

# **Recent Advances in Anticoagulant Therapy:**

## **Will New Oral Agents Render Warfarin a Thing of the Past?**

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# Objectives

- **Differentiate new anticoagulant agents with respect to their pharmacokinetics, pharmacodynamics, and recommended dosing strategies**
- **Outline current literature supporting the role of new anticoagulant agents in the prevention and treatment of thromboembolic disorders**
- **Given a patient who is receiving a new anticoagulant agent, assess whether current therapy is appropriate**

# Oral Anticoagulation - Warfarin

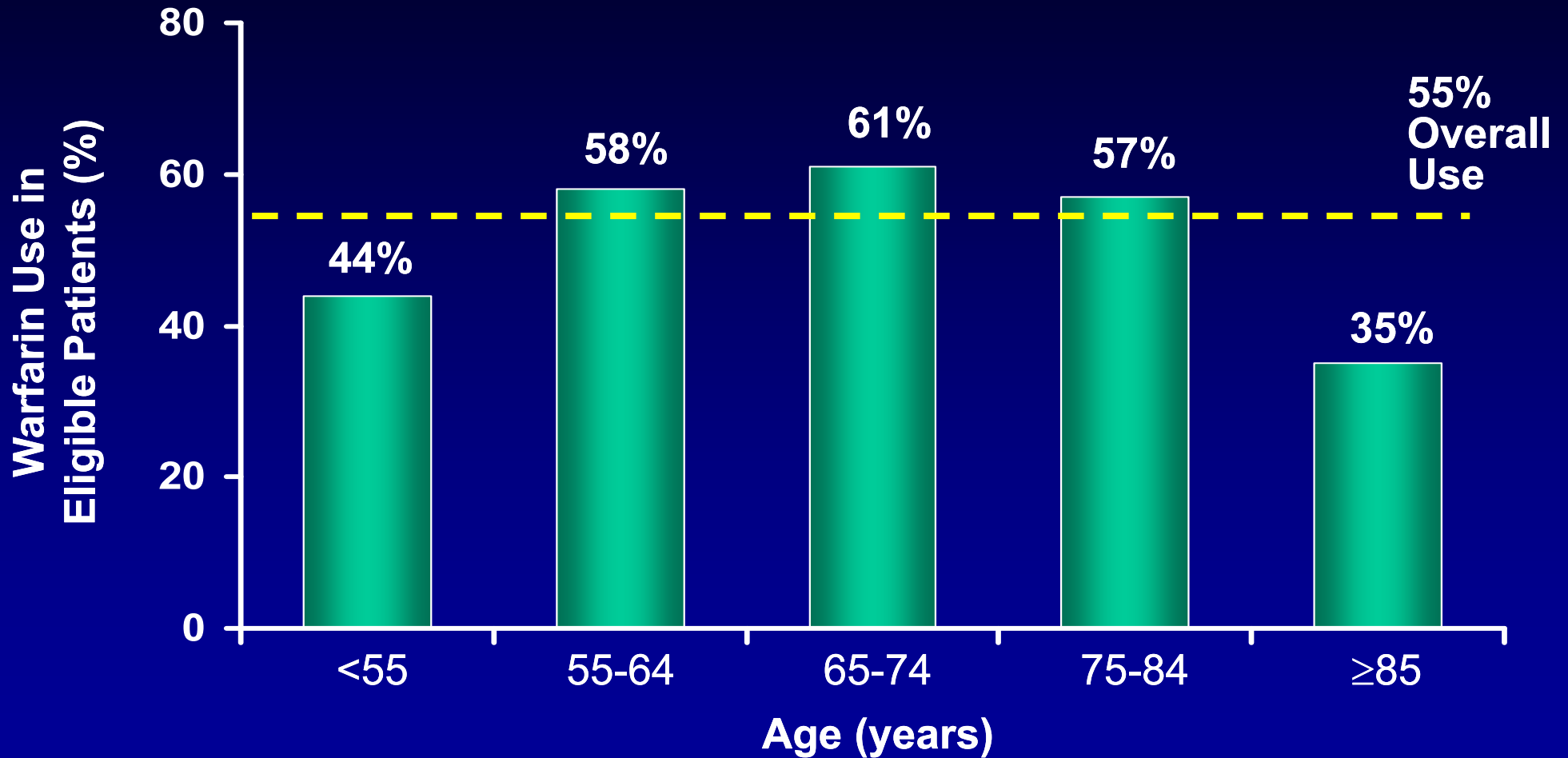
- Main oral agent for long term prevention and treatment of thromboembolic disease > 50 years
- Advances
  - INR
  - Anticoagulation Management Services
- Despite Advances
  - Challenges still exist in determining optimal and safest dose
    - *Individualized patient to patient*
  - Warfarin continues to rank among top 10 medications associated with adverse events
    - Bleeding
      - Cumulative increase over time
      - Rates vary depending on indication
      - *Rate is highest during initiation of therapy*

# Warfarin Key Variables for Dosing

- Metabolism
  - CYP system
  - Drug interactions
- Variable response
  - Food
  - Age
  - Concomitant disease states
  - ETOH
  - Ethnicity
- Half-life
  - 36-48 hours
  - Peak effect single dose
  - Steady state 2 weeks
- Initiation
  - Loading vs predicted maintenance dose
- Ethnicity and average daily dose
  - 6.1 mg: African-Americans
  - 5.1 mg: Caucasians
  - 3.4 mg: Asians

# Warfarin for Atrial Fibrillation

## *Limitations Lead to Under-treatment*



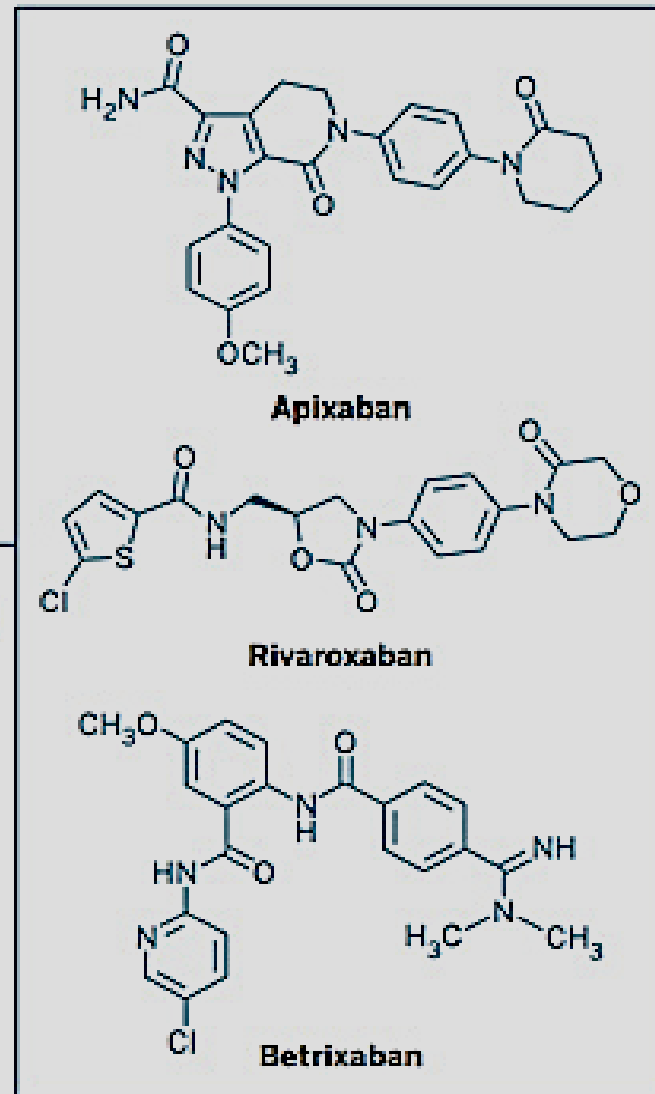
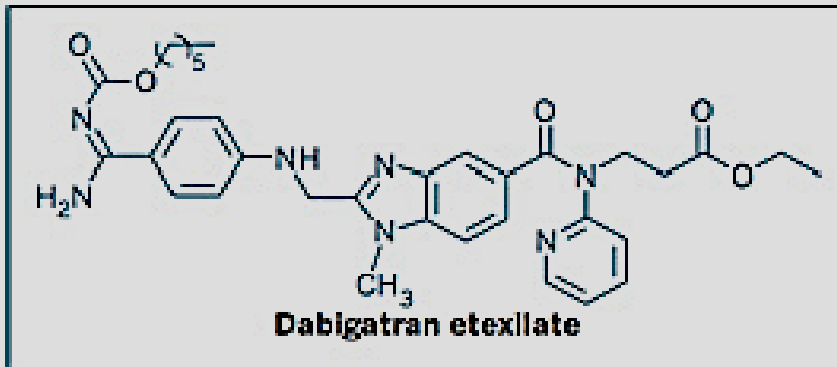
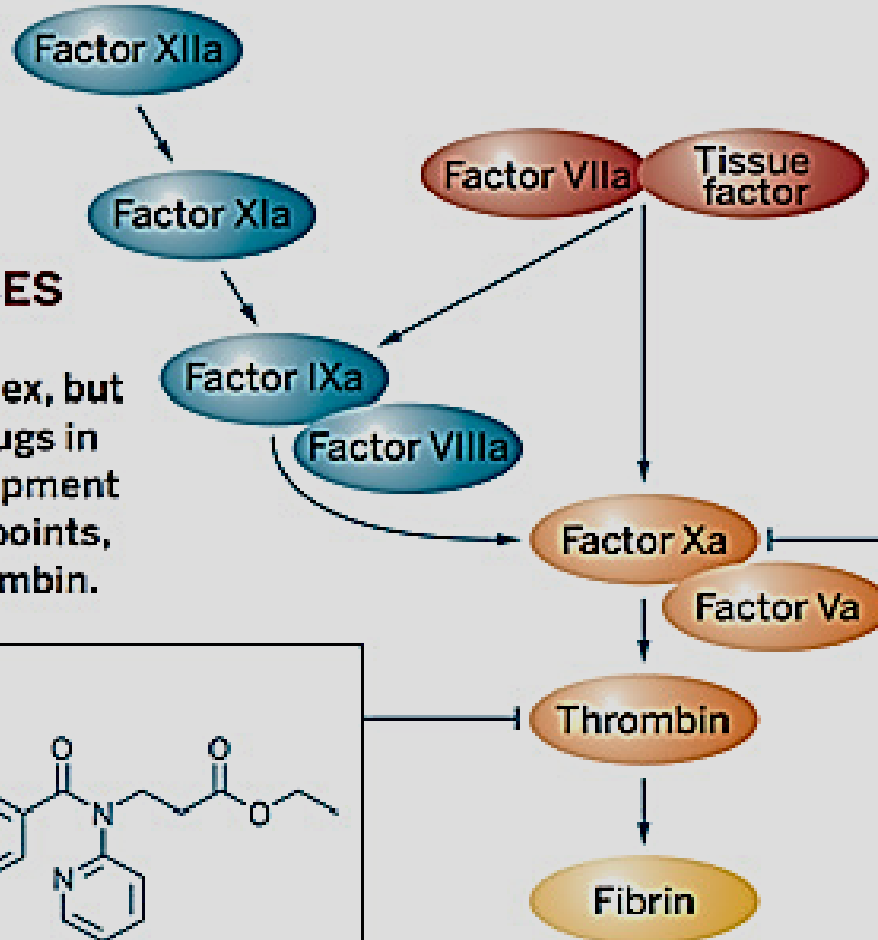
# Ideal Anticoagulant

