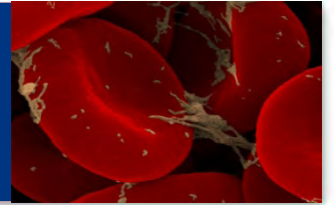




New Oral Anticoagulants: Have we found the Holy Grail?

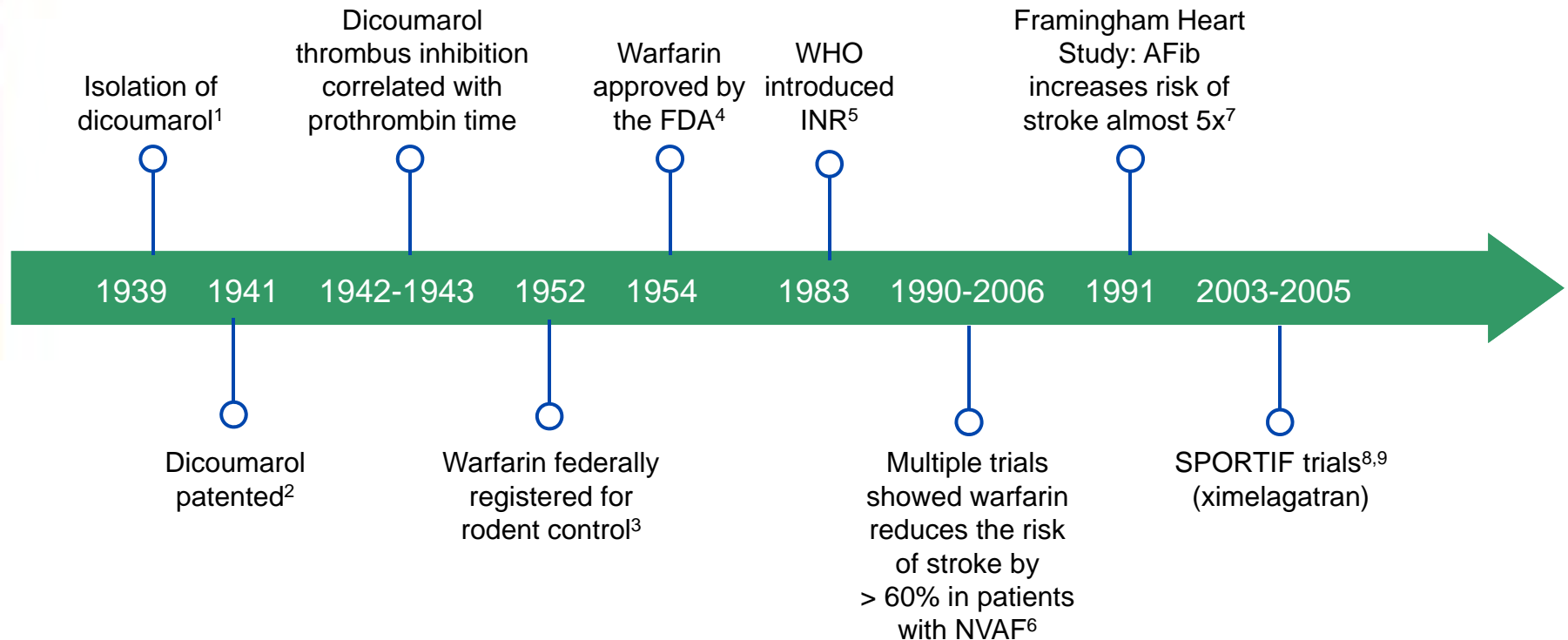
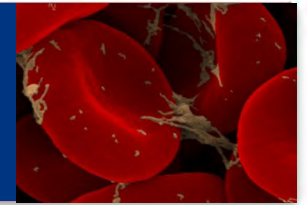
Allison Burnett, PharmD
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Objectives



- Recognize the efficacy of warfarin for stroke prevention in atrial fibrillation
- Describe the ideal anticoagulant
- Summarize new oral anticoagulants (OACs) in development & those already approved for use
- Discuss appropriate patient selection for warfarin vs. new options.
- Discuss the future of warfarin

OAC development



AFib: atrial fibrillation; **FDA:** Food and Drug Administration; **INR:** international normalized ratio; **NVAF:** non-valvular atrial fibrillation; **SPORTIF:** Stroke Prevention using ORal Thrombin Inhibitor for atrial Fibrillation.

1. Link KP. *Circulation*. 1959;19:97-107.
2. Wisconsin Alumni Research Foundation. <http://www.warf.org/about/index.jsp?cid=26&scid=34>. Accessed August 2, 2010.
3. Environmental Protection Agency. June 1991.
4. Food and Drug Administration. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist. Accessed August 19, 2010.
5. WHO Expert Committee on Biological Standardization, Thirty-third Report.
6. Hart RG, Pearce LA, Aguilar MI. *Ann Intern Med*. 2007;146:857-867.
7. Wolf PA, Abbott RD, Kannel WB. *Stroke*. 1991;22:983-988.
8. Olsson SB. *Lancet*. 2003;362:1691-1698.
9. Albers GW, Diener H-C, Frison L, et al. for the Executive Steering Committee for the SPORTIF V Investigators. *JAMA*. 2005;293:690-698.

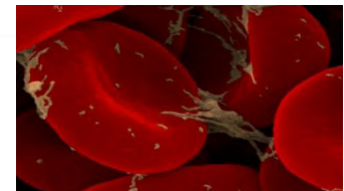
Warfarin vs. placebo: Efficacy in primary prevention of stroke in patients with non-valvular atrial fibrillation

Adjusted-dose warfarin versus placebo or no treatment

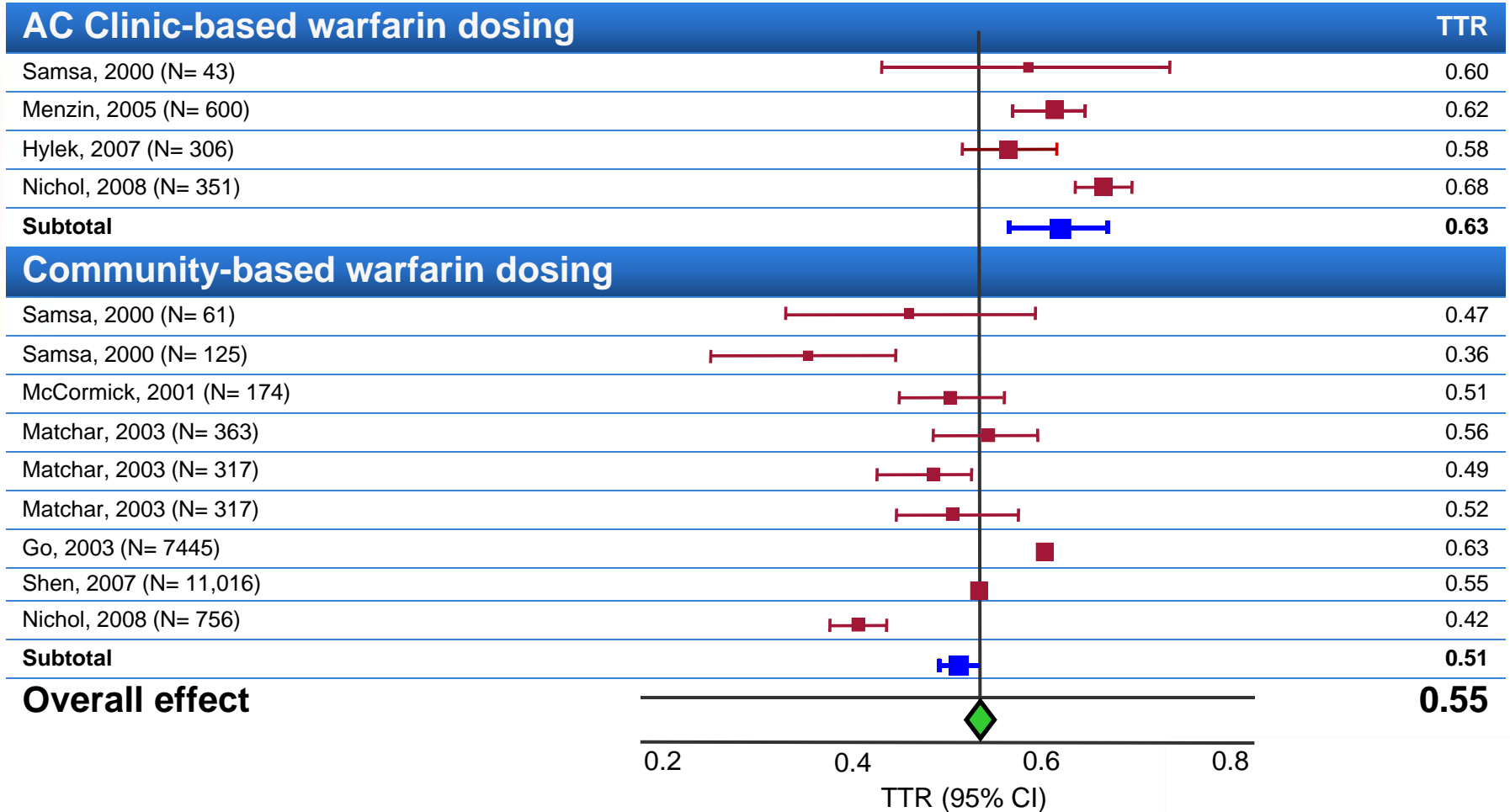
Study	Participants (N)	Target INR	Relative risk reduction (%)*
AFASAK	671	2.8-4.2	54
SPAF I	421	2.0-4.5	60 [†]
BAATAF	420	1.5-2.7	78 [†]
CAFA	378	2.0-3.0	33
SPINAF	571	1.4-2.8	70 [†]
EAFT	439	2.5-4.0	68 [†]
6 Trials	2900	—	64 (95% CI: 49 to 74)

*Risk reduction for combined ischemic and hemorrhagic strokes by intention-to-treat analysis.

