

NOVEL ORAL ANTICOAGULANTS

Jeffrey I. Weitz, MD, FRCP(C), FACP

**Professor of Medicine and Biochemistry
McMaster University
Canada Research Chair in Thrombosis
Heart & Stroke Foundation/ J.F. Mustard
Chair
in Cardiovascular Research**

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Overview

Limitations of warfarin

New oral anticoagulants

Role of new agents

Limitations of Warfarin

Limitation

Consequence

Slow onset of action

Overlap with a parenteral anticoagulant

Genetic variation in metabolism

Variable dose requirements

Multiple food and drug interactions

Frequent coagulation monitoring

Narrow therapeutic index

Frequent coagulation monitoring

New Oral Anticoagulants

**Direct inhibitors of factor Xa or
thrombin**

Comparison of the Features of New Oral Anticoagulants in Advanced Stages of Development

Features	Rivaroxaban	Apixaban	Dabigatran Etexilate
Target	Xa	Xa	Ila
Molecular weight	436	460	628
Prodrug	No	No	Yes
Bioavailability (%)	80	50	6
Time to peak (h)	3	3	2
Half-life (h)	9	9-14	12-17
Renal excretion (%)	65	25	80

Comparison of Features of New Anticoagulants With Those of Warfarin

Features	Warfarin	New Agents
Onset	Slow	Rapid
Dosing	Variable	Fixed
Food effect	Yes	No
Drug interactions	Many	Few
Monitoring	Yes	No
Half-life	Long	Short
Antidote	Yes	No

**How Do The New Oral
Anticoagulants Compare with
Warfarin?**

RE-LY: A Non-inferiority Trial

Atrial fibrillation with ≥ 1 Risk Factor
Absence of contra-indications
951 centers in 44 countries

Blinded Event Adjudication

R

Open

Blinded

Warfarin
Adjusted
INR 2.0 – 3.0
N=6000

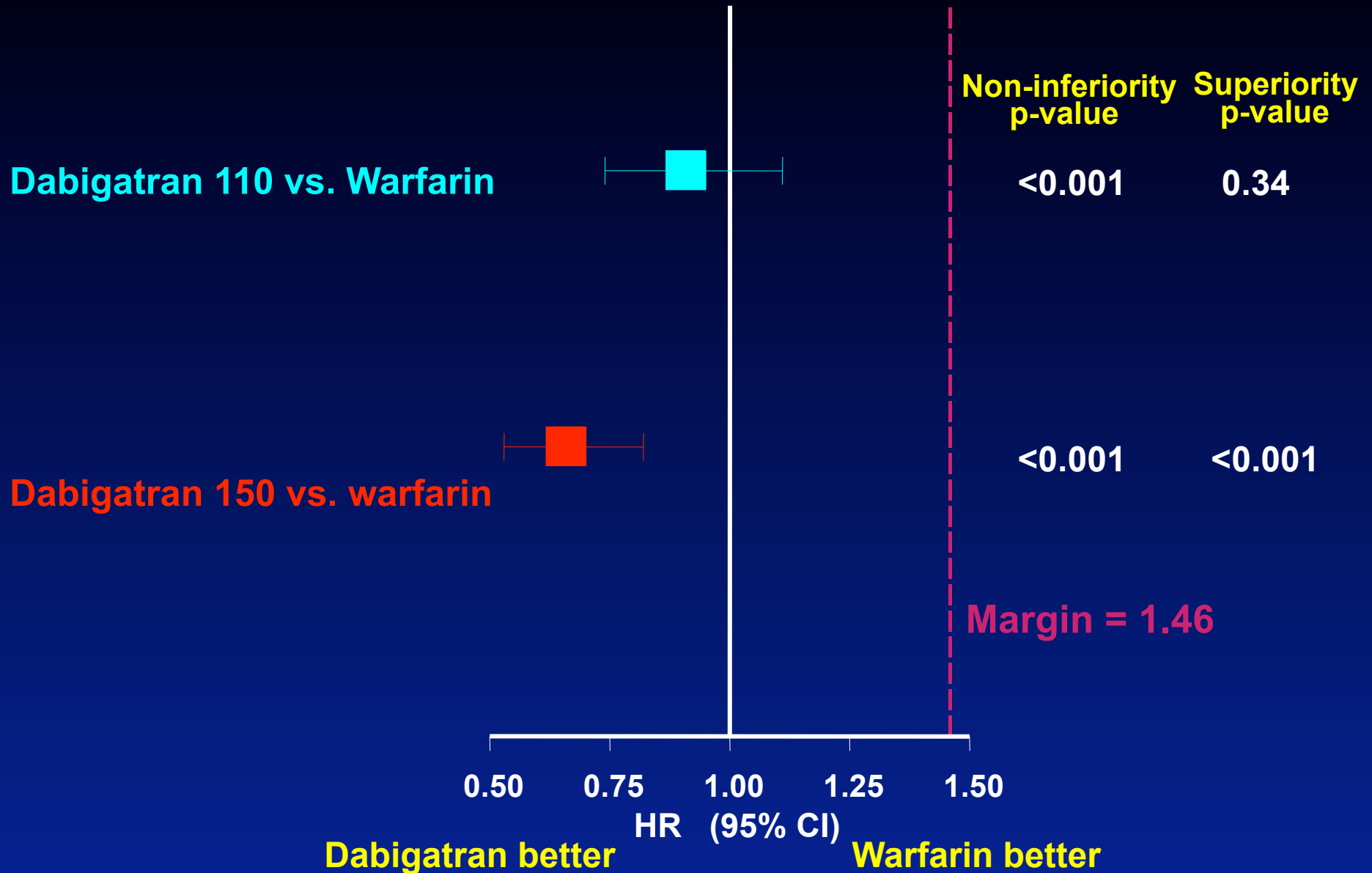
Dabigatran
etexilate 110 mg
BID
N=6000

Dabigatran
etexilate 150 mg
BID
N=6000

Baseline Characteristics

Characteristic	Dabigatran 110 mg	Dabigatran 150 mg	Warfarin
Randomized	6015	6076	6022
Mean age (years)	71.4	71.5	71.6
Male (%)	64.3	63.2	63.3
CHADS2 score (mean)	2.1	2.2	2.1
0-1 (%)	32.6	32.2	30.9
2 (%)	34.7	35.2	37.0
3+ (%)	32.7	32.6	32.1
Prior stroke/TIA (%)	19.9	20.3	19.8
Prior MI (%)	16.8	16.9	16.1
CHF (%)	32.2	31.8	31.9
Baseline ASA (%)	40.0	38.7	40.6
Warfarin Naïve (%)	49.9	49.8	51.4