<b>Disadvantage of Warfarin</b>	<b>Ideal Anticoagulant</b>
Slow onset of action <b>Need for Injectable agent</b>	Fast onset of action, allowing for acute treatment of VTE and use post-procedures
Slow resolution of action	Fast resolution of action, allowing for use pre-procedures
Regular blood monitoring	No routine blood monitoring
Many drug interactions	No drug interactions
Interactions with diet	No interactions with diet
Wide range of therapeutic doses	Narrow-ranged, fixed doses
Unpredictable dose-response	Predictable dose-response
Teratogenicity	Safe in pregnancy
Slow reversibility via vitamin K	Immediate reversibility

# New Oral Anticoagulants - Targets

## MANY CHOICES

The coagulation cascade is complex, but anticoagulant drugs in late-stage development hit it at just two points, Factor Xa or thrombin.



# **DABIGATRAN ETEXILATE**

## **(Pradaxa®), Boeringher-Ingelheim)**

- **PHARMACOLOGY:**

- Prodrug, converted to the active dabigatran moiety by hydrolysis via nonspecific esterases.
- Dabigatran is a reversible and selective direct thrombin inhibitor.
- Dabigatran inhibits human thrombin and thrombin-induced platelet aggregation.
- Dabigatran inhibits both clot-bound and fluid-phase thrombin.

- **FDA indication (Approved October 2010):**

- Dabigatran is a direct thrombin inhibitor indicated to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation

# RE-LY: Study Design

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

**Open**

N = 18,113

**Blinded**

Warfarin  
adjusted  
(INR 2.0-3.0)  
N=6000

Dabigatran  
Etexilate  
110 mg BID  
N=6000

Dabigatran  
Etexilate  
150 mg BID  
N=6000

Patients were eligible if they had atrial fibrillation documented on electrocardiography performed at screening or within 6 months beforehand and *at least one of the following* characteristics:

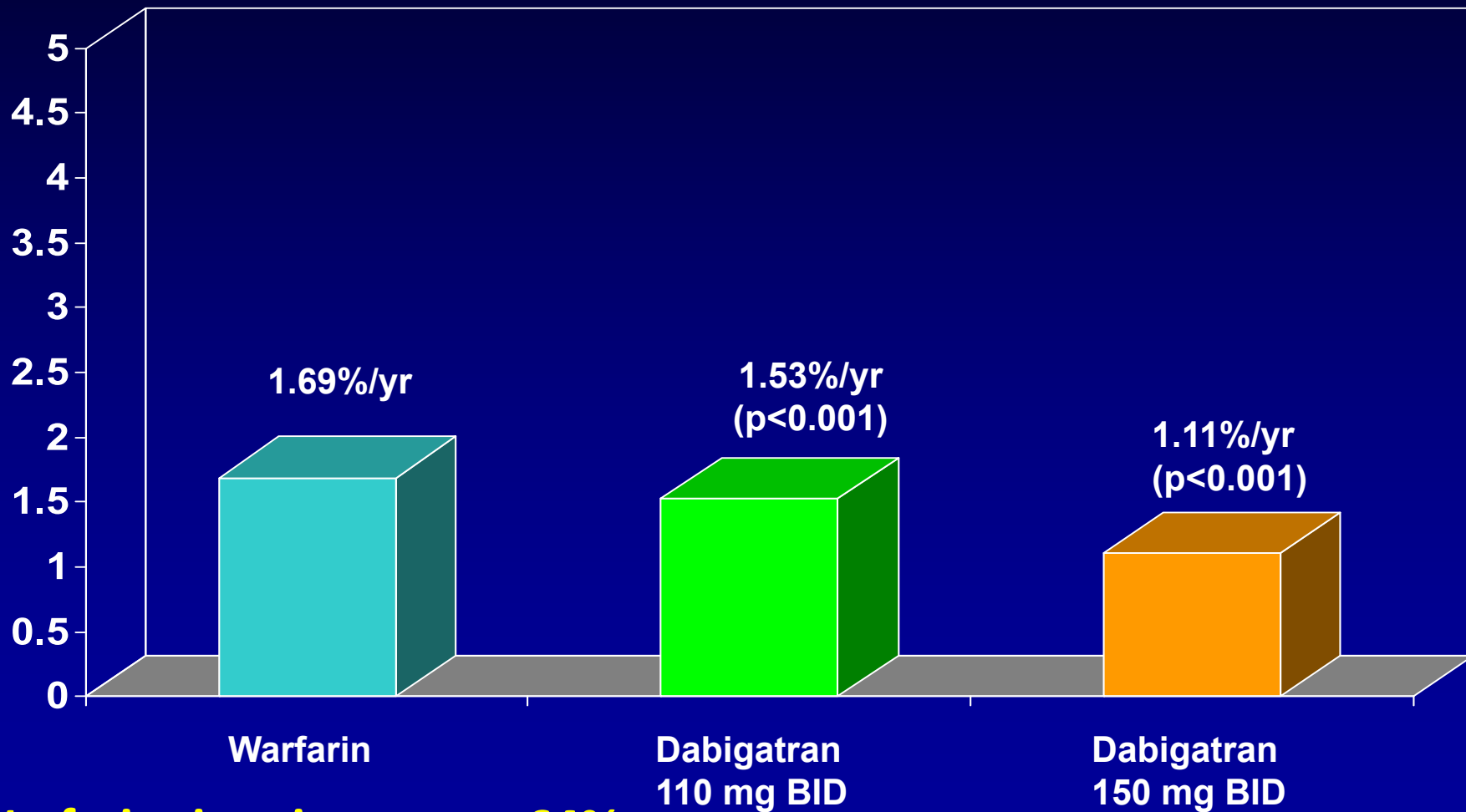
1. Previous stroke or transient ischemic attack
2. A left ventricular ejection fraction of less than 40%
3. New York Heart Association class II or higher heart-failure symptoms within 6 months before screening
4. An age of at least 75 years or an age of 65 to 74 years plus diabetes mellitus, hypertension, or coronary artery disease.

# RE-LY: 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

# RE-LY: Primary Outcome

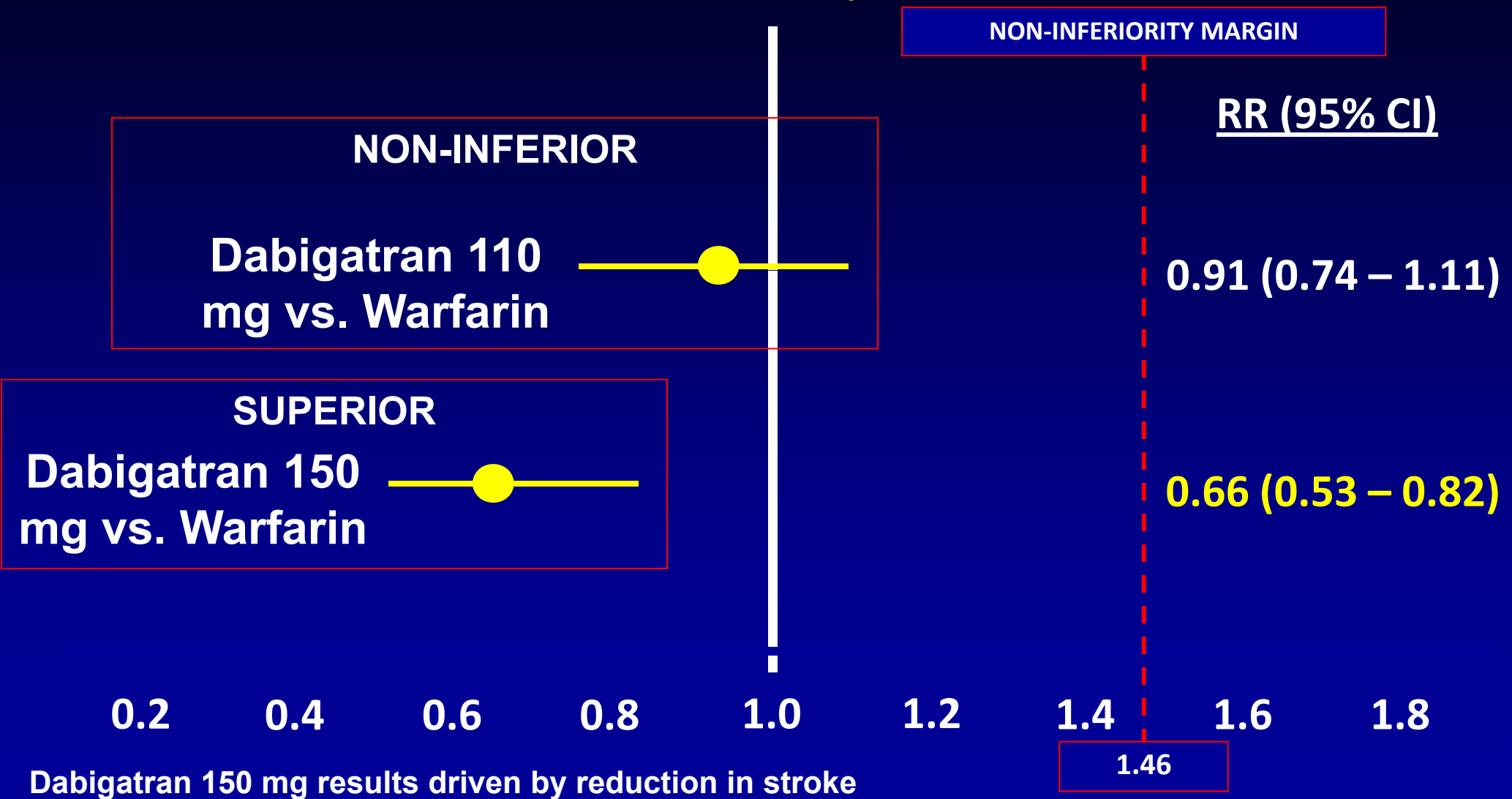
## Composite: Stroke or Systemic Embolism



