A New Era of Oral Anticoagulant Therapy

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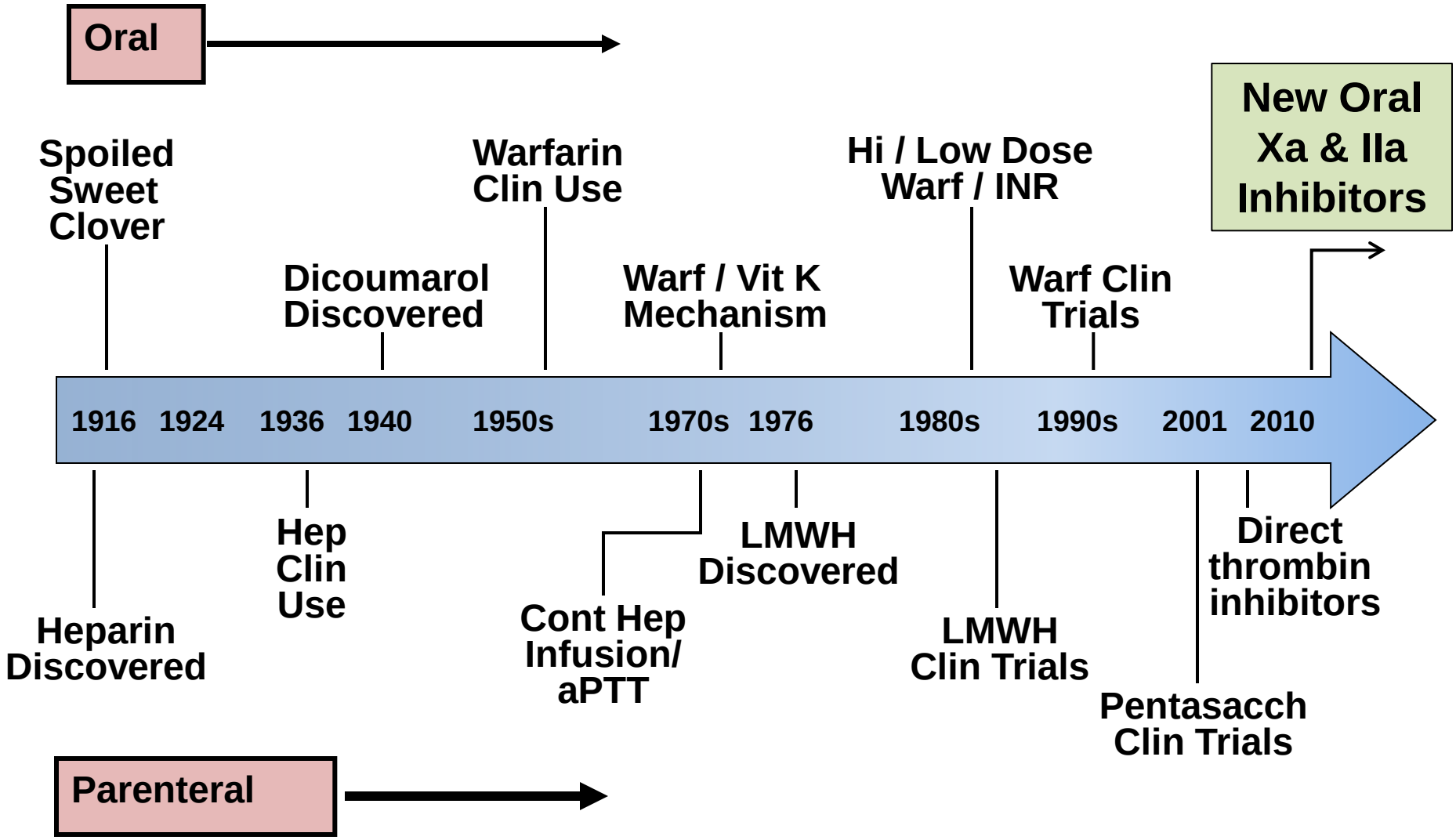
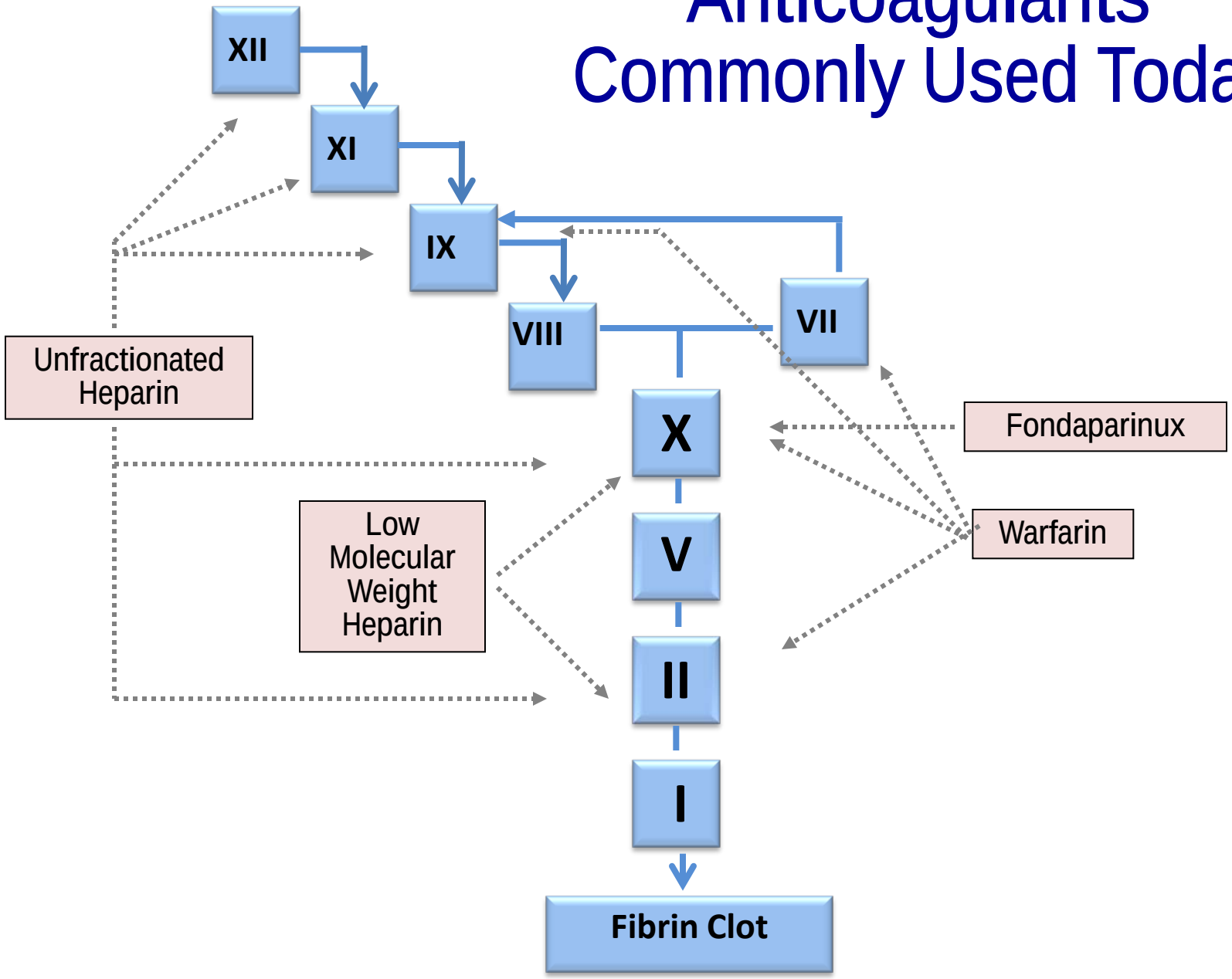
June 16, 2011

Disclosures: Consultant for
Ortho McNeil; Bristol Myers Squibb;
Boehringer Ingelheim; Daiichi

Anticoagulants – Highlights in Development



Anticoagulants Commonly Used Today



Problems with current therapy

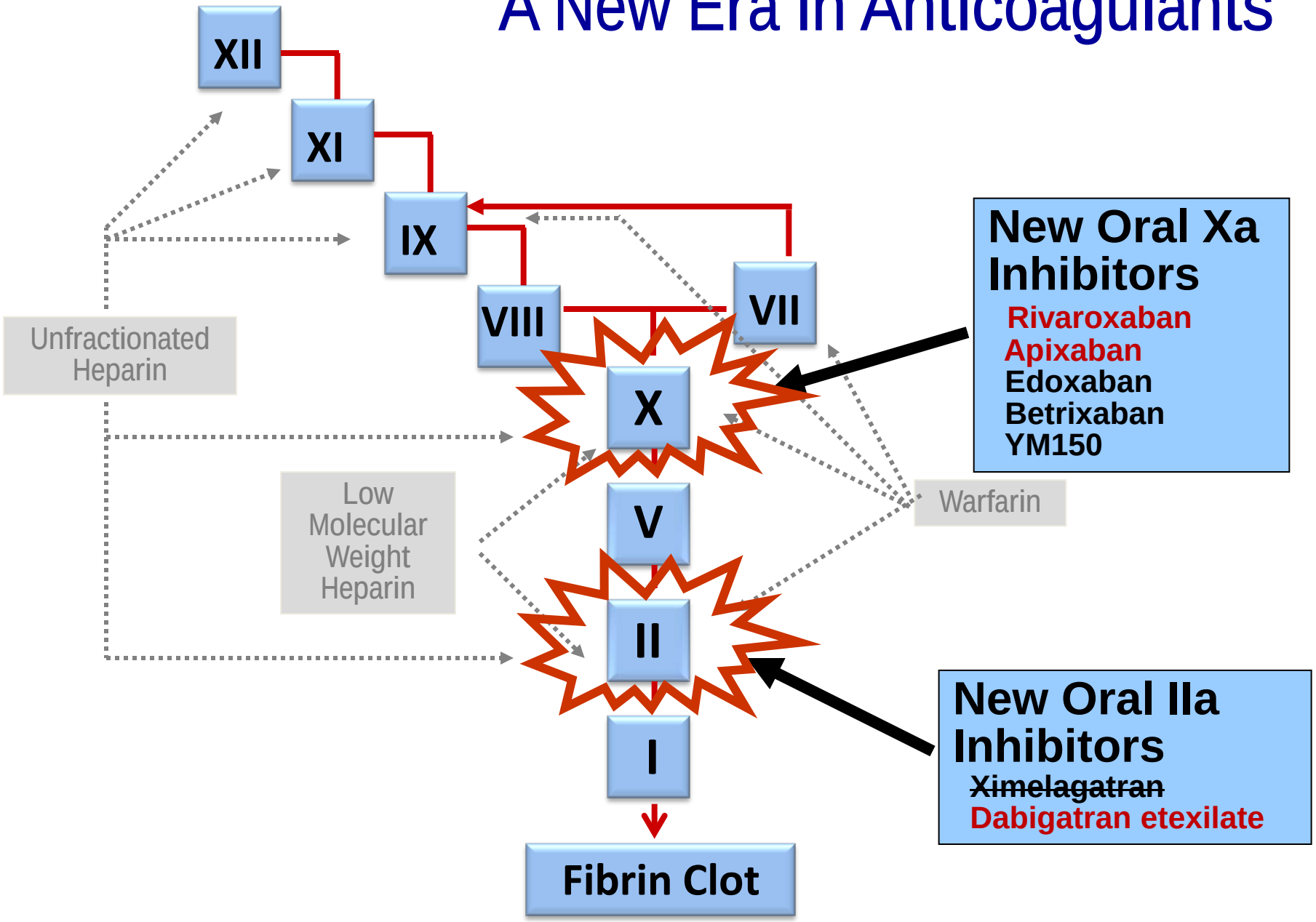
For Prevention

- Parenteral agents – no simple oral agent
- Expensive
- 2 drug regimen for selected indications (inpatient/outpatient)
- Side effects (e.g. HIT)

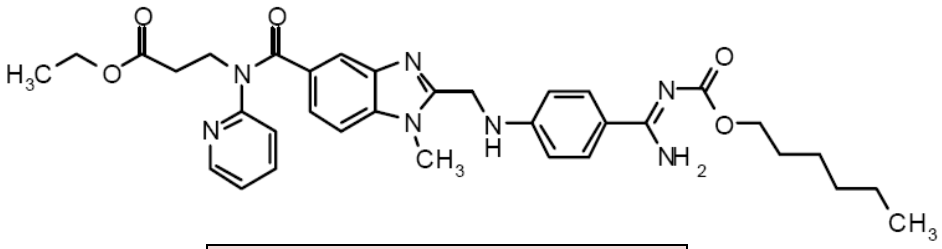
For Treatment

- 2 drug regimen: parenteral followed by oral agent
- Hospitalization often required
- Monitoring required
- Complex, burdensome therapy for both patient and doctor
- High rate of adverse events
- Under use of therapy

