New Age of Anticoagulants

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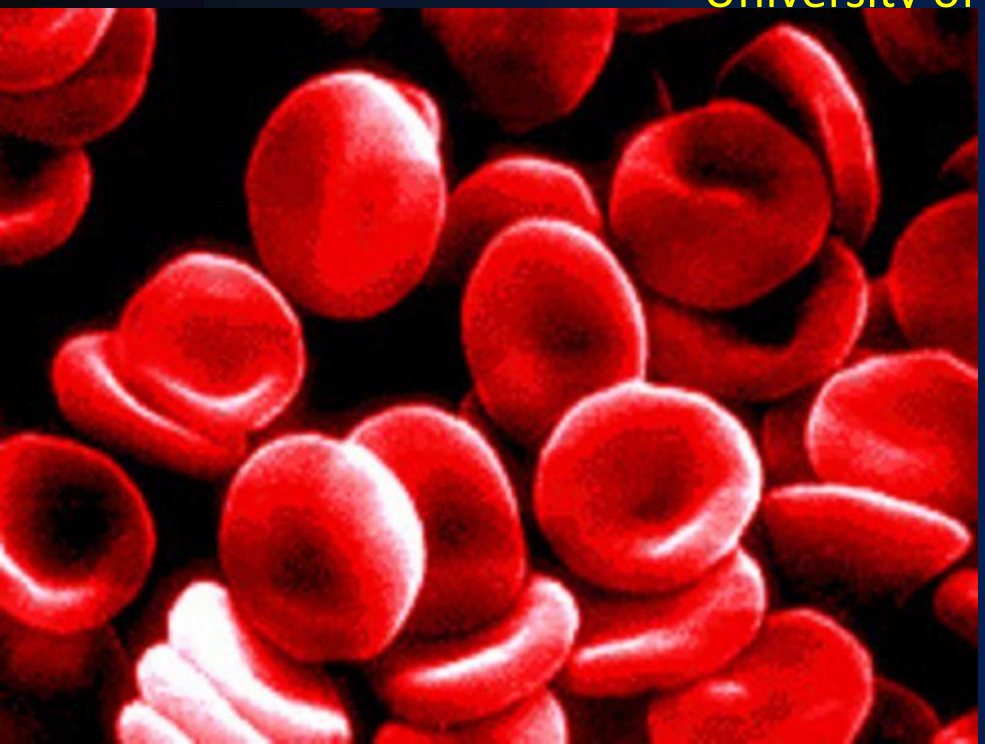
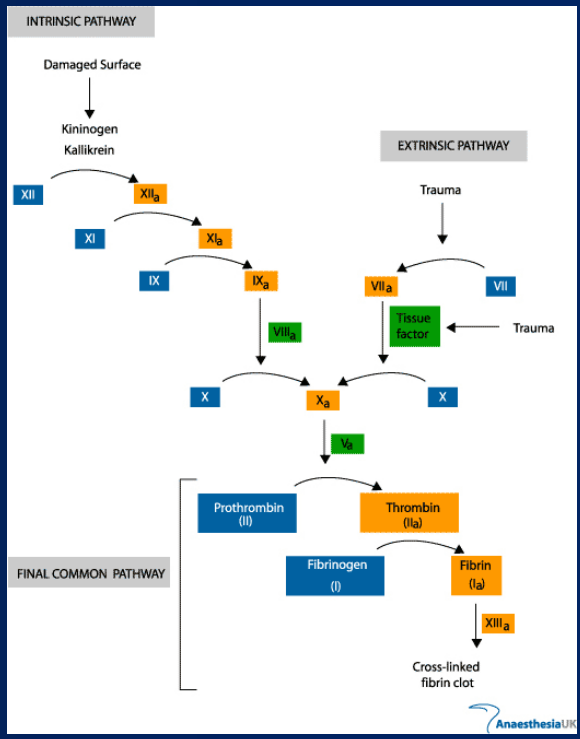
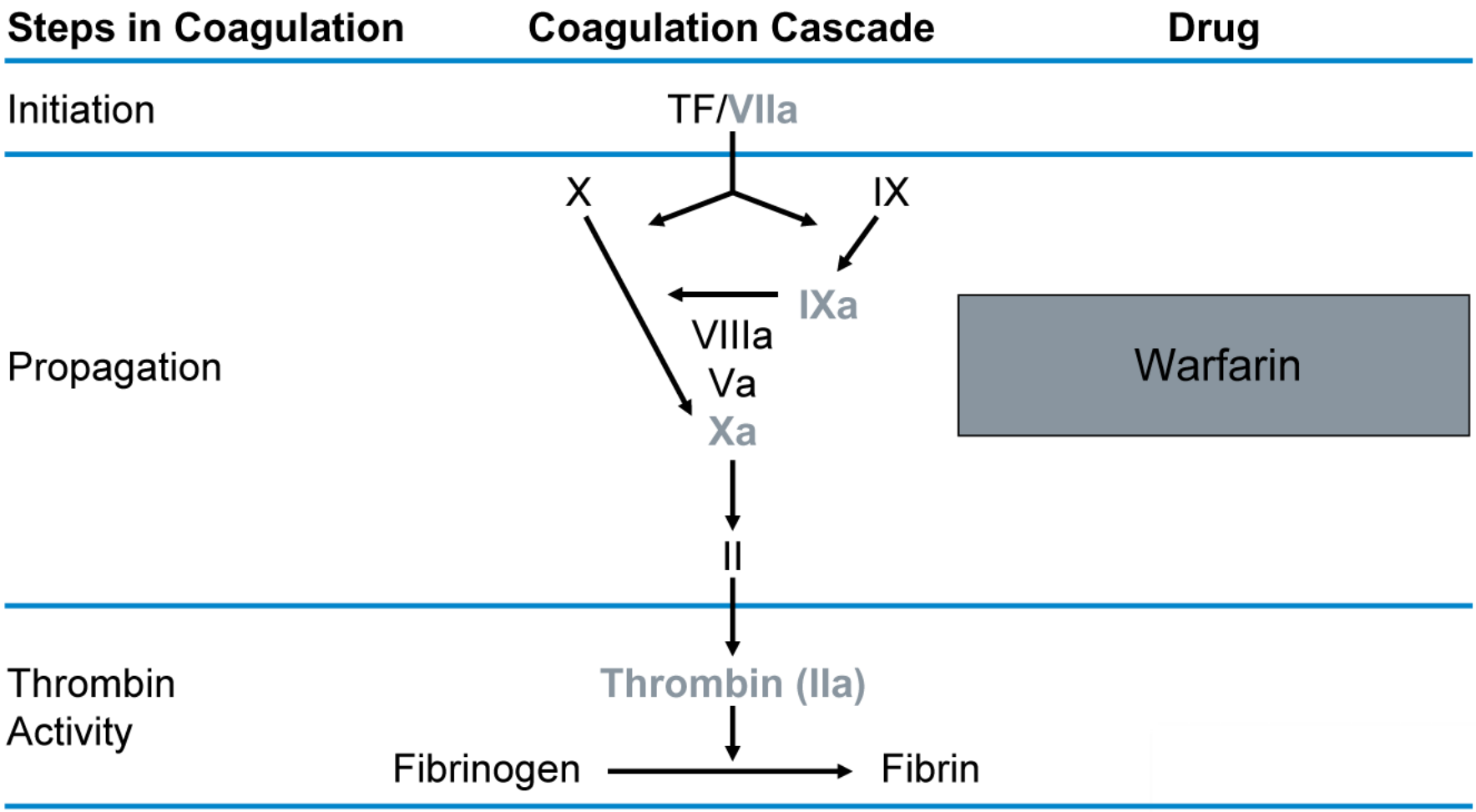