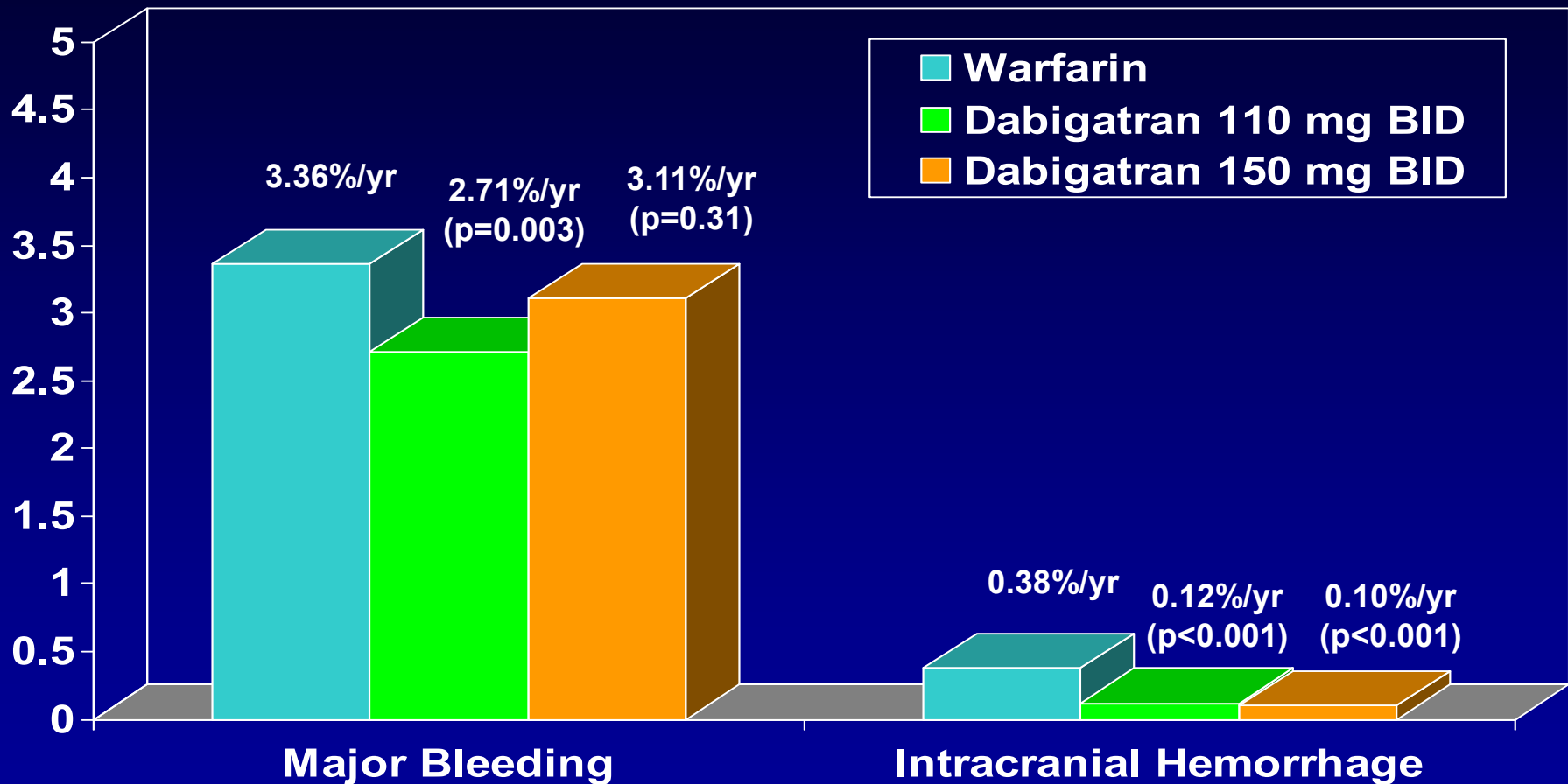
- Warfarin time-in-range = 64%

# RE-LY: Primary Outcome

Composite: Stroke or Systemic Embolism



# RE-LY: Primary Safety Outcome



# RE-LY: Bleeding Rates

	D 110mg	D 150mg	Warfarin	D 110mg vs. Warfarin		D 150mg vs. Warfarin	
	Annual rate	Annual rate	Annual rate	RR (95% CI)	p-value	RR (95% CI)	p-value
<b>Total</b>	14.6%	16.4%	18.2%	0.78 (0.74-0.83)	<0.001	0.91 (0.86-0.97)	0.002
<b>Major</b>	2.7%	3.1%	3.4%	0.80 (0.69-0.93)	0.003	0.93 (0.81-1.07)	0.31
<b>Life-threatening Major</b>	1.2%	1.5%	1.8%	0.68 (0.55-0.83)	<0.001	0.81 (0.66-0.99)	0.04
<b>Gastrointestinal Major</b>	1.1%	1.5%	1.0%	1.10 (0.86-1.41)	0.43	1.50 (1.19-1.89)	<0.001

# RE-LY: Adverse Events

Adverse event	D 110 mg (%)	D 150 mg (%)	Warfarin (%)
Dyspepsia *	11.8	11.3	5.8
Dyspnea	9.3	9.5	9.7
Dizziness	8.1	8.3	9.4
Peripheral edema	7.9	7.9	7.8
Fatigue	6.6	6.6	6.2
Cough	5.7	5.7	6.0
Chest pain	5.2	6.2	5.9
Arthralgia	4.5	5.5	5.7
Back pain	5.3	5.2	5.6
Nasopharyngitis	5.6	5.4	5.6
Diarrhea	6.3	6.5	5.7
Atrial fibrillation	5.5	5.9	5.8
Urinary tract infection	4.5	4.8	5.6
Upper respiratory tract infection	4.8	4.7	5.2

**\*Occurred more commonly with dabigatran  
(p<0.001)**

Connolly SJ et al. *New Engl J Med.* 2009; 361:1139-51.

# RE-LY: Effect of TTR on Primary Outcome

## Stroke and Systemic Embolism

	D 110mg	D 150mg	Warfarin	D 110mg vs. Warfarin		D 150mg vs. Warfarin	
cTTR	Rate*	Rate*	Rate*	RR (95% CI)	p-value	RR (95% CI)	p-value
<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

\* Rate per 100 person-years

cTTR = Centre's mean time in therapeutic range

# RE-LY: Effect of TTR on Safety Outcome

## Major Bleeding

cTTR	D 110mg	D 150mg	Warfarin	D 110mg vs. Warfarin		D 150mg vs. Warfarin	
	Rate*	Rate*	Rate*	RR (95% CI)	p-value	RR (95% CI)	p-value
<57.1%	2.36	2.54	3.59	0.65 (0.48-0.89)		0.71 (0.52-0.96)	
57.1-65.5%	3.38	3.33	4.13	0.82 (0.63-1.06)		0.81 (0.62-1.05)	
65.5-72.6%	2.82	3.80	3.40	0.83 (0.62-1.11)		1.13 (0.87-1.48)	
>72.6%	2.81	3.60	3.11	0.90 (0.67-1.21)	0.50	1.16 (0.88-1.54)	0.03

\* Rate per 100 person-years

cTTR = Centre's mean time in therapeutic range

# Role of Dabigatran for Stroke Prevention in AF

- 2011 ACCF/AHA/HRS Guidelines
  - Dabigatran given a Class I (LOE B) recommendation
    - Dabigatran is useful as an alternative to warfarin for prevention of stroke and systemic thromboembolism in patients with paroxysmal to permanent AF and risk factors for stroke or systemic embolization who do not have the following:
      - Prosthetic heart valve or hemodynamically significant valve disease
      - CrCl <15 mL/min
      - Advanced liver disease

# Role of Dabigatran for Stroke Prevention in AF

- 2011 ACCF/AHA/HRS guidelines also state the following:
  - Patients already taking warfarin with excellent INR control may have little to gain by switching to dabigatran because of dabigatran's:
    - Twice-daily dosing
    - Greater risk of nonhemorrhagic side effects,
  - Selection of patients with AF and  $\geq 1$  additional risk factor for stroke who could benefit from treatment with dabigatran as opposed to warfarin should consider individual factors, including:
    - Ability to comply with twice-daily dosing
    - Availability of an anticoagulation management program to sustain routine monitoring of INR
    - Patient preferences
    - Cost
    - Other factors

# RE-COVER: Dabigatran in Acute VTE Treatment

Acute, symptomatic, objectively verified proximal DVT of legs or PE and for whom 6 mos. of anticoagulant therapy was considered to be appropriate treatment