A New Era in Anticoagulants

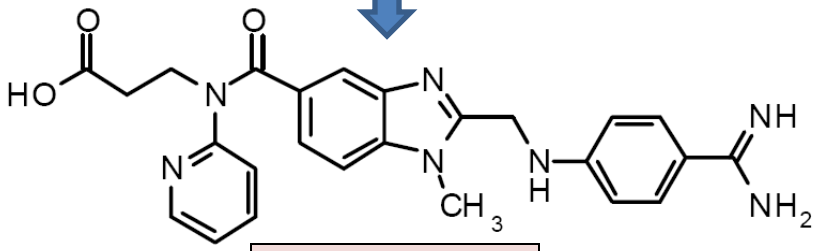


Factor IIa Inhibitors



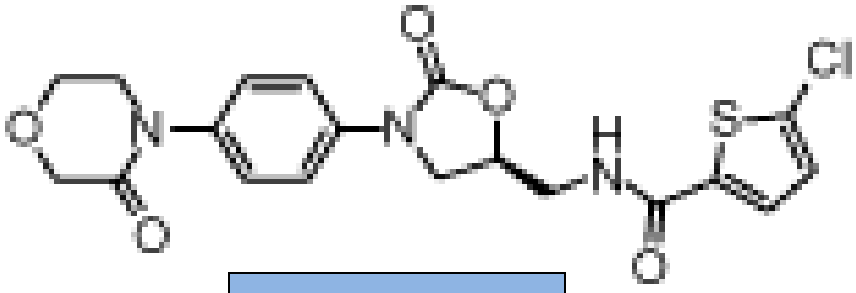
Dabigatran etexilate

Pro Drug

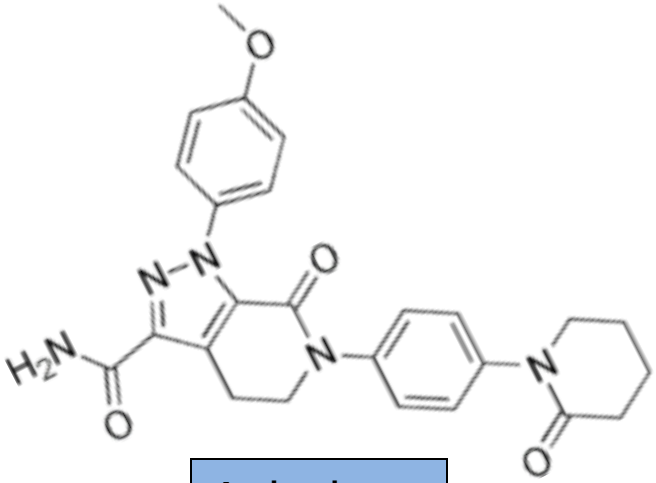


Dabigatran

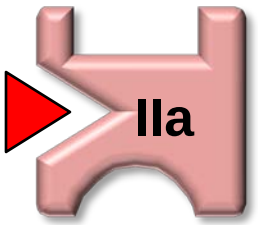
Factor Xa Inhibitors

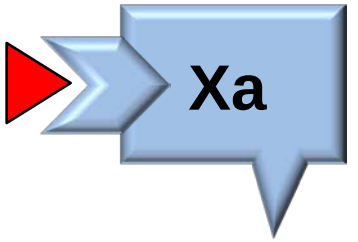


Rivaroxaban

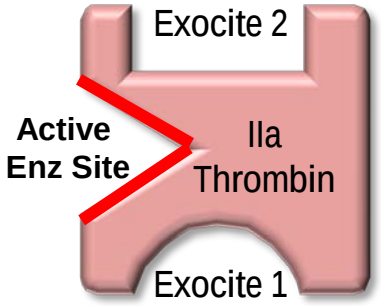


Apixaban





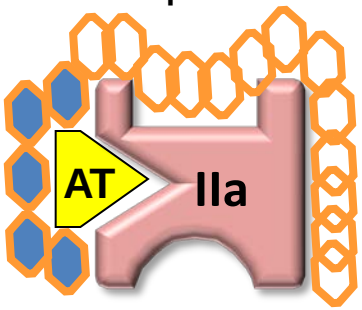
Thrombin (IIa)



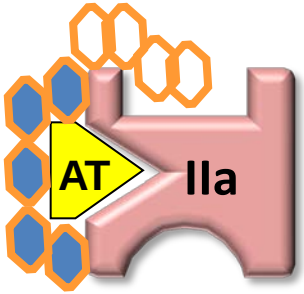
Exocite 1
Fibrin binding site

Exocite 2
Heparin binding site

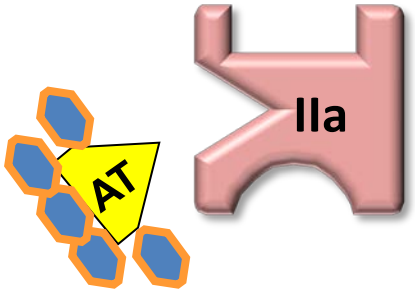
Unfractionated Heparin



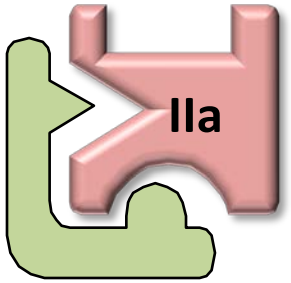
Low Molecular Weight Heparin



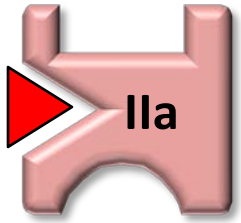
Fondaparinux



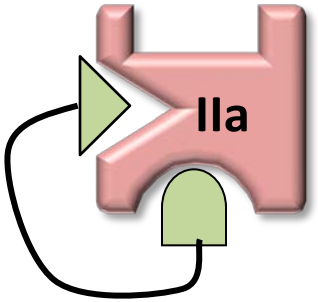
Lepirudin



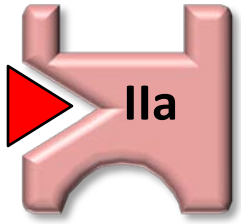
Argatroban



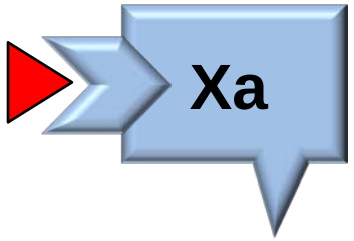
Bivalirudin



Dabigatran



Rivaroxaban
Apixaban



Comparative Features of Warfarin and New Oral Anticoagulants

	Warfarin	Dabigatran etexilate	Rivaroxaban	Apixaban
Target	Vit K epox reduc	Thrombin	Factor Xa	Factor Xa
Oral bioavailability	99%	6-7%	60-80%	80%
T (max)	72-96 h	2 h	2.5-4 h	3 h
Half-life	40 h	14-17 h	5-9 h healthy, 9-13 h elderly	8-15 h
Monitoring	INR-adjusted	Not needed	Not needed	Not needed
Administration	OD	OD or BID	QD or BID	BID
Metabolism / Elimination	Cytochrome P450	80% renal, 20% biliary	66% renal, 33% biliary	25% renal 75% biliary,
Antidote or treatment of bleeding	Vitamin K + FFP, APCC, or recFVIIa	Standard of Care (plasma or factor replacement; rVIIa)	Standard of Care (plasma or factor replacement; rVIIa) (Xa derivative)	Standard of Care (plasma or factor re placement; rVIIa) (Xa derivative)
Assay	PT/INR	Ecarin clotting time	Anti-factor Xa, PiCT®, HepTest®	Anti-factor Xa
Drug Interactions	CYP 2C9, 1A2, and 3A4	Potent P-gp inhibitors/ inducers; PPIs decrease absorp	Potent P-gp inhibitors/inducers; CYP3A4 inibitors	Potent P-gp inhibitors/inducers; CYP3A4 inibitors

Development Programs of New Oral Anticoagulants

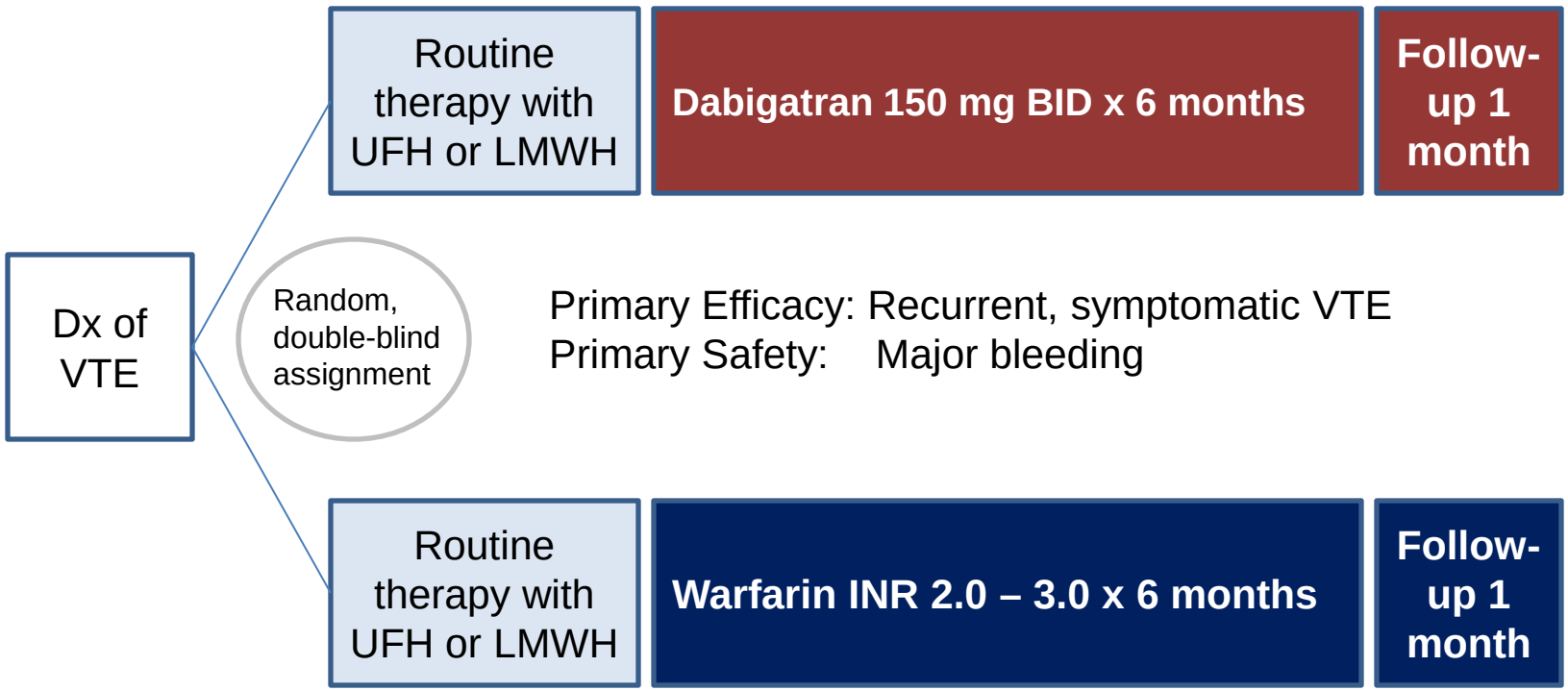
Condition	Dabigatran	Rivaroxaban	Apixaban
Hip Replacement	**Phase III**	**Phase III**	**Phase III**
Knee Replacement	**Phase III**	**Phase III**	**Phase III**
Stroke Prev in AF	**Phase III**	**Phase III**	Phase III **Phase III**
Medically Ill	----	**Phase III**	Phase III
ACS	Phase II	Phase III	**Phase III**
VTE Treatment Acute Chronic	 **Phase III** Phase III	 **Phase III** **Phase III**	 Phase III Phase III
Hip Fracture	----	----	----
Oncology	----	----	**Phase II**

Red: completed; **Green**: terminated early due to superiority; **Blue**: terminated early due to bleeding

Treatment of Acute DVT

Dabigatran vs Warfarin: RE-COVER Study

2539 patients with acute DVT treated initially with UFH/LMWH for a mean of10 days randomized to dabigatran, 150 mg BID vs warfarin (double blind); treatment for 6 months; Non-Inferiority Study (Abstract #1)



Dabigatran etexilate = **Pradaxa**

Schulman et al. NEJM 2009;361:2342

Treatment of Acute DVT

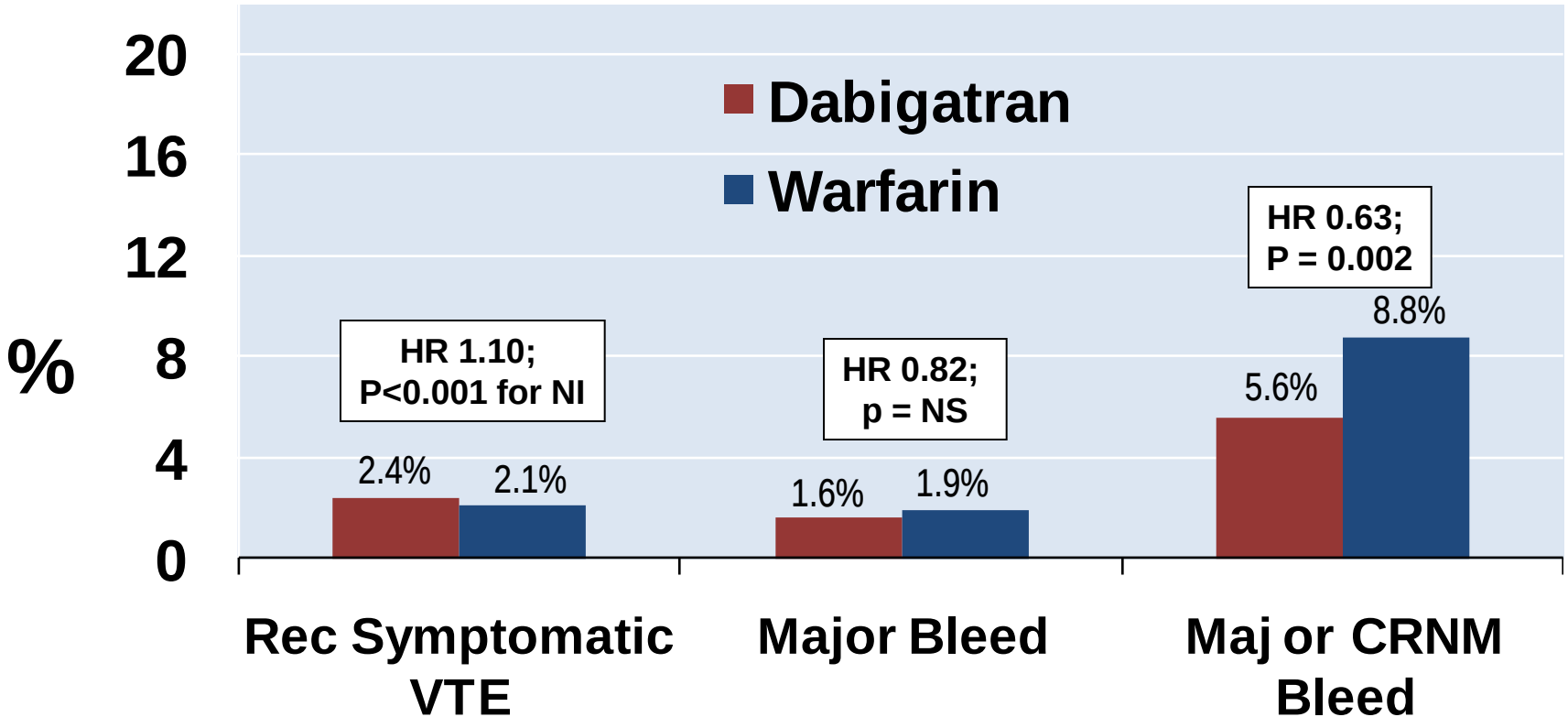
Dabigatran vs Warfarin: RE-COVER Study

	Dabigatran	Warfarin
#	**1,273**	**1,266**
DVT only	**69%**	**69%**
PE only	**21%**	**21%**
Cancer	**5%**	**5%**
Previous VTE	**26%**	**25%**
Parenteral AC pre-rand (days)	**2.8 d**	**2.8 d**
LMWH Rx	**89%**	**91%**
Time in Range	**-**	**60 %**

