

# **NOVEL ORAL ANTICOAGULANTS**

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# Disclosure

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# Overview

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**Limitations of warfarin**

**New oral anticoagulants**

**Role of new agents**

# Limitations of Warfarin

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## Limitation

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## Consequence

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**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**

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# **New Oral Anticoagulants**

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**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**

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

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

# RE-LY: A Non-inferiority Trial

Atrial fibrillation with  $\geq 1$  Risk Factor  
Absence of contra-indications  
*951 centers in 44 countries*

*Blinded Event Adjudication*



**Open**

**Blinded**

**Warfarin  
Adjusted  
INR 2.0 – 3.0  
N=6000**

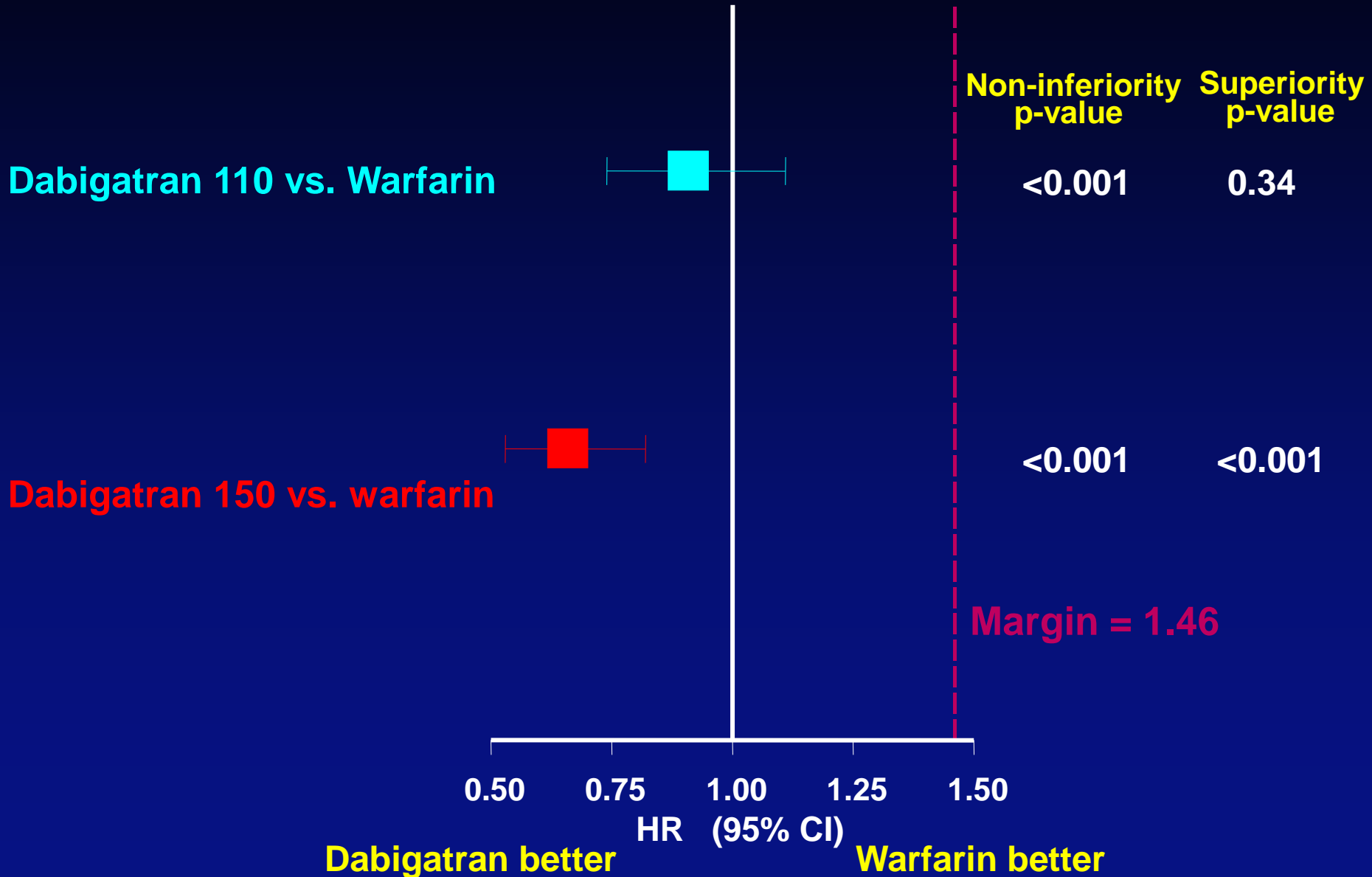
**Dabigatran  
etexilate 110 mg  
BID  
N=6000**