Mechanism of action of warfarin



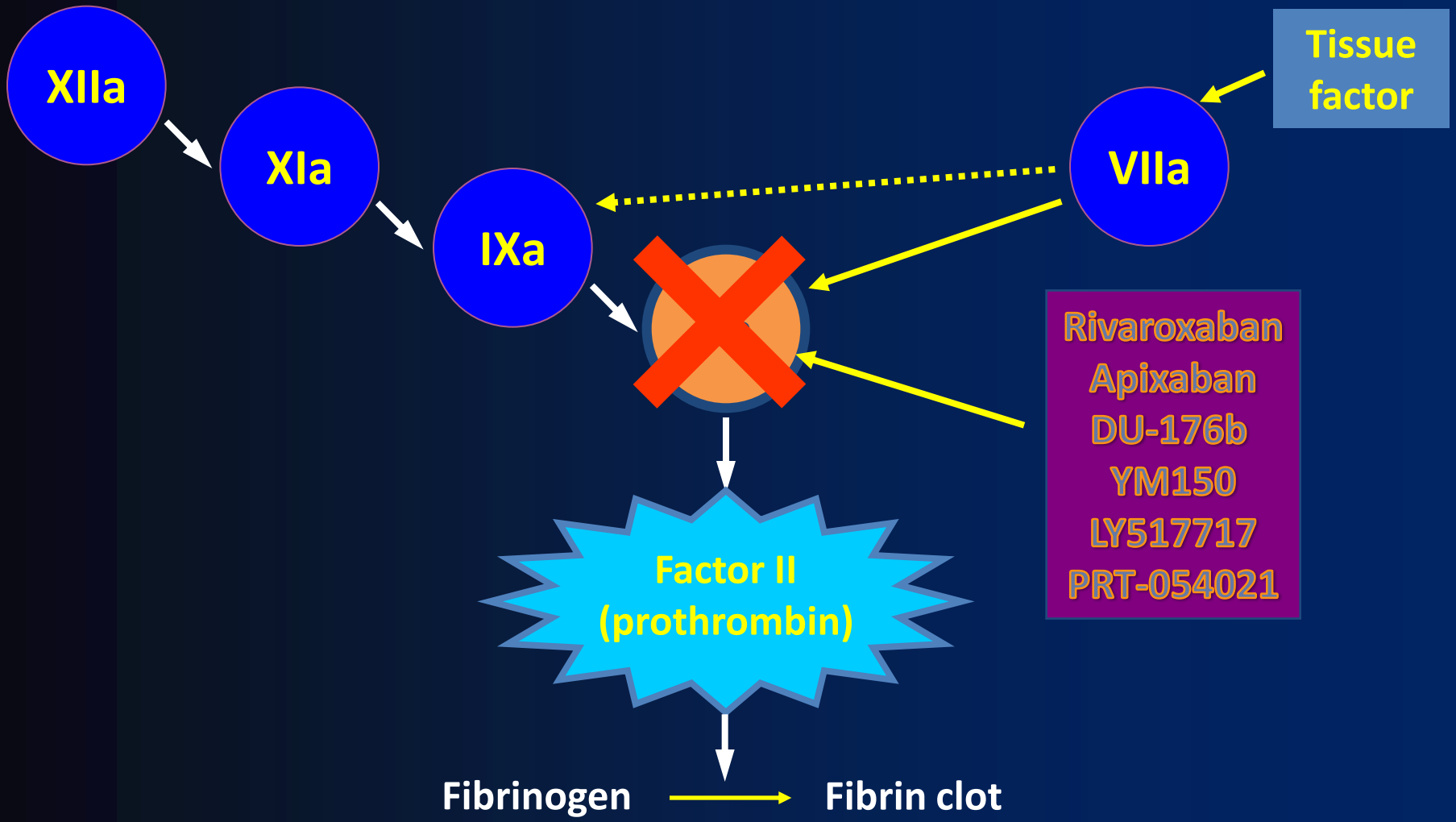
Adapted with permission from Weitz JI et al. *Chest*. 2004;126:265S-286S.

Low-Molecular-Weight Heparins

Potential Advantages:

- Lack of binding to plasma proteins and endothelium
- Good bioavailability
- Stable dose response
- Long half-life
- Resistance does not develop

Direct Factor Xa inhibition

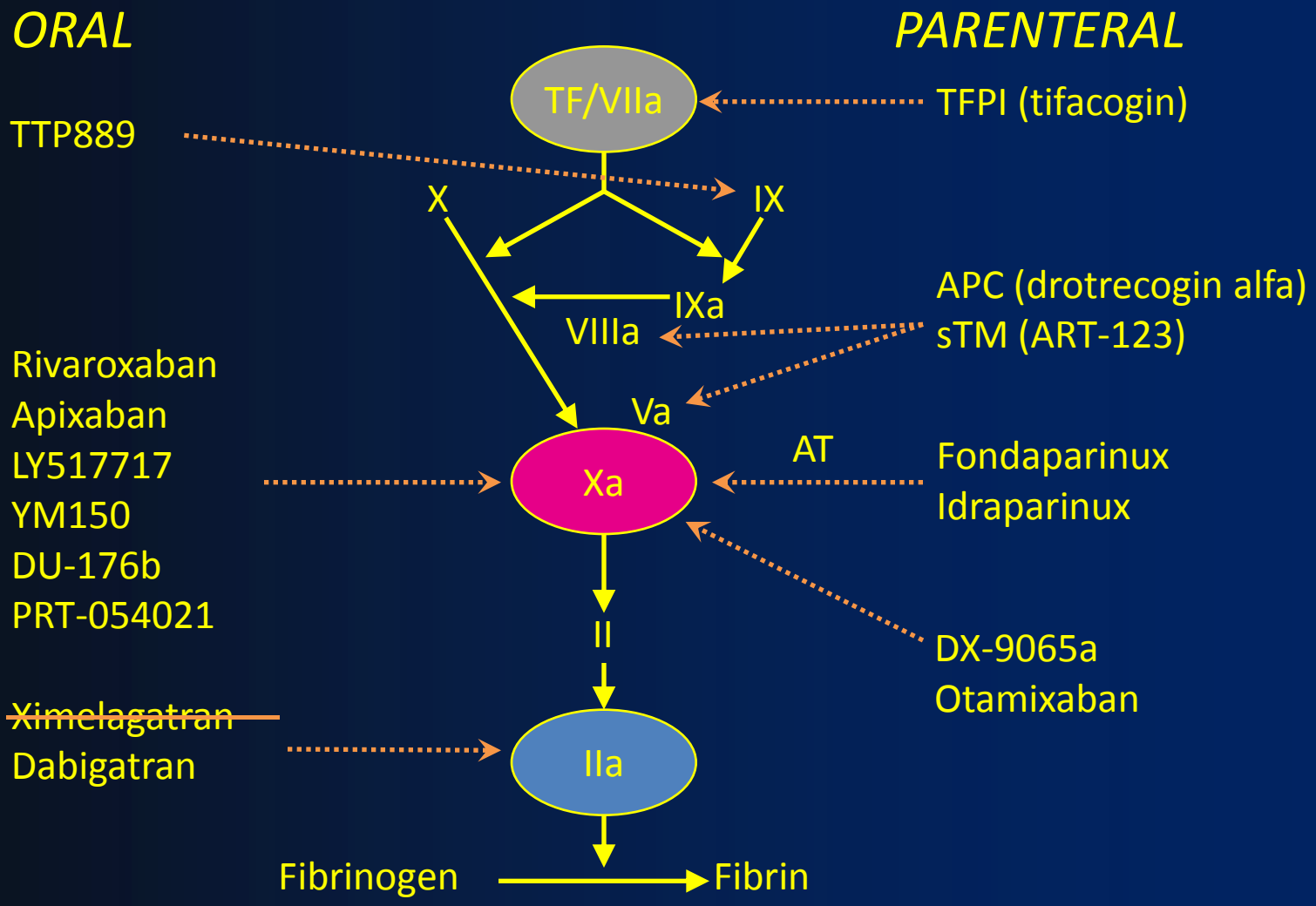


Factor Xa inhibitors

FXa may be a better target than thrombin

- Has few functions outside coagulation (compared with thrombin)
- Has a wider therapeutic window than thrombin (separation of efficacy and bleeding), *in vitro*
- Thrombin inhibitors are associated with rebound thrombin generation – no evidence with FXa inhibitors
- Efficacy of heparin-based anticoagulants improves as selectivity for FXa increases:
  UFH < LMWH < fondaparinux