[†] $p < 0.05$, 2-sided.



Time in therapeutic range (TTR) of atrial fibrillation patients on warfarin in the United States



Incidence of vascular events stratified by median time in therapeutic range (TTR) between treatment centers*

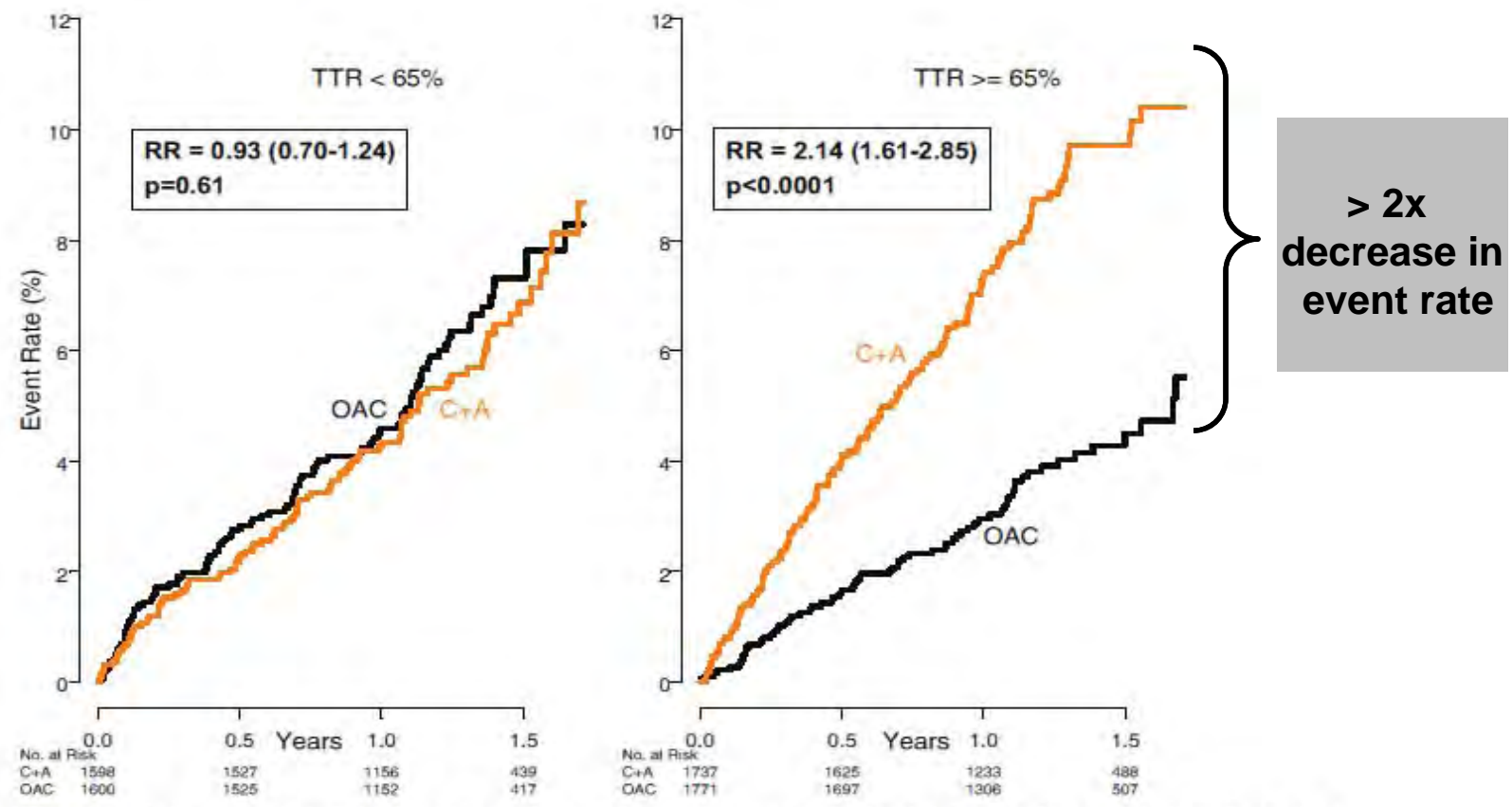


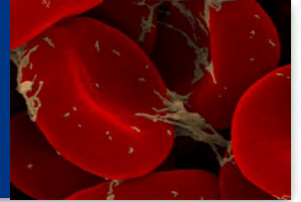
Figure 1. Cumulative risk of stroke, myocardial infarction, systemic embolism, or vascular death for patients treated at centers with a TTR below or above the study median (65%). RR indicates relative risk: C+A, clopidogrel plus aspirin.

OAC= oral anticoagulation (with vitamin K antagonist)

C+A= clopidogrel + aspirin

*Vascular events include stroke (ischemic and hemorrhagic), MI, vascular death, or systemic embolism over 1.5 years.

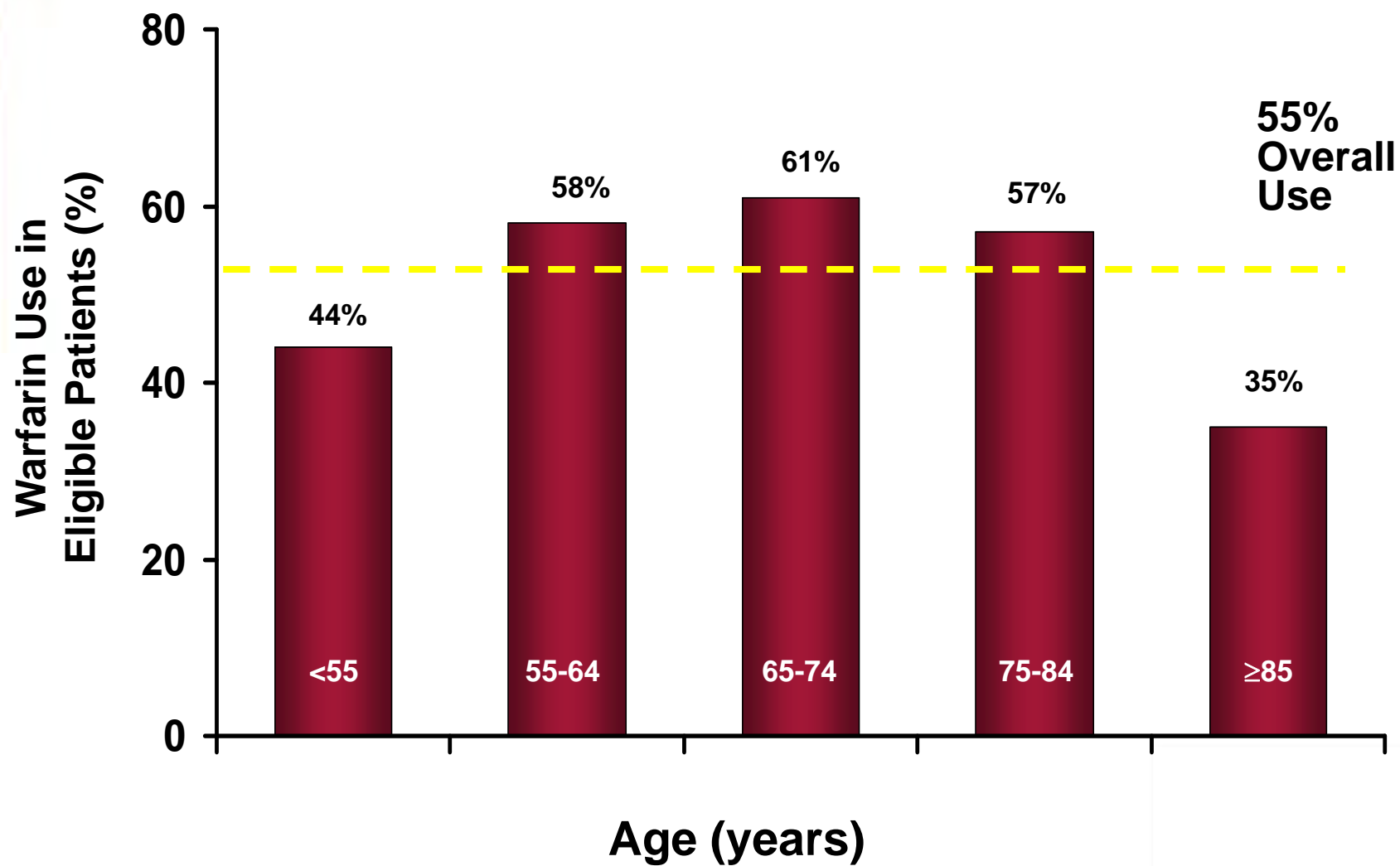
Limitations of warfarin



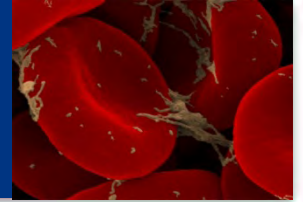
- Interactions (food, drug, disease state)
- Slow onset and offset of action
- Considerable inter- and inpatient variability
- Narrow therapeutic window
- Fear of hemorrhage
- Need for routine monitoring

Warfarin for Atrial Fibrillation

Limitations Lead to Under-treatment

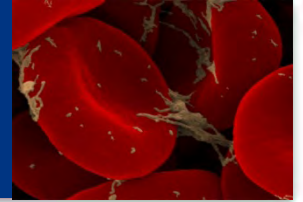


The ideal anticoagulant...