**Dabigatran  
etexilate 150 mg  
BID  
N=6000**

# Baseline Characteristics

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

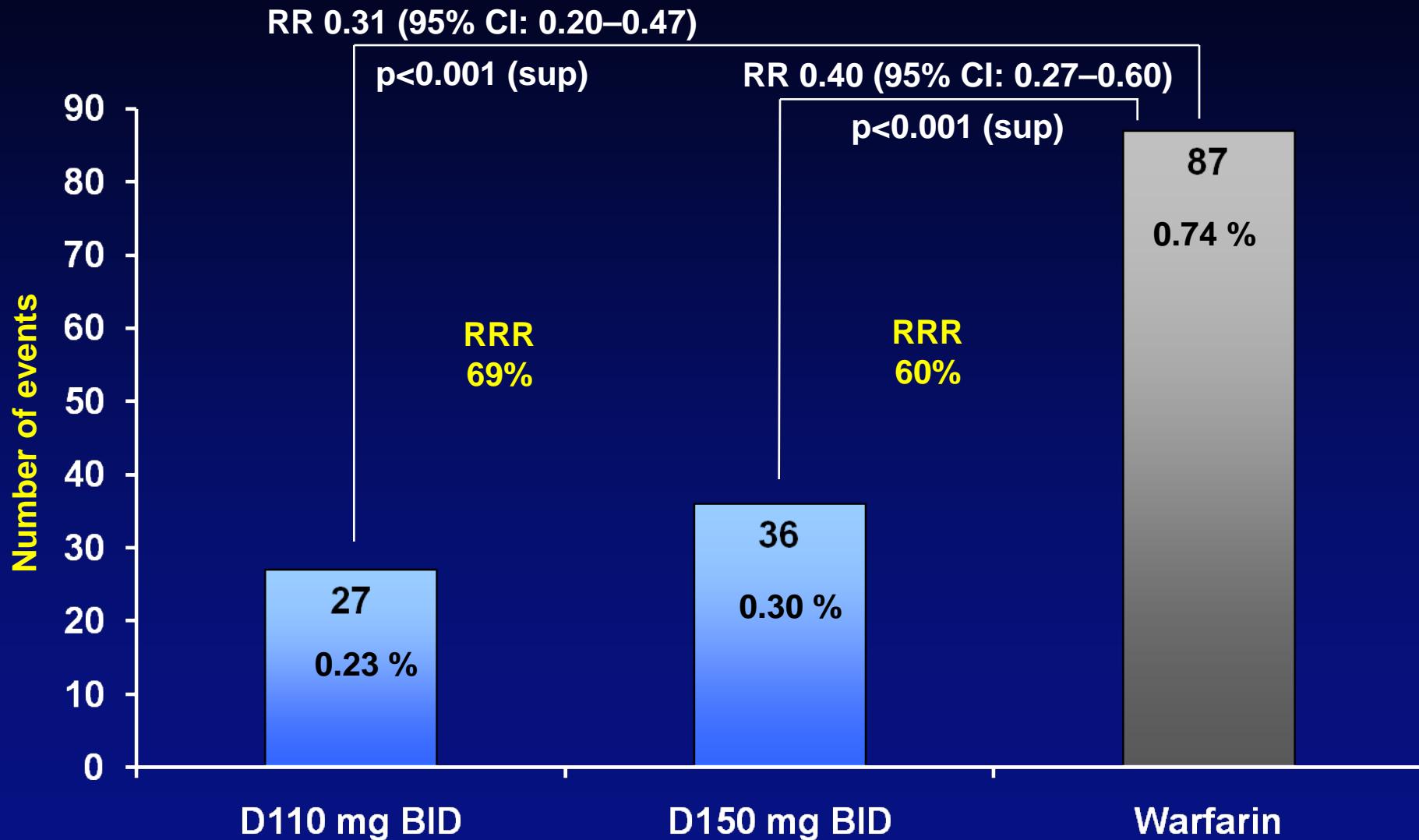
# Stroke or Systemic Embolism



# Annual Rates of Bleeding

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

# Intracranial Bleeding Rates



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

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**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?

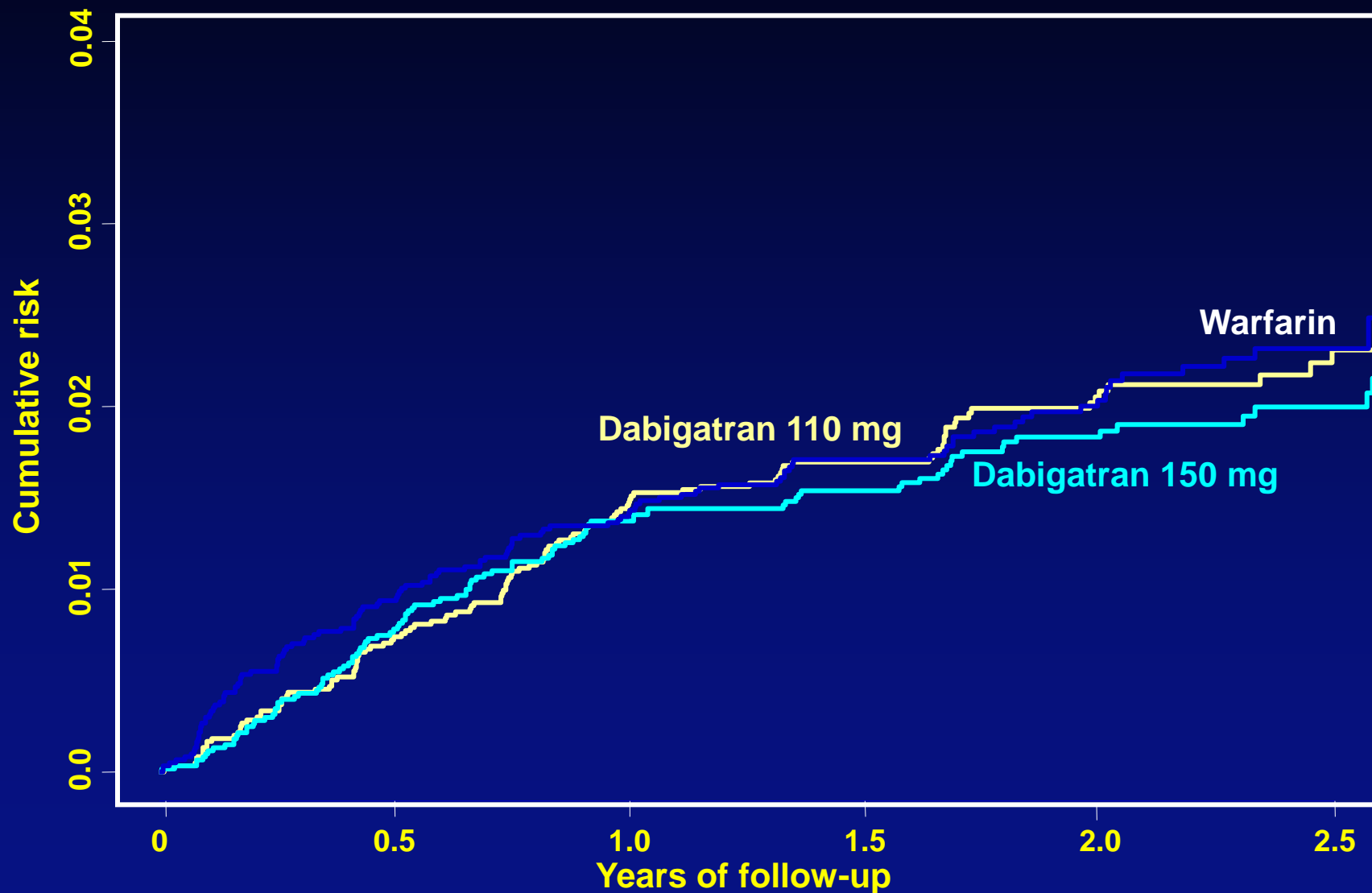
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Chance finding?