Stroke or Systemic Embolism



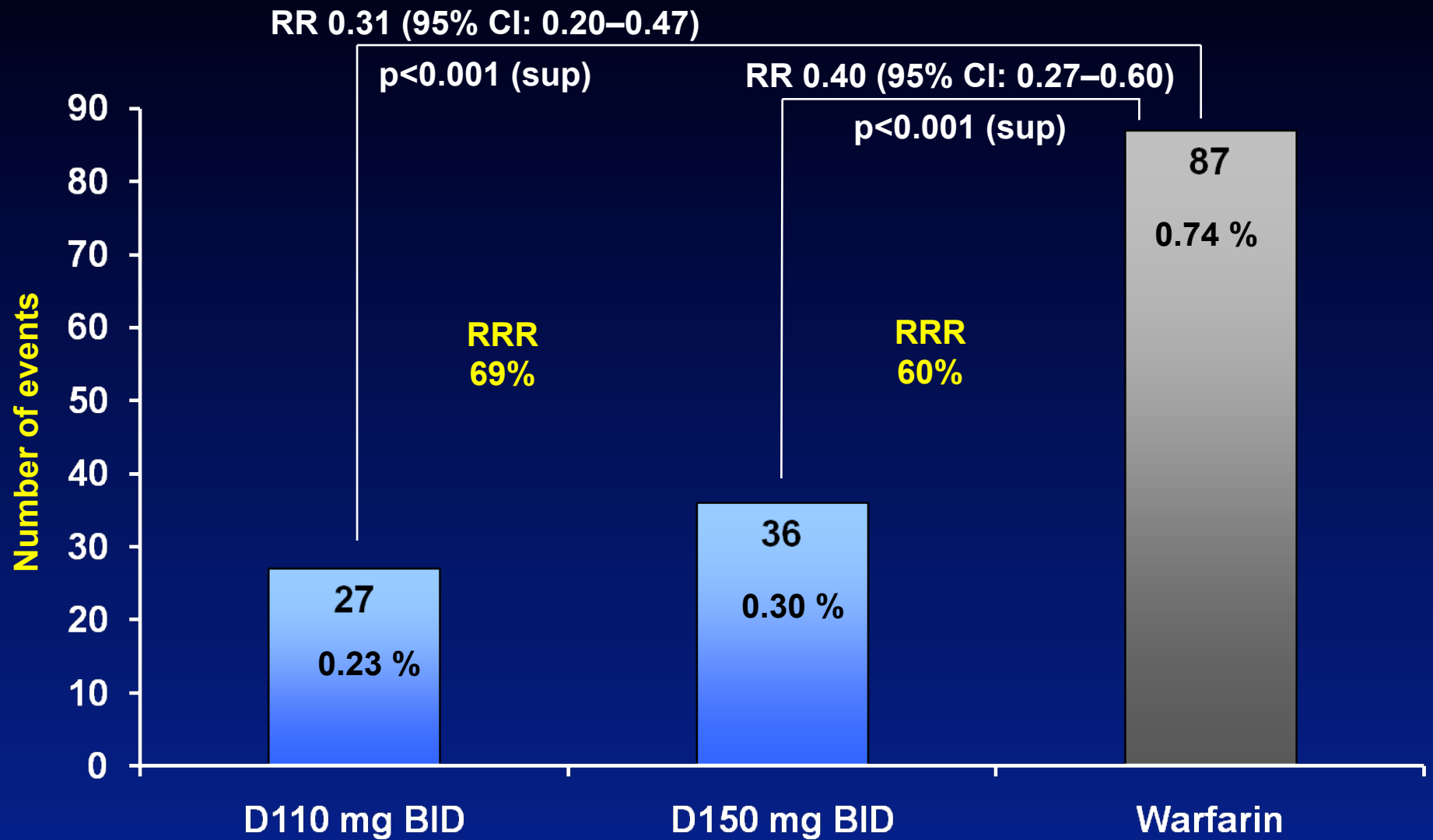
Connolly et al., *NEJM*, 2009

Annual Rates of Bleeding

	D 110mg	D 150mg	warfarin	D 110mg vs. warfarin		D 150mg vs. warfarin	
n	6015	6078	6022	RR 95% CI	p	RR 95% CI	p
Total	14.6%	16.4%	18.2%	0.78 0.74-0.83	<0.001	0.91 0.86-0.97	0.002
Major	2.7 %	3.1 %	3.4 %	0.80 0.69-0.93	0.003	0.93 0.81-1.07	0.31
Life- Threatening	1.2 %	1.5 %	1.8 %	0.68 0.55-0.83	<0.001	0.81 0.66-0.99	0.04
Gastro- intestinal	1.1 %	1.5 %	1.0 %	1.10 0.86-1.41	0.43	1.50 1.19-1.89	<0.001

Connolly et al., *NEJM*, 2009

Intracranial Bleeding Rates



How can dabigatran be more effective than warfarin yet cause less bleeding?

Targeted inhibition of thrombin

Consistent and predictable anticoagulant effect

Secondary Efficacy Outcomes According to Treatment Group

Event	Dabigatran 110 mg	Dabigatran 150 mg	Warfarin
		%	
Myocardial infarction	0.7	0.7	0.5
Vascular death	2.4	2.3	2.7
All-cause mortality	3.8	3.6	4.1