Schulman et al. NEJM 2009;361:2342

Treatment of Acute DVT

Dabigatran vs Warfarin: RE-COVER Study



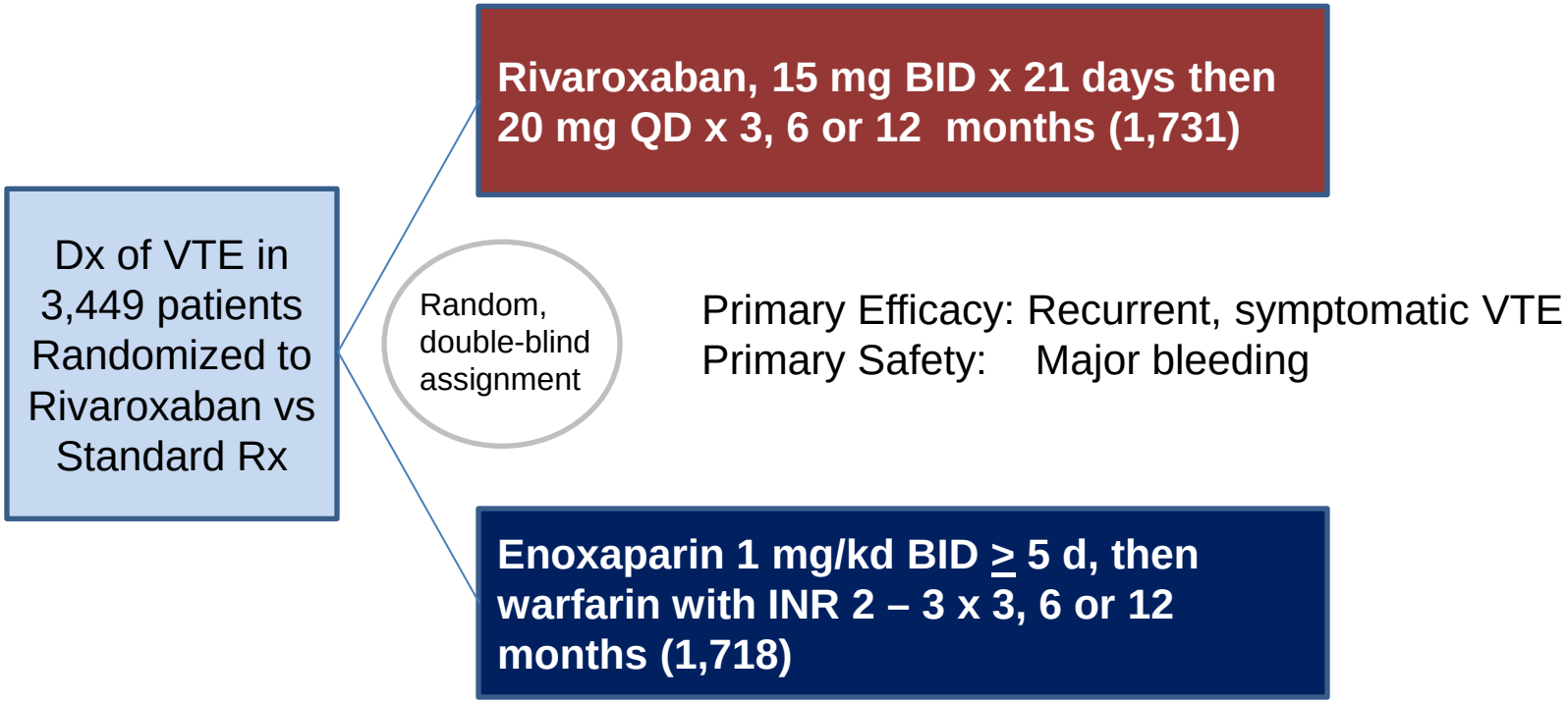
INR in range 60% of time; above range 19%; below range 21%

Schulman et al. NEJM 2009;361:2342

Treatment of Acute DVT

Rivaroxaban vs Standard Rx: EINSTEIN DVT

3,449 patients with acute DVT treated for 3 - 12 months with either rivaroxaban or enoxaparin followed by warfarin (open label).



rivaroxaban = **Xarelto**

Buller et al.ESC 2010; Session 708007 - 708008

Treatment of Acute DVT

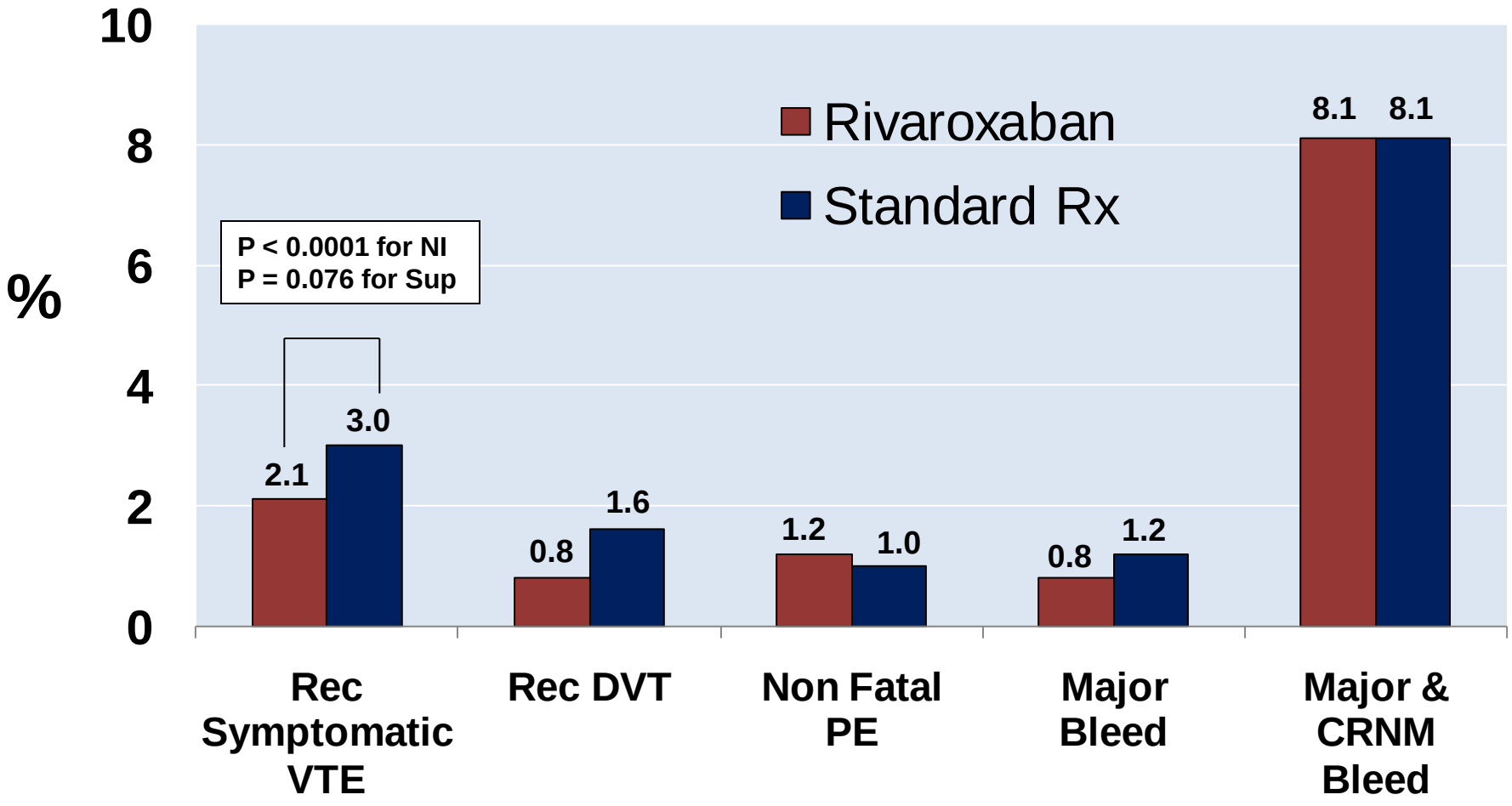
Rivaroxaban vs Standard Rx: EINSTEIN DVT

	Rivaroxaban	Warfarin
#	**1,731**	**1,718**
Age (mean)	**55.8**	**56.4**
Unprovoked DVT	**61%**	**63%**
Previous VTE	**19%**	**19%**
Parenteral AC pre-random	**73%**	**71%**
Duration Pre Rx	**4% >1 day**	**4% >1 day**
Time in Range	**-**	**58%**