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

Other factors?

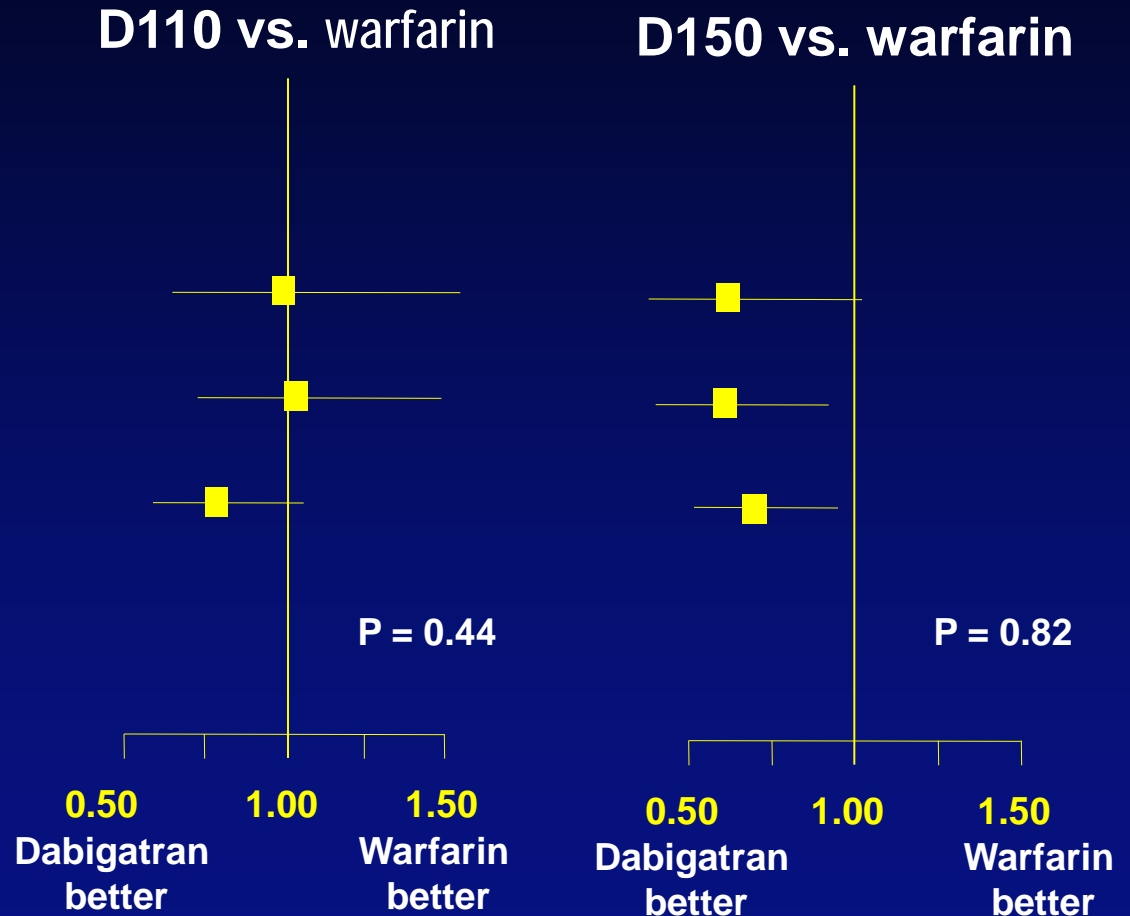
# Cumulative risk of ALT or AST >3x ULN after randomization



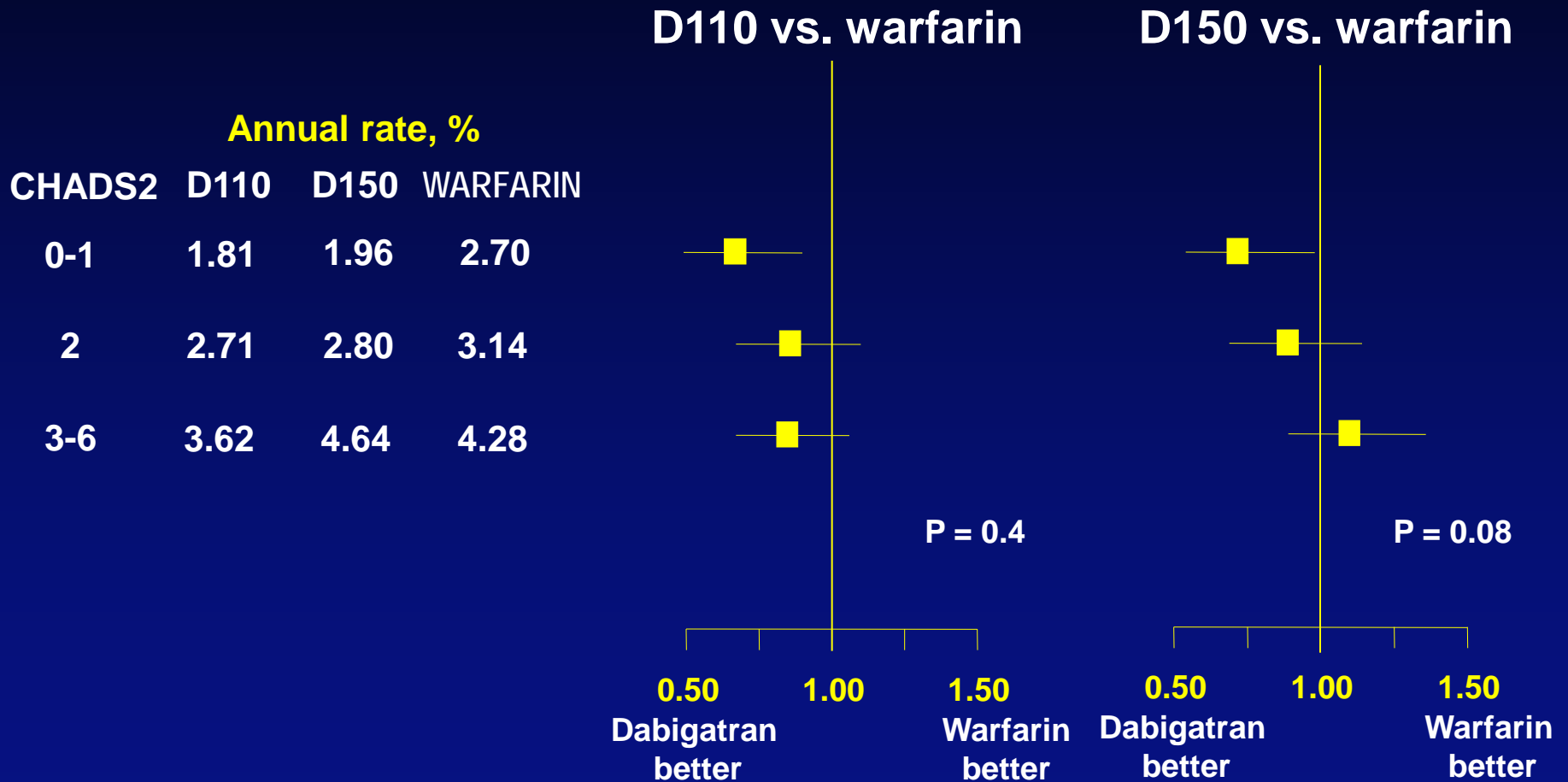
**Which dabigatran dose for  
which patient?**