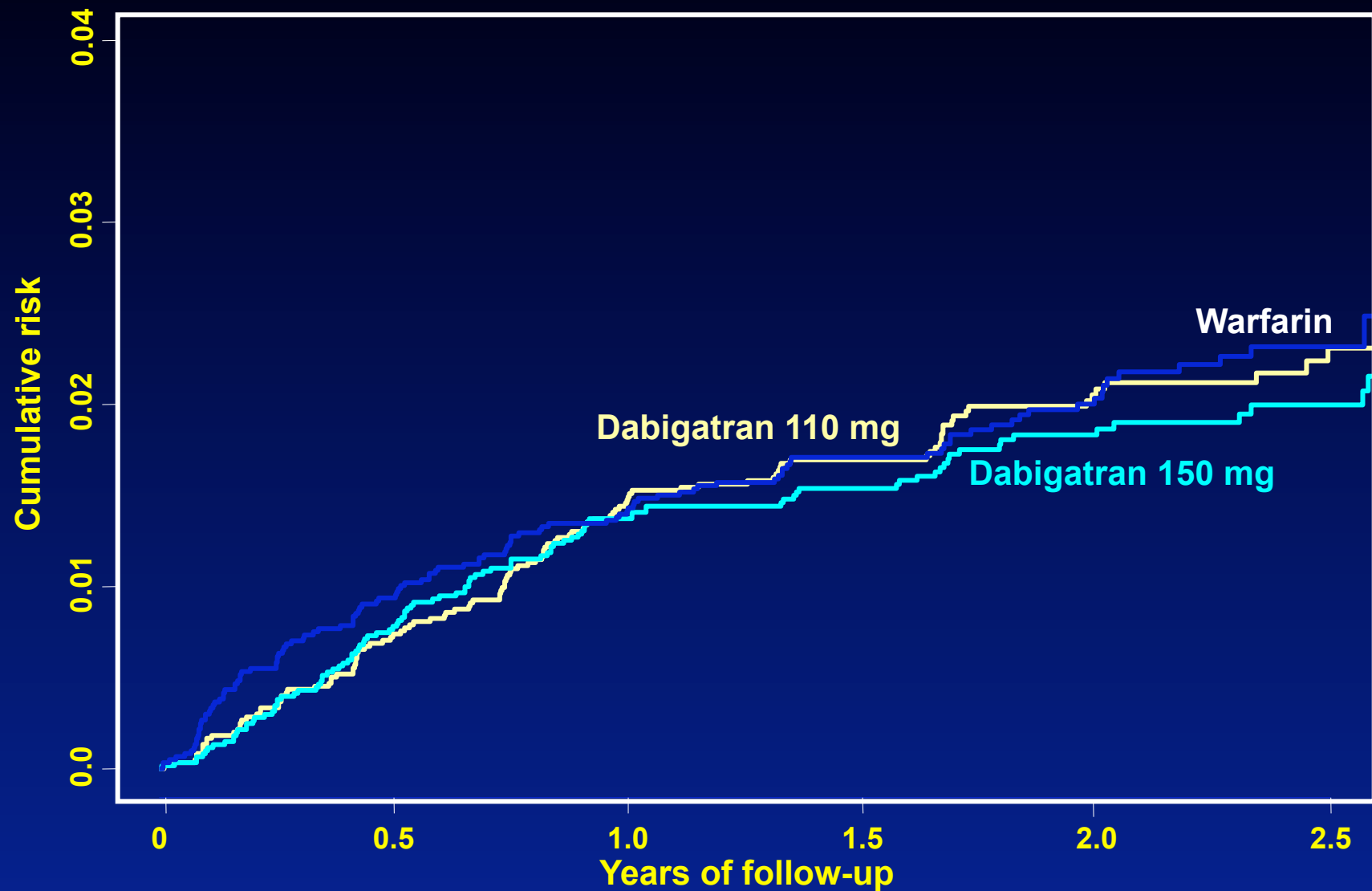
Why is there more MI with dabigatran?

Chance finding?

Warfarin superior to dabigatran for inhibition of clotting at sites of plaque disruption?

Other factors?