New anticoagulants

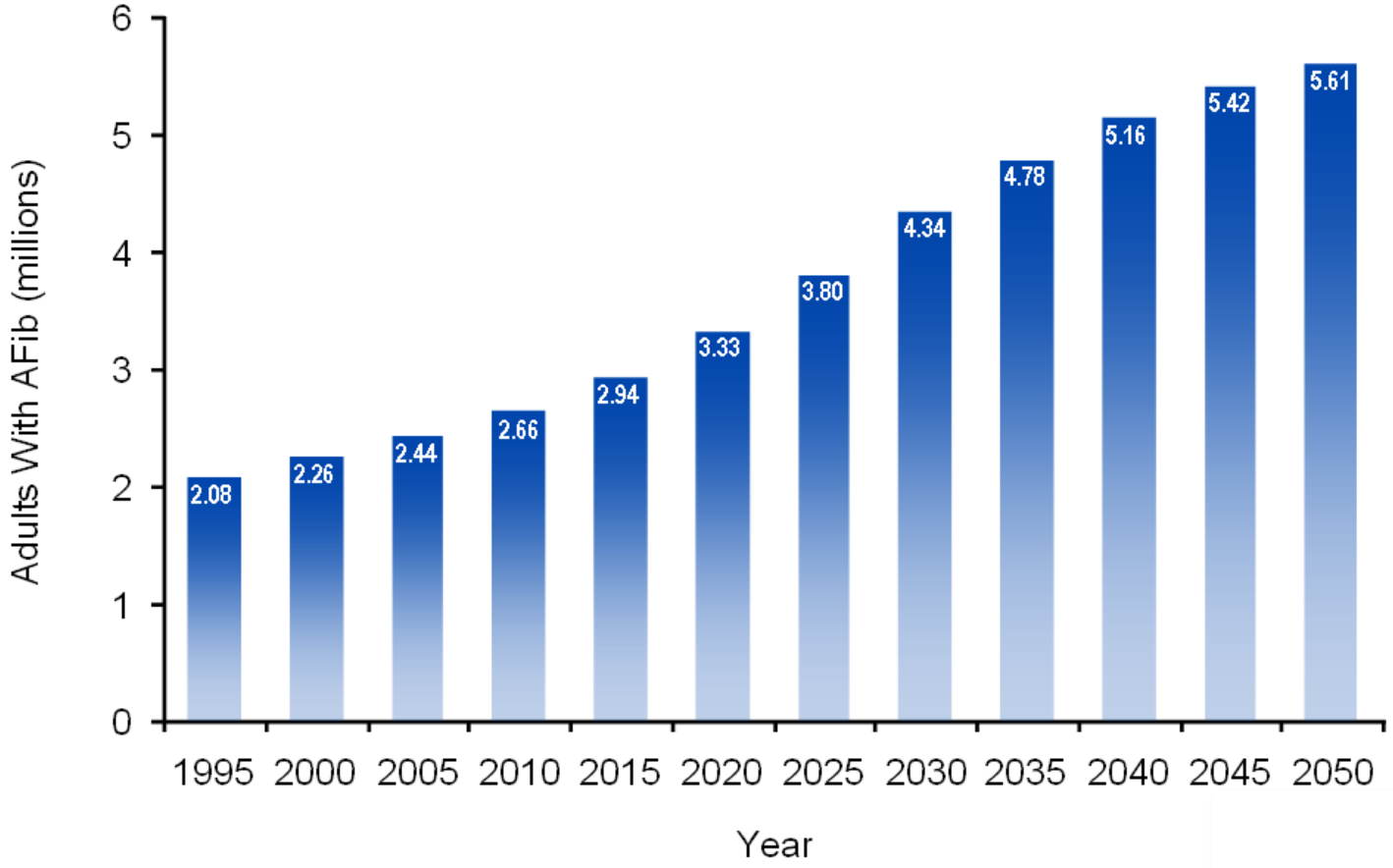


Adapted from Weitz & Bates, *J Thromb Haemost* 2005

Oral Factor Xa inhibitors
Clinical development

Rivaroxaban (JNJ/Bayer)	Phase IIb Phase III
Apixaban (BMS)	Phase III
YM150 (Astellas)	Phase IIb
DU-176b (Daiichi)	Phase IIb
LY517717 (Lilly)	Phase IIb
813893 (GSK)	Phase I/II
PRT054021(Portola)	Phase II

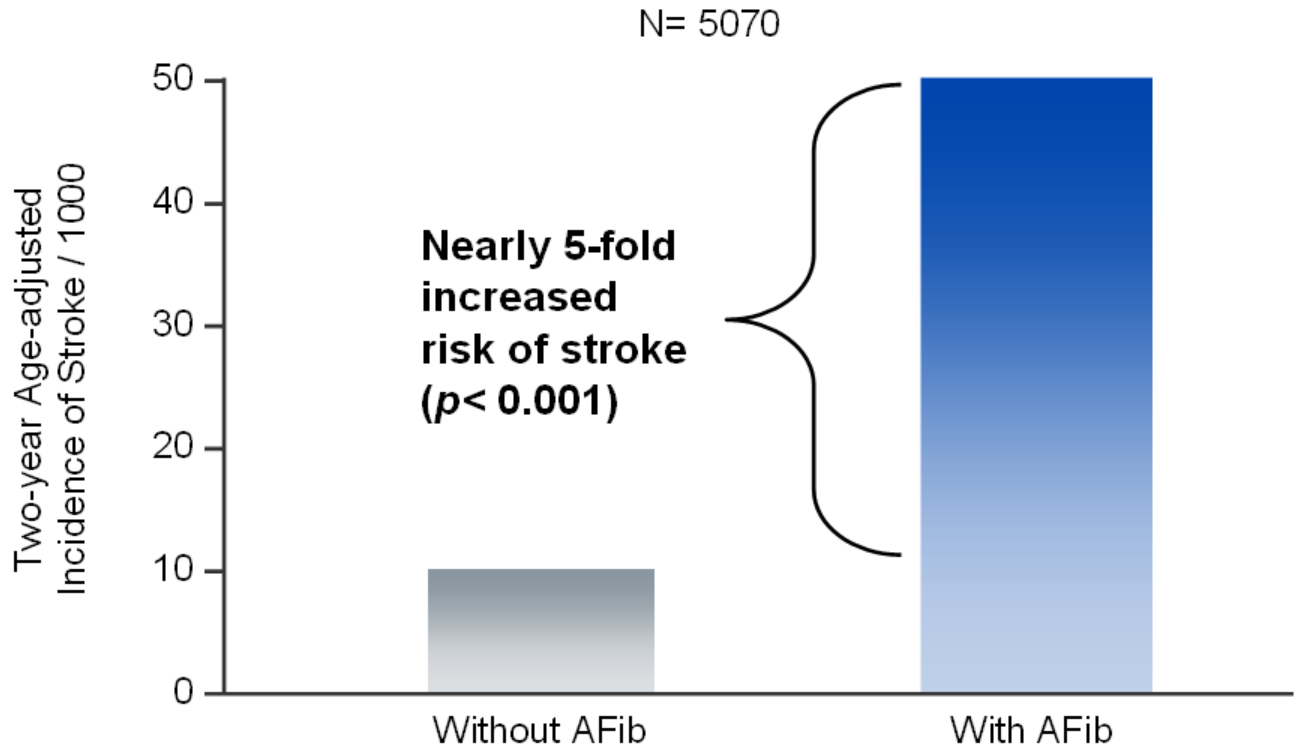
Estimated prevalence of atrial fibrillation (AFib) in the United States



Go AS et al. *JAMA*. 2001;285:2370-2375.

Pradaxa® dabigatran etexilate CAPSULES

Incidence of stroke* in patients with and without atrial fibrillation (AFib) in the Framingham study



*572 strokes (122 transient ischemic attacks, 256 nonembolic strokes, 114 embolic strokes, 27 intracerebral hemorrhages, 39 subarachnoid hemorrhages, 14 other causes) observed over 34 years in persons aged 50 to 89 years.

Adapted with permission from Wolf PA et al. *Stroke*. 1991;22:983-988.