# Stroke and systemic embolism

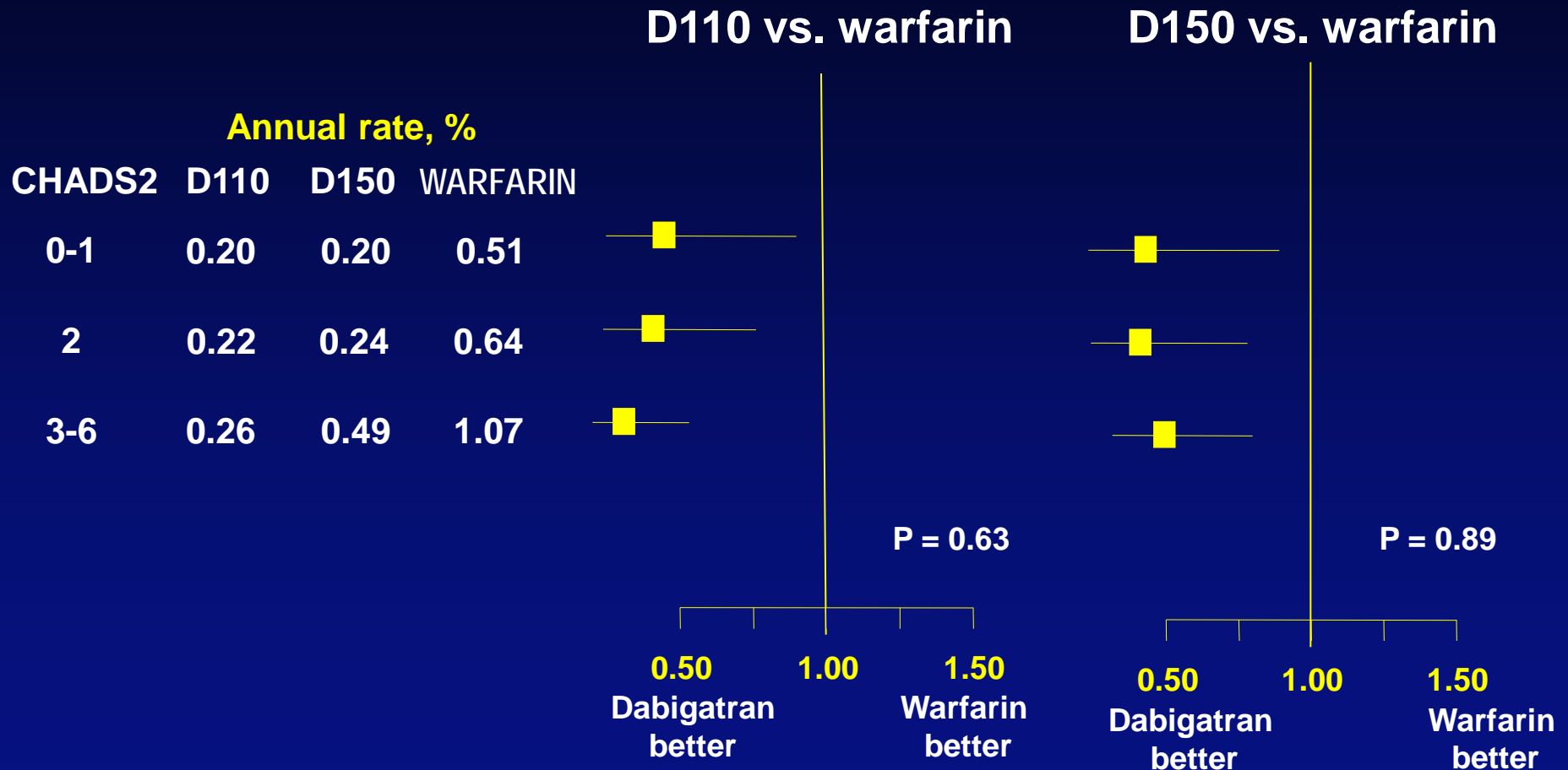
	Annual rate, %		
CHADS2	D110	D150	WARFARIN
0-1	1.06	0.65	1.05
2	1.43	0.84	1.38
3-6	2.12	1.88	2.68