Buller et al.ESC 2010

Treatment of Acute DVT

Rivaroxaban vs Standard Rx: EINSTEIN DVT

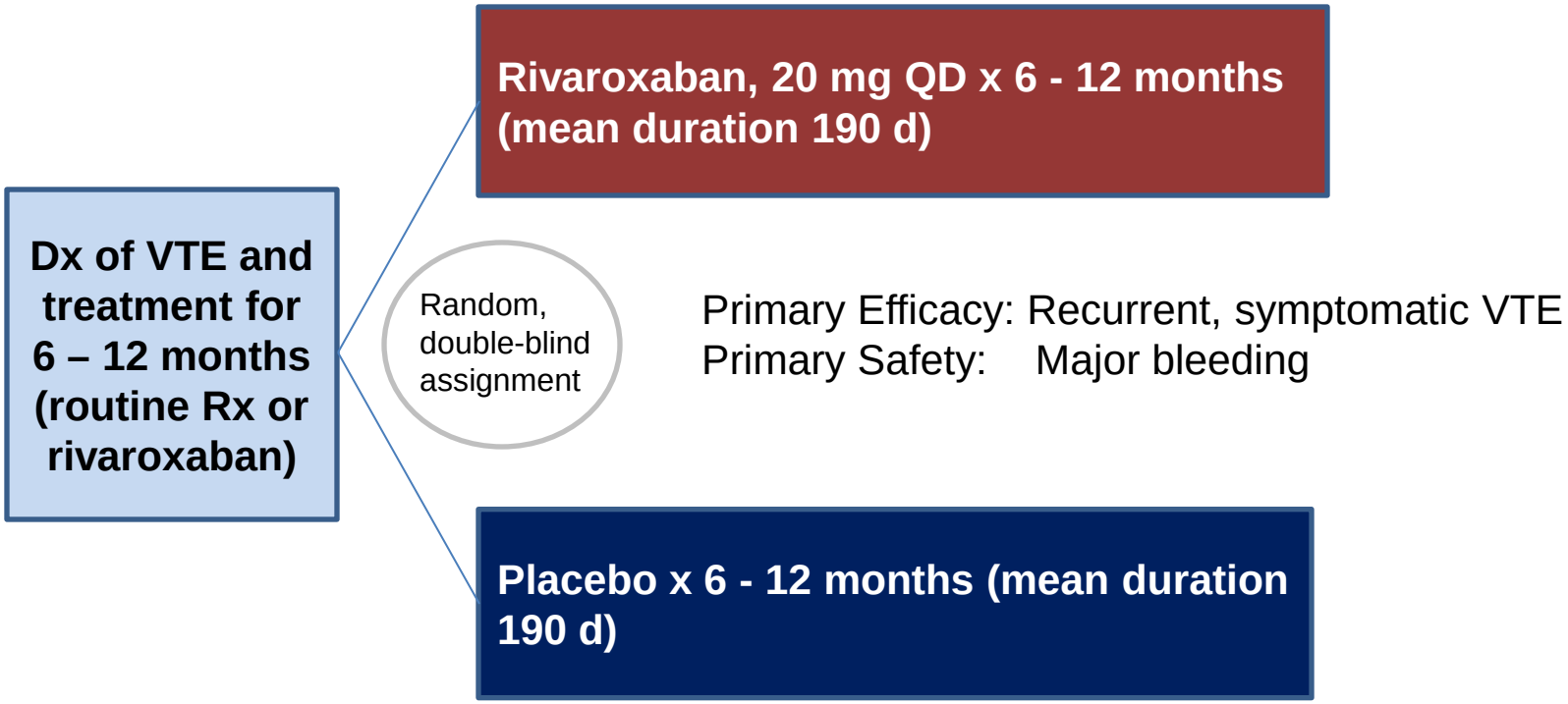


Buller et al.ESC 2010

Long-Term Treatment of DVT

Rivaroxaban vs Placebo EINSTEIN-Extension

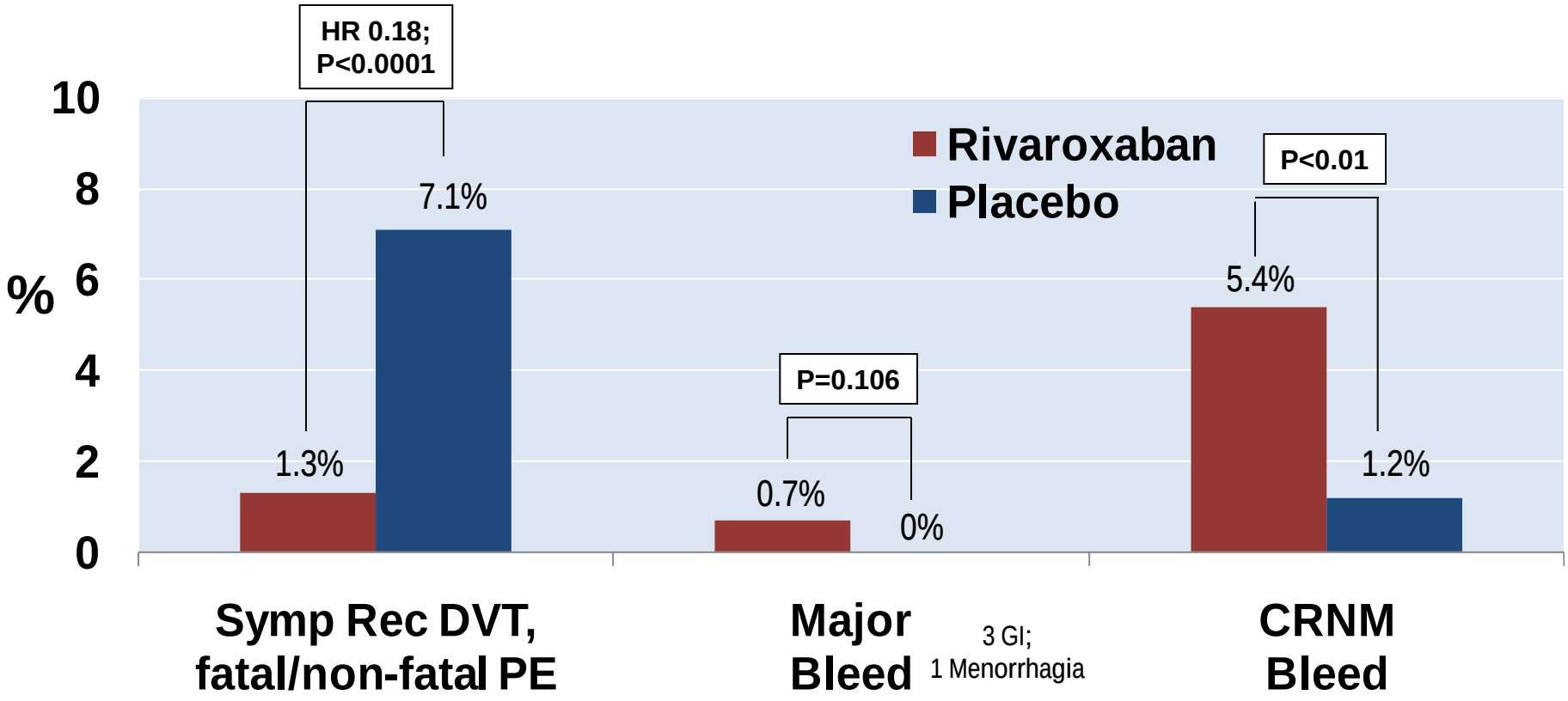
1197 patients with acute DVT treated for 6 - 12 mon with standard Rx or rivaroxaban and then randomized to rivaroxaban 20 mg QD vs placebo (double blind) and treated for 6 - 12 months; Superiority Study



Buller et al.Blood 2009;114:

Long-Term Treatment of DVT

Rivaroxaban vs Placebo EINSTEIN-Extension

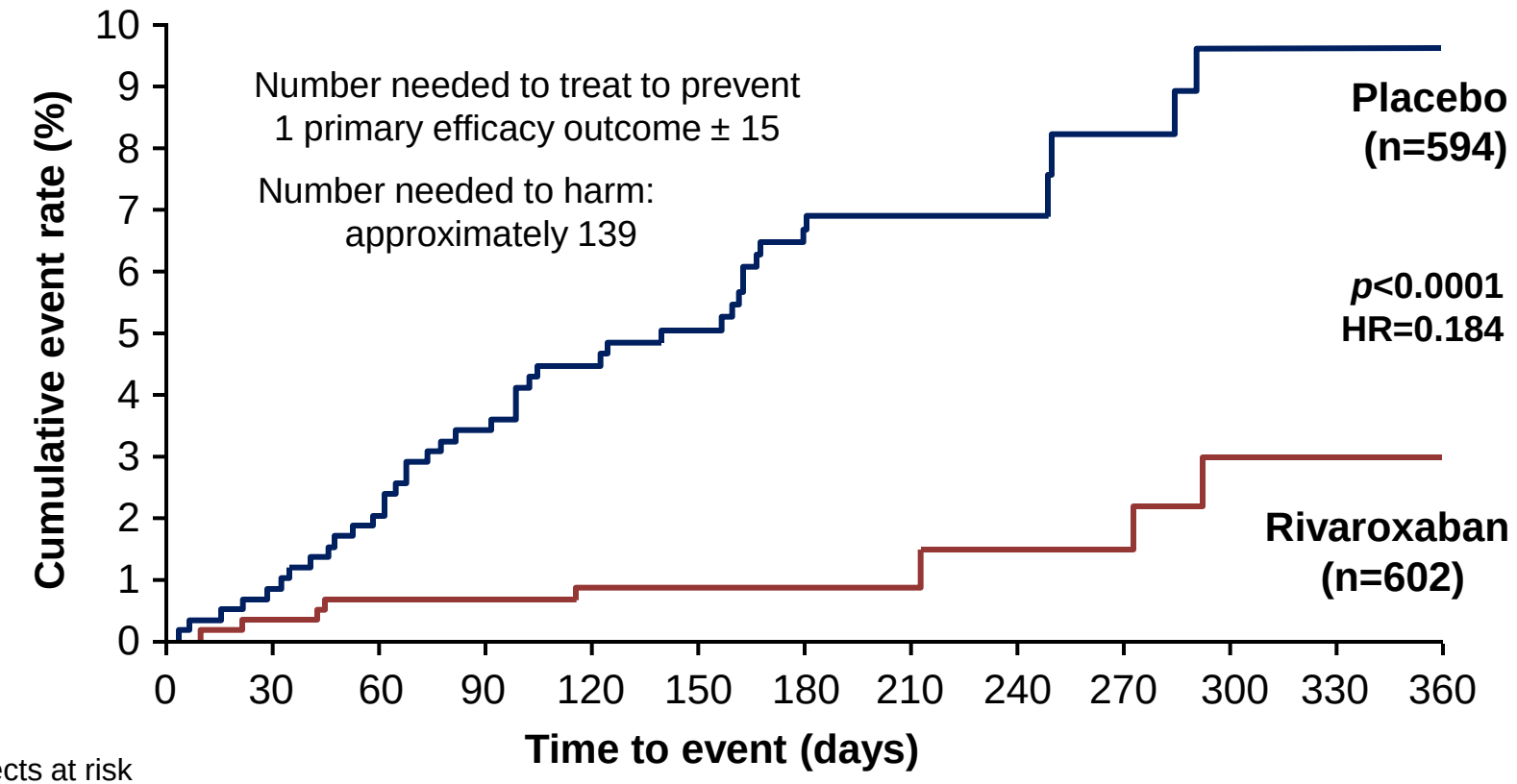


1197 patients with DVT treated for 6-12 months randomized to rivaroxaban, 20 mg QD vs placebo (double blind); mean duration of Rx 190 days

Buller et al.Blood 2009;114:

Long-Term Treatment of DVT

Rivaroxaban vs Placebo EINSTEIN-Extension



Subjects at risk

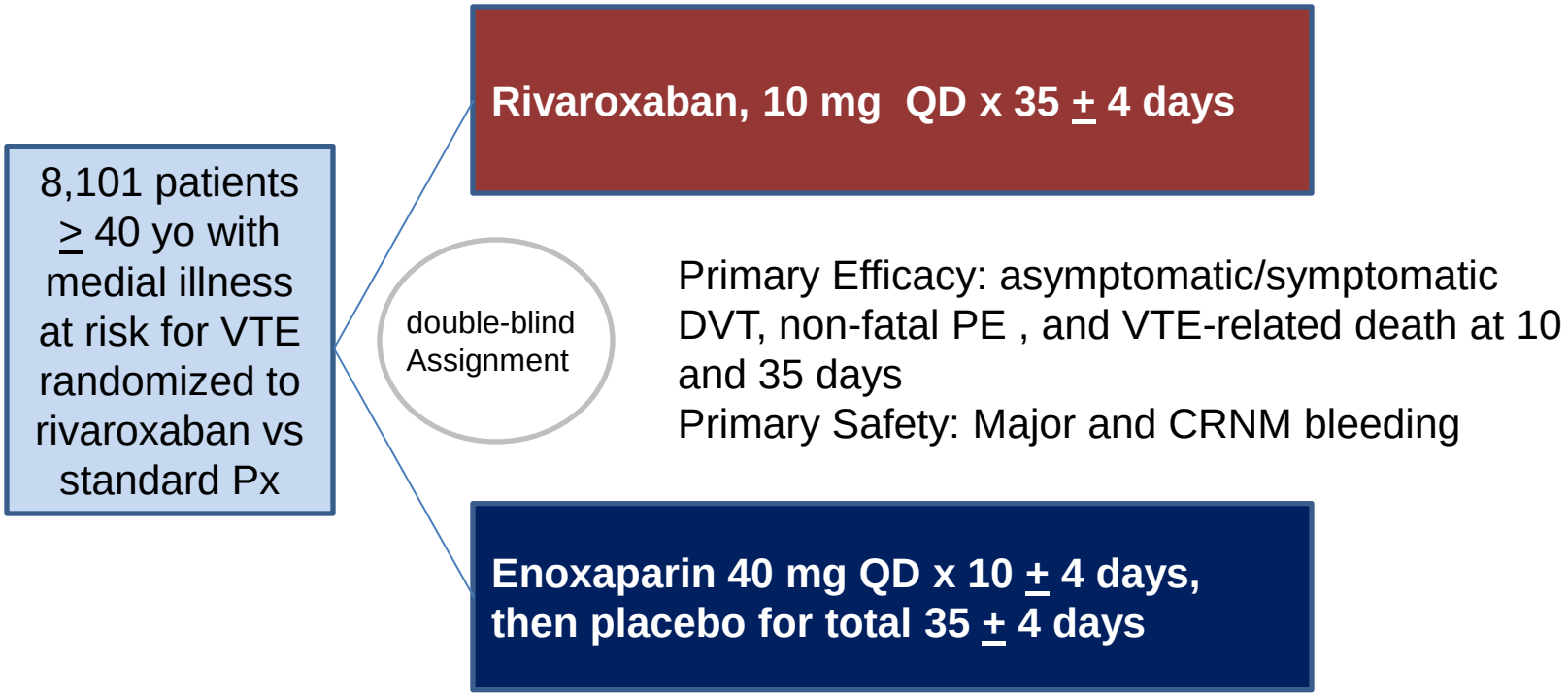
Rivaroxaban:	602	590	583	573	552	503	482	171	138	132	114	92	81
Placebo:	594	582	570	554	521	467	444	164	138	133	110	93	85

ITT population

Buller et al.Blood 2009;114:

Primary Post-Hospital Prophylaxis of VTE
Rivaroxaban vs Enoxaparin/Placebo: MAGELLAN

8,101 hospitalized patients with medical illness from 52 countries at risk for VTE treated for 35 ± 4 days with rivaroxaban vs enoxaparin (10 ± 4 d) followed by placebo. Ultrasound at d 10 ± 4 and d 35 ± 4



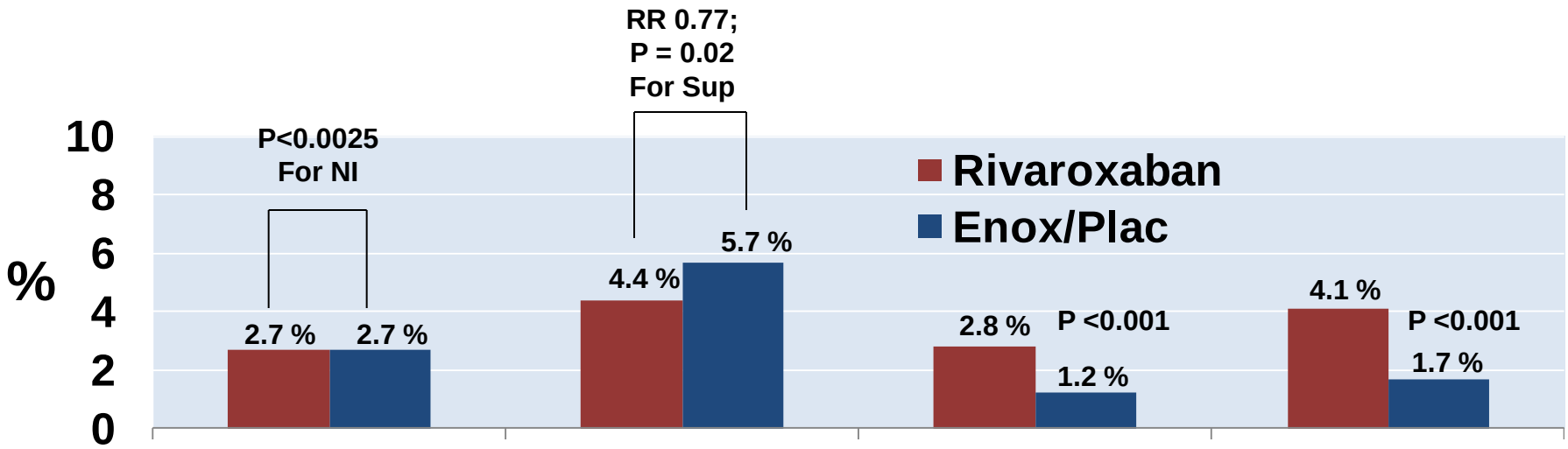
Approximately 45% acute infectious disease; 33% heart failure; 28% acute respiratory insufficiency; only 7% active cancer