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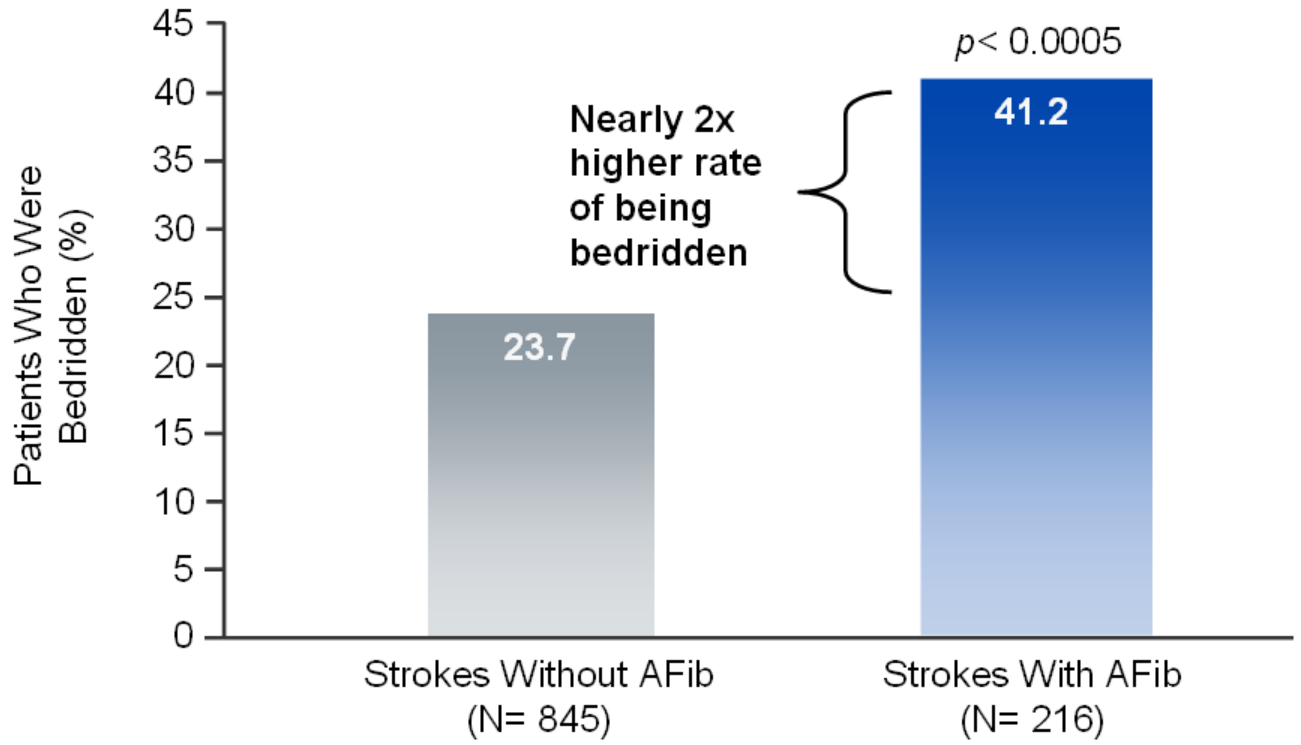
Severity of ischemic strokes in patients with and without atrial fibrillation (AFib)



Dulli DA et al. *Neuroepidemiology*. 2003;22:118-123.

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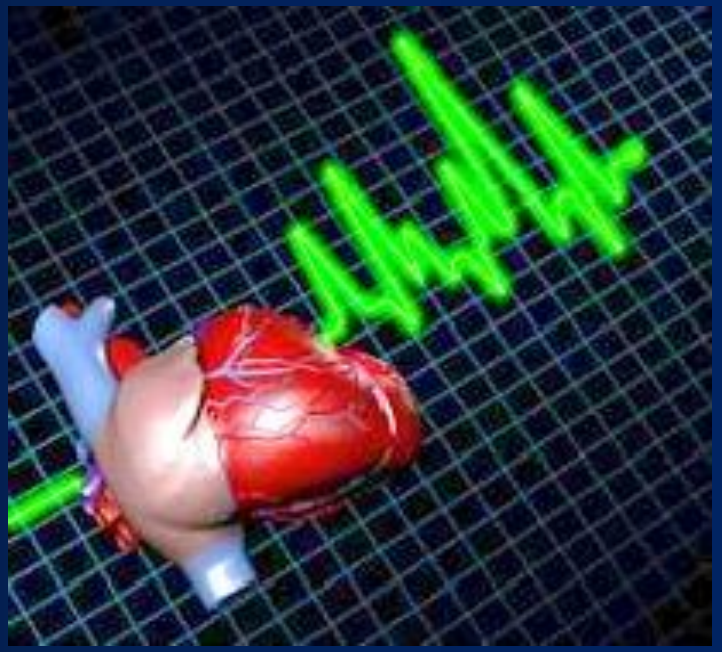
Stroke: A significant cause of poor health and Death

- Stroke accounts for nearly 10% of all deaths worldwide
- The number of strokes per year is predicted to rise dramatically as the population ages
- About 20-30% strokes are cardio embolic and 15% relate to AF
- Strokes in patients with AF are more severe and have worse outcomes than strokes in people without AF
- AF almost doubles the death rate from stroke. AF increases the risk of remaining disabled following stroke by almost 50%.

ESC Guidelines EHJ 2010; 31-2369 - Working Group Report, EU 2010

Sources of Cardioembolic Stroke

- 50% NVAF
- 10% Ventricular
- 10% Rheumatic
- 10% MI
- 5% Prosthetic
- 15% Other



MJ Schneck et al., eMedicine Neurology 2008

Stroke Risk Assessment in AF: CHADS-VASc

Stroke Risk Factors	Score
CHF/LV Dysfunction	1
HTN	1
Age ≥ 75 years	2
DM	1
Stroke/TIA /TE	2
Vascular Disease (prior MI, PAD, or Aortic Plaque)	1
Age 65-74 years	1
Sex Category (ie, female sex)	1

GY Lip et al. Chest 2010; 137-263 – ESC Guidelines EHJ 2010; 31:2369

Risk of Stroke by CHAD Score

	CHAD Index	**Antithrombotics**
High Risk	TE, MS, PHV, 2RF	Warfarin INR 2.0-3.5 Warfarin INR 2-3
Moderate Risk	1R	ASA 81-325mg Warfarin INR 2-3 (<EF)
Low Risk	0R	ASA 81-325mg

RF: C.Fail./EF < 35% 1, Hypert. 1, Age > 75 , Diabetes 1,
ACCIAHA/ESC (Fuster V et al) Circ 2006; 114:700

EHRA Score of AF-related symptoms

	Classification of AF-related symptoms (EHRA score)
EHRA class	Explanation
EHRA I	No Symptoms
EHRA II	Mild Symptoms; Normal daily activity not affected
EHRA III	Severe Symptoms; normal daily activity affected
EHRA IV	Disabling symptoms; normal daily activity discontinued

ESC (AJ Camm et. al.) Eur Heart J 2010; 31-2369 – ANSD!!!.

AF–Assessment of Bleeding Risk

HAS-BLED	
HTN (SBP > 160 mm Hg	1
Abnormal renal and liver function	1 or 2
Stroke	1
Bleeding	1
Labile INRs	1
Elderly (age > 65)	1
Drugs or alcohol (1 point each)	1 or 2
Maximum score	9

R Pisters et al. Chest 2010 (March 18) – DA Lane et. Al. Lancet. 2010; 376:935
HAS BLEED Score =3 > 3 Risk Bleed

Pre-admission Medications in Patients with known AF and Previous Ischemic Stroke/TIA History, Admitted with Acute Ischemic Stroke (High-Risk, N=323)

- Warfarin Subtherapeutic – 39%
- Single Antiplatelet Agent -25%
- Warfarin Therapeutic – 18%
- No Antithombotics – 15%
- Dual Antiplatelet Therapy –3%

REG. CANADIAN STORKE NETWORK
(D Gladstone et.al.) Stoke 2009; 40:235

Silent Cerebral Ischemia After TAVI

Diffusion-Weighted Magnetic Resonance Imaging Study

- Risk of stroke related to dislodgement of atheroma or calcified valve from aortic arch ranges 2-10%
- 32 patients underwent TAVI with the use of balloon expandable or self expandable stent valve prosthesis
- Early clinically silent new foci were detected in 84% patients undergoing TAVI