Initial parenteral anticoagulation

Dabigatran 150 mg twice daily x 6 months

N=1274

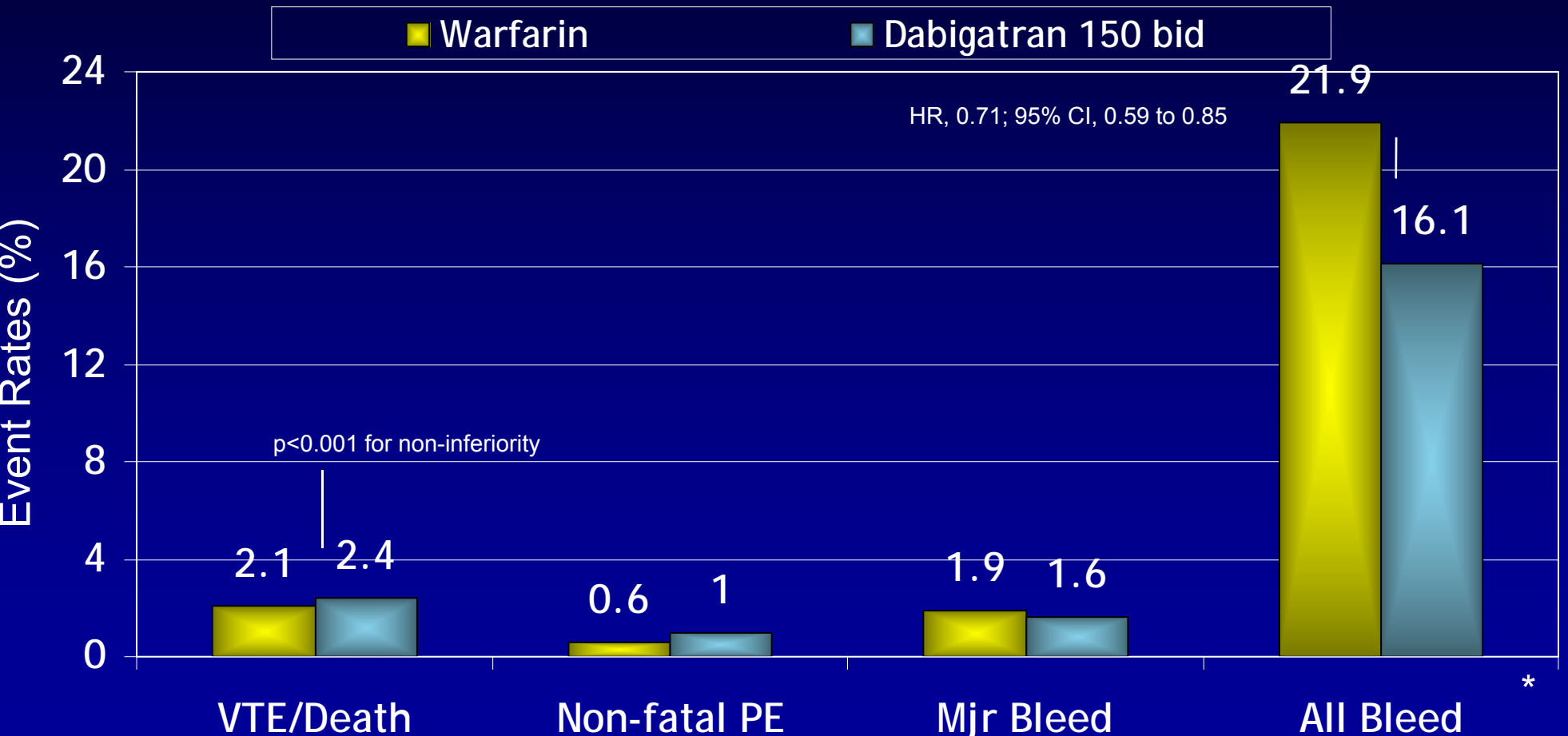
Dose-adjusted Warfarin for INR 2-3 x 6 months

N= 1265

- Double-blinded, double-dummy, randomized, non-inferiority trial
- Primary outcome: time to 1<sup>st</sup> occurrence of symptomatic VTE or death assoc. w/ VTE w/in 6 mos.
- Assessed at 7 days, then qmos. for 6 months

# RE-COVER: Dabigatran in Acute VTE

Open label, randomized non-inferiority trial of AT +Dabigatran 150mg BID versus AT+VKA (INR 2-3) for 6 months (n=2,564)



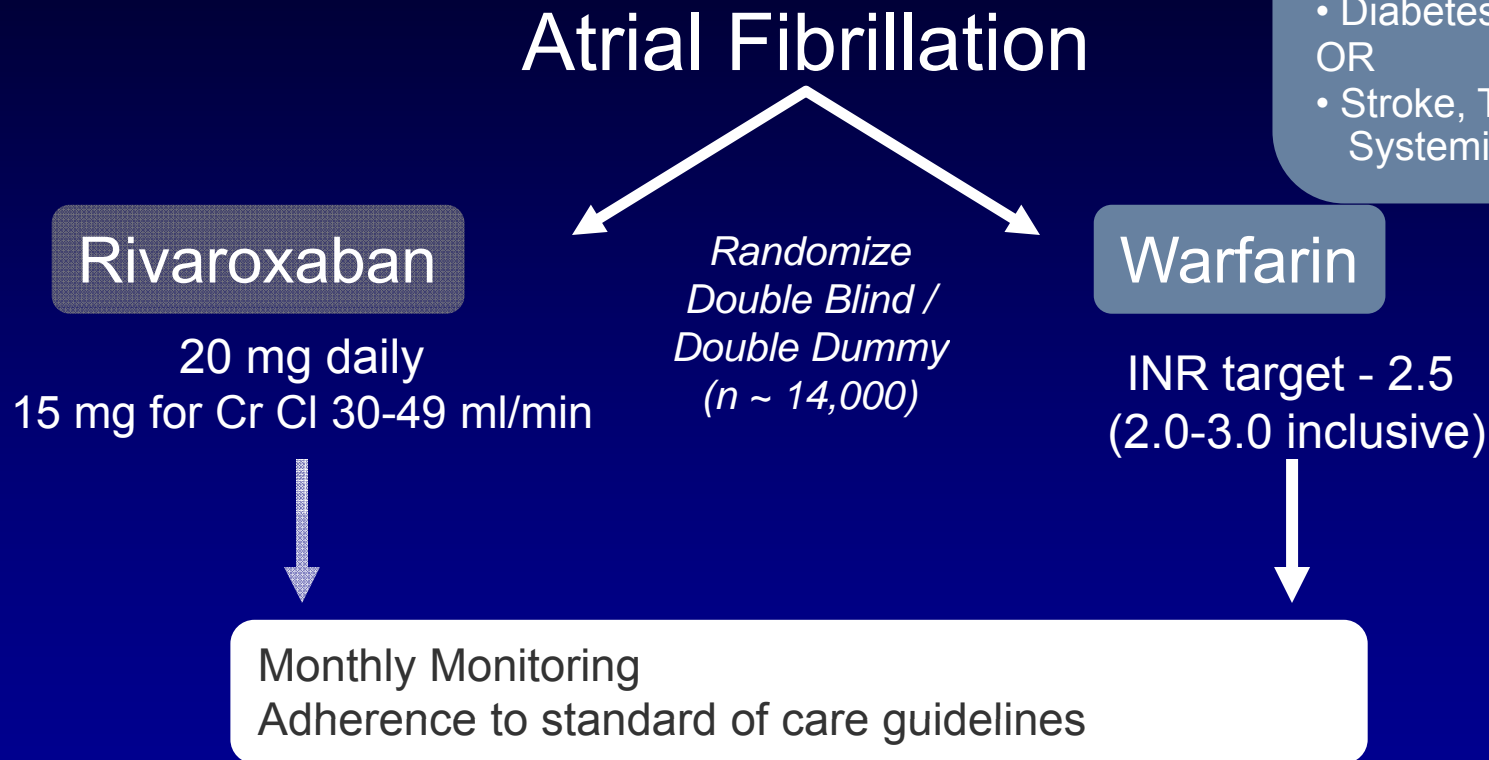
# Dabigatran for Prevention of VTE after Major Orthopaedic Surgery: Results

	Enoxaparin	Dabigatran (150 mg)	Dabigatran (220 mg)
<b>DVT, PE and all-cause mortality (%)</b>			
<b>RE-NOVATE</b>	6.7	8.6 <i>p</i> <0.0001*	6.0 <i>p</i> <0.0001*
<b>RE-MOBILIZE</b>	25.3	33.7 <i>p</i> =0.0009†	31.1 <i>p</i> =0.02†
<b>RE-MODEL</b>	37.7	40.5 <i>p</i> =0.0005*	36.4 <i>p</i> =0.0345*
<b>Major bleeding (%)</b>			
<b>RE-NOVATE</b>	1.6	1.3	2.0
<b>RE-MOBILIZE</b>	1.4	0.6	0.6
<b>RE-MODEL</b>	1.3	1.3	1.5

\*Non-inferior to enoxaparin; †inferior to enoxaparin

Eriksson *et al. Blood* 2006; Friedman *et al. J Thromb Haemost* 2007; Eriksson *et al. J Thromb Haemost* 2007

# ROCKET AF: Study Design



## Risk Factors

- CHF
- Hypertension
- Age  $\geq$  75
- Diabetes

$\geq 2$  required\*

OR

- Stroke, TIA or Systemic embolus

**Primary Endpoint: Stroke or non-CNS Systemic Embolism**

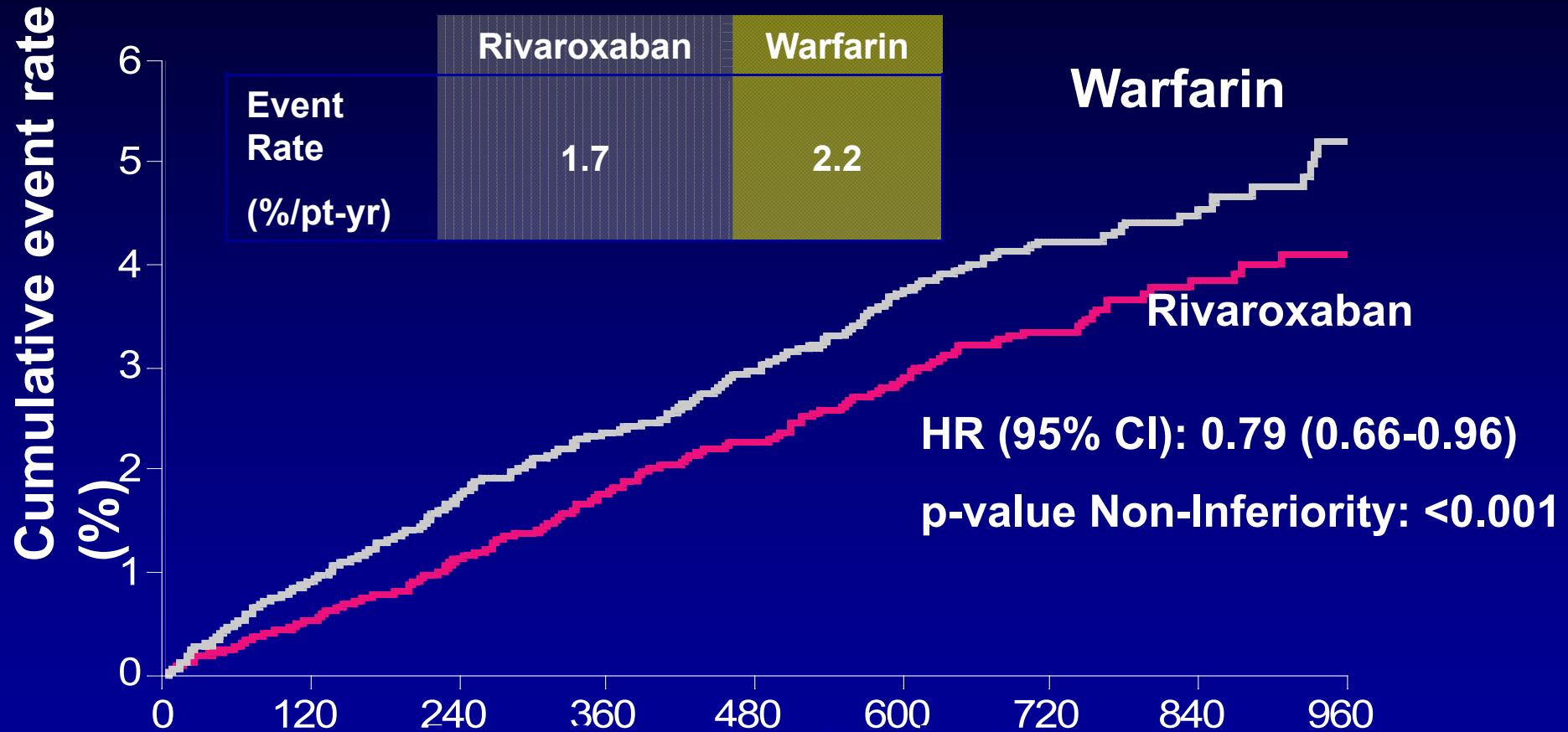
- Enrollment of patients without prior Stroke, TIA or systemic embolism and only 2 factors capped at 10%
- Remainder of patients with CHADS2  $\geq$  3