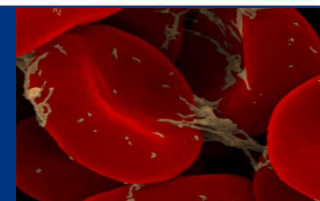
- Oral administration with rapid onset of action
- Broad therapeutic window
- Low inter- and intra-patient variability
- No routine monitoring
- No drug or food interactions
- Safe with minimal adverse events
- Easily reversible (with or without an antidote)
- Does not require bridging
- Target- or factor-specific (initiation, propagation, clot formation)
- Cost effective

Challenges in development



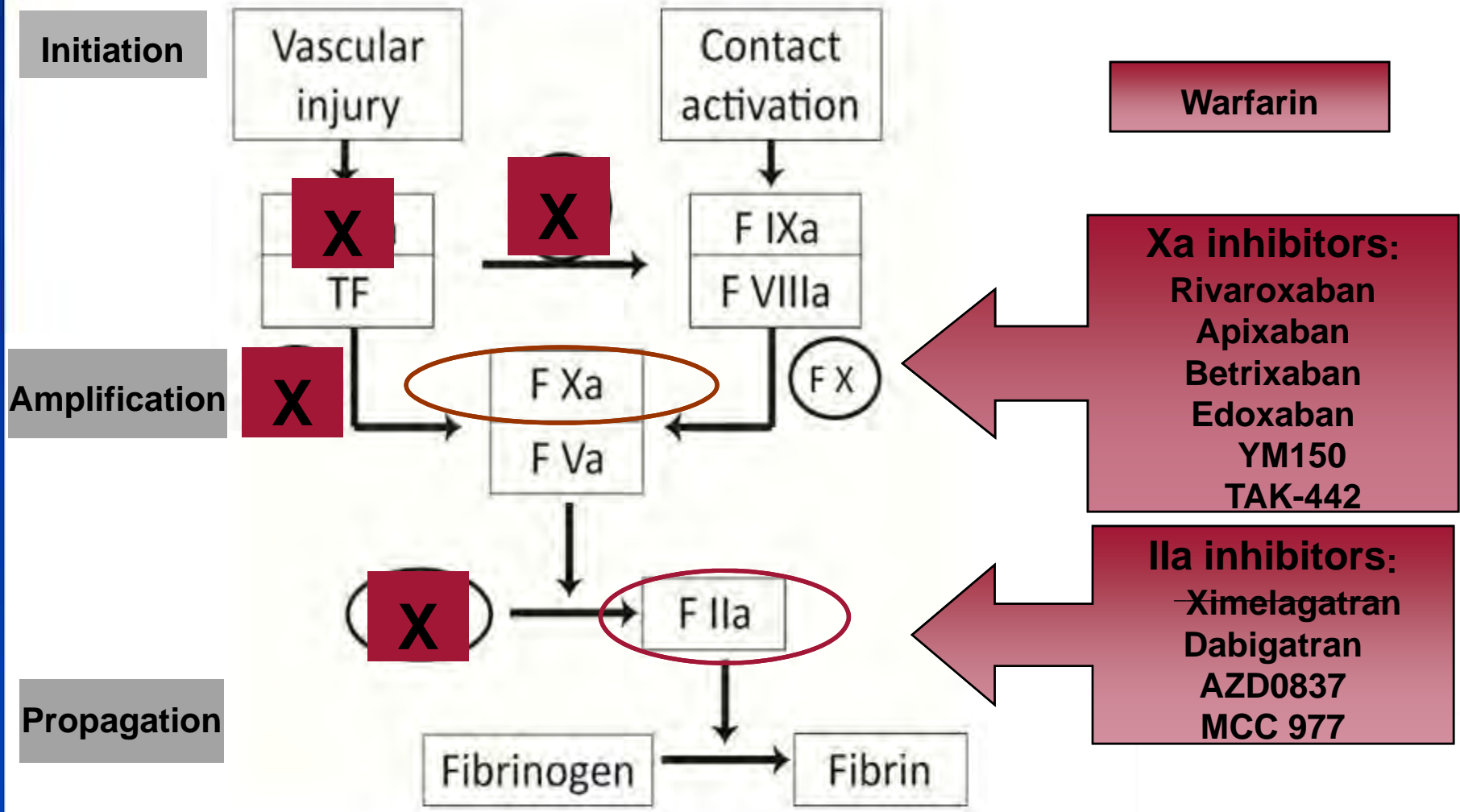
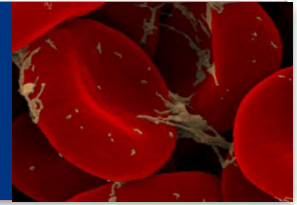
- Establish non-inferiority with existing agents
- Improve the risk-benefit profile
- Cost
- Efficacy in special populations (e.g. pregnancy, prosthetic valves)
- Standard progression of novel anticoagulant development
 - VTE prevention after major orthopedic surgery
 - VTE treatment
 - Stroke prevention in atrial fibrillation
 - Acute coronary syndromes

Anticoagulants in development

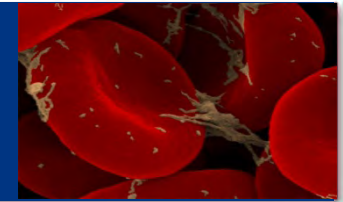


Agent	Route	Company	Status
Direct thrombin inhibitors (DTIs)			
Dabigatran	Oral	Boehringer Ingelheim	Phase III/IV
AZD0837	Oral	AstraZeneca	Phase II
MCC 977	Oral	Mitsubishi Pharma	Phase II
Direct Factor Xa Inhibitors			
Rivaroxaban	Oral	Bayer, Ortho-McNeill	Phase III/IV
Apixiban	Oral	Bristol-Myers Squibb, Pfizer	Phase III
Betrixaban	Oral	Portola	Phase II
YM150	Oral	Astellas	Phase II
Edoxaban	Oral	Daichi Sankyo	Phase III
TAK-442	Oral	Takeda	Phase II
Otamixaban	Inj	Sanofi-aventis	Phase II

Mechanism of action of new oral anticoagulants

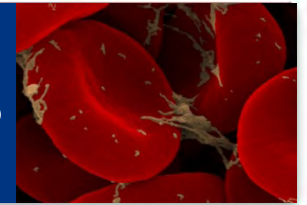


Comparative features: warfarin vs. new oral anticoagulants



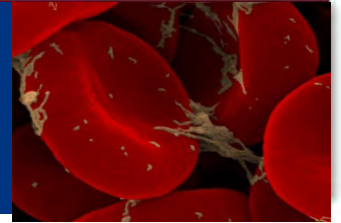
	Warfarin	Dabigatran etexilate	Rivaroxaban	Apixaban
Target	VKORC1 Factors II, VII, IX, X	Thrombin (Factor IIa)	Factor Xa	Factor Xa
T (max)	72-96 h	2 h	2.5-4 h	3 h
Half-life	40 h	14-17 h	5-9 h healthy, 9-13 h elderly	8-15 h
Monitoring	INR-adjusted	Not needed	Not needed	Not needed
Administration	Once daily	Once or twice daily	Once daily	Twice daily
Metabolism	Cytochrome P450	80% renal, 20% fecal	66% renal, 33% fecal	25% renal 75% fecal,
Possible assay	PT/INR	Ecarin clotting time, Thrombin time	Anti-factor Xa, PiCT [®] , HepTest [®]	Anti-factor Xa

Clinical trials of new oral anticoagulants



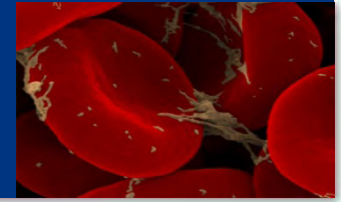
Drug	Orthopedic prophylaxis	VTE treatment	Stroke prevention in afib	ACS
Dabigatran FIIa inhibitor	BISTRO REMODEL RENOVATE REMOBILIZE	RECOVER REMEDY RESONATE	RELY	RE-DEEM
Rivaroxaban FXa inhibitor	RECORD 1 RECORD 2 RECORD 3 RECORD 4	EINSTEIN PE EINSTEIN DVT EINSTEIN-EXT	ROCKET AF	ATLAS
Apixaban FXa inhibitor	ADVANCE 1 ADVANCE 2 ADVANCE 3	AMPLIFY AMPLIFY-EXT	AVERROES (ASA) ARISTOTLE (W)	APPRAISE

Dabigatran (Pradaxa®)- Current Regulatory Status



- Approved in Europe and Canada in 2008 for thromboprophylaxis following THR/TKR (220 mg once daily)
- **Approved by US FDA for stroke prevention in atrial fibrillation on 10/19/10 based on results from the RE-LY trial**
- Approved dosing regimens for afib
 - 150 mg PO BID in normal renal function
 - 75 mg PO BID if CrCl <30 ml/min