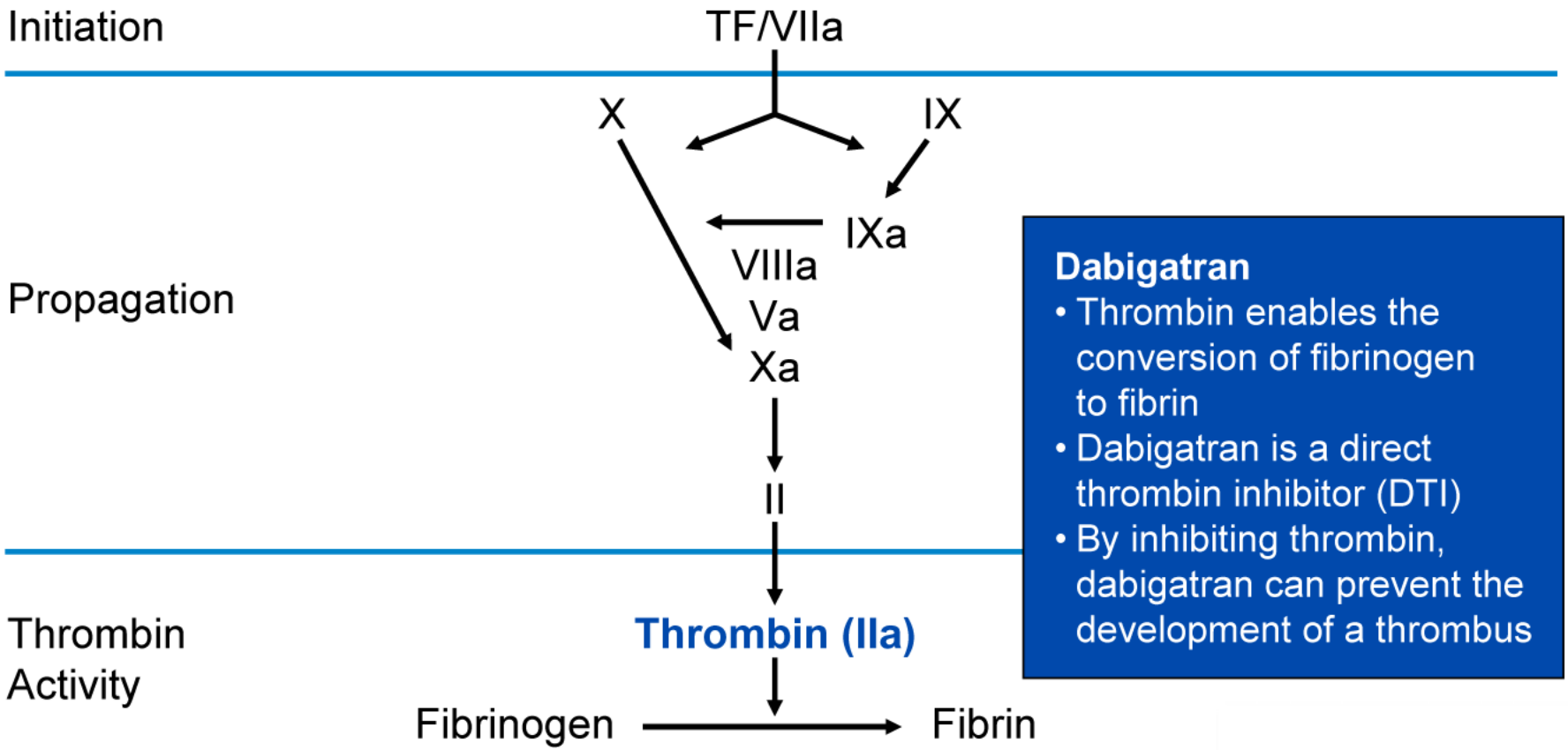
P Kahlert, R Erbel, H Eggebrecht, et al., Circ 2010; 121:878 (Essen, Germ)
A Ghanem et al JACC 2010; 55: 1427 – 72% (22 pts)
J Osorio, V Fuster Nature Rev. Card. 2010; 7:355 – TAVI, A Word of Caution

The Incidence of Dementia by the Patients AF Status

- AF
  - Nonspecific (about 3.3%)
  - Alzheimer's (about .5%)
  - Senile (about 1.5%)
  - Vascular (about .75%)
- No AF
  - Nonspecific (about 1.5%)
  - Alzheimer's (about .75%)
  - Senile (about .5%)
  - Vascular (about .3%)

TJ Bunch et al., Heart Rhythm 2010; 7:433 (Murray, Utah)

PRADAXA mechanism of action[1,2]



1. Adapted with permission from Weitz JI et al. *Chest*. 2004;126:2655-2865.
2. Pradaxa® (dabigatran etexilate mesylate) capsules [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; 2010.

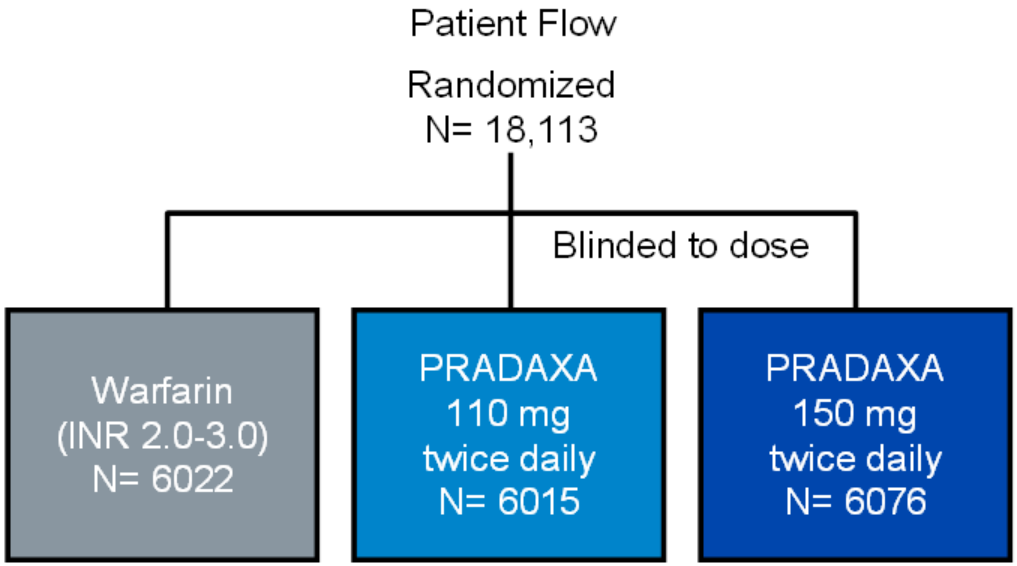
Please see full Prescribing Information.

Pradaxa® dabigatran etexilate CAPSULES

Design of the RE-LY® trial of PRADAXA[1,2]

Study Parameters

- Open label, noninferiority, intent-to-treat trial
- Blinded adjudication of outcome events
- 50% patients VKA-naïve*
- Primary outcome: incidence of stroke (ischemic and hemorrhagic) and systemic embolism in patients with non-valvular atrial fibrillation
- Primary safety outcome: incidence of major bleeds†



Minimum 1-year follow-up, maximum 3 years, median of 2 years of follow-up. INR: international normalized ratio; VKA: vitamin K antagonist.
*Total lifetime exposure of < 2 months.

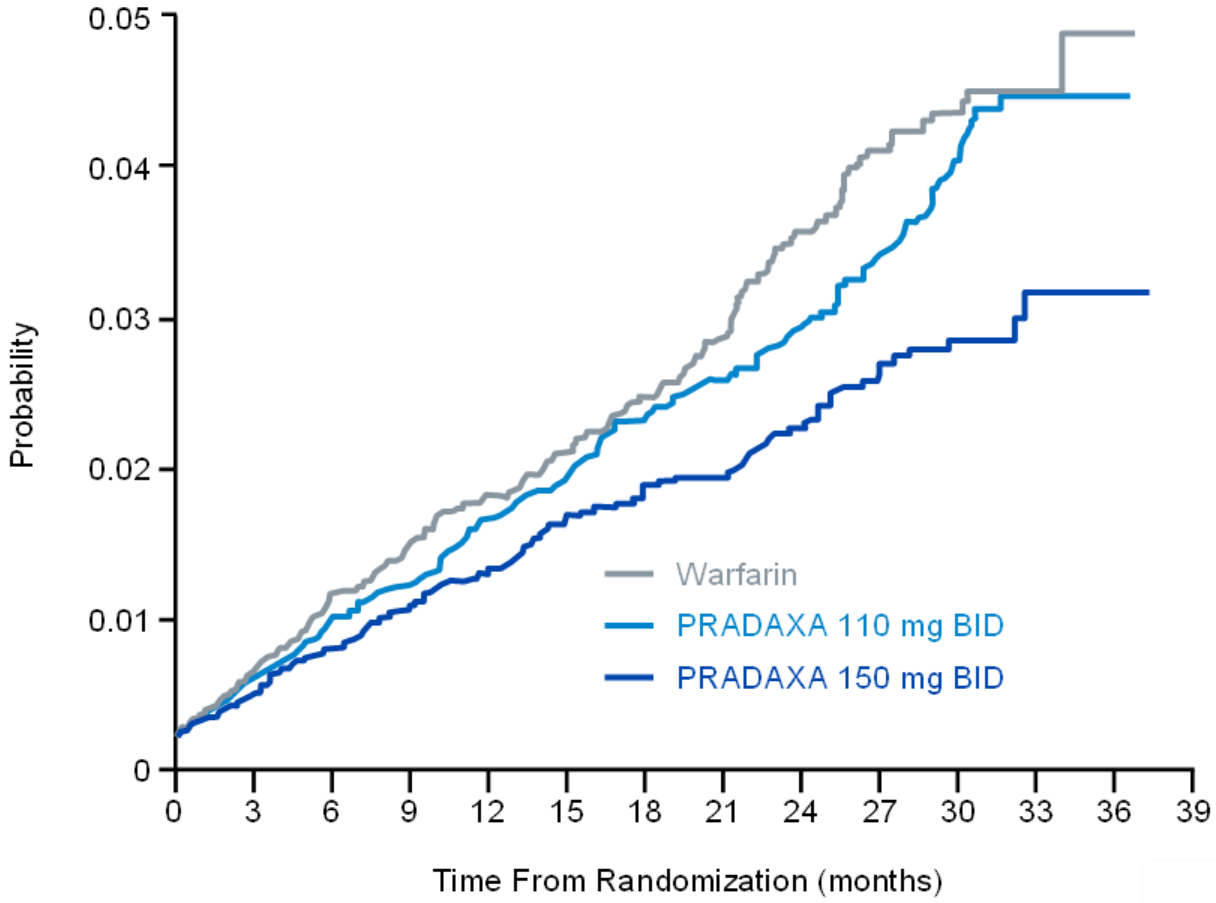
†Major bleeds fulfilled one or more of the following criteria: bleeding associated with a reduction in hemoglobin of at least 2 grams per deciliter or leading to a transfusion of at least 2 units of blood, or symptomatic bleeding in a critical area or organ. A life-threatening bleed met one or more of the following criteria: fatal, symptomatic intracranial bleed, reduction in hemoglobin of at least 5 grams per deciliter, transfusion of at least 4 units of blood, associated with hypotension requiring the use of intravenous inotropic agents, or necessitating surgical intervention. Intracranial hemorrhage included intracerebral (hemorrhagic stroke), subarachnoid, and subdural bleeds.