# Major bleeding



# Intracranial bleeding



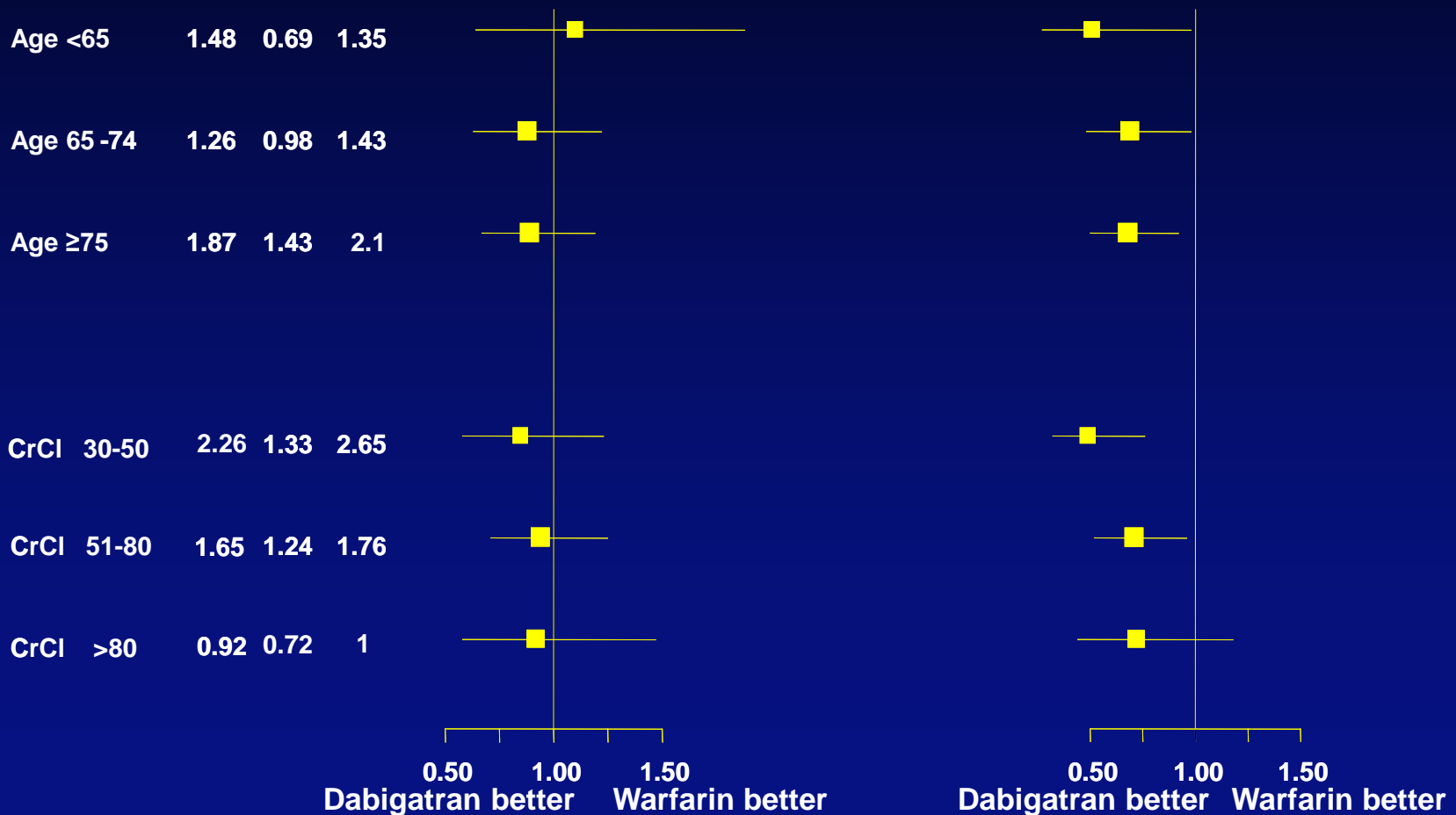
# Stroke or Systemic Embolism

## Dabigatran110 vs. warfarin

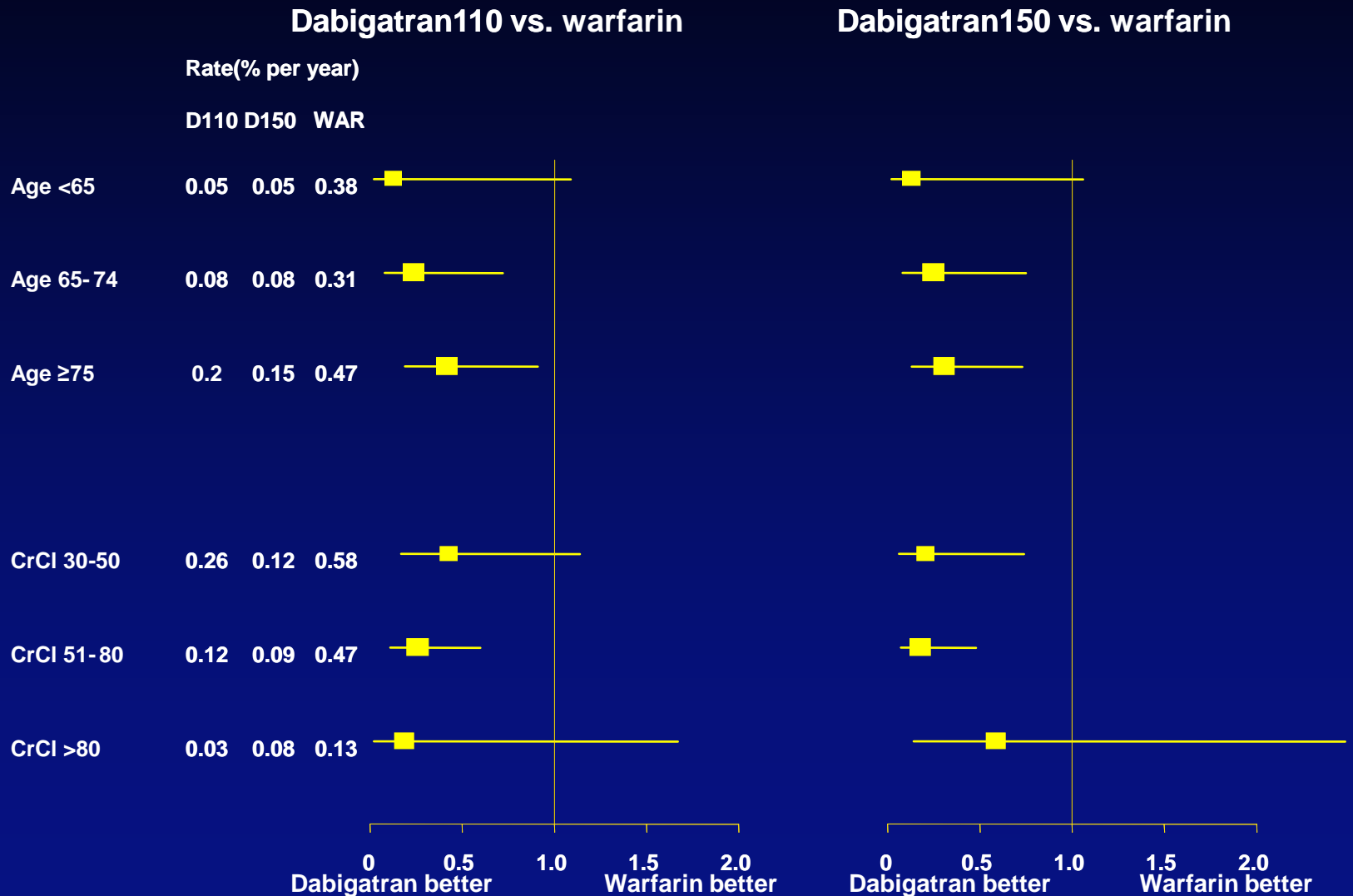
## Dabigatran150 vs. warfarin

Rate(% per year)