# ROCKET- AF: Baseline Characteristics

Characteristic	Rivaroxaban 20 mg	Warfarin
Randomized	7131	7133
Median age (years)	73	73
Female (%)	39.7	39.7
CHADS2 score (mean)	3.48	3.46
2 (%)	13	13.1
3 (%)	42.9	44.3
4 (%)	29.3	28.0
5 (%)	13.1	12.4
6 (%)	1.7	2.2
Prior stroke/TIA/Syst Embolism(%)	54.9	54.6
Prior MI (%)	16.6	18.0
CHF (%)	62.6	62.3
Baseline ASA (%)	36.3	36.7
Baseline Warfarin (%)	62.3	62.5

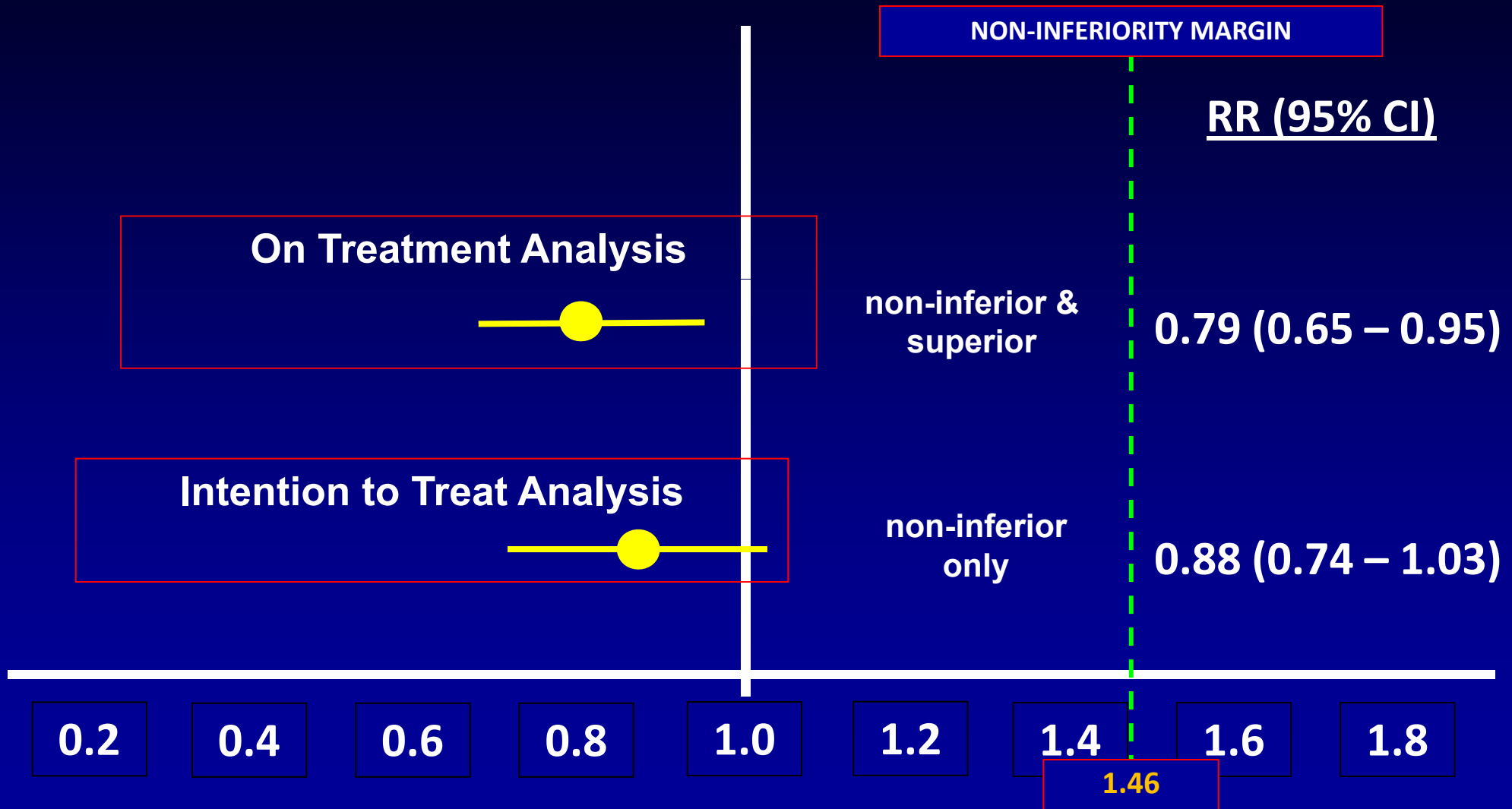
# ROCKET AF: Primary Endpoint

Composite: Stroke or Systemic Embolism  
On-Treatment Analysis



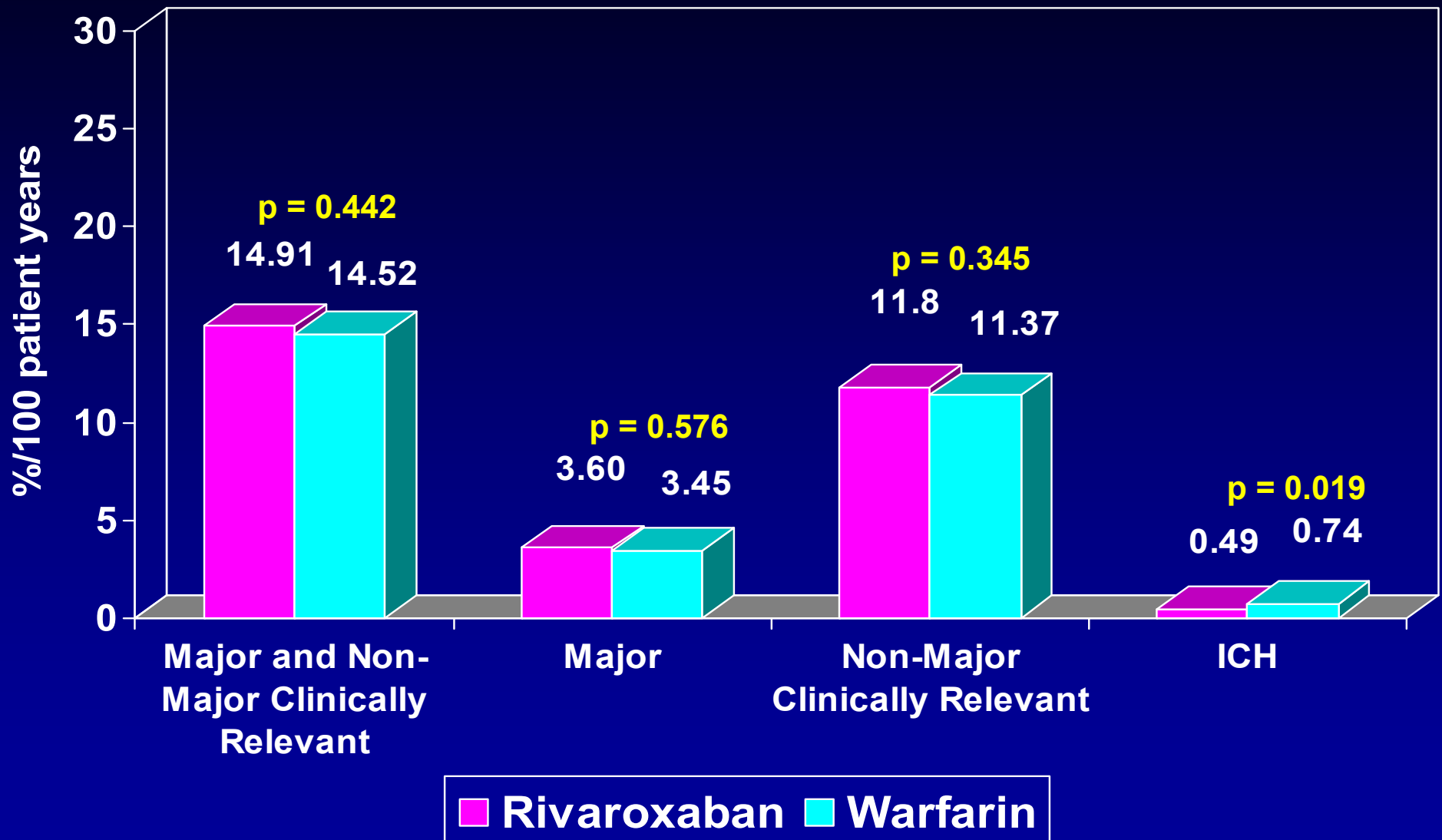
# ROCKET AF: Primary Endpoint Results

Composite: Stroke or Systemic Embolism



ROCKET AF Study Investigators. *Am Heart J.* 2010;159:340-7.  
Mahaffey KW et al. Presented at AHA Scientific Sessions; Nov. 2010.