1. Pradaxa® (dabigatran etexilate mesylate) capsules [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; 2010.
2. Connolly SJ, Ezekowitz MD et al. *N Engl J Med*. 2009;361:1139-1151.

Please see full Prescribing Information.

Pradaxa® dabigatran etexilate CAPSULES

Relative to warfarin, PRADAXA 150 mg twice daily significantly reduced the primary composite endpoint of stroke and systemic embolism



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Please see full Prescribing Information.

Pradaxa® dabigatran etexilate CAPSULES

First occurrence of stroke or systemic embolism in the RE-LY® study

	PRADAXA 150 mg twice daily	PRADAXA 110 mg twice daily	Warfarin
Patients randomized	6076	6015	6022
Patients with events	134 (2.2%)	183 (3%)	202 (3.4%)
Hazard ratio vs warfarin (95% CI)	0.65 (0.52, 0.81)	0.90 (0.74,1.10)	
p-value for superiority	0.0001	0.3	
Hazard ratio vs PRADAXA 110 mg (95% CI)	0.72 (0.58, 0.90)		
p-value for superiority	0.004		

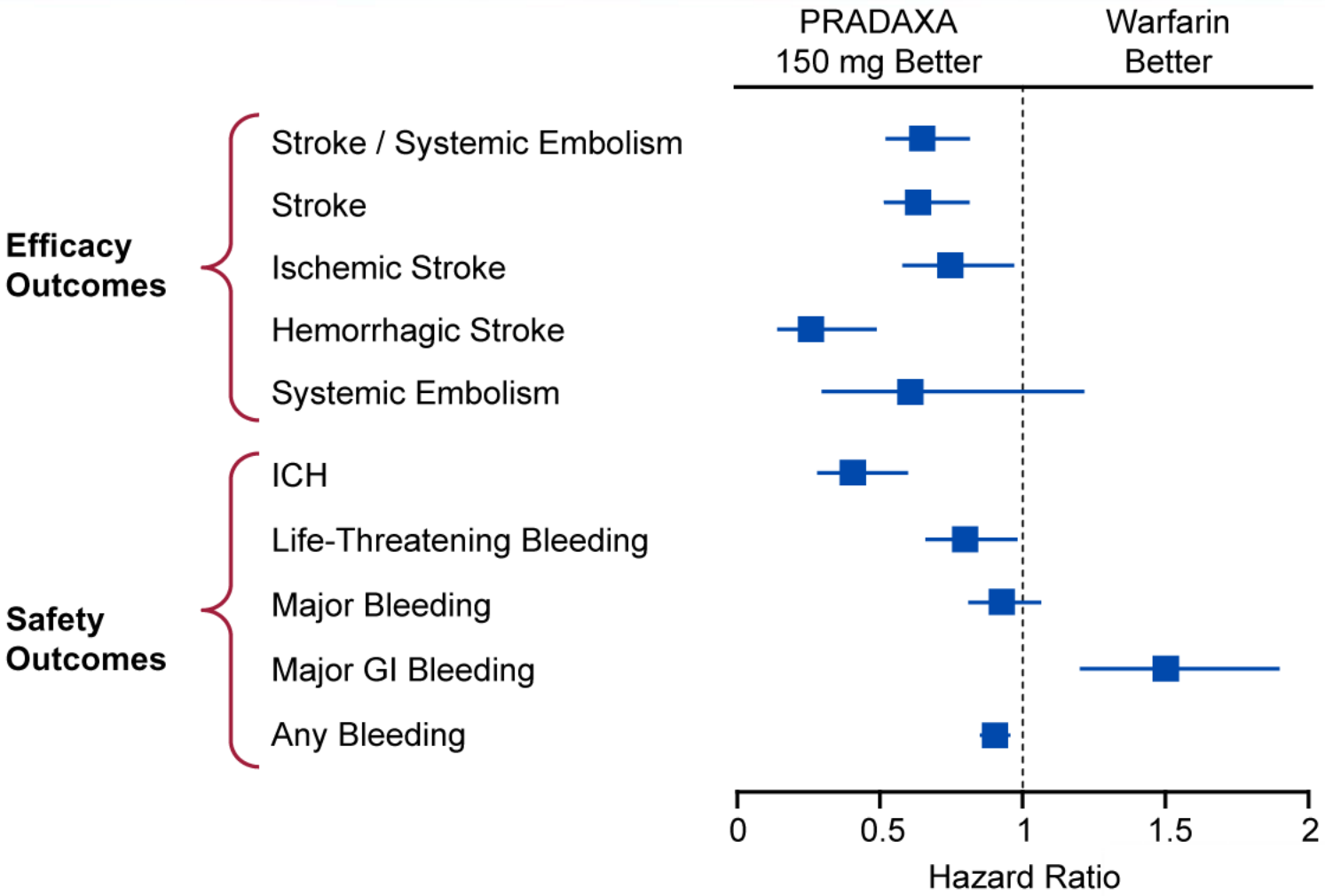
CI: confidence interval.

Pradaxa® (dabigatran etexilate mesylate) capsules [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; 2010.

Please see full Prescribing Information.

Pradaxa® dabigatran etexilate CAPSULES

Summary of clinical outcomes in patients treated with PRADAXA 150 mg twice daily or warfarin[1,2]



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Pradaxa® dabigatran etexilate CAPSULES

Dabigatran: An Oral Novel Potent Reversible Nonpeptide Inhibitor of Thrombin

- Dabigatran:
  - Highly selective
  - Reversible
  - Potent Thrombin Inhibitor
  - Plasma concentrations peak 1-2 hours after ingestion.
  - Half life, 12-14 hours
  - Does not interact with food.
  - Low potential for drug interactions
  - Excreted by kidneys
  - Chronic therapy prevents recurrence of venous thromboembolism and cardioembolic stroke
  - Effective and safe alternative to warfarin

WG Eisert et al., ATVB 2010; 30:1885

Dabigatran Summary

Pros

- Well tolerated
- Lower risk of intracranial hemorrhage
- Achieves therapeutic concentration in 0.5-2 hours (rapid onset)
- No routine monitoring
- Not as patient-dependent as warfarin
- Low potential for drug-drug and drug-diet interactions

Cons

- Higher risk of GI bleeds and dyspepsia
- Cost ($243/60 caps)
- Frequency- BID
- Medication must be used within 30 days of opening bottle
- Patients need to be extremely compliant due to rapid offset of effect
- Patients cannot utilize the drug if they cannot swallow the medication whole
- No reversal agent

Apixaban

- A highly potent, oral, direct FXa inhibitor (K_i 0.08 nM)
  - Follow-up to razaxaban (development halted due to bleeding concerns)
- Phase II study for VTE prevention after TKR: completed
  - Double-blind; dose-ranging; three od and three bid apixaban doses; comparator enoxaparin and warfarin; target enrolment n=1202
- Phase II pilot study for VTE prevention in patients with advanced metastatic cancer: ongoing

Apixaban versus Warfarin in Patients with Atrial Fibrillation

Results of the ARISTOTLE Trial

Presented on behalf of the ARISTOTLE Investigators and Committees

Sponsored by Bristol-Myers Squibb and Pfizer

Background

- Warfarin is very effective at preventing stroke in patients with atrial fibrillation.
- Warfarin has several limitations, including drug and food interactions, a narrow therapeutic range, need for anticoagulation monitoring, and bleeding.
- Apixaban is a novel oral factor Xa inhibitor with rapid absorption, a half life of about 12 hours, and 25% renal elimination.
- Apixaban has been shown to reduce stroke and systemic embolism by 55% compared with aspirin in patients with atrial fibrillation and not suitable for warfarin.