D110 D150 WAR



# Haemorrhagic stroke



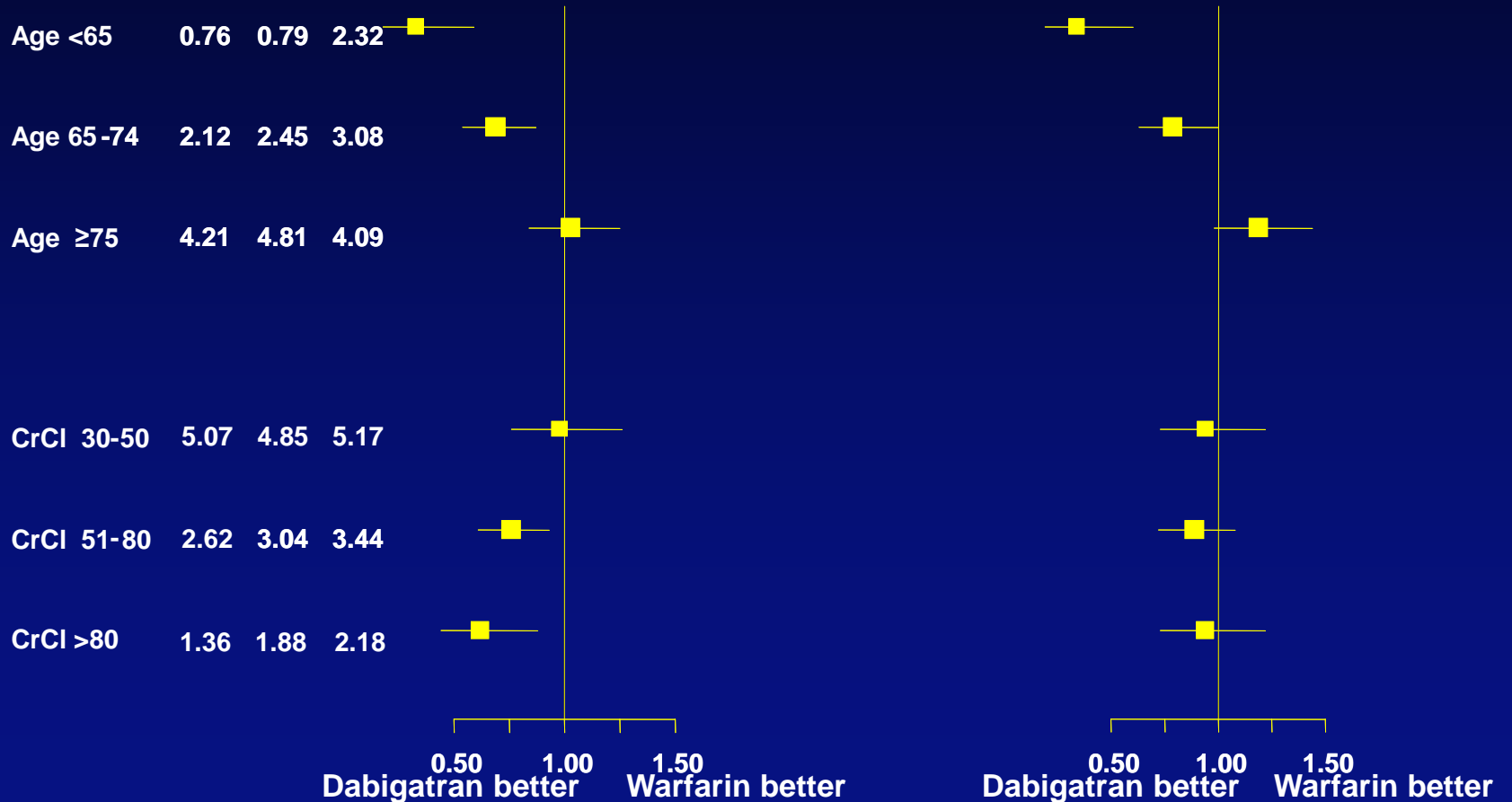
# Major bleeding

## Dabigatran110 vs. warfarin

## Dabigatran150 vs. warfarin

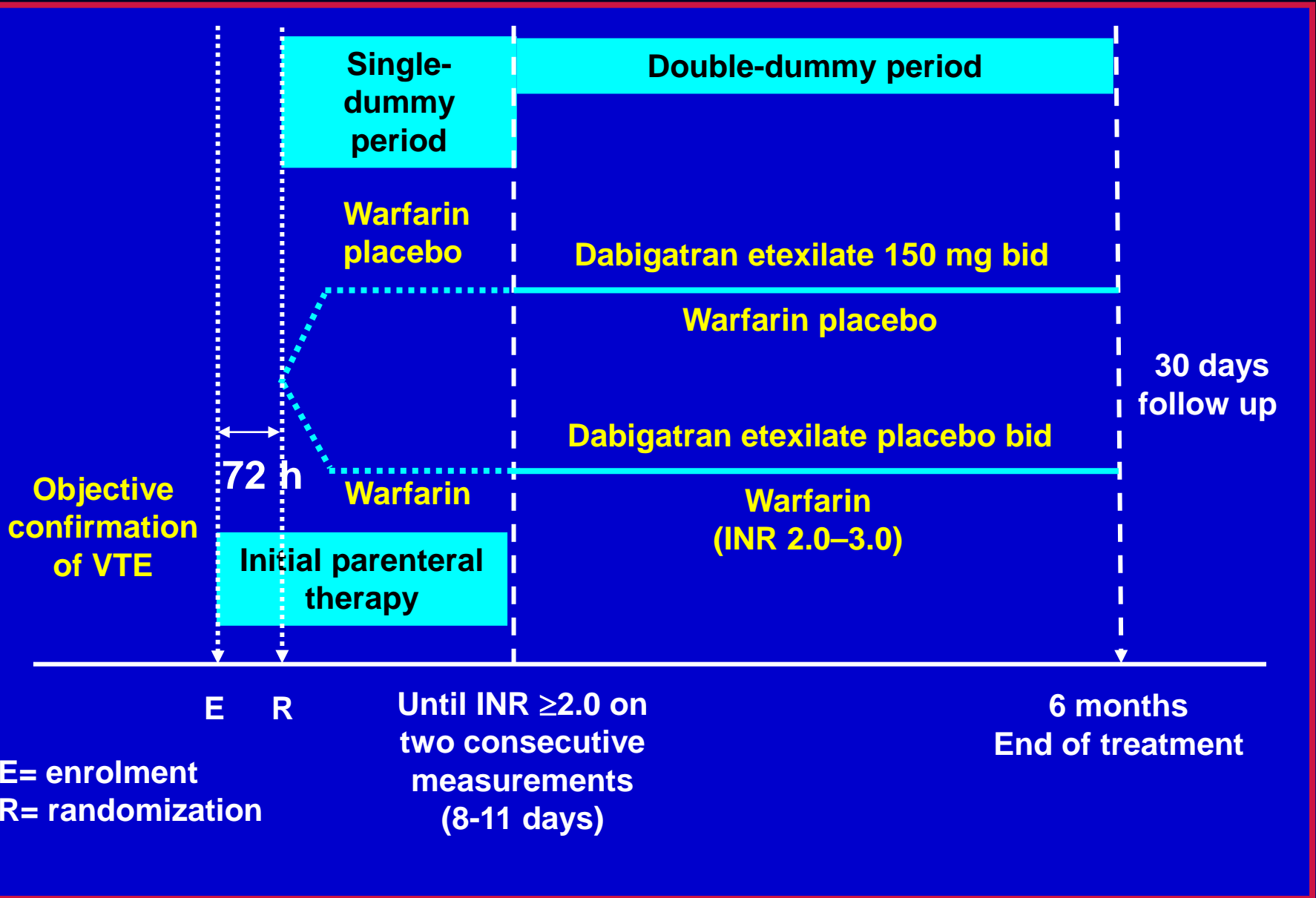
Rate(% per year)

D110 D150 WAR



**What About Other  
Indications?**