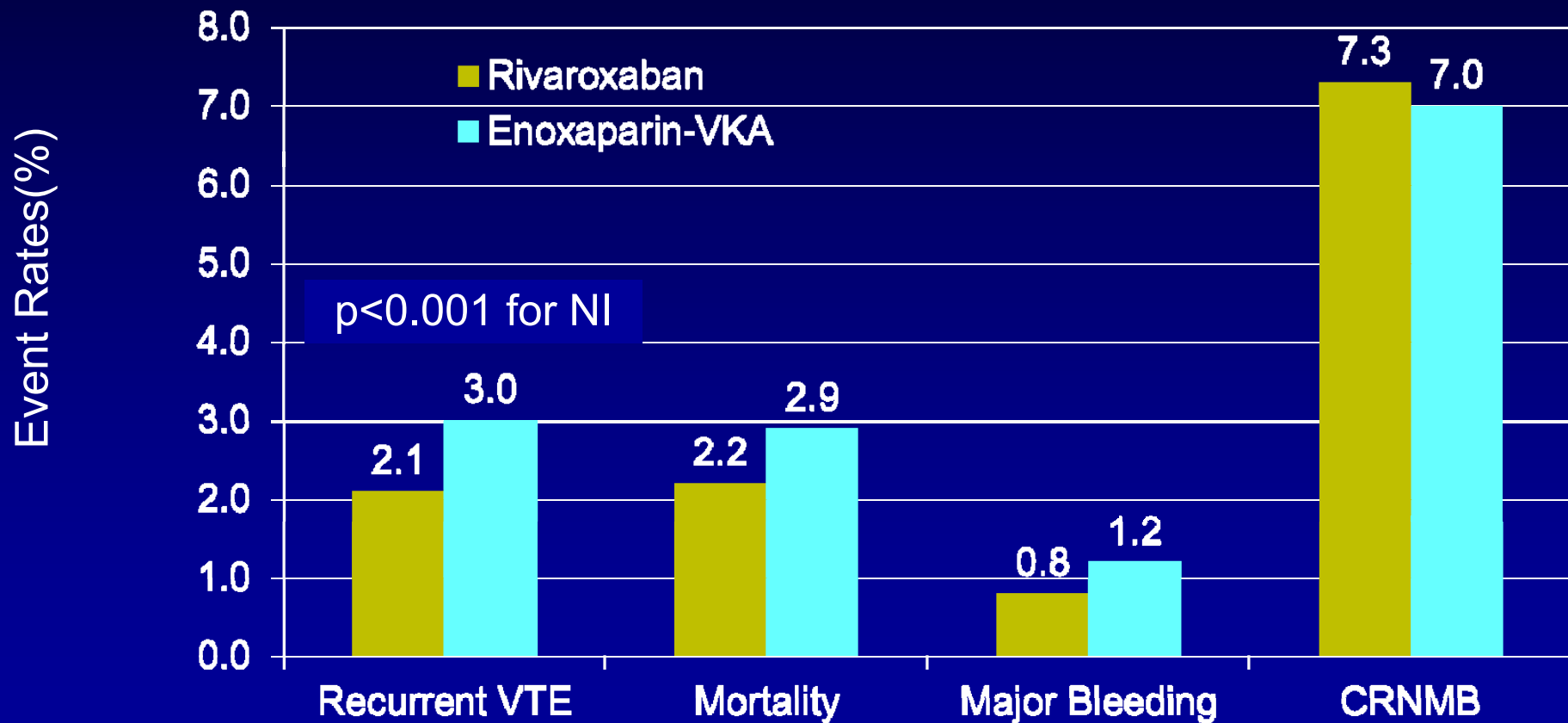
# ROCKET AF: Bleeding Rates



ICH = intracranial hemorrhage

# EINSTEIN: Rivaroxaban in Acute VTE

Open label, randomized non-inferiority trial of Rivaroxaban\* versus Enoxaparin + VKA (INR 2-3) for 6 months in 3,449 DVT/PE patients

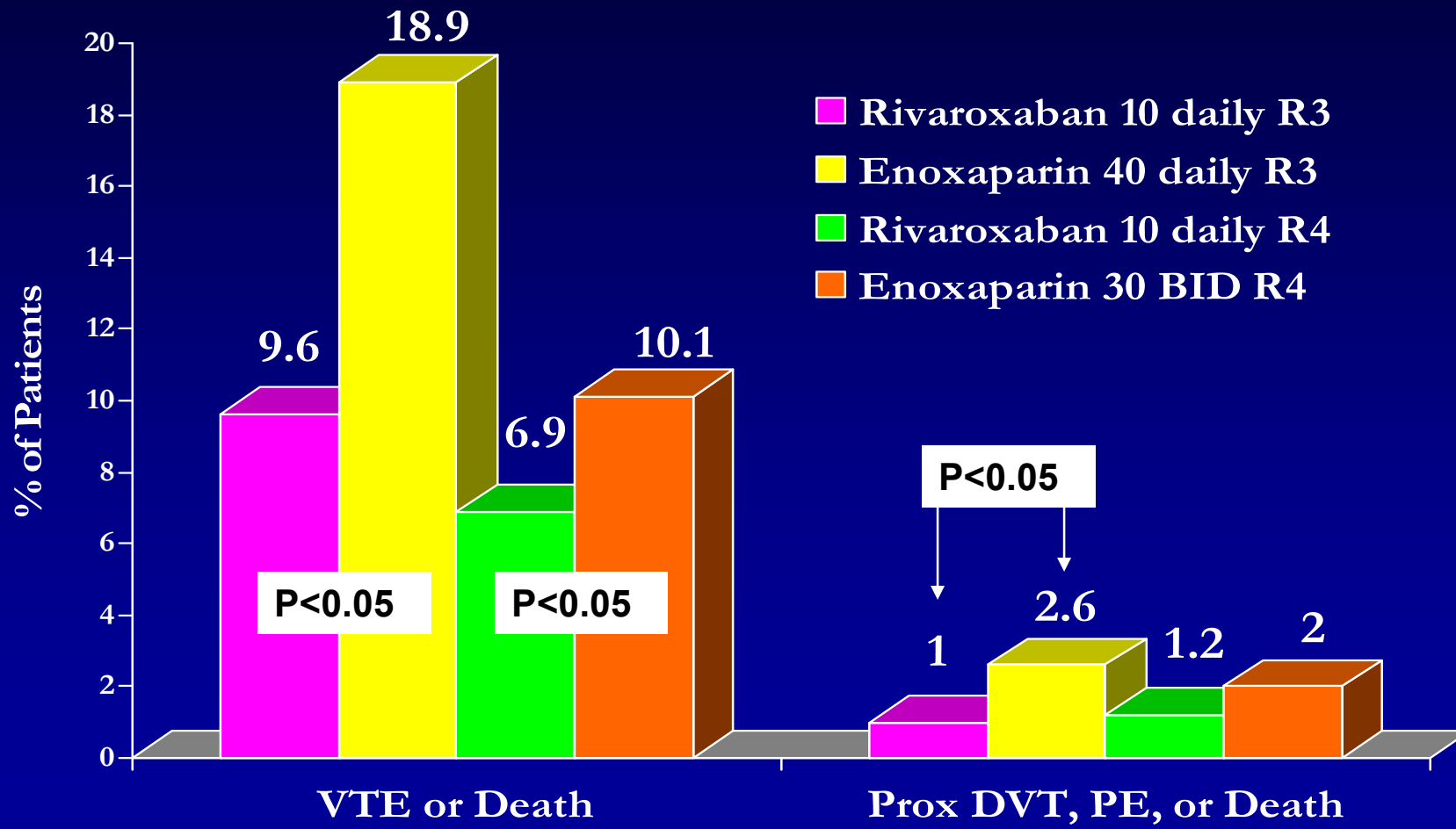


\*15mg BID x 3 weeks then 20mg QDay

# Rivaroxaban in Orthopedic Surgery

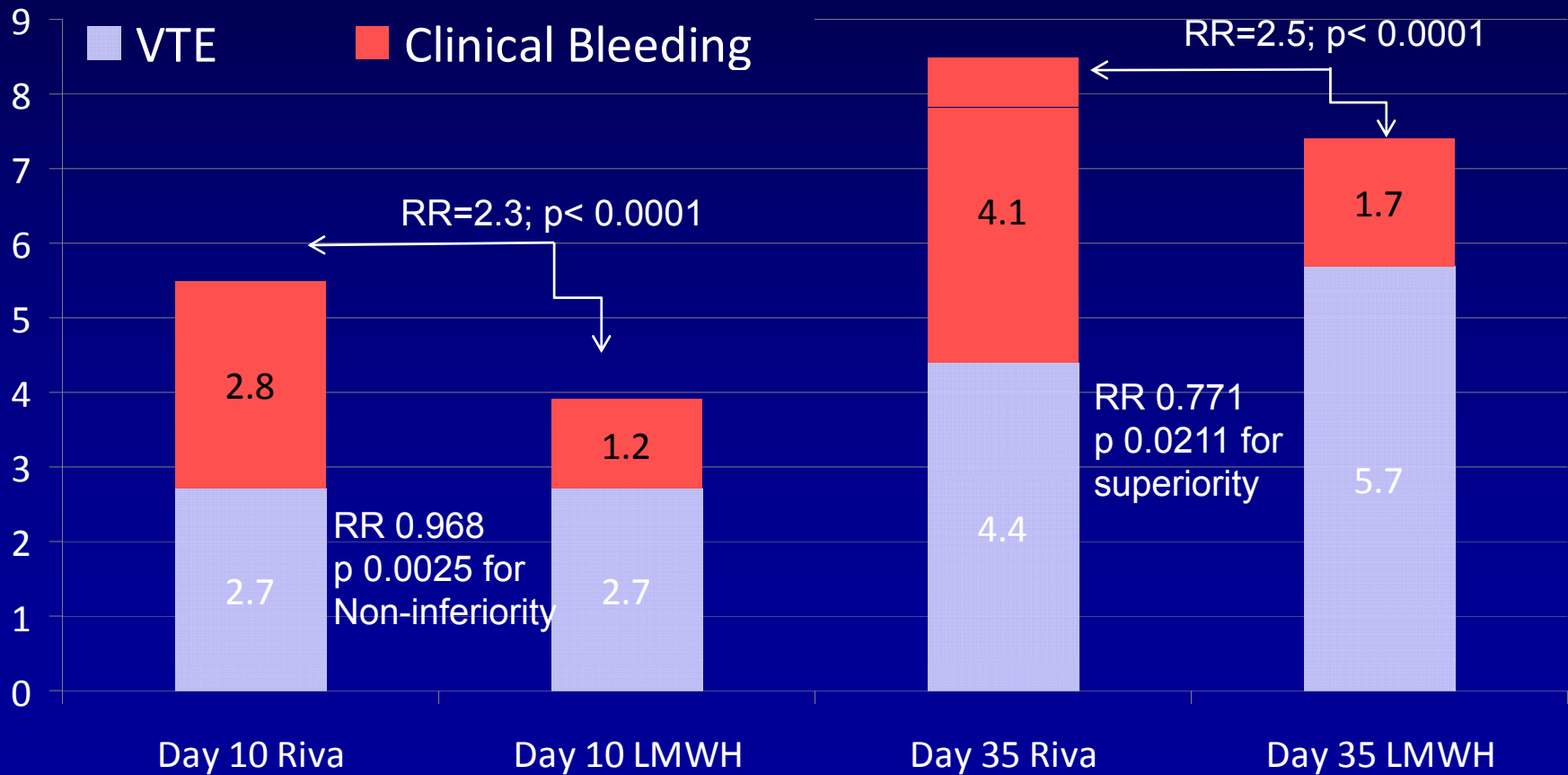
	Hip Trials		Knee Trials	
	RECORD 1	RECORD 2	RECORD 3	RECORD 4
Rivaroxaban dosing	10 mg qd	10 mg qd	10 mg qd	10 mg qd
Comparator dosing	Enoxaparin 40 mg qd	Enoxaparin 40 mg qd	Enoxaparin 40 mg qd	Enoxaparin 30 mg bid
Duration	Riva: 35 days Enox: 35 days	Riva: 35 days Enox: 14 days	14 days	14 days
Target or ongoing enrollment	4541	2509	2531	3148
Follow-up	40 ± 4 days	36 ± 4 days	12 ± 2 days	12 ± 2 days
Primary endpoint	Total VTE or death	Total VTE or death	Total VTE or death	Total VTE or death

# Rivaroxaban efficacy in TKA's RECORD 3 and 4 Results



# Magellan Medically Ill Trial

8,101 medical patients were randomized to either oral rivaroxaban 10mg once daily for 35 days or subcutaneous enoxaparin 40mg once daily for 10 days followed by placebo.