Cohen et. al. ACC 2011; abstract

Primary Post-Hospital Prophylaxis of VTE

Rivaroxaban vs Enoxaparin/Placebo: MAGELLAN

Primary efficacy at d 10 non-inferiority and at d 35 superiority

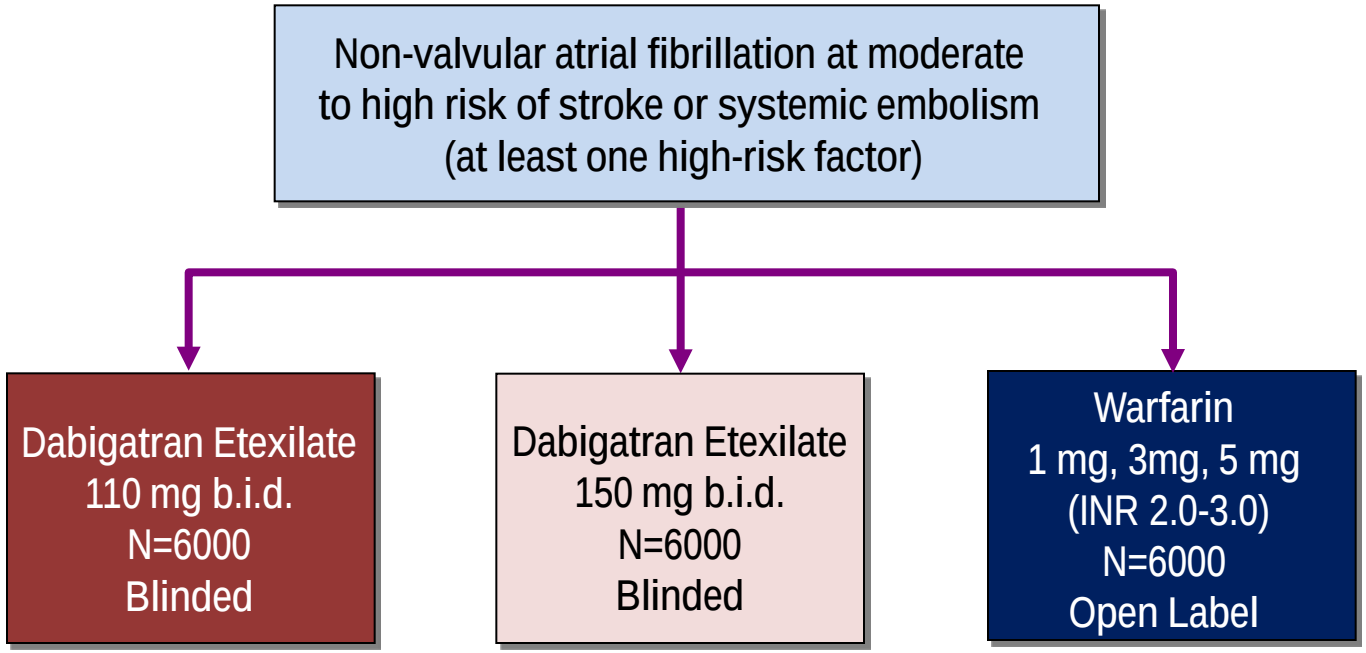


	Primary Efficacy at d10	Primary Efficacy at d35	Major/CRNM Bleeding at d 10	Major/CRNM Bleeding at d350
Important Events	Symp DVT, non-fatal PE, VTE-related death 16 vs 14 events	Symp DVT, non-fatal PE, VTE-related death 42 vs 59 events	Major Bleeding 24 vs 11 events P = 0.003 Fatal Bleeding 5 vs 1	Major Bleeding 19 vs 4 events P = 0.0004 Fatal Bleeding 2 vs 0

Cohen et. al. ACC 2011; abstract

Stroke Prevention in Atrial Fibrillation

Dabigatran etexilate vs warfarin (RE-LY)



- **Open label trial; blinded adjudication**
- **Primary objective: Noninferiority to warfarin**
- **Minimum 1 year follow-up, maximum of 3 years and mean of 2 years of follow-up**
- **Primary end point: Stroke + systemic embolism**

Connolly et al. NEJM 2009;361:1139

Stroke Prevention in Atrial Fibrillation

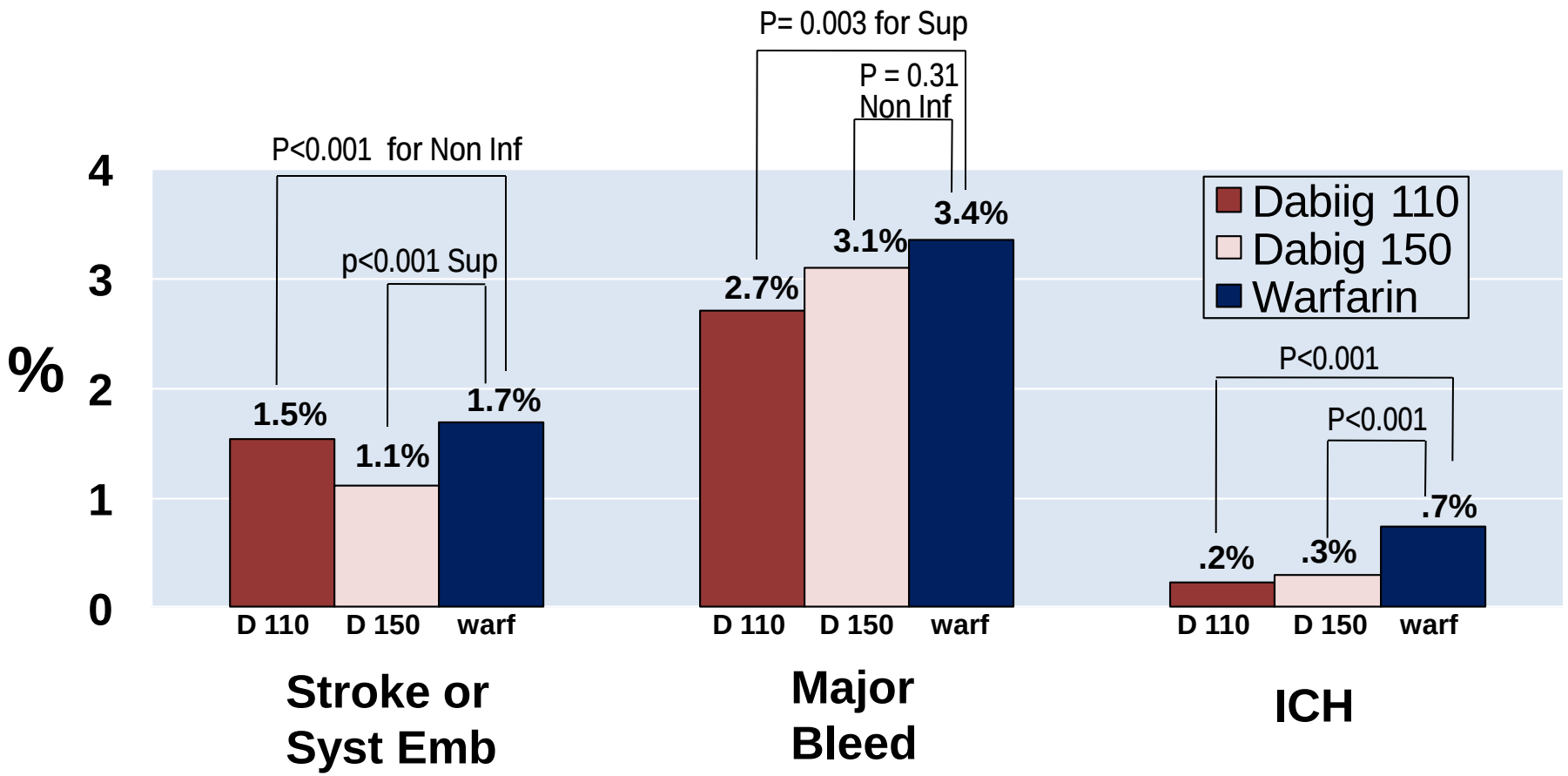
Dabigatran etexilate vs warfarin (RE-LY)

Characteristics	Dabigatran 110 mg BID (# 6,015)	Dabigatran 150 mg BID (# 6,076)	Warfarin (# 6,022)
Age (mean)	**71.4**	**71.5**	**71.6**
Gender (male)	**64%**	**63%**	**63%**
$CHADS_2$ (mean)	**2.1**	**2.2**	**2.1**
Warfarin Naive	**50%**	**50%**	**49%**
Time in Range	**-**	**-**	**64%**
Use of ASA (continuously)	**21%**	**20%**	**21%**

Connolly et al. NEJM 2009;361:1139

Stroke Prevention in Atrial Fibrillation

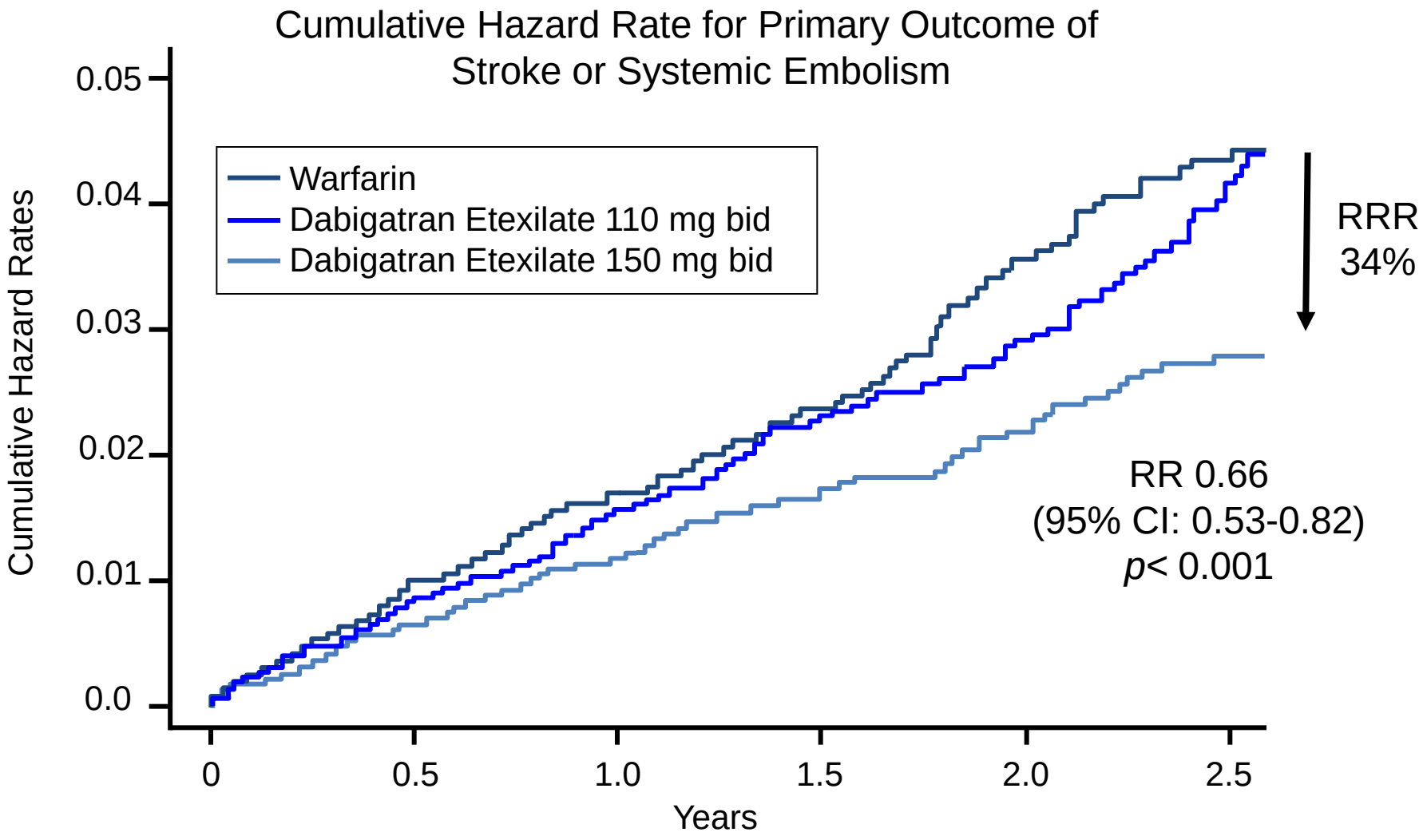
Dabigatran etexilate vs warfarin (RE-LY)



18,113 patients; Dabigatran BID; CHADS Score: ~1/3rd 0-1, 2, 3-6;
AF = ~1/3rd each w/ persistent; parox; permanent