Dabigatran in Afib: RE-LY trial

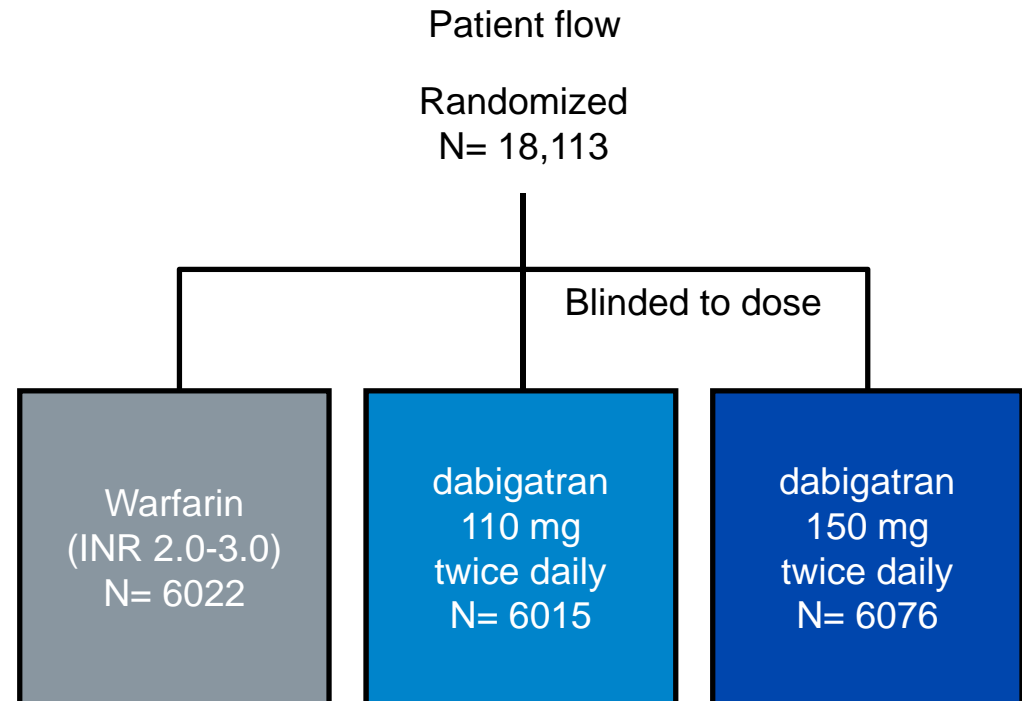


Study Parameters

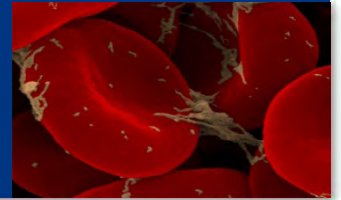
- Open label, noninferiority, intent-to-treat trial
- Blinded adjudication of outcome events
- 50% patients VKA-naïve*
- Primary outcome: incidence of stroke (ischemic and hemorrhagic) and systemic embolism in patients with non-valvular atrial fibrillation
- Primary safety outcome: incidence of major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

VKA: vitamin K antagonist.

*Total lifetime exposure of < 2 months

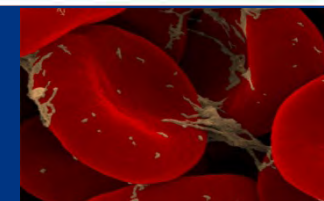


Inclusion/Exclusion Criteria of RE-LY



- Inclusion
 - Non-valvular persistent, paroxysmal, or permanent atrial fibrillation AND
 - One or more additional risk factors for stroke
 - Concomitant medications allowed, including antiplatelets
- Exclusion
 - History of heart valve disorders
 - Severe disabling stroke within the previous 6 months or any stroke within the previous 14 days
 - Conditions associated with an increased risk of bleeding
 - Contraindication to warfarin treatment
 - ***Severe renal impairment (creatinine clearance < 30 mL/min)***

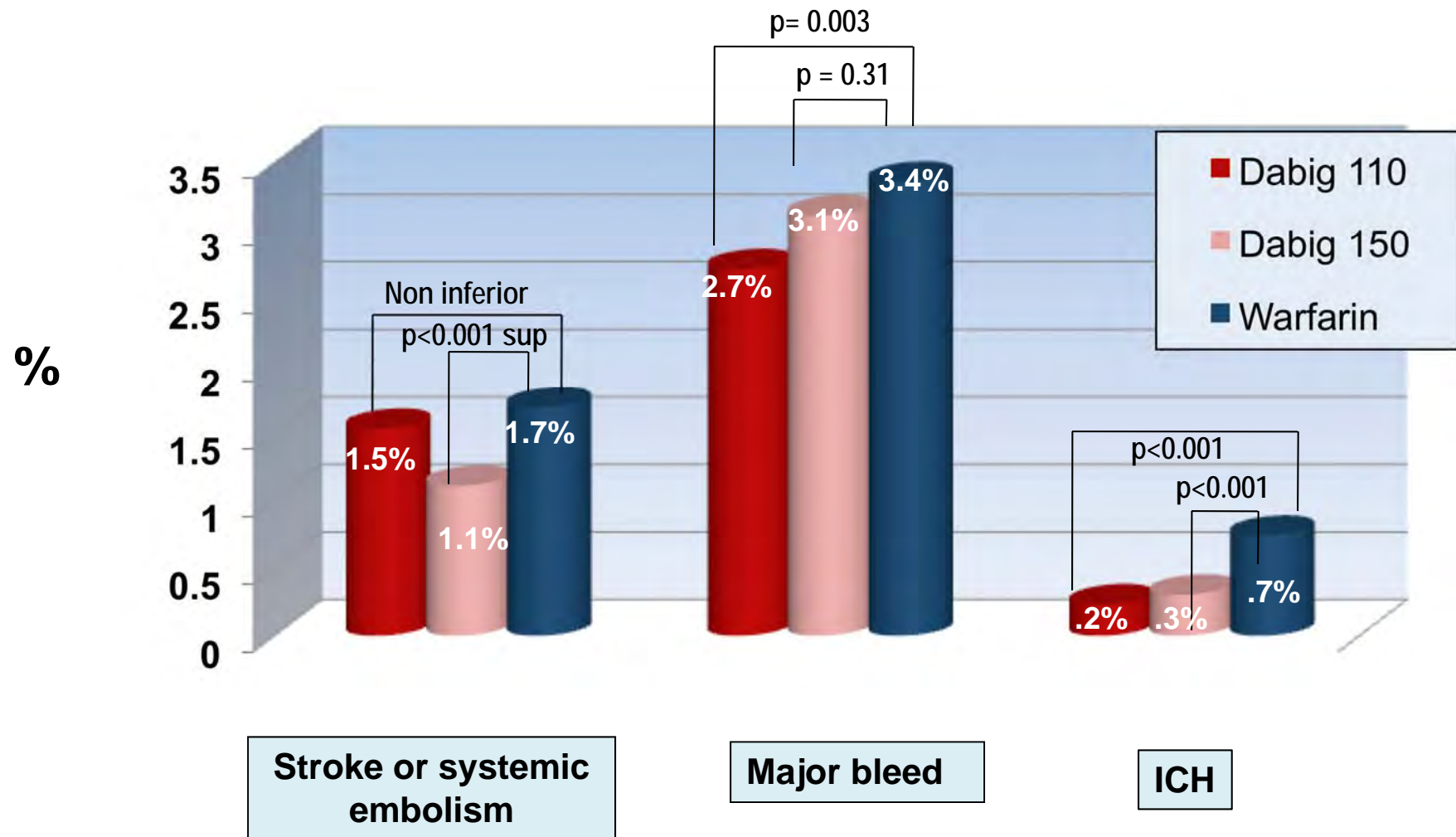
Baseline characteristics of patients in the RE-LY trial