# RE-COVER™ Trial Design



# Efficacy and Safety Outcomes

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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)

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

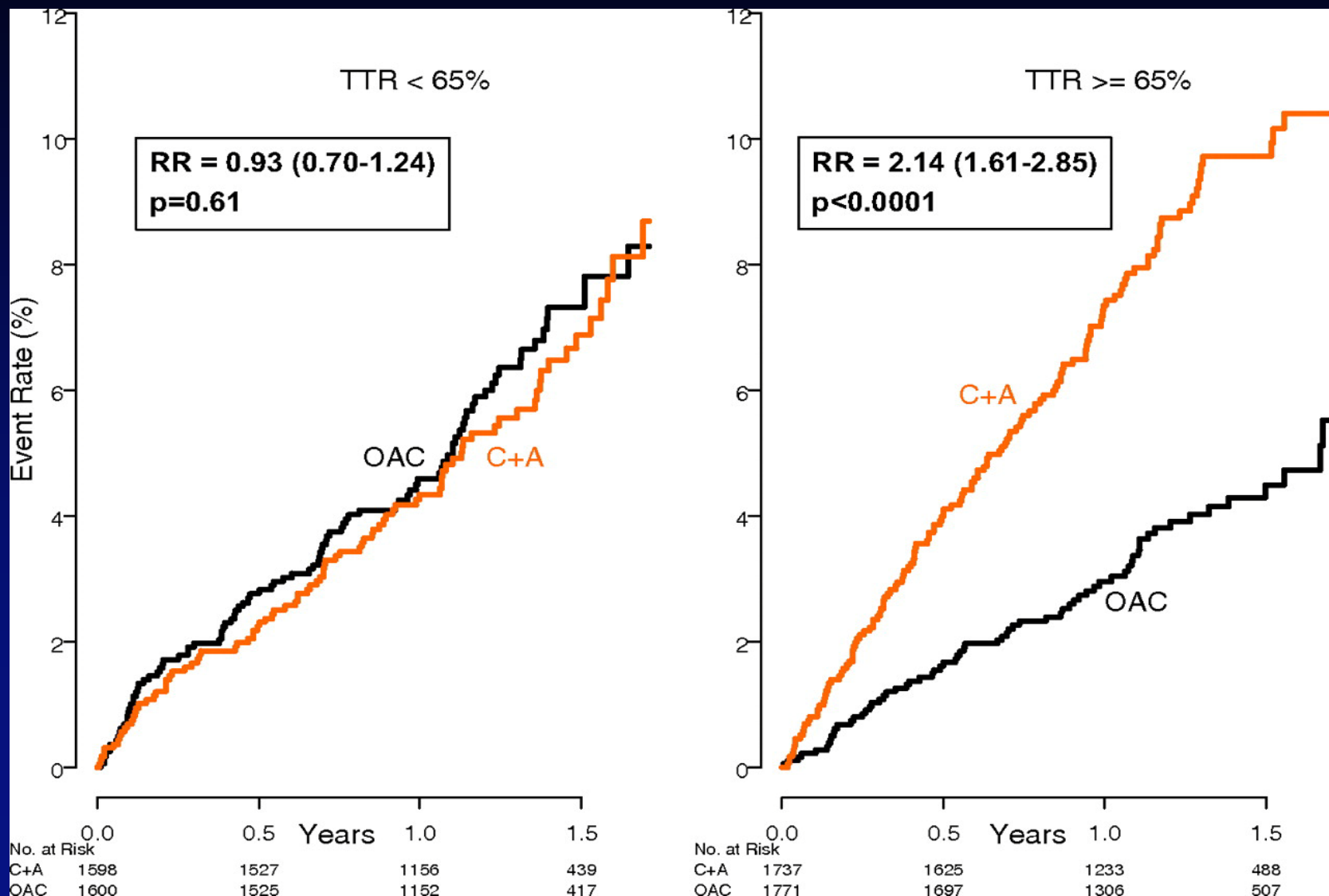
# Is Warfarin Obsolete?