Connolly et al. NEJM 2009;361:1139

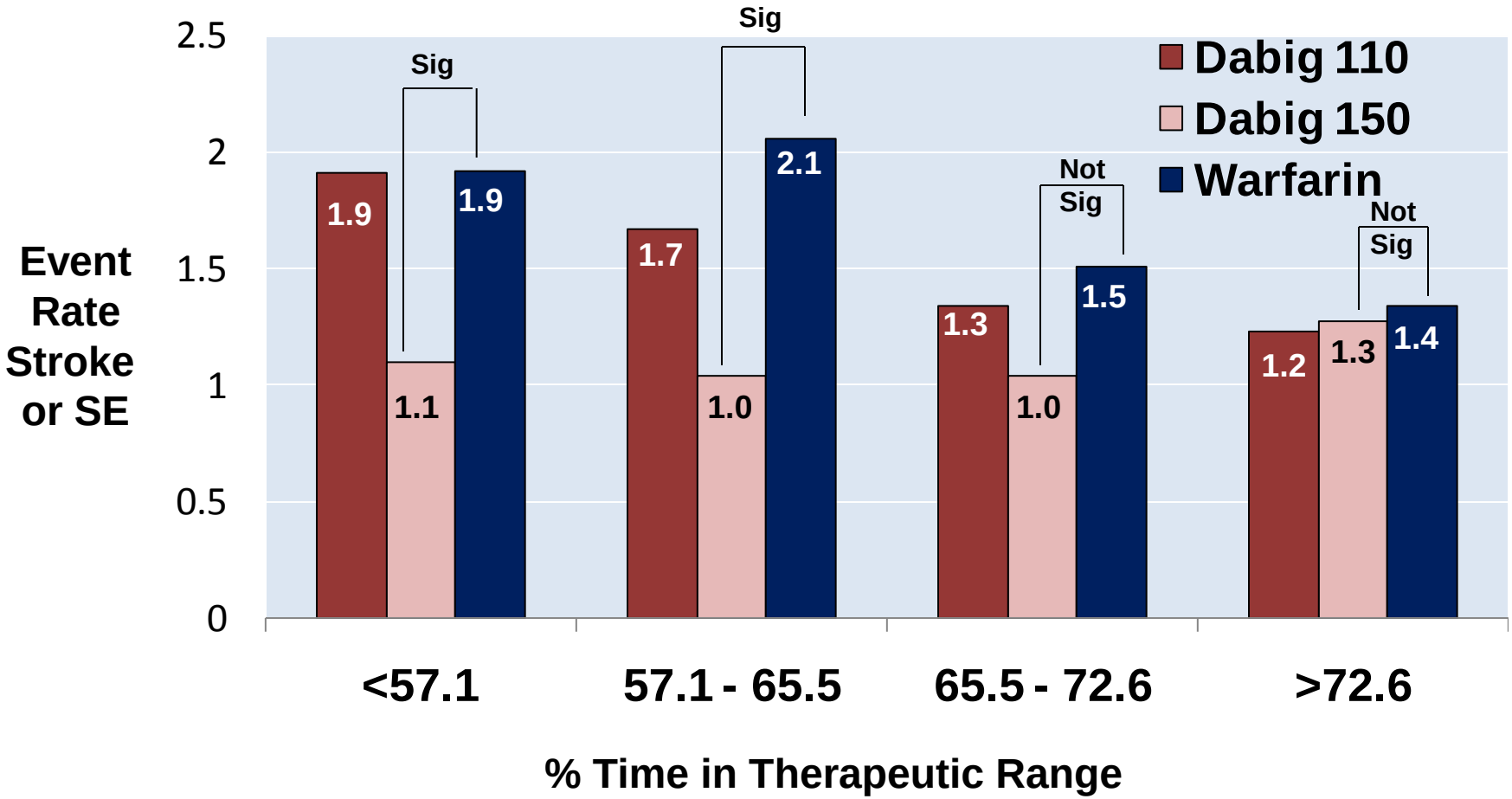
The Incidence of Stroke or Systemic Embolism Is Significantly Lower in Patients Treated With Dabigatran Etexilate 150 mg bid Than Patients Treated With Warfarin



Adapted with permission from Connolly SJ et al. *N Engl J Med.* 2009;361:1139-1151.

Stroke prevention in Atrial Fibrillation

Dabigatran vs warfarin (RE-LY)

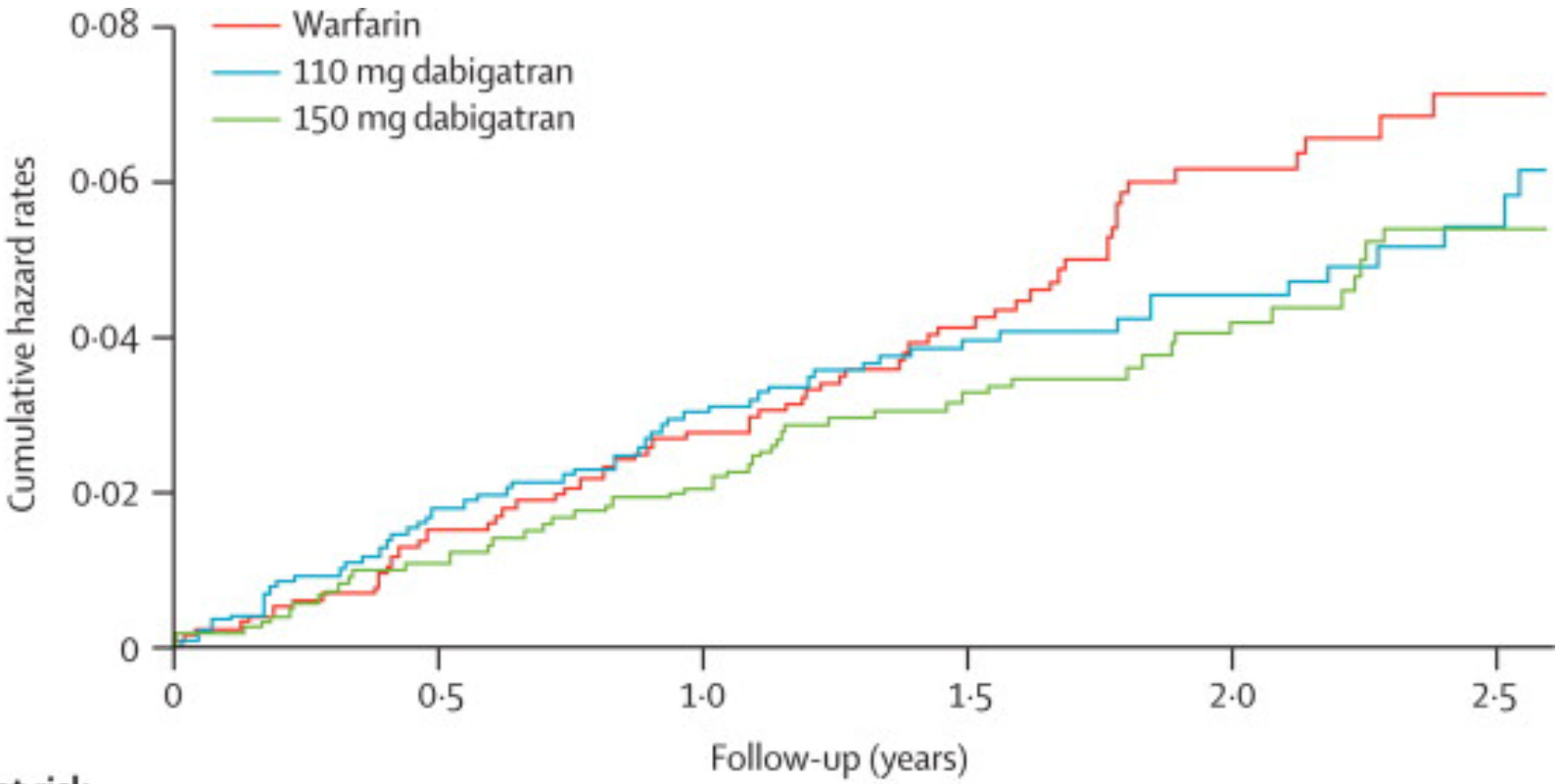


Wallentin et al. Lancet 2010;376:975

Stroke Prevention in Atrial Fibrillation

Dabigatran etexilate vs warfarin (RE-LY)

Time to outcome in patients with previous stroke or TIA

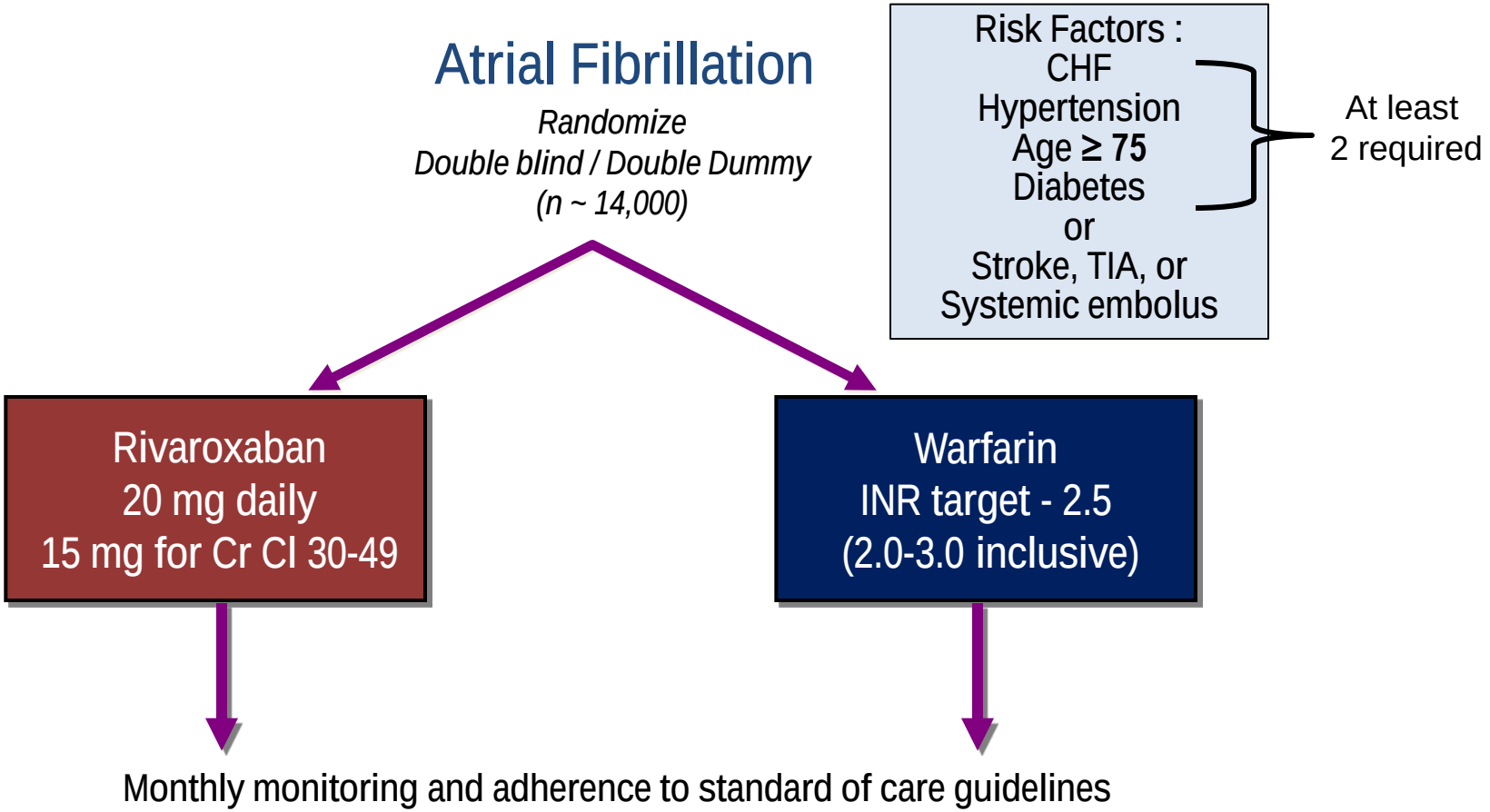


Number at risk						
110 mg dabigatran	1195	1159	1131	908	573	289
150 mg dabigatran	1233	1200	1163	938	517	321
Warfarin	1195	1159	1125	895	565	251

Diener et al. Lancet Neurol 2010;9:1157

Stroke prevention in Atrial Fibrillation

Rivaroxaban vs warfarin (ROCKET AF)