Atrial Fibrillation with at Least One Additional Risk Factor for Stroke

Inclusion risk factors
- Age ≥ 75 years
- Prior stroke, TIA, or SE
- HF or LVEF ≤ 40%
- Diabetes mellitus
- Hypertension

Randomize
double blind, double dummy
(n = 18,201)

Major exclusion criteria
- Mechanical prosthetic valve
- Severe renal insufficiency
- Need for aspirin plus thienopyridine

Apixaban 5 mg oral twice daily
(2.5 mg BID in selected patients)

Warfarin
(target INR 2-3)

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

Primary outcome: stroke or systemic embolism

Hierarchical testing: non-inferiority for primary outcome, superiority for primary outcome, major bleeding, death

Objectives

Primary objective

- To determine whether apixaban is non-inferior to warfarin at reducing stroke (ischemic or hemorrhagic) or systemic embolism in patients with atrial fibrillation and at least one additional risk factor for stroke.

Primary safety outcome

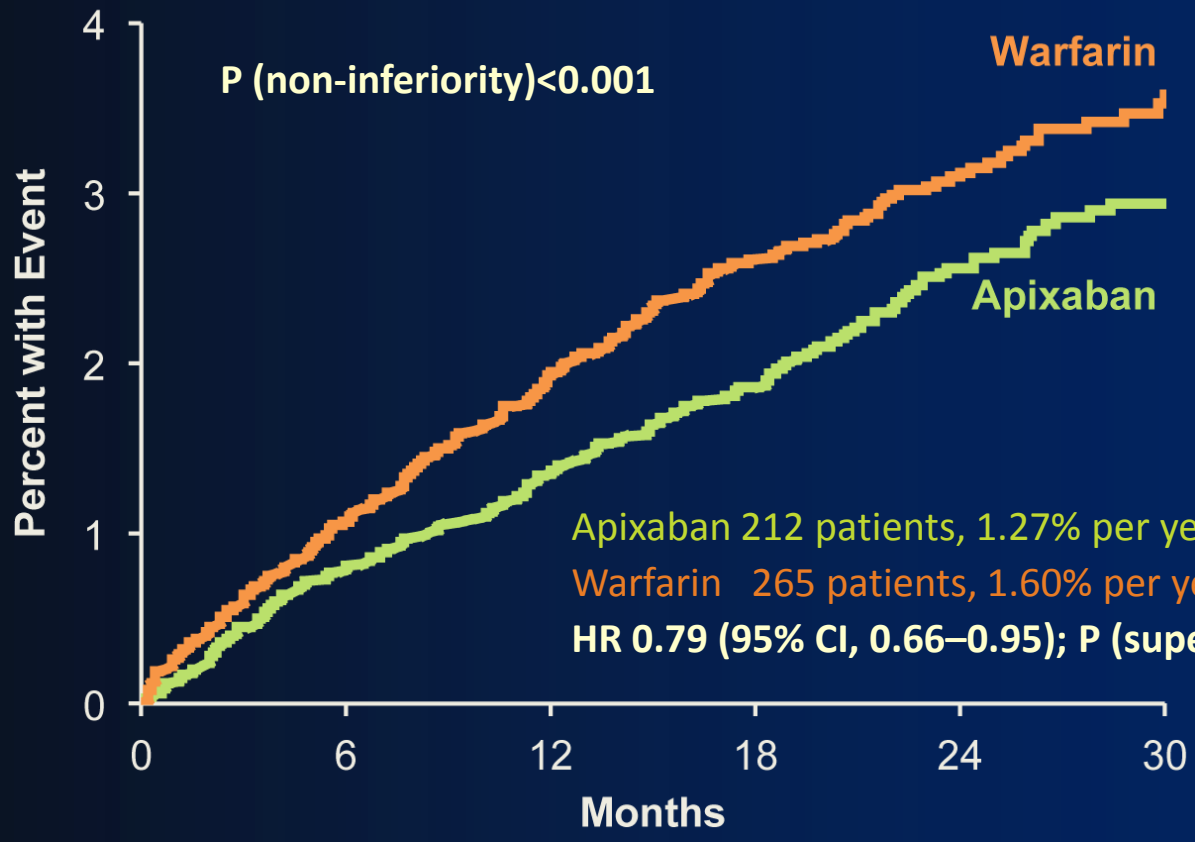
- Major bleeding according to the International Society of Thrombosis and Hemostasis (ISTH) definition.

Apixaban and Warfarin Dosing

- Apixaban (or matching placebo) was dosed at 5 mg twice daily, or 2.5 mg twice daily for a subset of patients with 2 or more of the following criteria: age ≥ 80 years, body weight ≤ 60 kg, serum creatinine ≥ 1.5 mg/dL (133 µmol/L).
- Warfarin (or matching placebo) was dosed guided by blinded encrypted INR point-of-care device, with target INR of 2.0–3.0.

Primary Outcome

Stroke (ischemic or hemorrhagic) or systemic embolism



No. at Risk						
Apixaban	9120	8726	8440	6051	3464	1754
Warfarin	9081	8620	8301	5972	3405	1768