Cumulative risk of ALT or AST >3x ULN after randomization

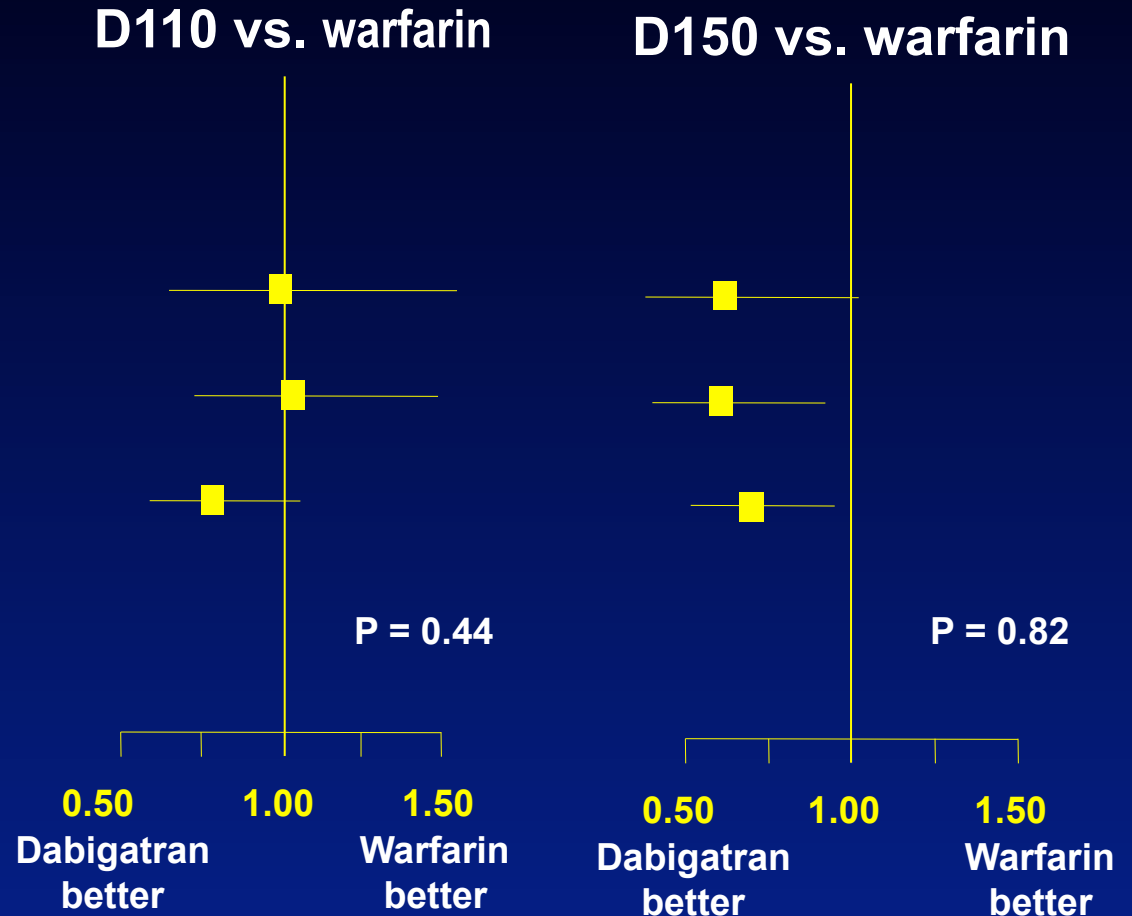


Connolly et al., *NEJM*, 2009

**Which dabigatran dose for
which patient?**

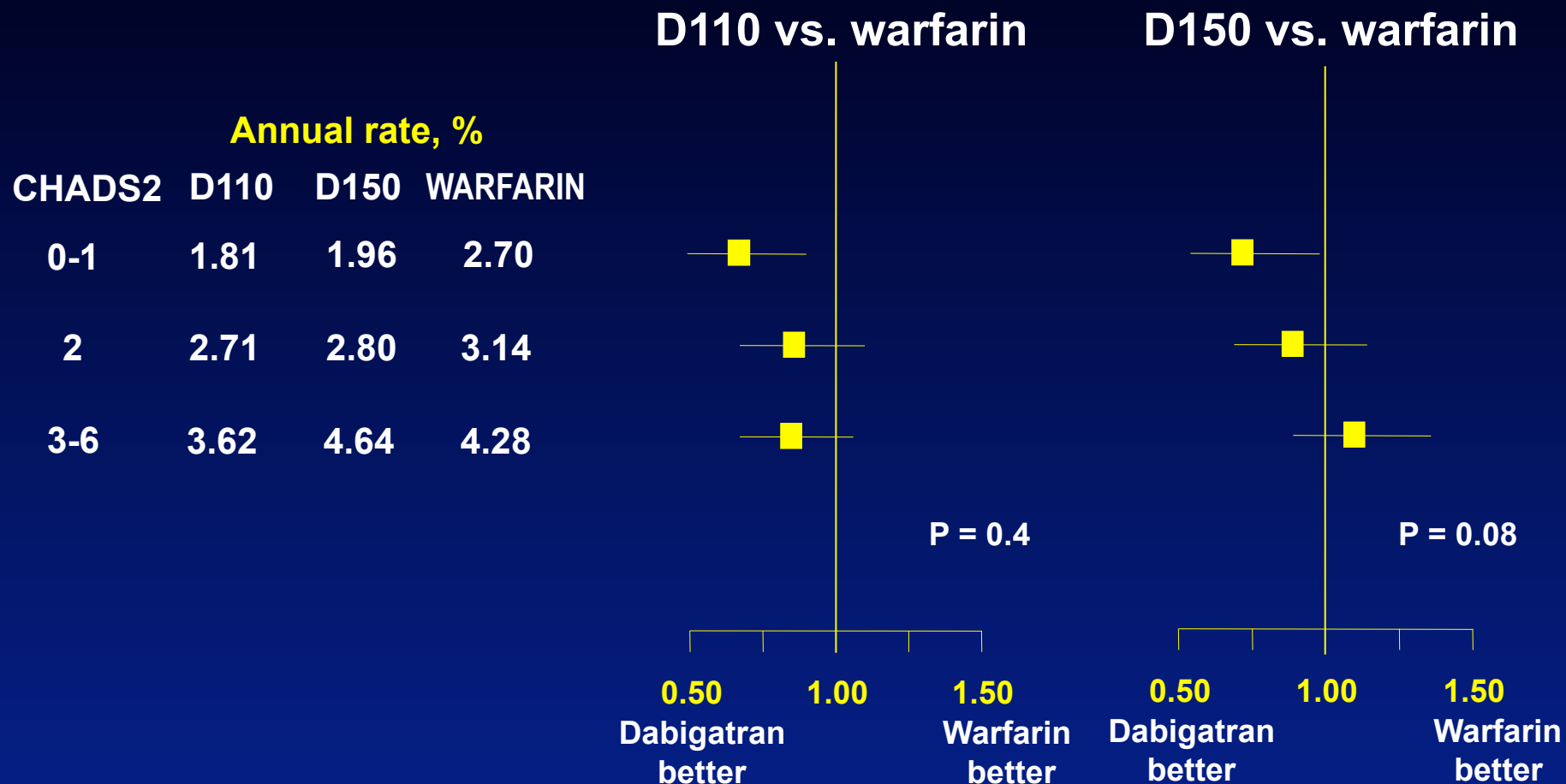
Stroke and systemic embolism

CHADS2	Annual rate, %		
	D110	D150	WARFARIN
0-1	1.06	0.65	1.05
2	1.43	0.84	1.38
3-6	2.12	1.88	2.68