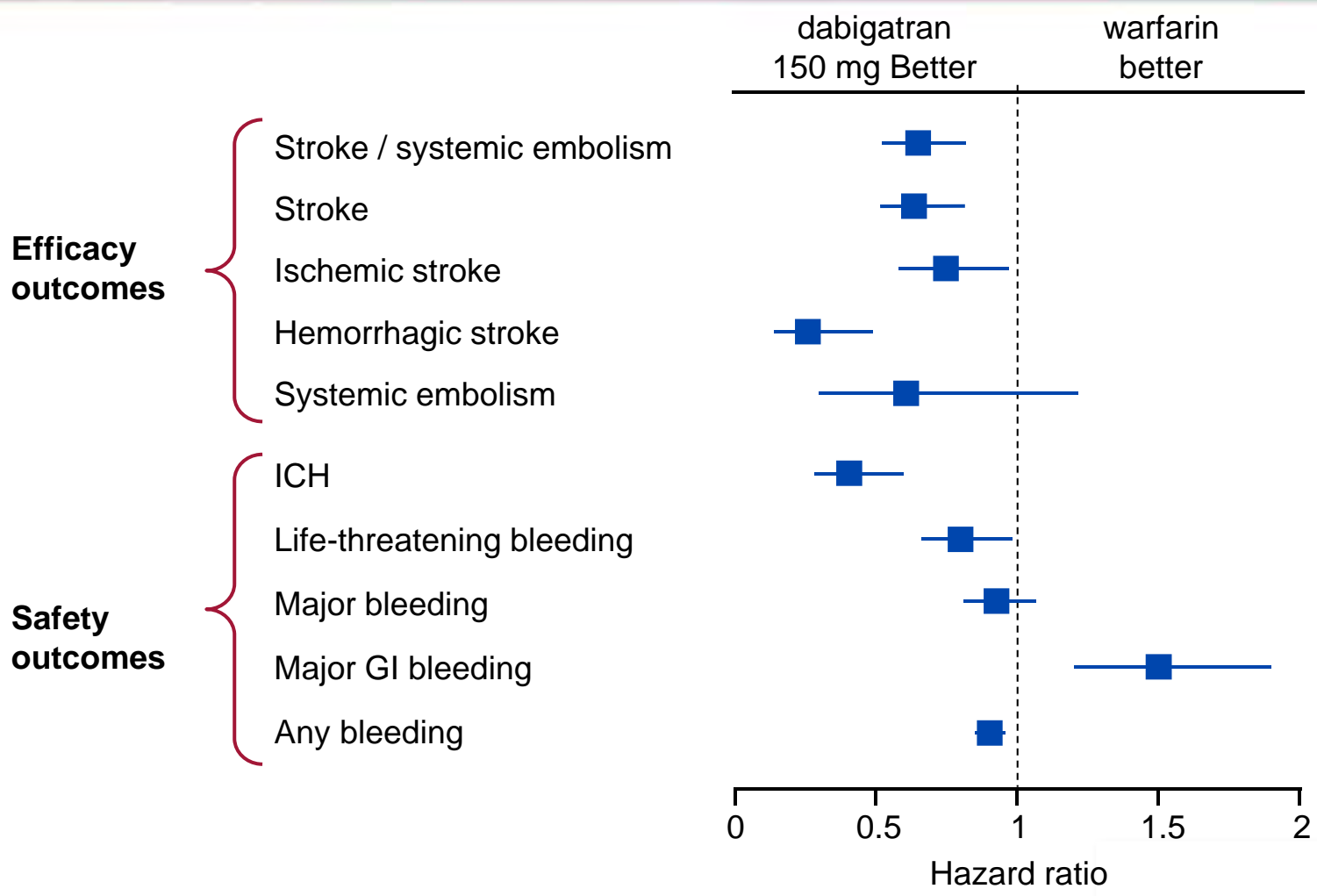
Characteristic	dabigatran 150 mg twice daily (N= 6076)	Warfarin (N= 6022)
Age, mean (years)	71.5	71.6
Age ≥ 75 years (%)	40.6	40.2
Male (%)	63.2	63.3
CHADS ₂ score, mean	2.2	2.1
0-1 (%)	32.2	30.9
2 (%)	35.2	37.0
3+ (%)	32.6	32.1
Prior stroke / TIA (%)	20.3	19.8
Diabetes (%)	23.1	23.4
Hypertension (%)	78.9	78.9
Baseline aspirin (%)	38.7	40.6
VKA-naive (%)	49.8	51.4

Stroke Prevention in Atrial Fibrillation

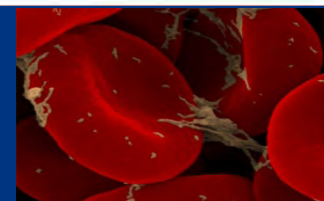
Dabigatran etexilate vs. warfarin (RE-LY)



Summary of clinical outcomes in patients treated with dabigatran 150 mg twice daily or warfarin



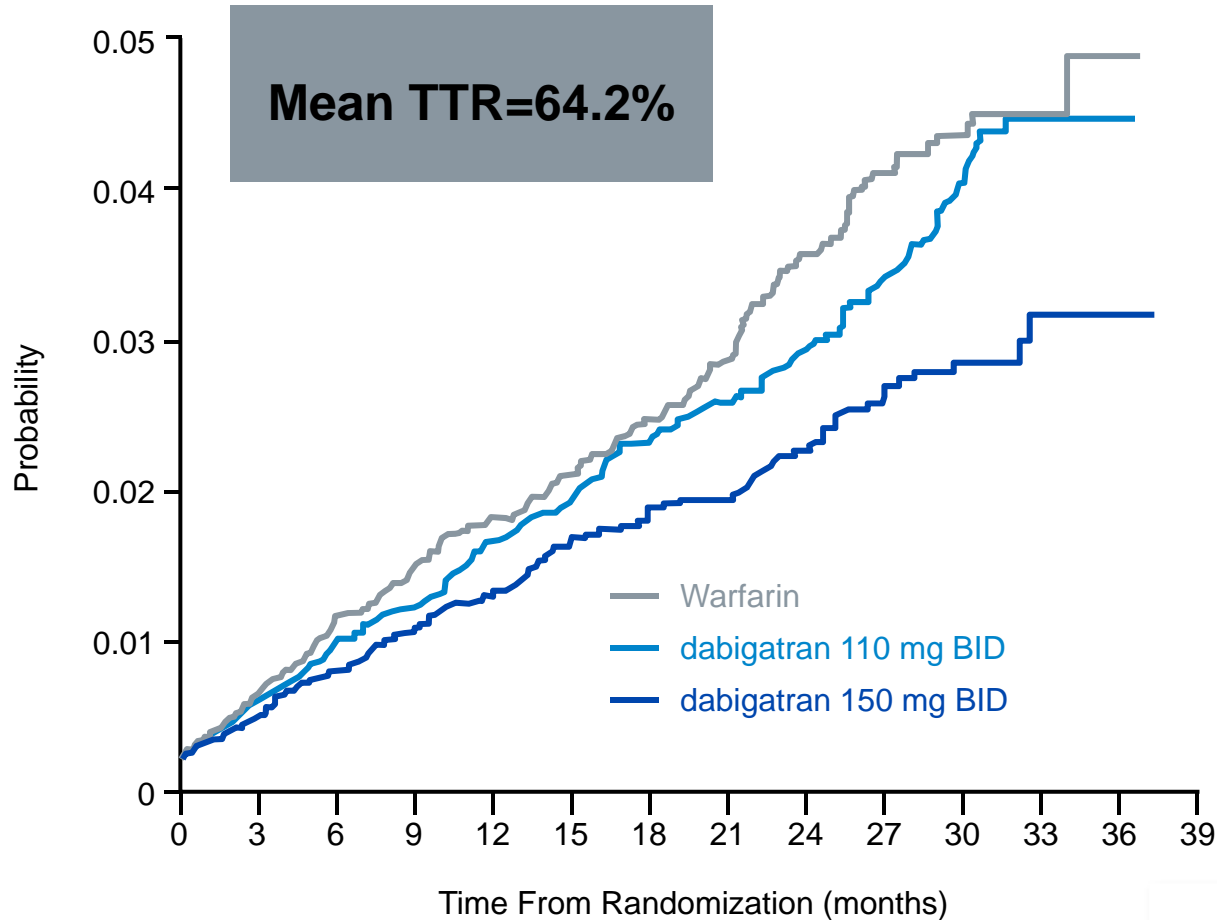
Adverse Events- RELY



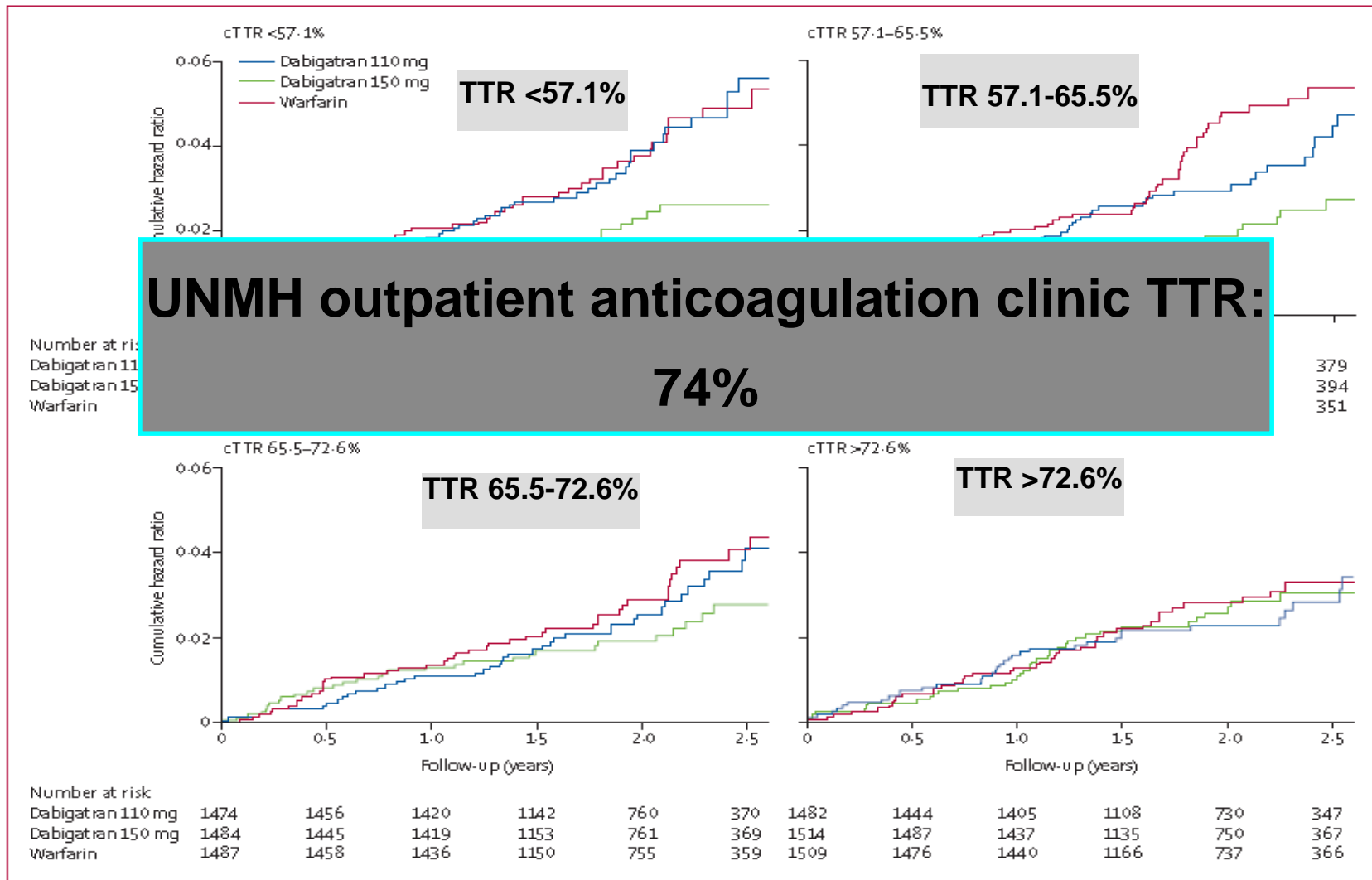
	Dabigatran 150 mg BID	Warfarin
Incidence of GI adverse effects	35%	24%
Drug discontinuation	21%	16%