Primary Endpoint: Stroke or non-CNS systemic embolism

Statistics: non-inferiority, >95% power, 2.3% warfarin event rate

Mahaffey et al. AHA , Nov 2010

Stroke prevention in Atrial Fibrillation

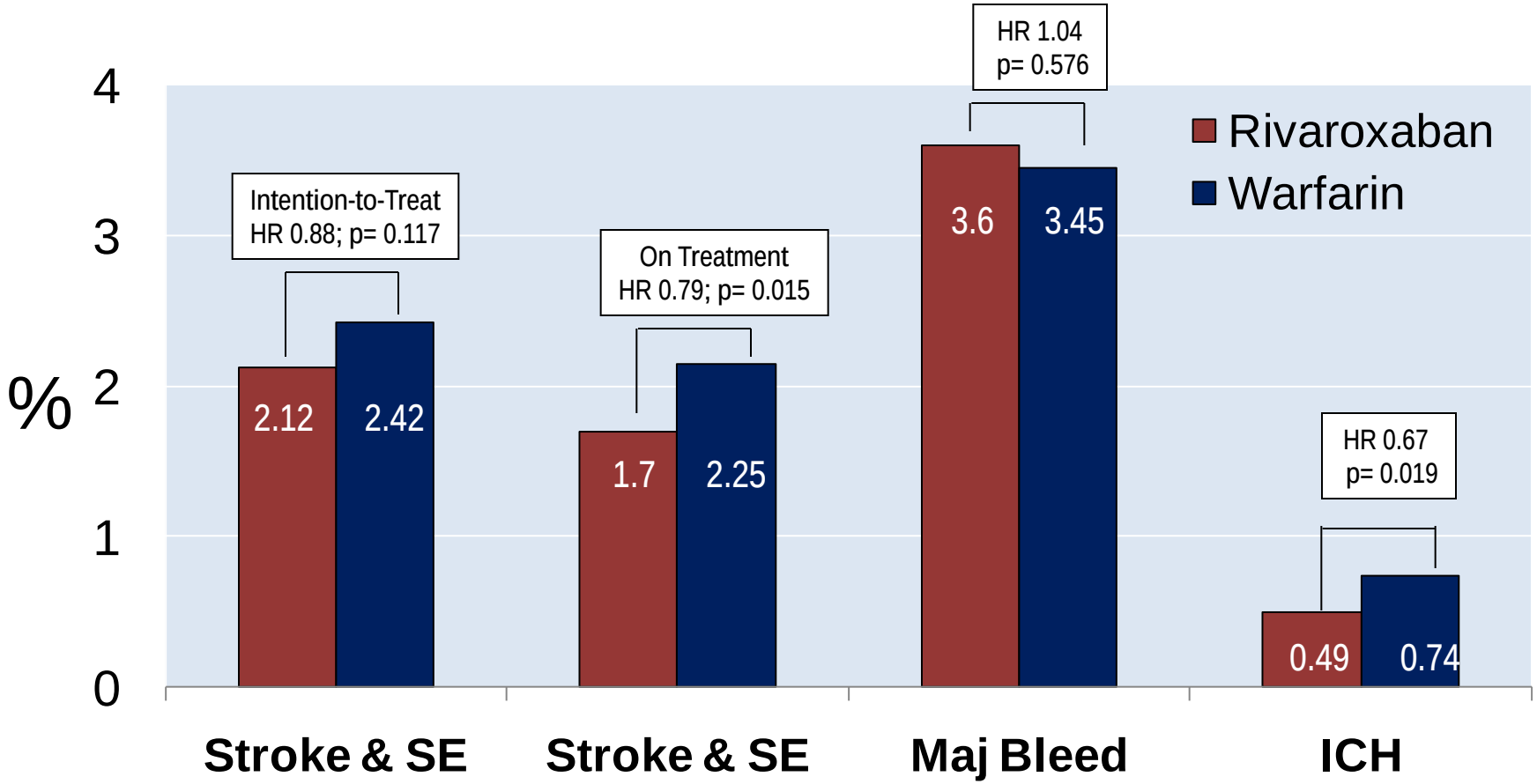
Rivaroxaban vs warfarin (ROCKET AF)

Characteristics	Rivaroxaban (# 7,081)	Warfarin (# 7,090)
Age	**73**	**73**
Gender (male)	**60%**	**60%**
Creatinine Clearance ≥50 30 - 50	 **79%** **21%**	 **79%** **21%**
$CHADS_2$ (mean) 4 - 6	**3.48** **44%**	**3.46** **42%**
Warfarin Naive	**28%**	**27%**
Time in Range	-	**57.8%**

Mahaffey et al. AHA , Nov 2010

Stroke prevention in Atrial Fibrillation

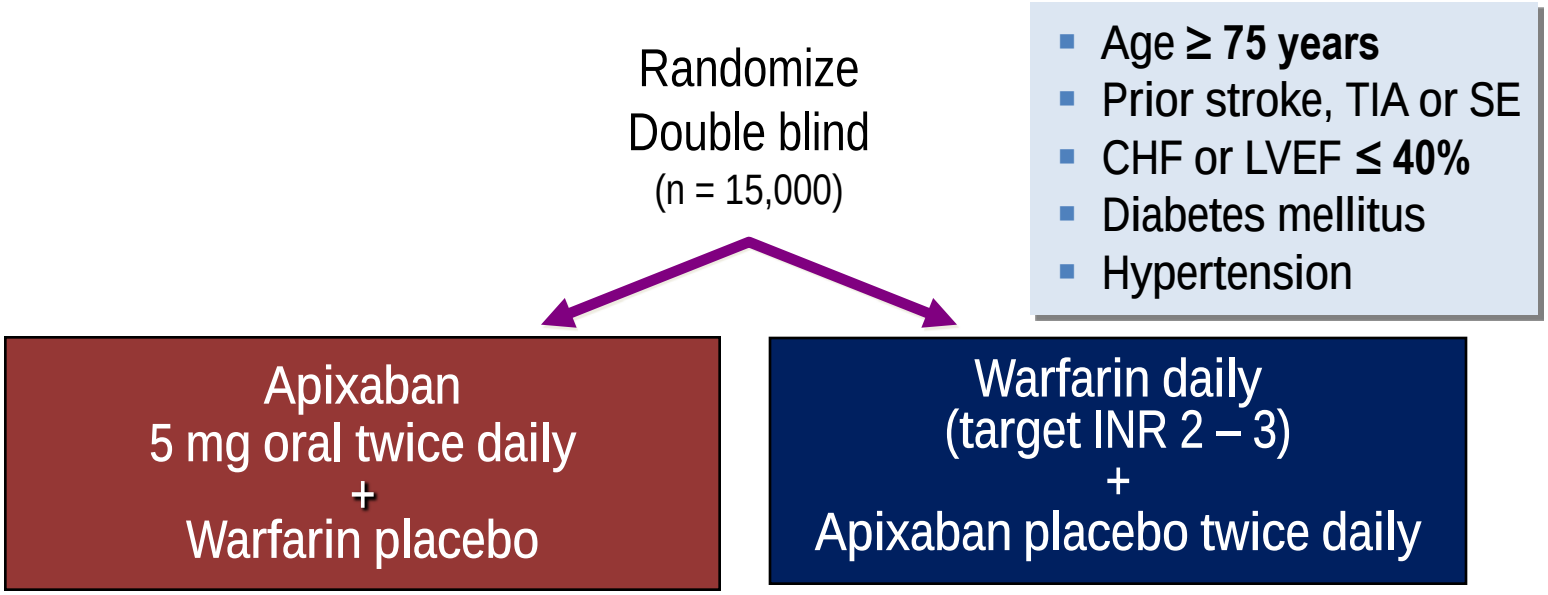
Rivaroxaban vs warfarin (ROCKET AF)



Mahaffey et al. AHA , Nov 2010

Stroke prevention in Atrial Fibrillation

Apixaban vs warfarin (ARISTOTLE)



Warfarin/warfarin placebo adjusted by INR/sham INR based on encrypted point-of-care testing device

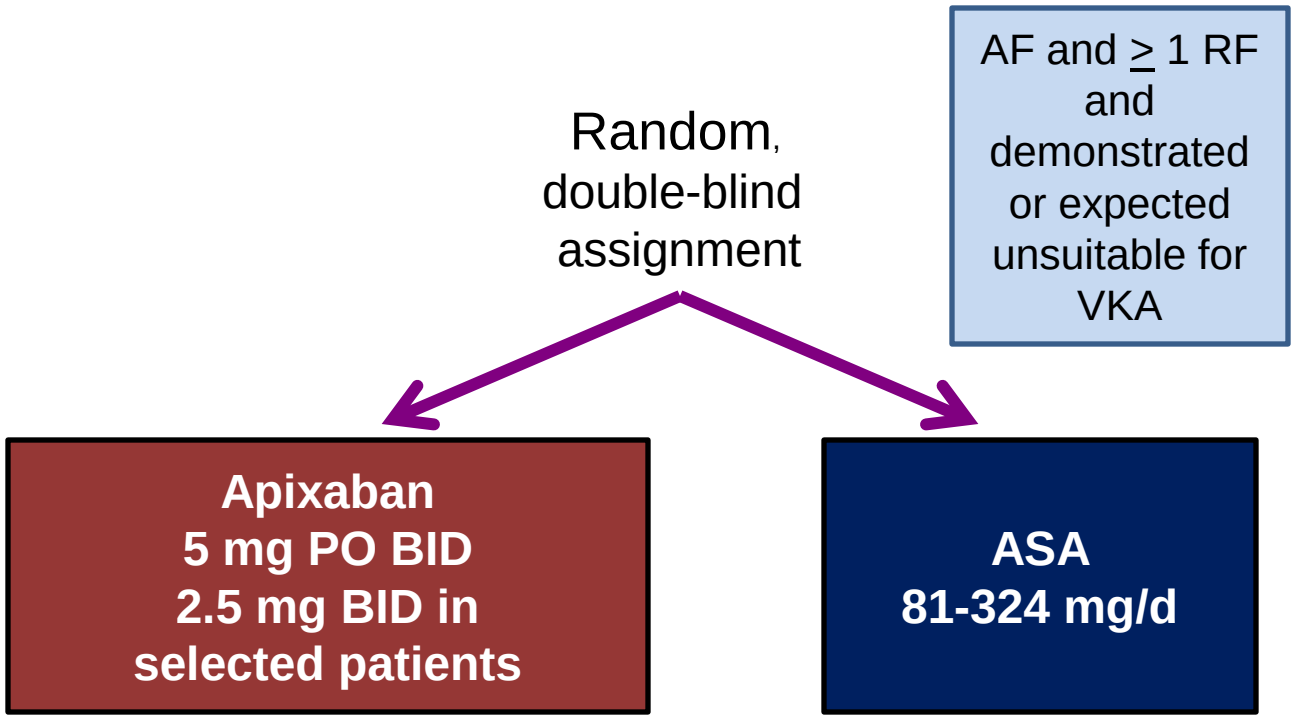
Primary outcome: stroke and systemic embolism

Other outcomes: Death, MI, bleeding

Stratified by warfarin-naïve status

Stroke Prevention in Atrial Fibrilltion

Apixaban vs ASA: AVERROES Study



5,600 patients with AF felt not to be suitable for VKA therapy
Terminated early; median follow up 1 year

Primary Efficacy: Stroke or Systemic Embolic Event
Primary Safety: Major bleeding

S Connolly. ESC 2010

Stroke Prevention in Atrial Fibrilltion

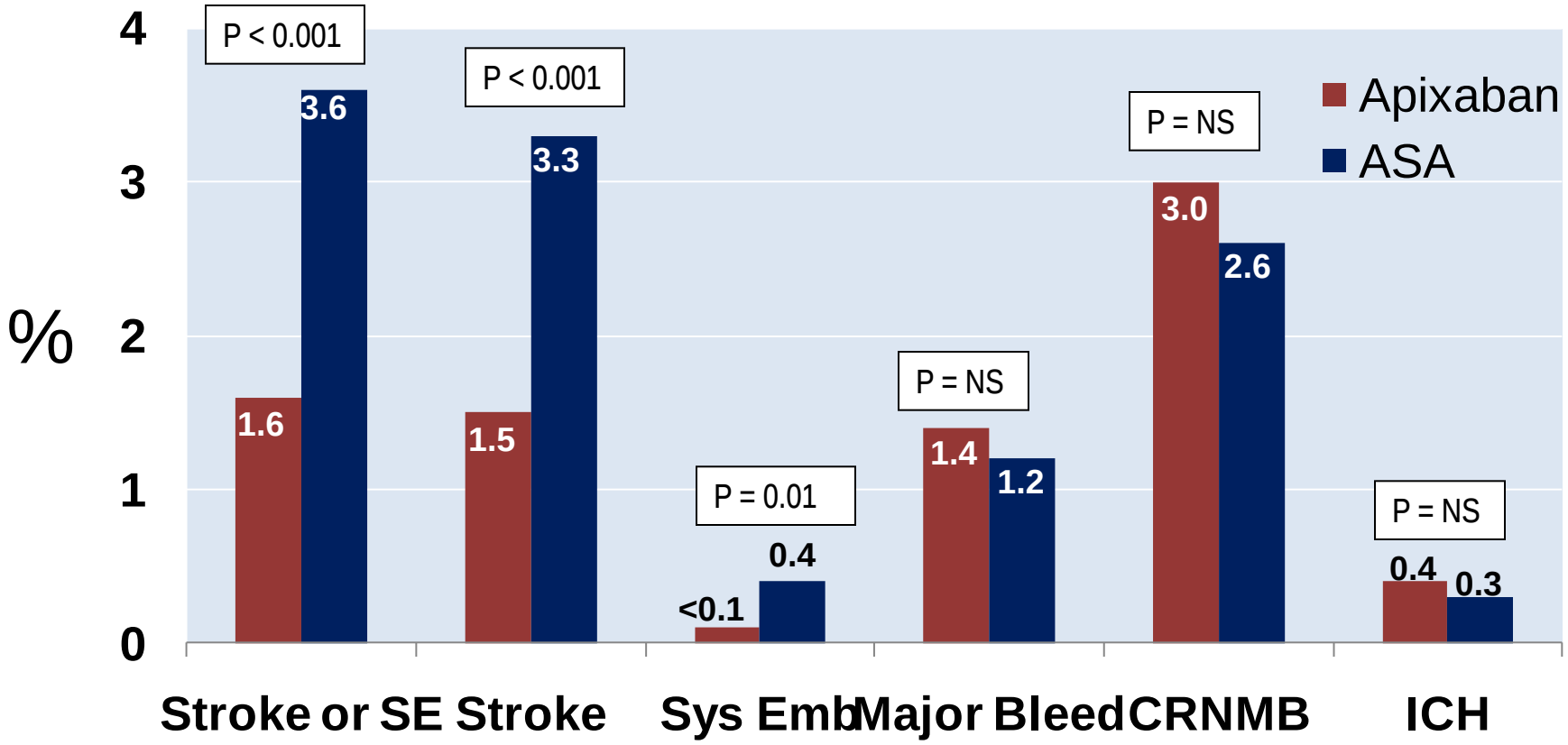
Apixaban vs ASA: AVERROES Study

Characteristic	Apixaban	ASA
Randomized	2,809	2,791
Age (mean/SD)	70 ± 10	70 ± 10
Male	59%	58%
CHADS2 score (mean/SD) **0-1** **2** **3+**	**2.1 ± 1.1** **36%** **37%** **27%**	**2.1 ± 1.1** **37%** **34%** **29%**
Prior stroke/TIA	14%	13%
Diabetes	19%	20%
Hypertension	86%	87%
CHF	40%	38%
Baseline ASA	76%	74%

S Connolly. ESC 2010

Stroke Prevention in Atrial Fibrilltion

Apixaban vs ASA: AVERROES Study



S Connolly. ESC 2010

Stroke Prevention in AF

The value of new oral ACs

- Dabigatran offers 2 dose levels, one for patients with normal and one for patients with impaired renal function. Once again, it offers simple therapy without monitoring and the other drawbacks of warfarin. Most importantly, there appears to be superior efficacy with the higher dose and a decrease in ICH, but overall bleeding is the same.
- Rivaroxaban, (not yet approved), offers equivalent therapy as warfarin without the headache. There is also a decrease in ICH.
- Both drugs raise concern about compliance and rivaroxaban's once daily dosing may offer advantages to dabigatran's twice daily dosing.
- For patients deemed too risky for warfarin, apixaban (not yet approved), may be a good alternative, more effective, yet just as safe.
- Studies of apixaban and other agents are pending.