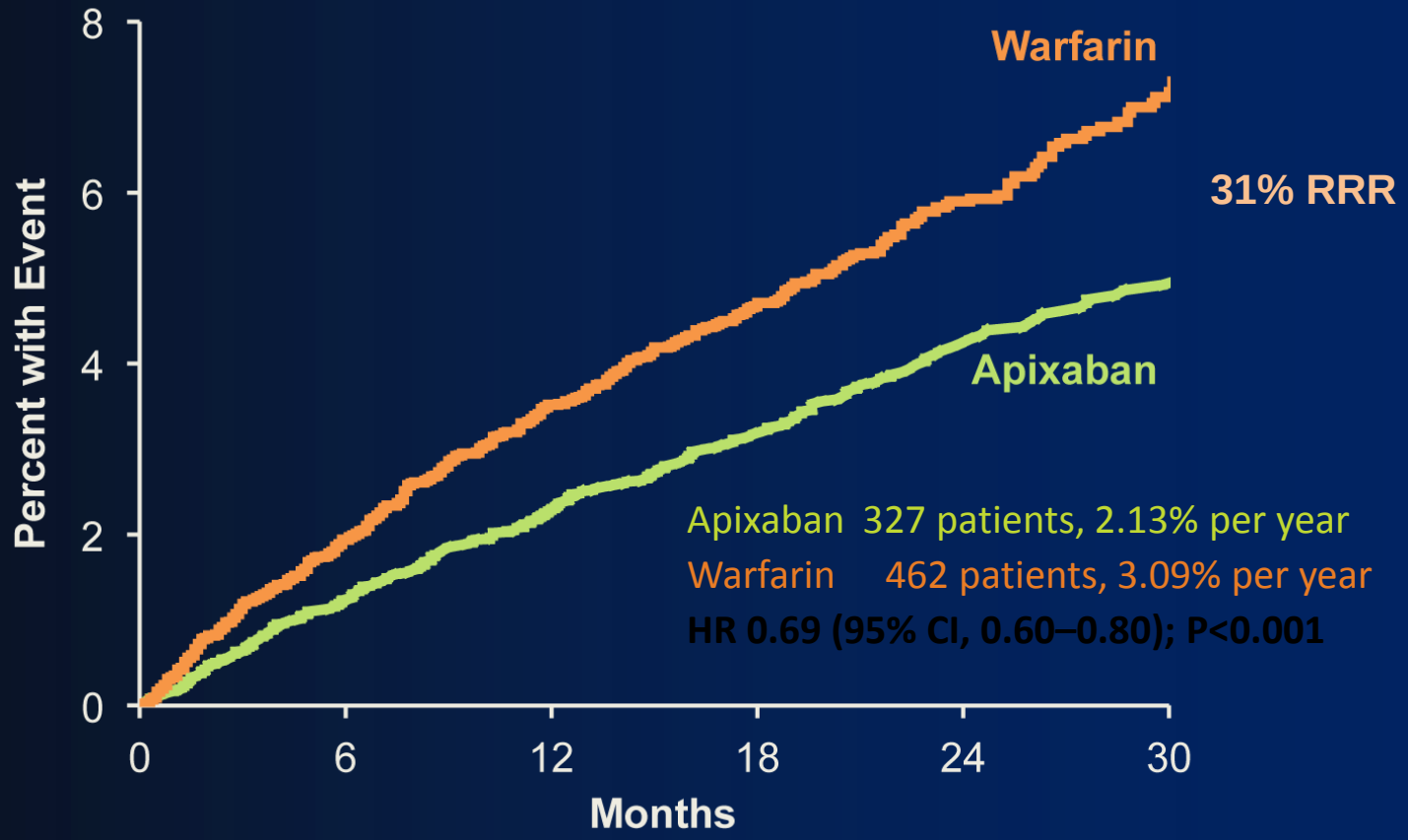
Efficacy Outcomes

Outcome	Apixaban (N=9120) Event Rate (%/yr)	Warfarin (N=9081) Event Rate (%/yr)	HR (95% CI)	P Value
Stroke or systemic embolism*	1.27	1.60	0.79 (0.66, 0.95)	0.011
Stroke	1.19	1.51	0.79 (0.65, 0.95)	0.012
Ischemic or uncertain	0.97	1.05	0.92 (0.74, 1.13)	0.42
Hemorrhagic	0.24	0.47	0.51 (0.35, 0.75)	<0.001
Systemic embolism (SE)	0.09	0.10	0.87 (0.44, 1.75)	0.70
All-cause death*	3.52	3.94	0.89 (0.80, 0.998)	0.047
Stroke, SE, or all-cause death	4.49	5.04	0.89 (0.81, 0.98)	0.019
Myocardial infarction	0.53	0.61	0.88 (0.66, 1.17)	0.37

* Part of sequential testing sequence preserving the overall type I error

Major Bleeding

ISTH definition



No. at Risk						
Apixaban	9088	8103	7564	5365	3048	1515
Warfarin	9052	7910	7335	5196	2956	1491

Compared with warfarin, apixaban (over 1.8 years) prevented

- 6 Strokes
  - 4 hemorrhagic
  - 2 ischemic/uncertain type
- 15 Major bleeds
- 8 Deaths

per 1000 patients treated.

Summary

Treatment with apixaban as compared to warfarin in patients with AF and at least one additional risk factor for stroke:

- Reduces stroke and systemic embolism by 21% ($p=0.01$)
- Reduces major bleeding by 31% ($p<0.001$)
- Reduces mortality by 11% ($p=0.047$)

with consistent effects across all major subgroups and with fewer study drug discontinuations on apixaban than on warfarin, consistent with good tolerability.

Conclusion

In patients with atrial fibrillation, apixaban is superior to warfarin at preventing stroke or systemic embolism, causes less bleeding, and results in lower mortality.

Rivaroxaban vs. Warfarin
for Prevention of Stroke and Emboli

- ROCKET AF aims to establish the noninferiority of rivaroxaban compared with warfarin in patients with nonvalvular AF who have a hx of stroke or risk factors.
- Randomly assigned to Rivaroxaban vs. Warfarin
- Primary efficacy and point is a composite of all-cause stroke and noncentral nevrvous system embolism.
- 14,000 patients randomized at 1,100 sites in 45 countries.
- Will be followed until 405 primary outcomes are observed.

ROCKET AF – Am Heart J 2010; 159:340

Rivaroxaban Cont'd

Pharmacokinetics/ Dynamics

- Absorption: rapid
- Protein binding: 92-95%
- Metabolism: hepatic (CYP 3A4, 3A5, 2J2)
- Bioavailability: ~100%
- Half life: 5-9 hours
- Excretion: urine and feces

Contraindications/ Precautions

- Contraindications
  - Hypersensitivity to rivaroxaban or any formulation component
  - Hepatic disease
  - Active bleeding
  - Concomitant systemic treatment with strong CYP 3A4 and P-glycoprotein inhibitors
  - Pregnancy and lactation
- Precautions
  - **Black Box Warning:** epidural or spinal hematomas may occur in anticoagulated patients who receive neuraxial anesthesia or undergo spinal puncture, may result in long term/ permanent paralysis
  - Monitor for neurological impairment
  - Renal impairment
  - Lactose intolerance

Rivaroxaban Clinical Trials

- Rivaroxaban Versus Warfarin in Nonvalvular Afib
  - Rivaroxaban 20 mg daily, rivaroxaban 15 mg daily (dose adjusted for renal function), and warfarin
  - Patients had substantial rates of coexisting illnesses (mean $CHADS_2$ score of ~3.5 +/- 0.95)
  - Rivaroxaban was noninferior to warfarin for the prevention of stroke or systemic embolism
    - In patients actively receiving treatment, rivaroxaban was found to be superior to warfarin
  - The efficacy of rivaroxaban, as compared with warfarin, was as favorable in centers with the best INR control as in those with poorer control
    - Warfarin INR control was suboptimal

Summary

Pros

- Significant decrease in ICH
- Significant decrease in fatal bleeding
- No routine lab monitoring
- Fewer interactions compared to warfarin

Cons

- Bleeding from GI sites (including: upper, lower, and rectal) occurred more frequently
- One 10mg tablet/$6.75
- 92-95% protein bound (not dialyzable)
- Lactose intolerance
- No reversal agent

Edoxaban

Pharmacokinetics/ Dynamics

- Absorption: rapid
- Protein binding: ~80%
- Metabolism: hepatic (CYP 3A4)
- Bioavailability: ~50%
- Half life: ~8-10 hours
- Excretion: 35% urine and 65% feces

Contraindications/ Precautions

- Will be similar to rivaroxaban
- Hypersensitivity to edoxaban or any formulation component
- Active bleeding
- Concomitant systemic treatment with strong CYP 3A4 and P-glycoprotein inhibitors
- Renal impairment

Edoxaban Clinical Trials (in progress)

- Phase III ENGAGE AF-TIMI 48 trial- Edoxaban vs. warfarin in Non-valvular atrial fibrillation and stroke risk factor/s ($CHADS_2$ 2-3 vs. 4-6)
  - Primary end point: Time to stroke or systemic embolism *****Study Ongoing******
- Phase III HOKUSAI VTE trial- Edoxaban vs LMWH/Warfarin in treatment and prevention of recurrent thromboembolic events
  - Primary end point: Symptomatic recurrent VTE (the composite of DVT, non-fatal PE, and fatal PE)
  - *****Study Ongoing(enrolling through September 2012)*****

Possible Reversal Agent for the Anti-Xa Medications

- Portola Pharmaceuticals is currently investigating a drug known as PRT064445
- A novel recombinant protein
- Capable of reversing Factor Xa inhibitors
- As of 2010 the company was still undergoing preclinical studies

Summary Apixaban and Edoxaban

Pros

- Offers a more convenient alternative to LMWH for VTE prophylaxis after TKR or THR
- No routine lab monitoring
- Fewer known interactions compared to warfarin
- Rapid onset

Cons

- Apixaban-increased bleeding in combination with combination antiplatelet therapy following ACS- APPRAISE II trial
- Cost (when approved)
- Renal dose
- No reversal agent

New VKA on the horizon- Tecarfarin

- Tecarfarin is a single enantiomer, novel warfarin analogue with improved pharmacological properties
  - T ½ -136 hrs
  - Highly protein bound
  - Metabolized by carboxylesterases in the hepatic microsomes (not CYP450)
  - 100% hepato-biliary clearance
  - Less drug-drug interactions than warfarin
  - Monitored by INR

Challenges in the Clinical Adoption of New Anticoagulants

- No validated tests to measure anticoagulation effect
- No established therapeutic range
- No antidote for most agents (yet…)
- Assessment of compliance more difficult than for vitamin K antagonists
- Potential for unknown long-term adverse effects
- Balancing cost against efficacy
- Lack of head-to-head studies comparing new agents

AF, Antithrombotics and Challenges – 2010-2020

- 1. Challenge by ESC of ACC/AHA Guidelines in AF
- 2. Challenge by INR- TE/Bleeding
- 3. Challenge of Age – TE/Bleeding
- 4. Challenge of Brain – Micro vascular Disease
- 5. Challenge of Multiple Antithrombotics
- 6. Challenge of Novel Platelet Inhibitors
- 7. Challenge of Nobel Anticoagulants
- 8. Challenge of Ablation and LAA Exclusion in AF

ACC/AHA/ESC (Fuster V et al) Circ 2006; 114:700
ESC Guidelines, EHJ 2010; 31:2369 – Working Group Report, EU 2010

The End

Damodhar P. Suresh, M.D., F.A.C.C., F.S.C.A.I.