- There was a trend towards a higher incidence of bleeding on dabigatran for patients ≥ 75 years of age (HR 1.2, 95% CI:1.0 to 1.4)
- Increased incidence of myocardial infarction in dabigatran patients (0.74% vs 0.53% p=0.048, RR 1.38 (1-1.91 95%CI))
- No difference in elevation of liver transaminases

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



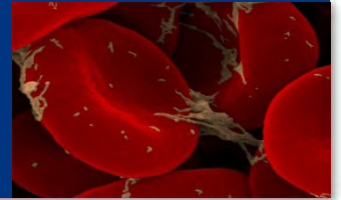
Dabigatran vs. warfarin, stratified by center-based TTR



Time to stroke or systemic embolism

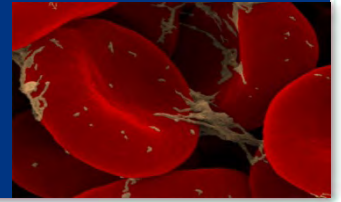
Wallentin et al. Lancet 2010. 376:975-83

ACC/AHA guideline on atrial fibrillation- 2010



- Revised to include dabigatran as an alternative to warfarin for stroke or systemic embolism prevention in NVAF (1B)
- “because of twice-daily dosing and greater risk of non-hemorrhagic side effects with dabigatran, patients already taking warfarin with excellent INR control may have little to gain by switching...”

Considerations for formulary addition of dabigatran



- Stability
 - 60 days for bottles
 - blister packs won't fit in pill boxes
- Insurance issues
 - high co-pay/prior auth required by most local insurances
 - cost will put most Medicare patients into the doughnut hole
 - who will triage these issues prior to discharge
- Possible restrictions
 - Cardiology
 - NVAf
 - Warfarin failure (how to define this?)
 - Renal impairment or age >75?
- TTR of your outpatient clinic
- Cost
 - Retail price \$175-275 per month

Dabigatran: Transitioning and Peri-operative Management

Transitioning

- Changing from warfarin: discontinue warfarin; start dabigatran when $\text{INR} < 2$.
- Changing to warfarin:
 - CrCl > 50 : start warfarin 3 days before discontinuing dabigatran
 - CrCl 31-50: 2 days before
 - CrCl 15-30: 1 day before

Peri-operative management

- Discontinue dabigatran 1-2 days (CrCl > 50) or 3-5 days (CrCl < 50) before scheduled invasive or surgical procedures
- Consider longer time intervals for major surgery or spinal/epidural punctures

Post-marketing Surveillance- Dabigatran

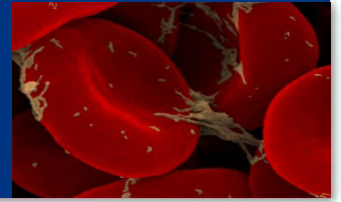
heartwire
ARRHYTHMIA
Cautio... in the elderly
AUGUST 4

Tweet 0 +1 0 Share

From Heartwire > Alerts, Approvals
Deaths Prompt Dabigatran Sa...
Shelley Wood
Authors and Disclosures
Posted: 08/17/2011

**This is NOT
“Anticoagulation for Dummies”!**

Who Is a Candidate for Dabigatran?



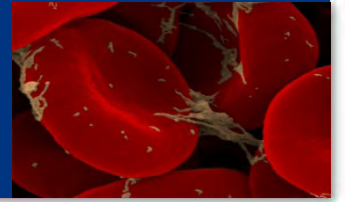
- Good candidates

- Have NVAF and meet CHADS2 criteria for anticoagulation AND ≥ 1 of the following
 - Poor INR control in spite of good compliance with warfarin
 - Unusual difficulty with regular INR checks
 - True warfarin allergy
 - Understand disadvantages and are willing to trade them for convenience of no lab monitoring

- Less compelling candidates

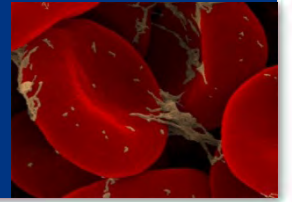
- Have indications other than NVAF for anticoagulation or an unacceptable risk-benefit ratio for warfarin use
- Are stable on warfarin with TTR > 72%
- Have CrCl < 30 ml/min
- Have poor INR control due to poor compliance
- Age ≥ 75 yoa?

Dabigatran Monitoring



- Check SCr and estimated CrCl prior to starting dabigatran, and with any change in health status that might affect renal function
- Follow-up is required to monitor for:
 - Side effects
 - Compliance
 - Ability to afford consistent supply of medication

Rivaroxaban (Xarelto®)- Current Regulatory Status



- Approved in Europe and Canada in 2008 for thromboprophylaxis following THR/TKR
- **FDA-approved in July 2011 for same indication**
- 10 mg once daily

ROCKET-AF Study Design

Risk Factors

- CHF
 - Hypertension
 - Age \geq 75
 - Diabetes
- At least 2 or 3 required*
- OR
- Stroke, TIA or Systemic embolus

Atrial Fibrillation

Rivaroxaban

20 mg daily
15 mg for Cr Cl 30-49 ml/min

*Randomize
Double Blind /
Double Dummy
(n ~ 14,000)*

Warfarin

INR target - 2.5
(2.0-3.0 inclusive)

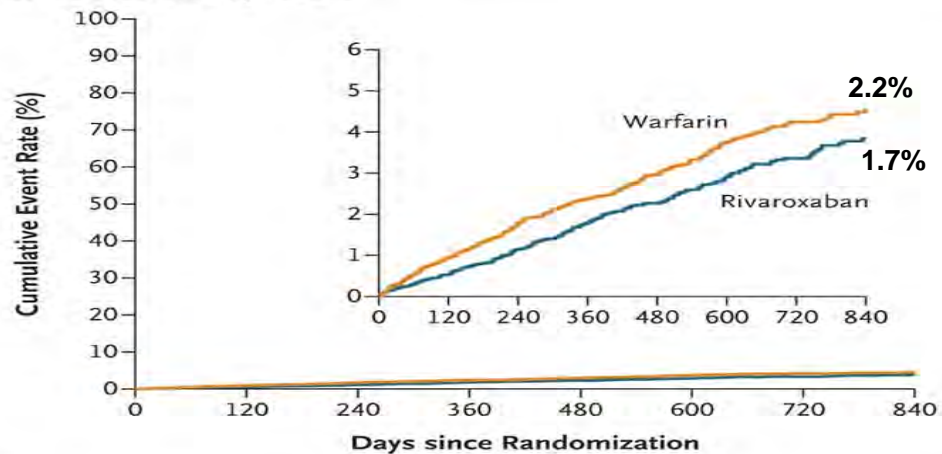
**Monthly Monitoring
Adherence to standard of care guidelines**

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%

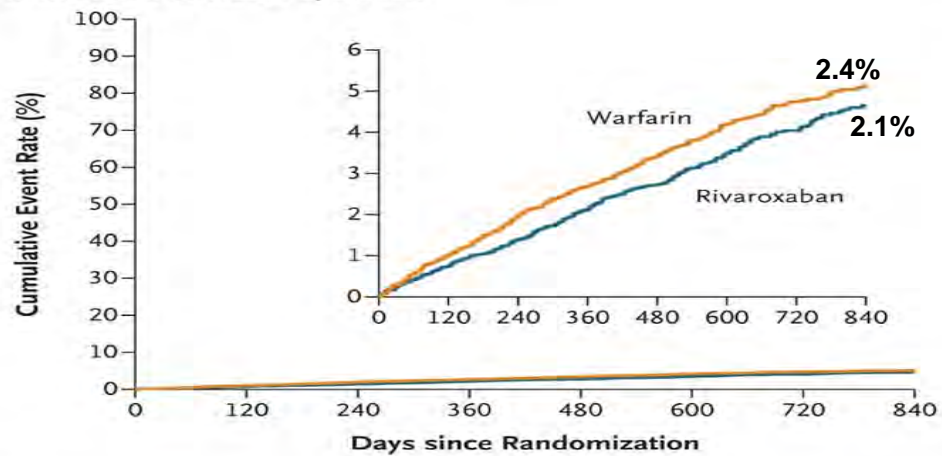
ROCKET-AF: Cumulative Rates of the Primary End Point (Stroke or Systemic Embolism)

A Events in Per-Protocol Population



No. at Risk	0	120	240	360	480	600	720	840
Rivaroxaban	6958	6211	5786	5468	4406	3407	2472	1496
Warfarin	7004	6327	5911	5542	4461	3478	2539	1538