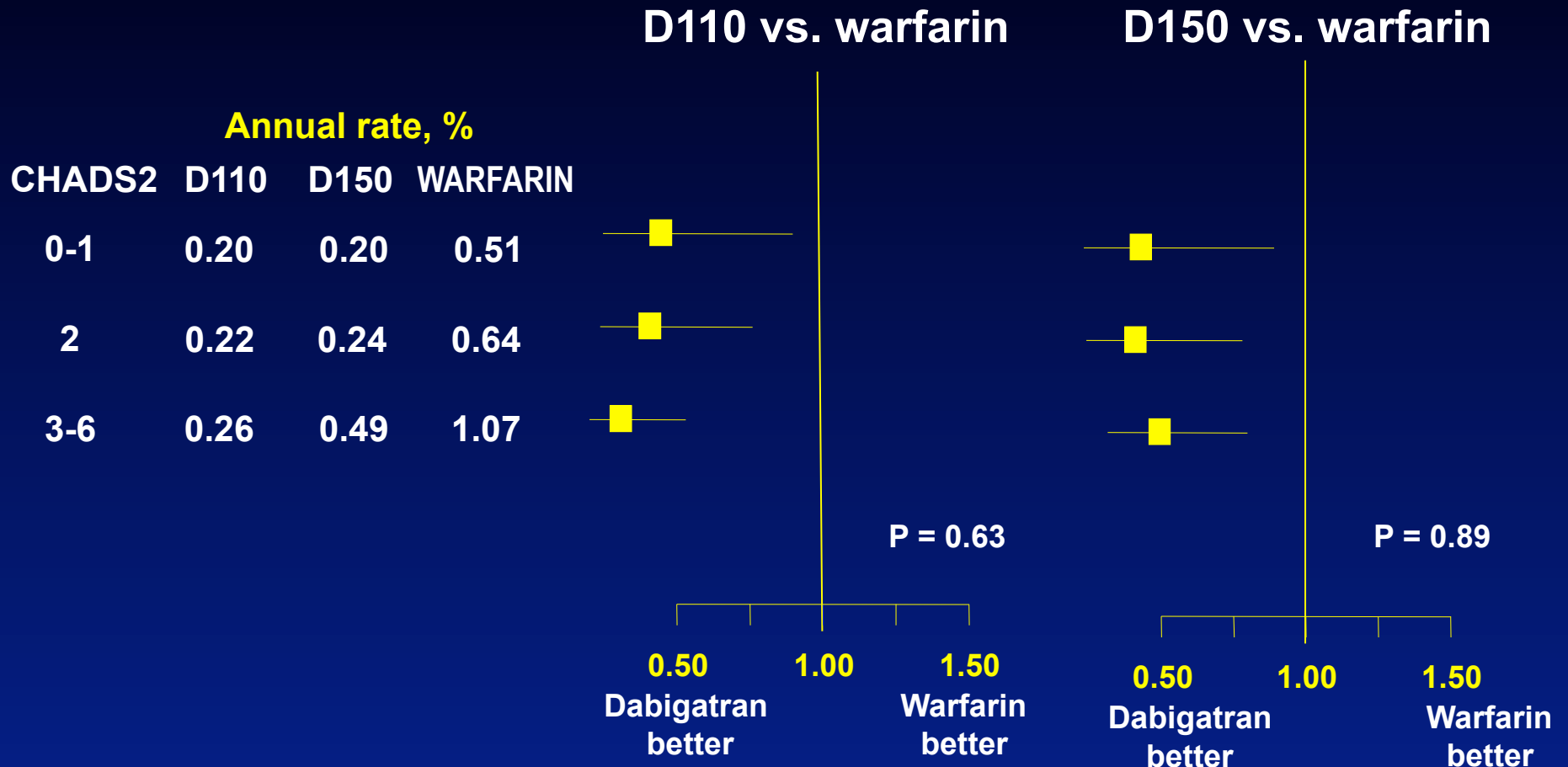


Oldgren et al., *JACC*, 2010

Major bleeding



Intracranial bleeding

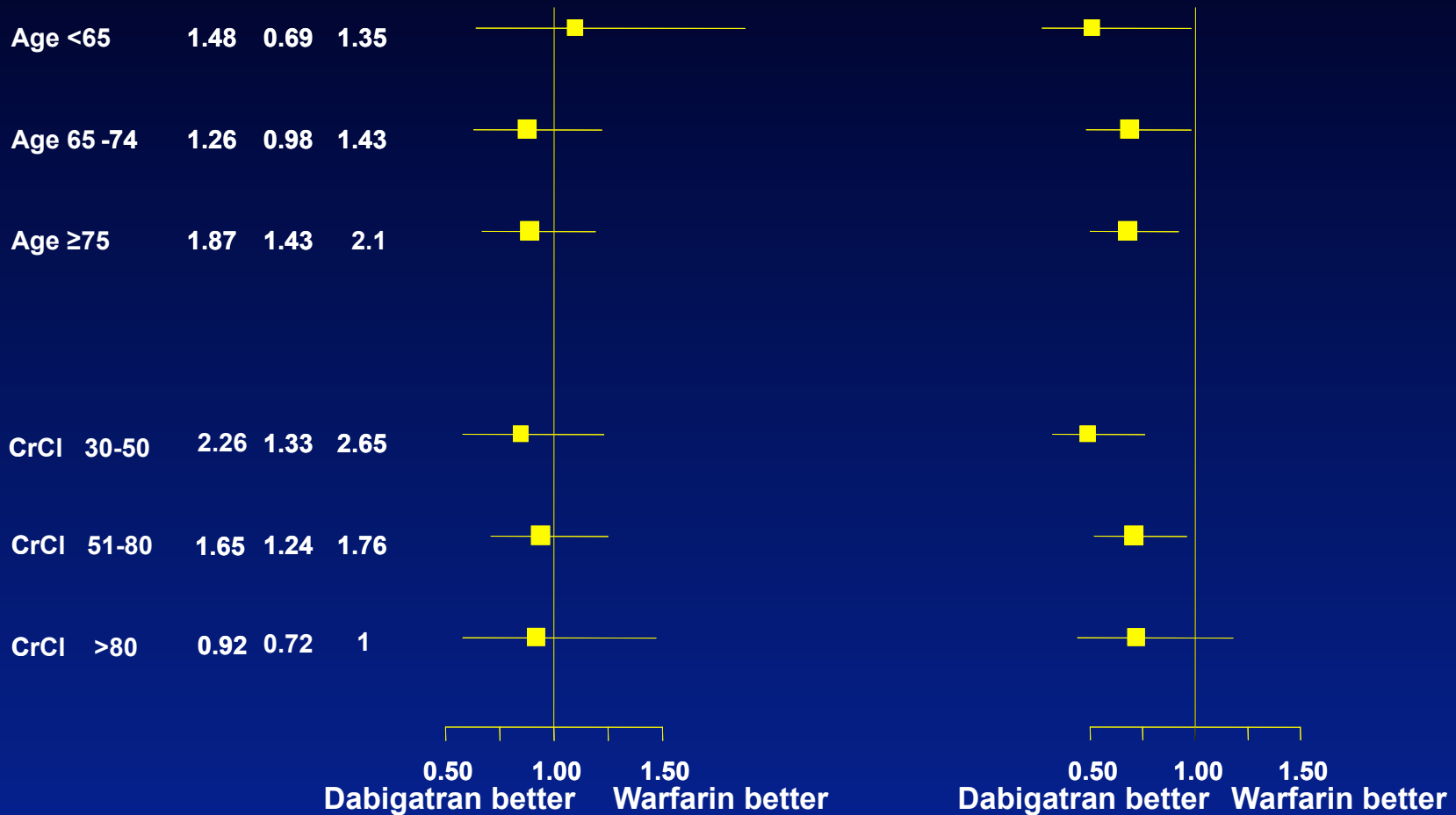


Stroke or Systemic Embolism

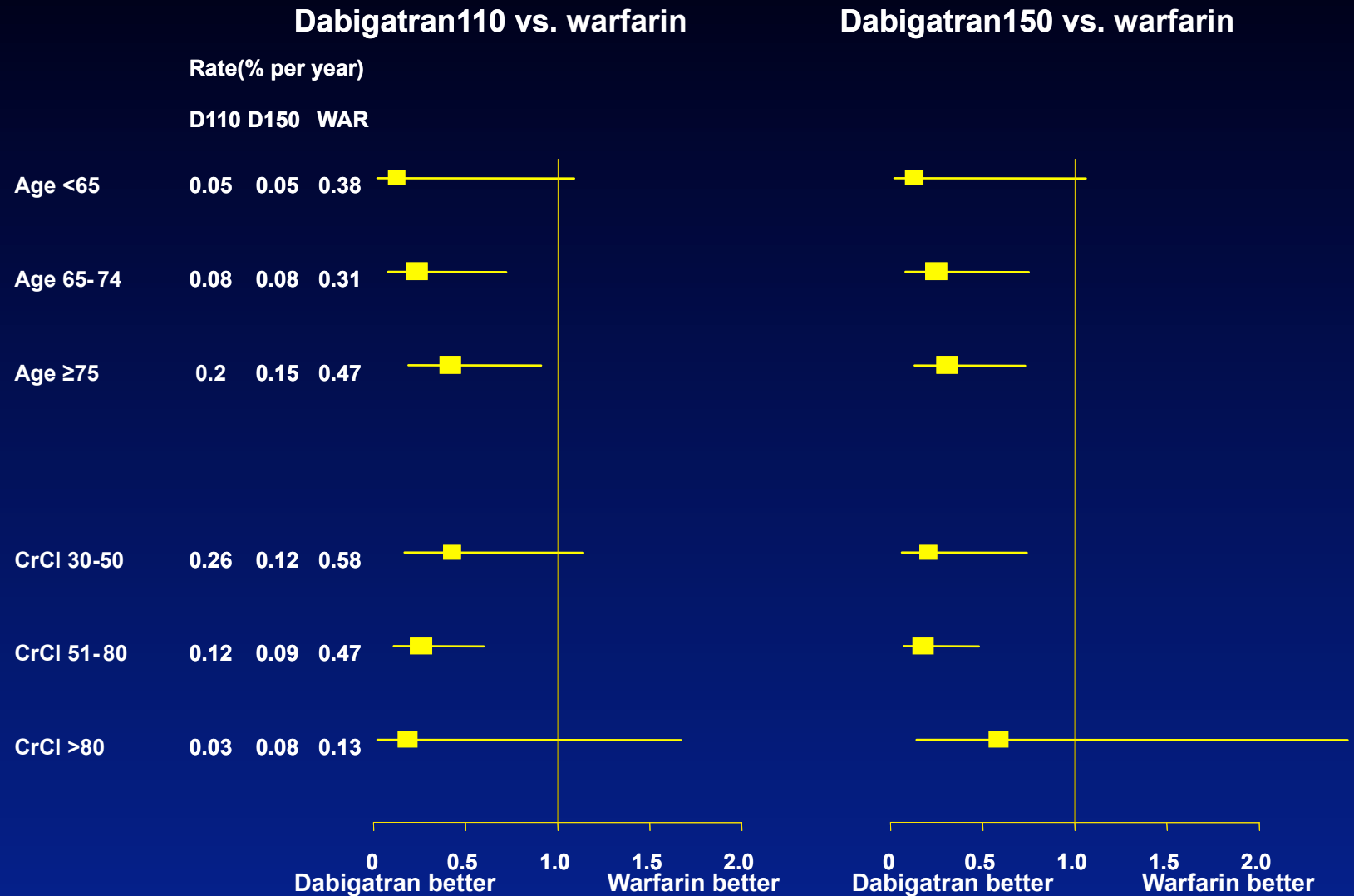