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**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%)



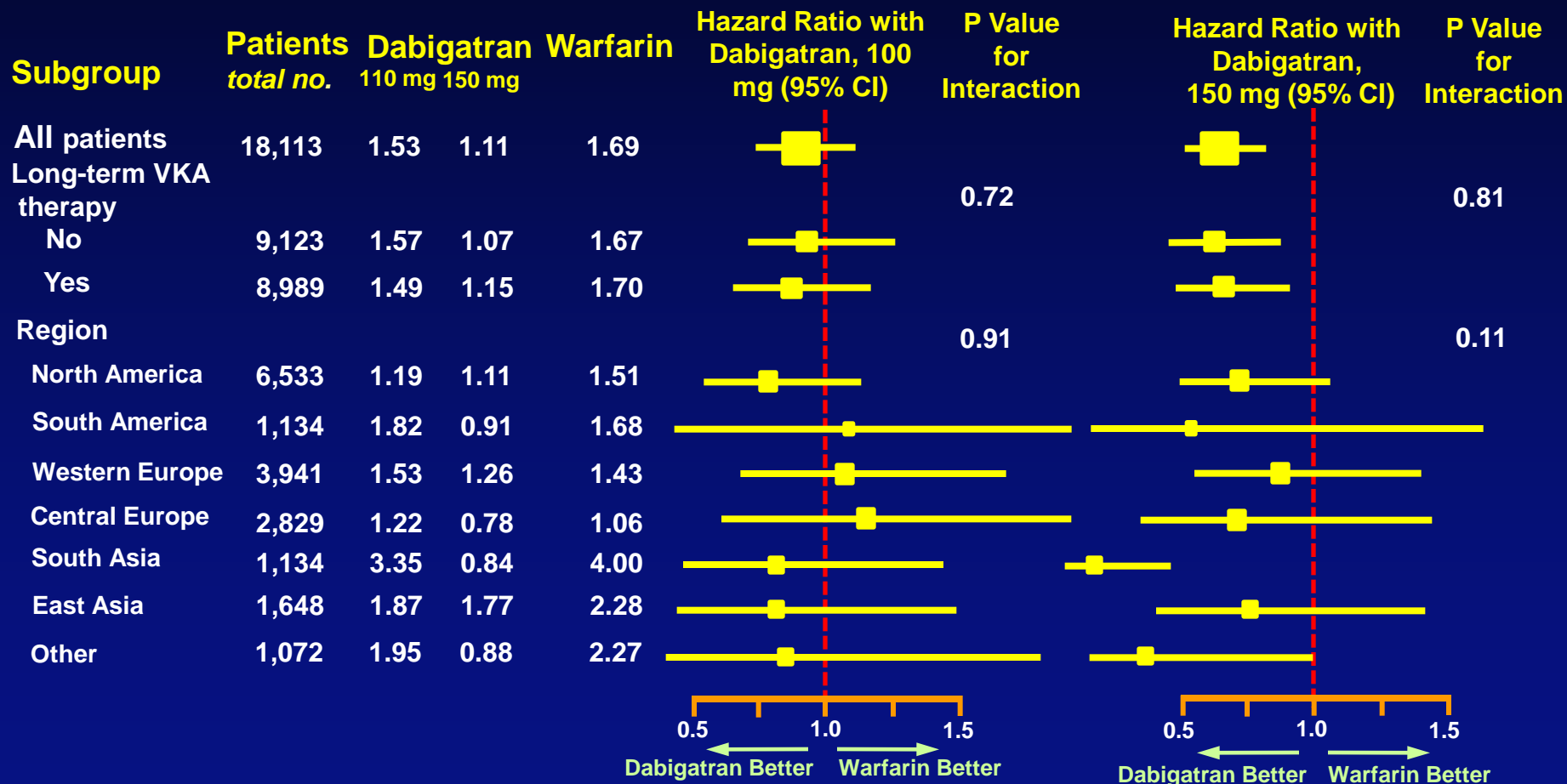
# Time in Therapeutic Range (TTR) with Warfarin in the RE-LY Trial

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

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



# Who is Not a Candidate for Dabigatran?

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**Stable on warfarin**

**Renal impairment**

**Severe hepatic disease**

**Poor compliance**

# Unanswered Questions

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**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?

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

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# Challenges for New Oral Anticoagulants?

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**Costs will be high – who will pay?**

**How will we assess compliance?**

**How will we treat bleeds?**

# Conclusions

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**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*