B Events in Intention-to-Treat Population



No. at Risk	0	120	240	360	480	600	720	840
Rivaroxaban	7081	6879	6683	6470	5264	4105	2951	1785
Warfarin	7090	6871	6656	6440	5225	4087	2944	1783

Per-protocol, as-treated population

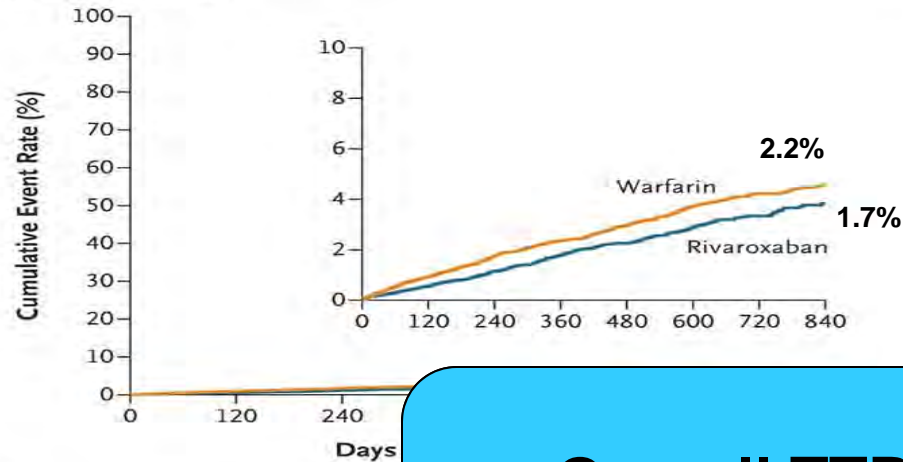
**p <0.001 for non-inferiority
HR 0.79 (95%CI 0.66-0.96)**

Intention-to-Treat (ITT) population total

**p <0.001 for non-inferiority
p= 0.12 for superiority
HR 0.88 (95%CI 0.75-1.03)**

Cumulative Rates of the Primary End Point During Treatment and after Discontinuation in the Intention-to-Treat Population

A Events during Treatment

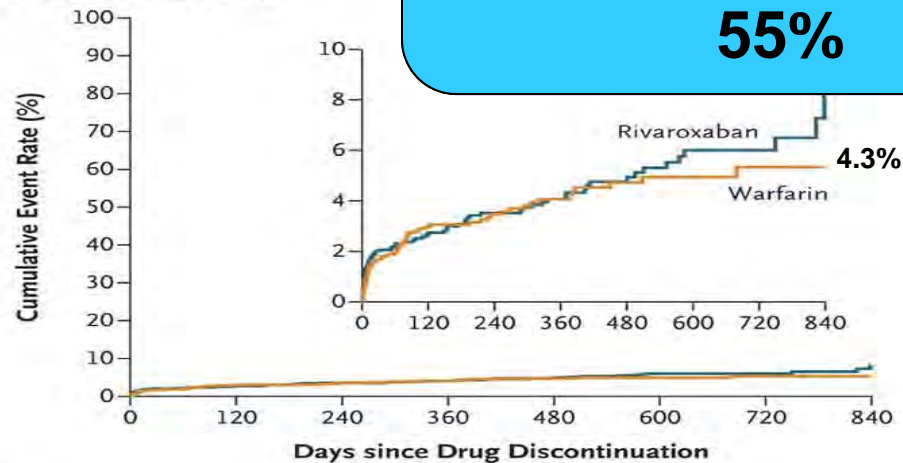


No. at Risk	0	120	240
Rivaroxaban	7081	6309	5874
Warfarin	7090	6397	5976

p=0.02 for superiority
HR 0.79 (95%CI 0.66-0.96)
21% risk reduction

Overall TTR in ROCKET-AF
55%

B Events after Discontinuation



No. at Risk	0	120	240	360	480	600	720	840
Rivaroxaban	2088	1270	986	775	543	364	211	101
Warfarin	1962	1193	880	681	470	326	196	96

p=0.58 for superiority
HR 1.1 (95%CI 0.79-1.52)
10% risk increase

ROCKET-AF: Rates of Bleeding Events

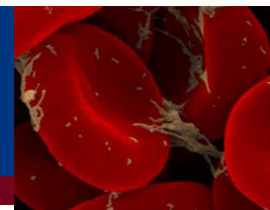


Table 3. Rates of Bleeding Events.*

Variable	Rivaroxaban (N=7111)		Warfarin (N=7125)		Hazard Ratio (95% CI) [†]	P Value [‡]
	Events	Event Rate	Events	Event Rate		
	no. (%)	no./100 patient-yr	no. (%)	no./100 patient-yr		
Principal safety end point: major and nonmajor clinically relevant bleeding [§]	1475 (20.7)	14.9	1449 (20.3)	14.5	1.03 (0.96–1.11)	0.44
Major bleeding						
Any	395 (5.6)	3.6	386 (5.4)	3.4	1.04 (0.90–1.20)	0.58
Decrease in hemoglobin \geq 2 g/dl	305 (4.3)	2.8	254 (3.6)	2.3	1.22 (1.03–1.44)	0.02
Transfusion	183 (2.6)	1.6	149 (2.1)	1.3	1.25 (1.01–1.55)	0.04
Critical bleeding [¶]	91 (1.3)	0.8	133 (1.9)	1.2	0.69 (0.53–0.91)	0.007
Fatal bleeding	27 (0.4)	0.2	55 (0.8)	0.5	0.50 (0.31–0.79)	0.003
Intracranial hemorrhage	55 (0.8)	0.5	84 (1.2)	0.7	0.67 (0.47–0.93)	0.02
Nonmajor clinically relevant bleeding	1185 (16.7)	11.8	1151 (16.2)	11.4	1.04 (0.96–1.13)	0.35

* All analyses of rates of bleeding are based on the first event in the safety population during treatment.

[†] Hazard ratios are for the rivaroxaban group as compared with the warfarin group and were calculated with the use of Cox proportional-hazards models with the study group as a covariate.

[‡] Two-sided P values are for superiority in the rivaroxaban group as compared with the warfarin group.

[§] Minimal bleeding events were not included in the principal safety end point.

[¶] Bleeding events were considered to be critical if they occurred in intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular (with compartment syndrome), or retroperitoneal sites.

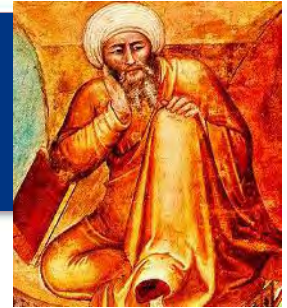
**Increased GI bleeding with rivaroxaban
(3.15%) vs warfarin (2.16%) p<0.001**

Will Rivaroxaban Get Nod From FDA for AF?

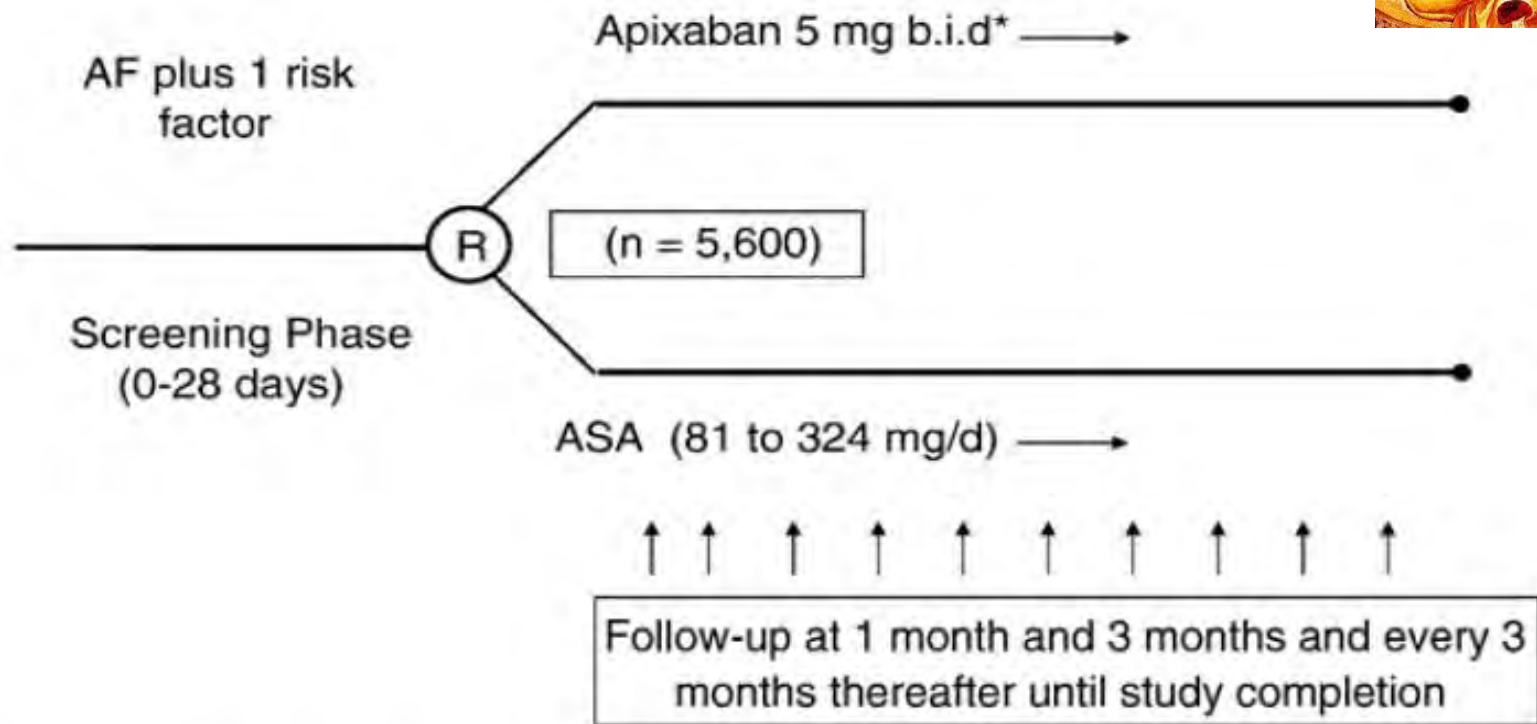
- 9/6/2011- “FDA Reviewer Slams Xarelto for Stroke Prevention in Afib”
- Criticisms of ROCKET-AF
 - Study design of “on treatment” vs. “intention-to-treat” analysis
 - More strokes and embolisms in rivaroxaban group in transition period to open-label therapy
 - Poorly managed warfarin patients (TTR 55%) not a good comparator
 - Study failed to show that rivaroxaban better than warfarin when warfarin is used “skillfully”
- 9/8/2011- “ FDA Advisory Panel Endorses Xarelto for Stroke Prevention” (with one abstention)