# **FDA approves oral anticoagulant rivaroxaban for DVT prevention at surgery**

July 1, 2011 | [Steve Stiles \(www.theheart.org\)](http://www.theheart.org)

## **• INDICATIONS AND USAGE**

- XARELTO is a factor Xa inhibitor indicated for the prophylaxis of deep vein thrombosis (DVT) which may lead to pulmonary embolism (PE) in patients undergoing knee or hip replacement surgery. (1)

## **• DOSAGE AND ADMINISTRATION**

- The recommended dose of XARELTO is 10 mg taken orally once daily with or without food. The initial dose should be taken at least 6 to 10 hours after surgery once hemostasis has been established.
- For patients undergoing hip replacement surgery, treatment duration of 35 days is recommended.
- For patients undergoing knee replacement surgery, treatment duration of 12 days is recommended.

**OK, so how do we make this work in  
the real world???**

# Pharmacokinetics of New Antithrombotic Agents

	Dabigatran	Rivaroxaban	Apixaban
<b>Tmax</b>	1.25-3 hours	2-4 hours	1-3 hours
<b>T 1/2</b>	12-14 hours	5-9 hours	8-15 hours
<b>Metabolism</b>	Conjugation (no CYP involvement)	Oxidation (via CYP3A4 and CYP2J2) and hydrolysis	Oxidation (via CYP3A4) and conjugation
<b>Renal Excretion of Unchanged Drug</b>	80%	36%	25%
<b>Dialyzability</b>	Yes	Not expected	Unlikely
<b>Reversibility</b>	No antidote	No antidote	No antidote

# Dosing Regimens for Stroke Prevention in AF

Drug	Dose
Dabigatran	CrCl >30 mL/min: 150 mg po BID CrCl 15-29 mL/min: 75 mg po BID <sup>1</sup> CrCl <15 mL/min: Not recommended
Rivaroxaban <sup>2</sup>	CrCl ≥50 mL/min: 20 mg po daily CrCl 30-49 mL/min: 15 mg po daily CrCl <30 mL/min: Excluded from ROCKET AF
Apixaban <sup>2</sup>	5 mg po BID Dose adjusted to 2.5 mg po BID based on age, wt, and SCr in ARISTOTLE (CrCl <25 mL/min excluded)

<sup>1</sup> Based on pharmacokinetic modeling. Not studied clinically

<sup>2</sup> Not FDA approved

# Dabigatran Dosing and Risk for Bleeding

- Major bleeding in overall population
  - 110 mg: 2.71%
  - 150 mg: 3.11%
  - Warfarin: 3.36%
- Major bleeding in patients > 75 years of age
  - 110 mg: 4.17%
  - 150 mg: 4.81%
  - Warfarin: 4.09%

# Drug Interactions: CYP 450 enzymes

	Apixaban (Eliquis <sup>®</sup> )	Rivaroxaban (Xarelto <sup>®</sup> )	Dabigatran (Pradaxa <sup>®</sup> )	Warfarin (Coumadin <sup>®</sup> )
<b>CYP Inducers</b> ↓ AC effect	None	Rifampin Phenytoin Carbamazepine St John's Wort	None	Many
<b>CYP Inhibitors</b> ↑ AC effect	Azole antifungals* Macrolide abx Ritonavir	Azole antifungals* Ritonavir	None	Many

# Drug Interactions: P-glycoprotein

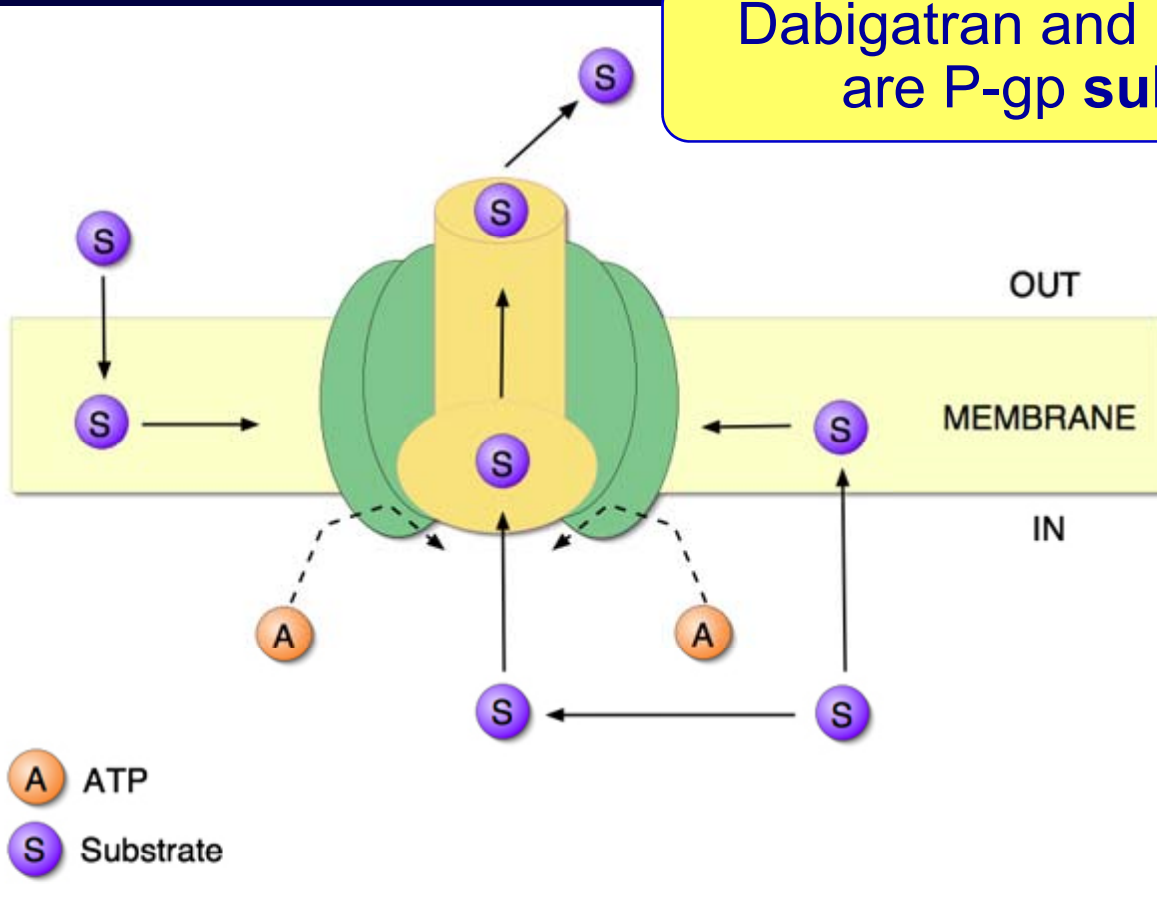
Dabigatran and Rivaroxaban  
are P-gp **substrates**

P-gp inducers  
↓ AC effect

Rifampin

P-gp inhibitors  
↑ AC effect

Amiodarone  
Verapamil  
Dronedarone



# Dabigatran: Drug Interactions

- Not a substrate of CYP P450
- P-glycoprotein substrate
  - P-gp inhibitors
    - Ketoconazole – AUC ↑ by 153%
    - Verapamil – Effect dependent on formulation and timing of administration of verapamil.
      - 1 hr before dabigatran → ↑ AUC by 250%
      - Concurrent administration → ↑ AUC by 170%
      - 2 hr after dabigatran → No change in AUC
    - Amiodarone – AUC ↑ by 58%; renal clearance ↑ 65% to compensate
    - Quinidine – AUC ↑ by 53%
  - P-gp inducers
    - Rifampin – AUC ↓ by 66% (AVOID combination with dabigatran)
- No interaction with PPIs, H<sub>2</sub> antagonists, or digoxin

# Rivaroxaban: Drug Interactions

## 7.1 Drugs that Inhibit Cytochrome P450 3A4 Enzymes and Drug Transport Systems

- In drug interaction studies evaluating the concomitant use with drugs that are combined P-gp and CYP3A4 inhibitors, increases in rivaroxaban exposure and pharmacodynamic effects (i.e., factor Xa inhibition and PT prolongation) were observed. Significant increases in rivaroxaban exposure may increase bleeding risk.
  - *Ketoconazole (combined P-gp and strong CYP3A4 inhibitor)*: Steady-state rivaroxaban AUC and C<sub>max</sub> increased by 160% and 70%, respectively. Similar increases in pharmacodynamic effects were also observed.
  - *Ritonavir (combined P-gp and strong CYP3A4 inhibitor)*: Single-dose rivaroxaban AUC and C<sub>max</sub> increased by 150% and 60%, respectively. Similar increases in pharmacodynamic effects were also observed.
  - *Clarithromycin (combined P-gp and strong CYP3A4 inhibitor)*: Single-dose rivaroxaban AUC and C<sub>max</sub> increased by 50% and 40%, respectively. The smaller increases in exposure observed for clarithromycin compared to ketoconazole or ritonavir may be due to the relative difference in P-gp inhibition.
  - *Erythromycin (combined P-gp and moderate CYP3A4 inhibitor)*: Both the single-dose rivaroxaban AUC and C<sub>max</sub> increased by 30%.
- Avoid concomitant administration of XARELTO with combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir/ritonavir, and conivaptan) which cause significant increases in rivaroxaban exposure that may increase bleeding risk.