Dabigatran110 vs. warfarin

Dabigatran150 vs. warfarin

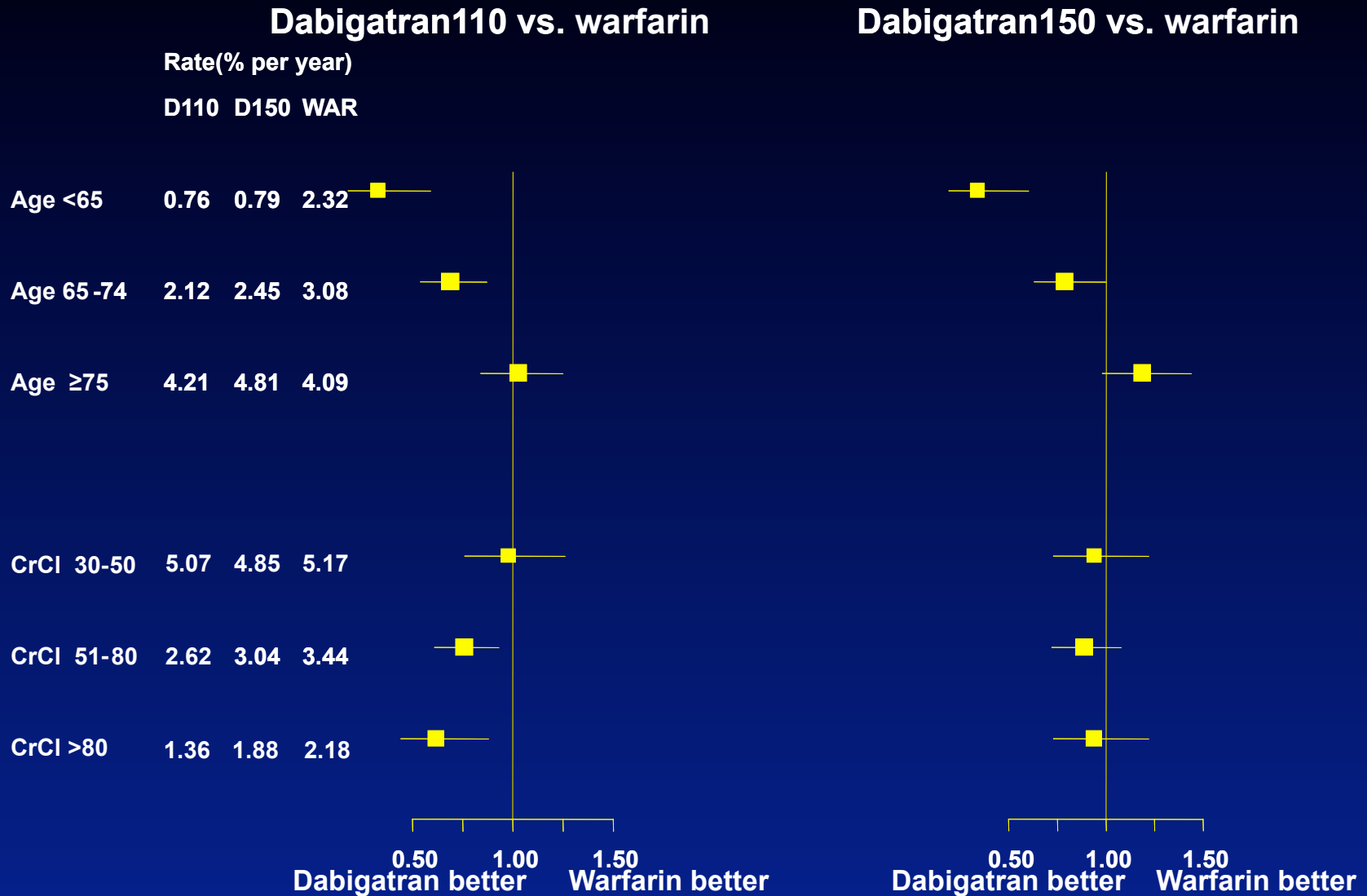
Rate(% per year)
D110 D150 WAR



Haemorrhagic stroke

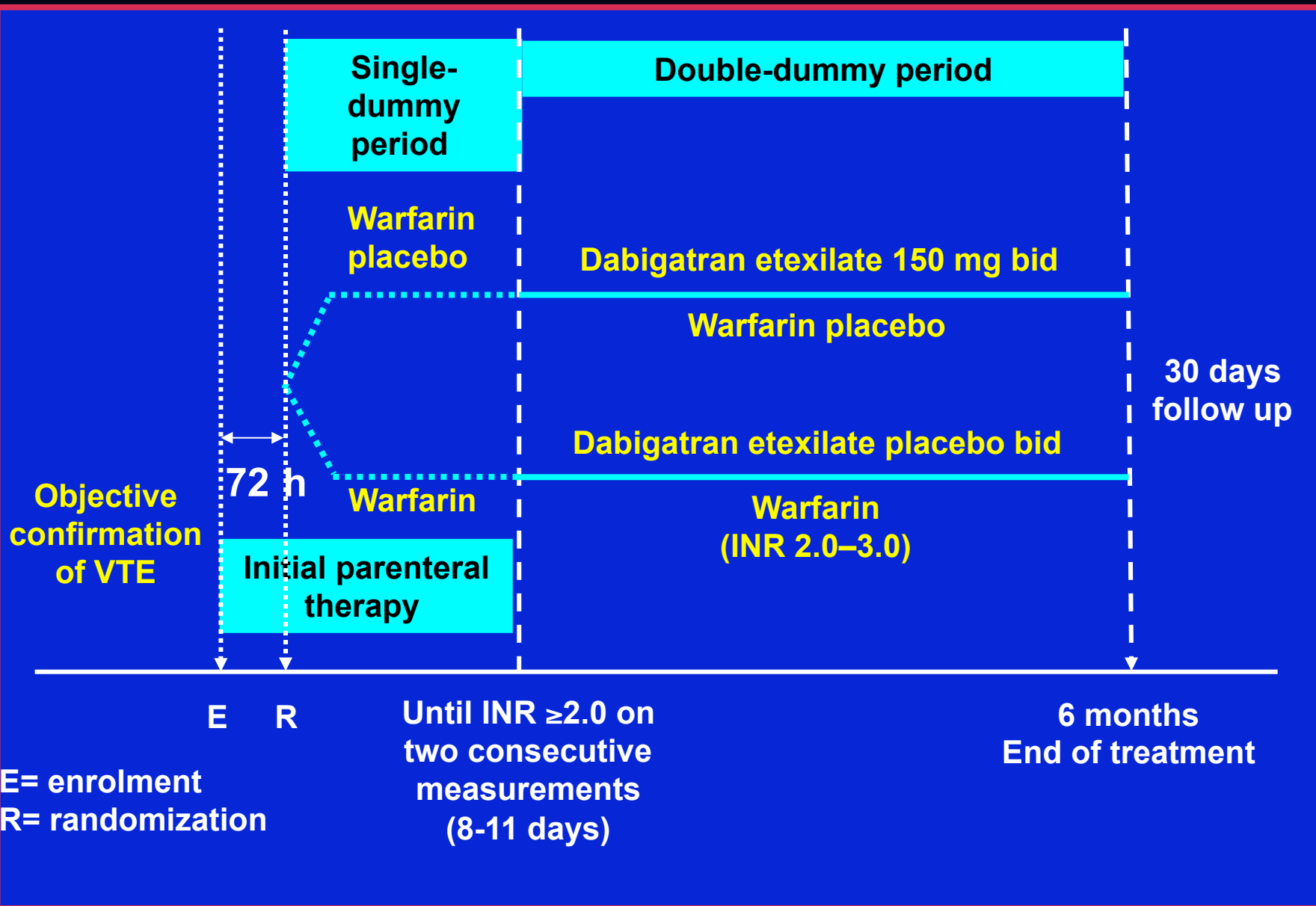


Major bleeding



**What About Other
Indications?**

RE-COVER™ Trial Design



Efficacy and Safety Outcomes

Outcome	Dabigatran (n=1274)	Warfarin (n=1265)	HR (95%CI)
			%
Recurrent VTE and VTE-related death	2.4	2.1	1.10 (0.65-1.84)
Major bleeding	1.6	1.9	0.82 (0.45-1.48)