Apixaban (Eliquis®)- Current Regulatory Status-

- Approved in Europe and Canada for thromboprophylaxis following THR/TKR
May 2011
- 2.5 mg twice daily



AVERROES: Apixaban vs. ASA for Stroke Prevention in AFib



Study outline. *The dose of apixaban is reduced to 2.5 mg twice daily in selected patients (at least two of the following criteria: age ≥ 80 years, body weight ≤ 60 kg, serum creatinine ≥ 1.5 mg/dL or $133 \mu\text{mol/L}$).

AVERROES: Apixaban vs ASA for Stroke Prevention in AFib

Outcomes	Apixaban (n=2809)	Aspirin (n=2791)	Relative risk (95% CI)
Stroke or systemic embolic event	1.6	3.6	0.46 (0.33–0.64)
Stroke, embolic event, MI, or vascular death	4.1	6.2	0.66 (0.53–0.83)
•MI	0.7	0.8	0.85 (0.48–1.50)
•Vascular death	3.4	2.9	0.86 (0.64–1.16)
Cardiovascular hospitalizations	14.9	14.9	0.79 (0.68–0.91)
Total death	5.4	4.4	0.79 (0.62–1.02)
Major bleeding	1.4	1.2	1.14 (0.74–1.75)
Clinically relevant non-major bleeding	3.0	2.6	1.18 (0.88–1.58)
Minor bleeding	5.2	4.1	1.27 (1.01–1.61)
Fatal bleeding	0.1	0.1	0.84 (0.26–2.75)
Intracranial	0.4	0.3	1.09 (0.50–2.39)

NNT=50

ARISTOTLE: Apixaban vs Warfarin for Stroke Prevention in AFib



Atrial Fibrillation with At Least One Additional Risk Factor for Stroke

Randomized
Double-blind
(n = 18,206)

- Age ≥ 75 years
- Prior stroke, TIA, or SE
- CHF or LVEF $\leq 40\%$
- Diabetes mellitus
- Hypertension

Apixaban 5 mg oral twice daily
+
Warfarin placebo

Apixaban placebo twice daily
+
Warfarin (target INR 2–3)

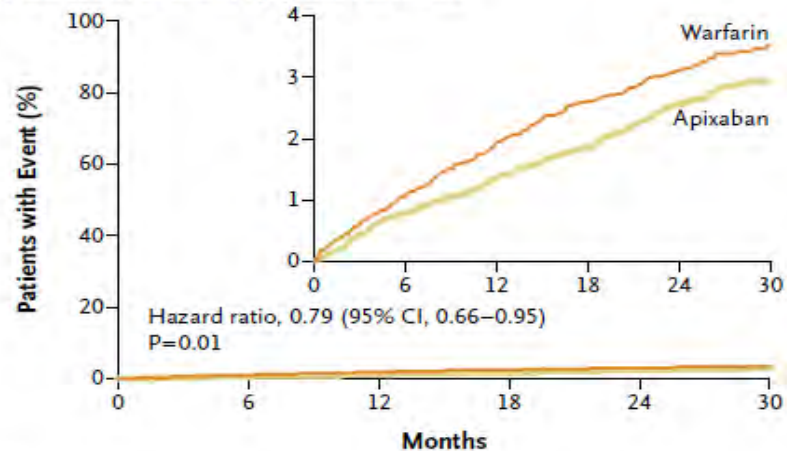
Warfarin/warfarin placebo adjusted by INR/sham INR
based on encrypted point-of-care testing device

Primary outcome: stroke and systemic embolism

Other outcomes: death, MI, bleeding (stratified by warfarin-naïve status)

ARISTOTLE: Efficacy Outcomes

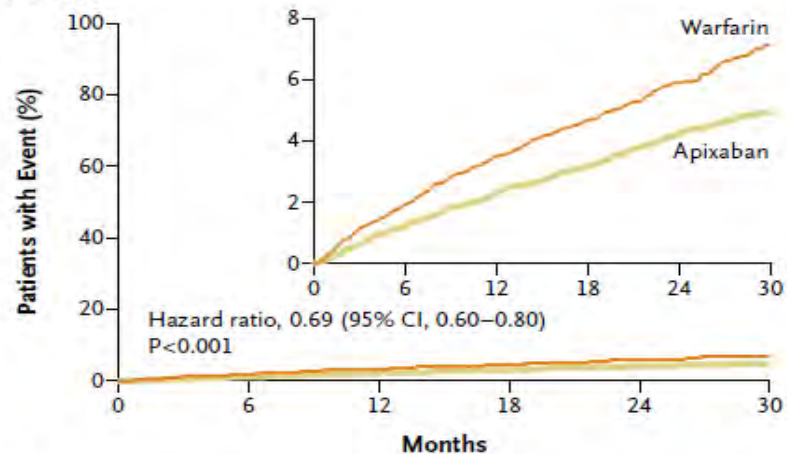
A Primary Outcome: Stroke or Systemic Embolism



No. at Risk

	0	6	12	18	24	30
Apixaban	9120	8726	8440	6051	3464	1754
Warfarin	9081	8620	8301	5972	3405	1768

B Major Bleeding



No. at Risk

	0	6	12	18	24	30
Apixaban	9088	8103	7564	5365	3048	1515
Warfarin	9052	7910	7335	5196	2956	1491

Intention-to-Treat Analysis
p<0.001 for non-inferiority
p=0.01 for superiority
HR 0.79 (0.66-0.95 95%CI)
(21% reduction)

Statistically significantly less bleeding with apixaban compared to warfarin by ISTH, GUSTO and TIMI bleeding criteria

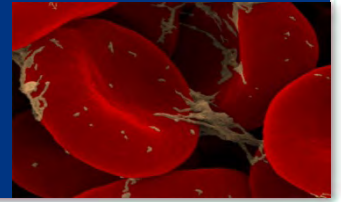
ICH: HR 0.42 (58% reduction)

Hemorrhagic stroke: HR 0.51 (49% reduction)

Other Pertinent Findings from ARISTOTLE

- TTR 62.2%
- No increase in GI bleeding
- Rates of myocardial infarction lower with apixaban, although not statistically significant
- No differences in elevation of transaminases
- No significant differences in adverse events
- Fewer patients discontinued apixaban (25.3%) than warfarin (27.5%) (p=0.001)
- Rate of death from any cause with apixaban vs warfarin 3.52% vs 3.94% annually (HR 0.89; 95% CI 0.8-0.99; p=0.047)- 11% reduction
- Net clinical outcome (stroke, systemic embolism, major bleed or death from any cause) 6.13% vs 7.2% in favor of apixaban (p<0.001;HR 0.85 (95% CI 0.78-0.92))

Importance of anticoagulants

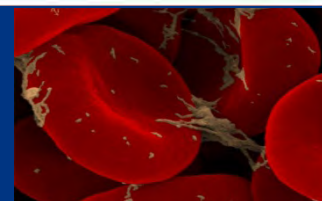


- Thrombosis is a major cause of morbidity and mortality
- Anticoagulants widely used
 - Prevention and treatment of VTE
 - Acute management of ACS
 - Stroke prevention
 - Atrial fibrillation/flutter
 - Mechanical valves
- Aging population so incidence likely to increase

Potential Pros and Cons of New OACs

Pros	Cons
Potential superior efficacy and/ or safety	<ul style="list-style-type: none">• Lack of experience• Potential dose adjustment(s) for renal or hepatic impairment
Do not require routine monitoring	<ul style="list-style-type: none">• No lab marker available• Cannot monitor and adjust the intensity of anticoagulation
Increased compliance (both providers and patients)	Medication adherence <ul style="list-style-type: none">• Twice daily dosing• Non-hemorrhagic side effects (MI, GI)
Rapid onset of action and shorter half-lives	Cost/ insurance coverage
Limited or no food/drug interactions	No specific antidote yet (only supportive measures such as PCCs)

The future of warfarin...



- Indications for new oral anticoagulants are currently limited to orthopedics and cardiology
- Multitude of experience with dosing, monitoring and reversing warfarin
- Not much “bang for your buck” if TTR > 72%
- Cost and insurance coverage of new agents may be prohibitive
- Warfarin will likely remain the mainstay of treatment until more efficacy and safety data emerge
- New OACs may be a good alternative for patients that fail existing therapies

Thank you



"Hold it, I wonder if I might try the warfarin again?"