# Rivaroxaban: Drug Interactions

## 7.2 Drug-Disease Interactions with Drugs that Inhibit Cytochrome P450 3A4 Enzymes and Drug Transport Systems

- Based on simulated pharmacokinetic data, patients with renal impairment receiving XARELTO with drugs that are combined P-gp and weak or moderate CYP3A4 inhibitors (e.g., erythromycin, azithromycin, diltiazem, verapamil, quinidine, ranolazine, dronedarone, amiodarone, and felodipine), may have significant increases in exposure compared with patients with normal renal function and no inhibitor use, since both pathways of rivaroxaban elimination are affected. Since these increases may increase bleeding risk, use XARELTO in this situation only if the potential benefit justifies the potential risk [*see Use in Specific Populations (8.7)*].

# Patients Not Necessarily Represented in Clinical Trials

An 88-year-old woman with atrial fibrillation was rhythm controlled with sustained-release verapamil and amiodarone. Her antithrombotic therapy with warfarin had been stable for more than 2 years without a change in dosage. A recent hospital admission for anxiety-related shortness of breath, unrelated to her atrial fibrillation or antithrombotic therapy, prompted a review of her therapy

# Additional Considerations

- Missed Doses
- Managing transitions from other anticoagulant agents
- Peri-operative Management
- Treatment of Bleeding
- Monitoring
- Agent specific considerations

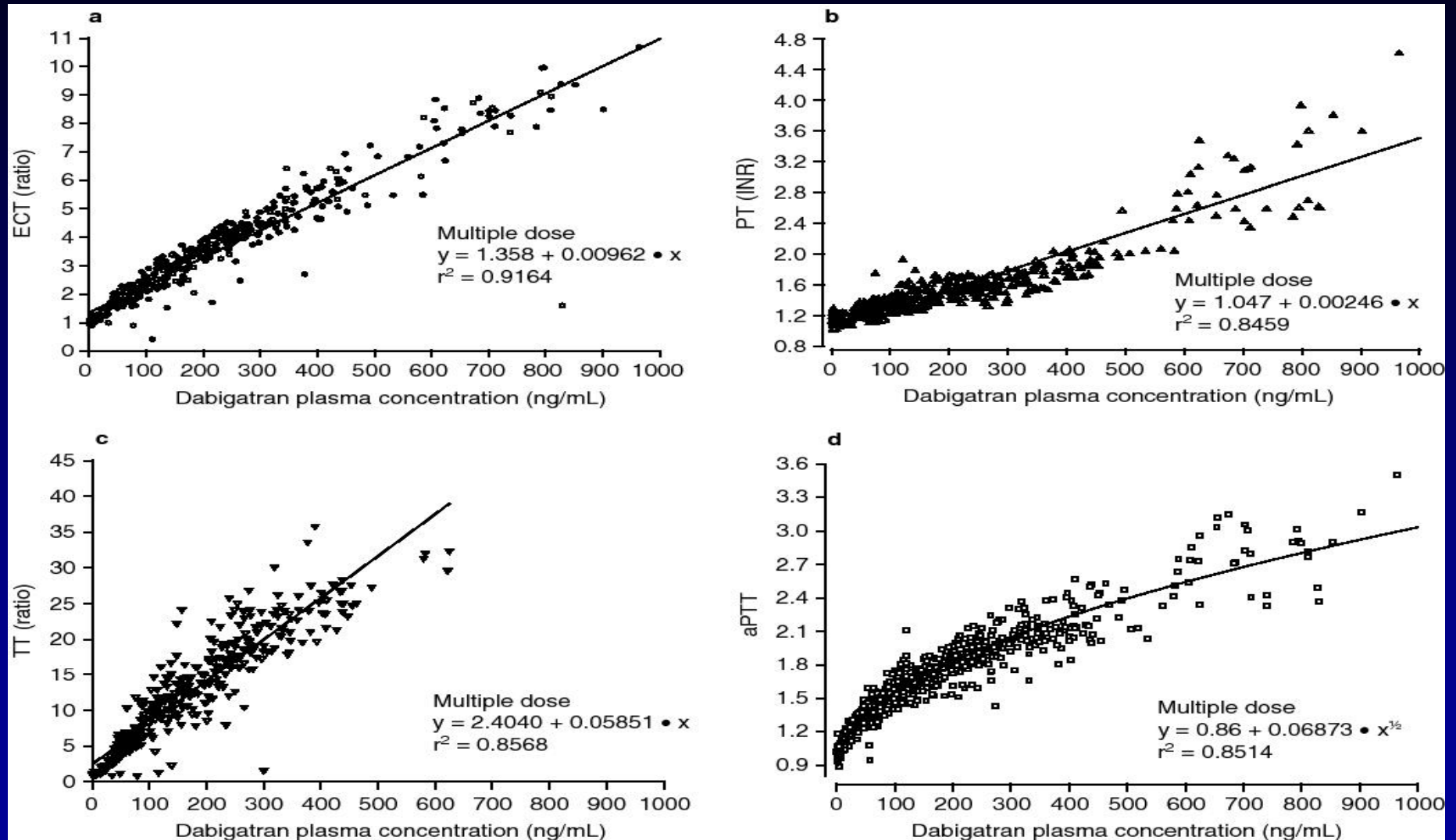
# Monitoring – new oral agents

- “OK, so I don’t need to monitor”
- “But, can I monitor if the clinical situation dictates that I have some knowledge of the extent of anticoagulation?”
  - Overdose
  - Pregnancy
  - Extremes of body weight
  - Major bleeding
  - Urgent surgical procedure
  - Assessment of compliance
  - Thromboembolic event
  - Titration of therapy if therapeutic failure
  - Organ dysfunction
  - Drug Interactions

# Monitoring - Issues

- Unlike warfarin, new oral agents exhibit circadian peak and trough activities
  - Need to know when in relation to dosing coagulation parameter was checked
  - Need to know when and how much last dose was

# Dabigatran – Effect on Clotting Assays



Stangier J. *Clin Pharmacokinet.* 2008; 47:285-95.

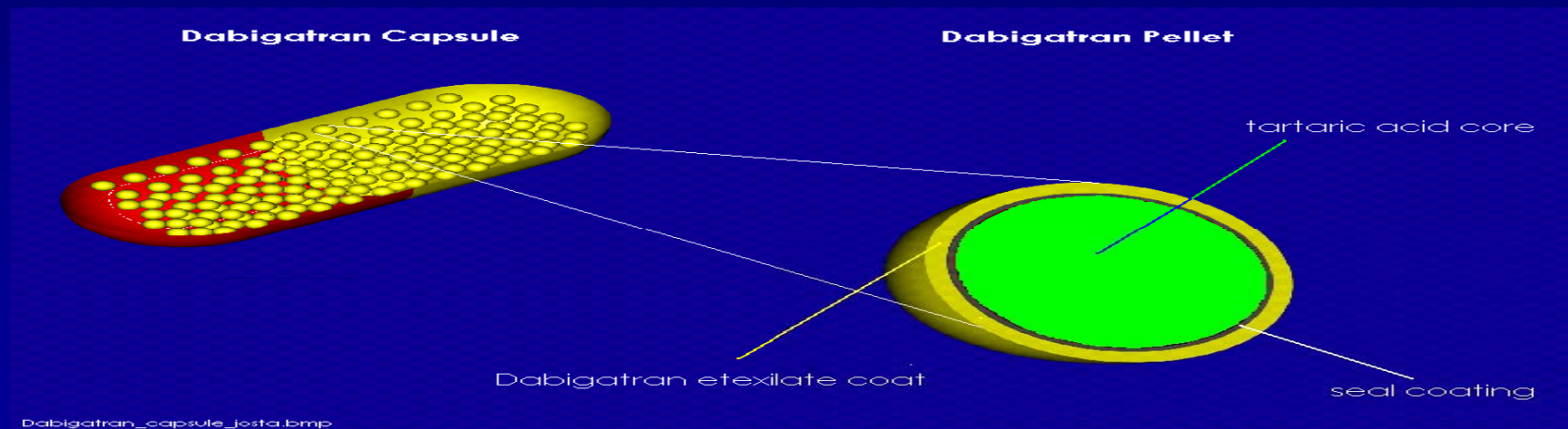
# Management of Bleeding on Dabigatran

- No antidote available
- In overdose setting
  - Activated charcoal has been demonstrated to work in vitro
- Local control measures should be employed
- Adequate diuresis should be maintained
- Administration of blood-products or FFP
- One study suggested dabigatran can be dialyzed
  - 62% removed at 2 hours
  - 68% removed at 4 hours
- Recombinant Factor VIIa has been shown to reverse effects of dabigatran ex vivo (rat model)

# Dabigatran: Ensuring Appropriate Use

## Capsule Stability

- Dabigatran exetilate requires an acid environment for absorption
- Capsules contain multiple drug pellets
- Each pellet has a tartaric acid core (coated with drug) that creates an acidic microenvironment to improve dissolution and absorption independent of gastric pH



**DO NOT CRUSH, CHEW OR BREAK CAPSULES**

# Dabigatran: Ensuring Appropriate Use Capsule Stability

- Once bottle is opened, contents must be used within 30 days
  - Cap on bottle contains dessicant to reduce moisture and avoid degradation
- Blister packs should be used in inpatient setting



# Potential Advantages of New Oral Anticoagulants

- Oral administration
- Rapid onset of action
  - Eliminates 2 AC regimen
- Predictable effect with fixed or weight-based dosing
  - No monitoring
- Less food/drug interactions
- Short half- life
  - Ease of reversal/ no bridging
- More convenient
  - Potentially leading to greater use
- More cost effective
  - No routine monitoring
  - Fewer ADEs requiring ER visits and hospitalizations
- Possible superior efficacy
- Possible superior safety

# Attributes May Also Be Disadvantages

## Clinical Management Attributes

### PK / PD Attributes

- Short half-life
- Disadvantage for elderly population
- AC effect poor
- Poor compliance than with V
- No antidote
- No evidence
- Immediate

- No routine lab marker available to monitor drug activity
  - Decreases early detection of issues/ education
  - Determine 'therapy failure' vs. poor compliance
  - No ability to tailor intensity of therapy (esp. with drug interactions)
- Inability to titrate when needed
  - 'One dose fits all' may be limiting
- Dose adjustment for renal/hepatic impairment? Varying weights?
  - No INR to guide therapy

## Societal Attributes

- Cost
- No generics available

# The Future for Warfarin?



- Warfarin will not disappear!
- Use will continue in many circumstances, including:
  - Mechanical heart valves and other un-studied indications
  - Patients who ‘fail’ therapy on a new AC
  - A monitored drug may be preferred for patients with:
    - Compliance issues
    - Drug interaction issues
    - Changing/ poor renal or hepatic function (dialysis?)
  - There may be initial resistance to new agents
    - Especially to convert over a stable warfarin patient
- More data
  - Head-to-head anti-Xa vs. DTI!