FDA Approves Dabigatran for Stroke Prevention in Atrial Fibrillation

Indication

Prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation

Dosage forms

75 mg and 150 mg

Dosing

150 mg BID for all patients except:

75 mg BID for Renal impairment: Clcr 15-30 mL/min

No dose adjustment for hepatic impairment

Misc Guidelines

Use without regard to meals

Monitoring: aPTT > 2.5 x control may indicate over anticoagulation

Instruct patients not to chew, break, or open capsules

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

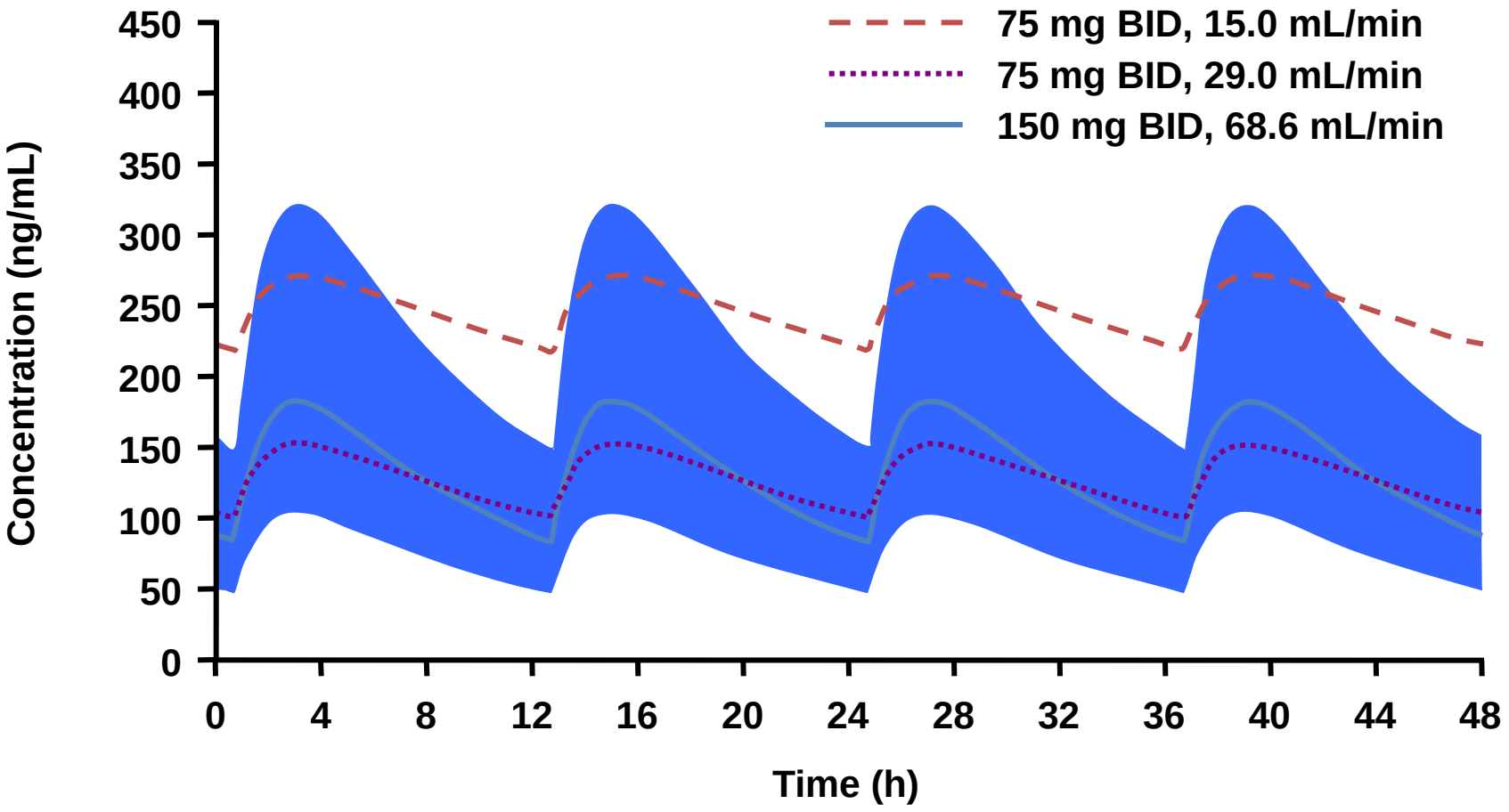
Anticoagulant Options — Why the FDA Approved a Higher but Not a Lower Dose of Dabigatran

B. Nhi Beasley, Pharm.D., Ellis F. Unger, M.D., and Robert Temple, M.D.

On October 19, 2010, the Food and Drug Administration (FDA) approved dabigatran for the reduction of the risk of stroke and systemic embolism in patients with nonvalvular atrial

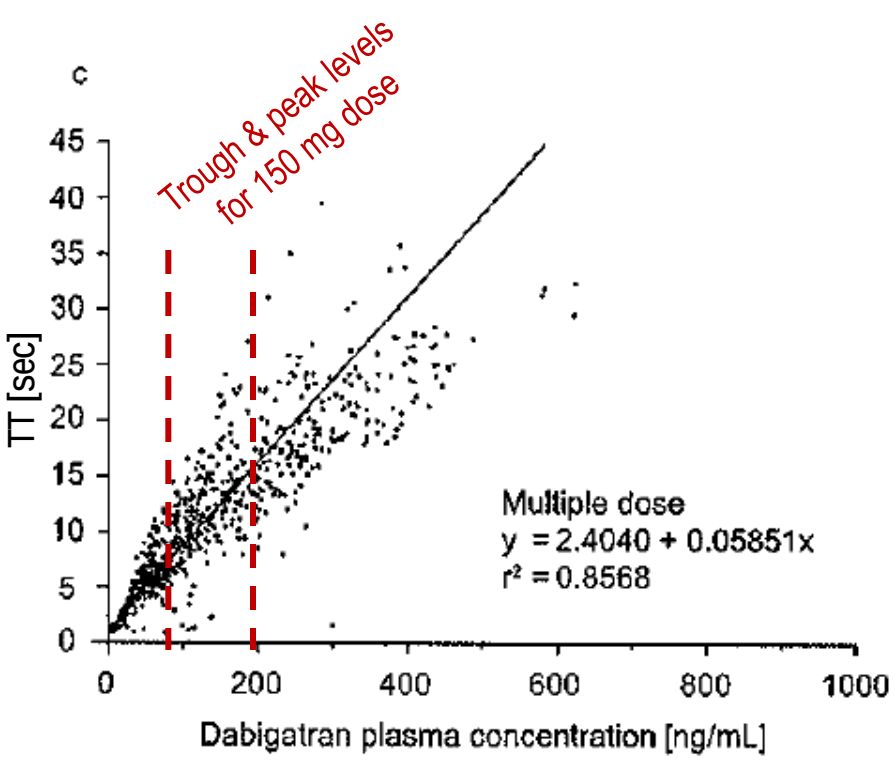
sidered safe and effective if studied alone in comparison with warfarin, although the noninferiority finding for the 110-mg dose is somewhat less compelling. But

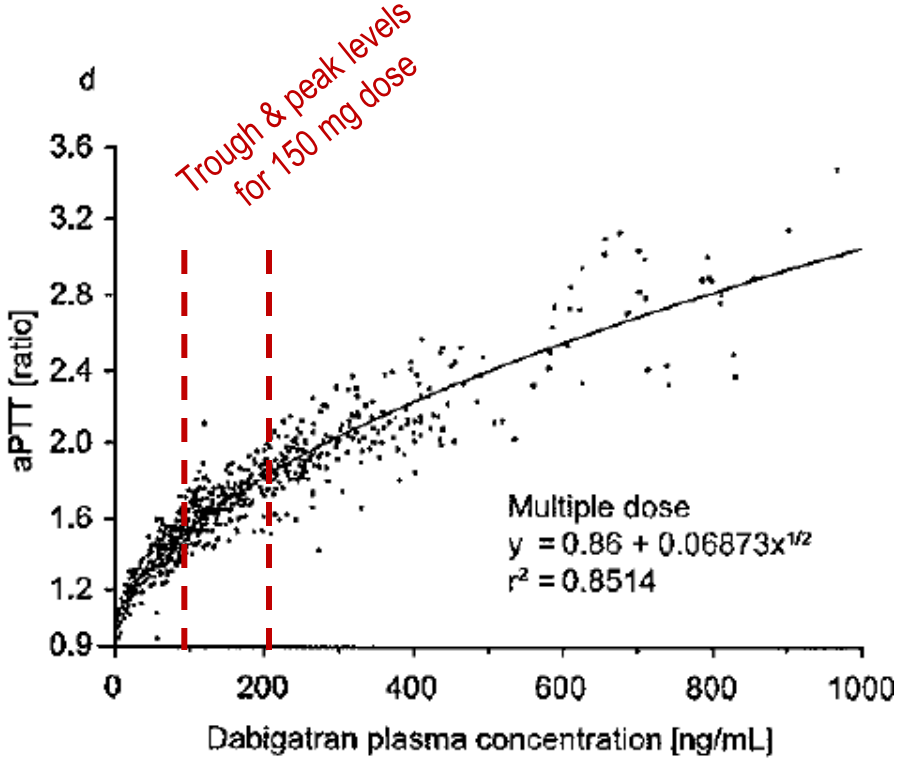
Rationale for Selection of Dabigatran 75 mg Twice Daily in Patients With Renal Impairment



Data on file. Boehringer Ingelheim Pharmaceuticals, Inc.

Monitoring the effect of dabigatran





Van Ryn et al. Thromb Haemost 2010;103:1116

FDA Approves Dabigatran for Stroke Prevention in Atrial Fibrillation

Conversions

From parenteral AC to dabigatran:

UFH: when continuous infusion stopped

LMWH/Fondaparinux: 2 hr before next SQ dose

From dabigatran to parenteral AC:

12 hours (Clcr > 30) or 24 hours(Clcr < 30) after last dabigatran dose

From warfarin to dabigatran:

When the INR is < 2.0

From dabigatran to warfarin:

Clcr > 50	start warfarin 3 days before dabigatran stopped
Clcr 31-50	start warfarin 2 days before dabigatran stopped
Clcr 15-30	start warfarin 1 day before dabigatran stopped

FDA Approves Dabigatran for Stroke Prevention in Atrial Fibrillation

From package insert

OVERDOSAGE

Accidental overdose may lead to hemorrhagic complications. There is no antidote to dabigatran etexilate or dabigatran.

In the event of hemorrhagic complications, initiate appropriate clinical support, discontinue treatment with PRADAXA, and investigate the source of bleeding.

Dabigatran is primarily excreted in the urine; therefore, maintain adequate diuresis. Dabigatran can be dialyzed (protein binding is low), with the removal of about 60% of drug over 2 to 3 hours; however, data supporting this approach are limited.

Consider surgical hemostasis or the transfusion of fresh frozen plasma or red blood cells. There is some experimental evidence to support the role of activated prothrombin complex concentrates (e.g., FEIBA), or recombinant Factor VIIa, or concentrates of coagulation factors II, IX or X; however, their usefulness in clinical settings has not been established.

Consider administration of platelet concentrates in cases where thrombocytopenia is present or long-acting antiplatelet drugs have been used. Measurement of aPTT or ECT may help guide therapy *[see Clinical Pharmacology (12.2)].*

Potential Drawbacks of New Oral Anticoagulants

- Cannot easily assess compliance without monitoring assay
- Cannot easily assess treatment failure without monitoring assay
- Cannot easily titrate dose to lower or higher level of anticoagulation without monitoring assay
- Cannot easily reverse anticoagulant affect
- Unclear how to treat major hemorrhage
- Cost may be a factor in utilization

Considerations in the next year

- Hospital formulary?
- Education of Emergency Department physicians?
- Treatment of overdoses?
- Treatment of major bleeding?
- Management of failure of therapy?
- Transitions of care: -warfarin to new agent
  -new agent to warfarin
  -heparin to new agent
  -new agent to heparin
- Bridging for invasive procedures?
- Routine use of new AC in hospitalized patients?

What is the Future for Warfarin?

Vitamin K antagonists (warfarin and others) will not completely go away. Their use will continue in selected circumstances. For example -

1. Mechanical heart valves will be the last of the indications studied for new AC.
2. Patients who fail therapy on a new AC will likely be switched to a VKA.
3. When there is a question of compliance, a physician may prefer a monitored drug, i.e. VKA
4. There may be some physician resistance to convert a stable patient to a new AC.