction)
<57.1%	7.65	6.83	10.13	0.74 (0.62–0.89)	-	0.67 (0.56–0.80)	-
57.1–65.5%	7.84	7.09	8.03	0.97 (0.81–1.16)	-	0.87 (0.73–1.05)	-
65.5–72.6%	6.88	7.41	7.13	0.97 (0.80–1.17)	-	1.05 (0.87–1.27)	-
>72.6%	6.85	7.07	6.42	1.07 (0.87–1.30)	0.036	1.11 (0.91–1.35)	0.0006

* (stroke, embolism, MI, PE, Bleeding, Death)

Lancet 2010

Which pts should not receive dabigatran

1. Pts who cannot afford it!
2. Pts with advanced renal failure (CrCl < 30 ml/min)

Which pts might not receive dabigatran

1. Pts who are already on AVK and have excelent INR control

   especially if

2. They have rather low embolic risk ($CHADS_2$ <2) and relatively low bleeding risk (HASBLED <3)

Which pts should rather receive dabigatran

1. Pts with high embolic risk (choice:150 mg)

2. Pts with high haemorrhagic risk (choice: 110 mg)

Which pts should receive dabigatran

1. Pts already on AVK and difficult INR control
2. Pts with embolic event while on AVK (choice: 150 mg) or haemorrhage while on AVK (choice:110 mg)
3. Pts on other drugs and possible interactions with AVK
4. Pts with an indication for AVK and receive (“wrongly”) antiplatelet therapy

NICE (October 2011)

1. Dabigatran recommended as an option
2. Decision to start should be made after an informed discussion about risk/benefit compared to W
3. D 150 mg clinically more effective than W, D 110 mg non-inferior to W
4. Cost within the range normally considered a cost-effective use of NHS resources
5. Evidence for stratifying by INR control is insufficient to exclude the minority of pts with very good INR control from considering D as a potential treatment option