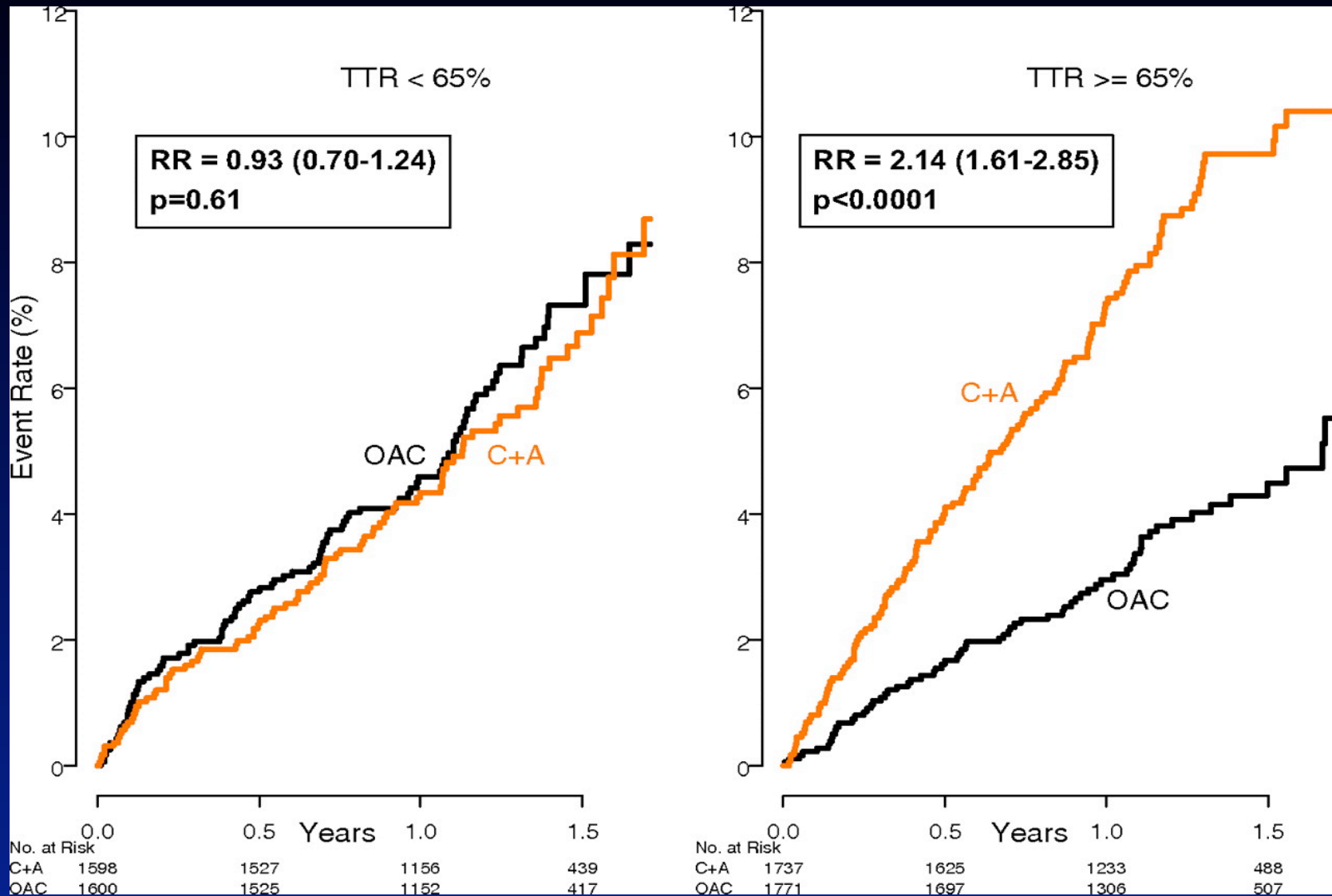
Schulman et al., *N Engl J Med*, 2009

Is Warfarin Obsolete?

New oral anticoagulants are more convenient

But, warfarin effective when time in therapeutic range is high

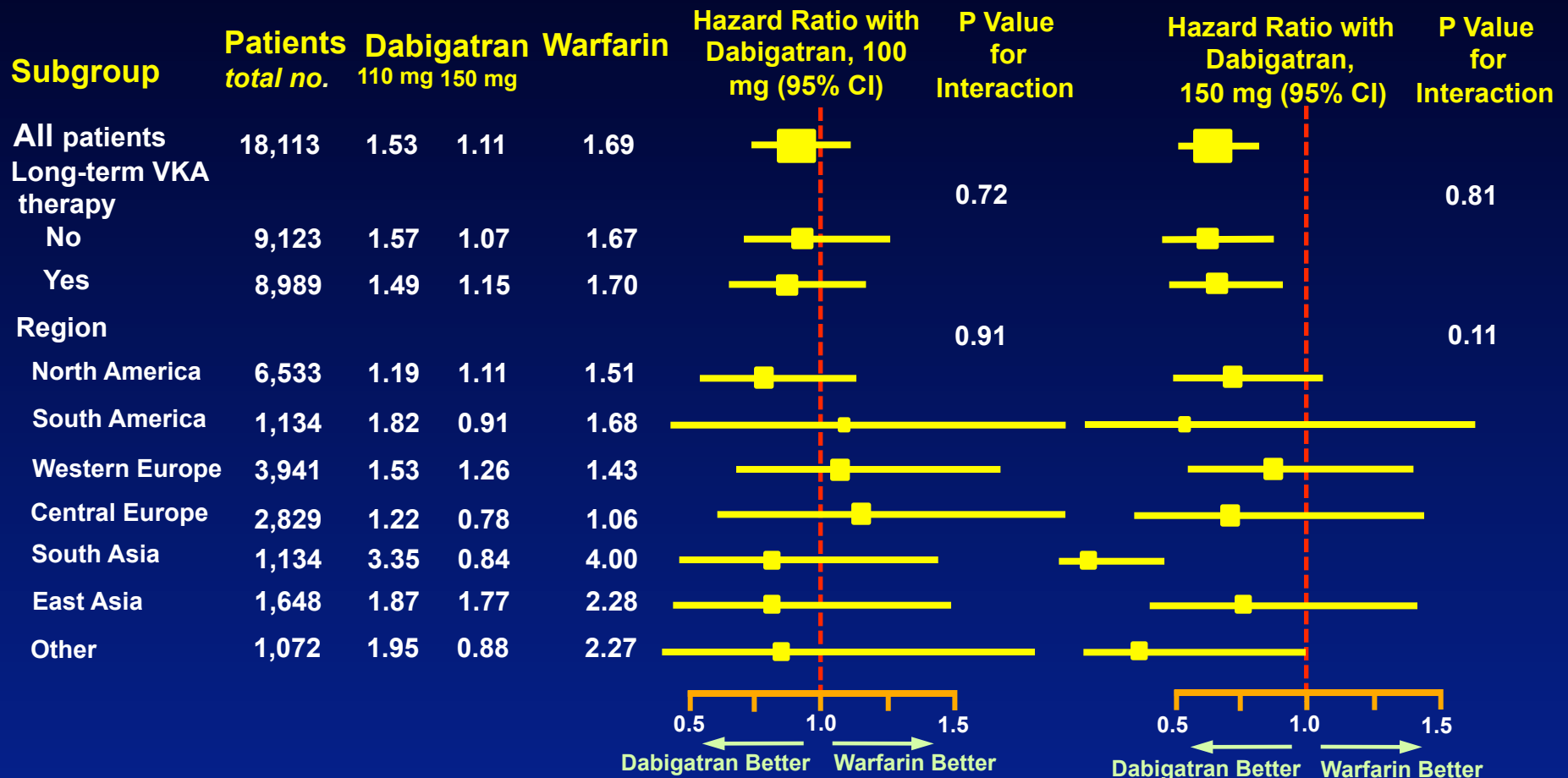
Cumulative risk of stroke, myocardial infarction, systemic embolism, or vascular death for patients treated at centers with a TTR below or above the study median (65%)



Time in Therapeutic Range (TTR) with Warfarin in the RE-LY Trial

Group	TTR
Overall	64%
VKA experienced	67%
VKA naïve	61%

Relative Risk of Stroke or Systemic Embolism with Dabigatran Versus Warfarin According to Geographical Region



Who is Not a Candidate for Dabigatran?

Stable on warfarin

Renal impairment

Severe hepatic disease

Poor compliance

Unanswered Questions

Will elimination of monitoring adversely impact patient care?

Will short half-life obviate need for an antidote?

How will we manage patients with a history of cardiac disease or GI bleeding?

What About Other Agents?

Agent	Indication	
	AF	VTE
Rivaroxaban	ROCKET	EINSTEIN
Apixaban	ARISTOTLE	AMPLIFY
Edoxaban	ENGAGE	HOKUSAI

Challenges for New Oral Anticoagulants?

Costs will be high – who will pay?

How will we assess compliance?

How will we treat bleeds?

Conclusions

Results with dabigatran are promising

Dosing of new oral anticoagulants is critical: Are the doses of the factor Xa inhibitors optimal?

New oral anticoagulants will replace warfarin, but transition likely to be slow

From Fermented Sweet Clover to Molecular Targeting of Coagulation

Delivering the Promise of New Anticoagulants

