Atrial Fibrillation Care
New Anti-Thrombotic Strategies

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Disclosures

Research Grants:

Johnson and Johnson PRD

NIH – PROMISE trial

AHRQ – Comparative Effectiveness

Advisory Board / Consultant: Ikaria, Cardiostem, Bayer, Genzyme, Jansen, theheart.org, DukeTV.org, Ortho McNeil Jansen, Pleuristem

Research Faculty at DCRI

Why are VKAs underused?

High degree of inter and intra-patient variability in dose-response

- Numerous interactions with food and concomitant drugs
- Genetic polymorphisms
- Comorbid conditions

Narrow therapeutic window (INR 2–3)

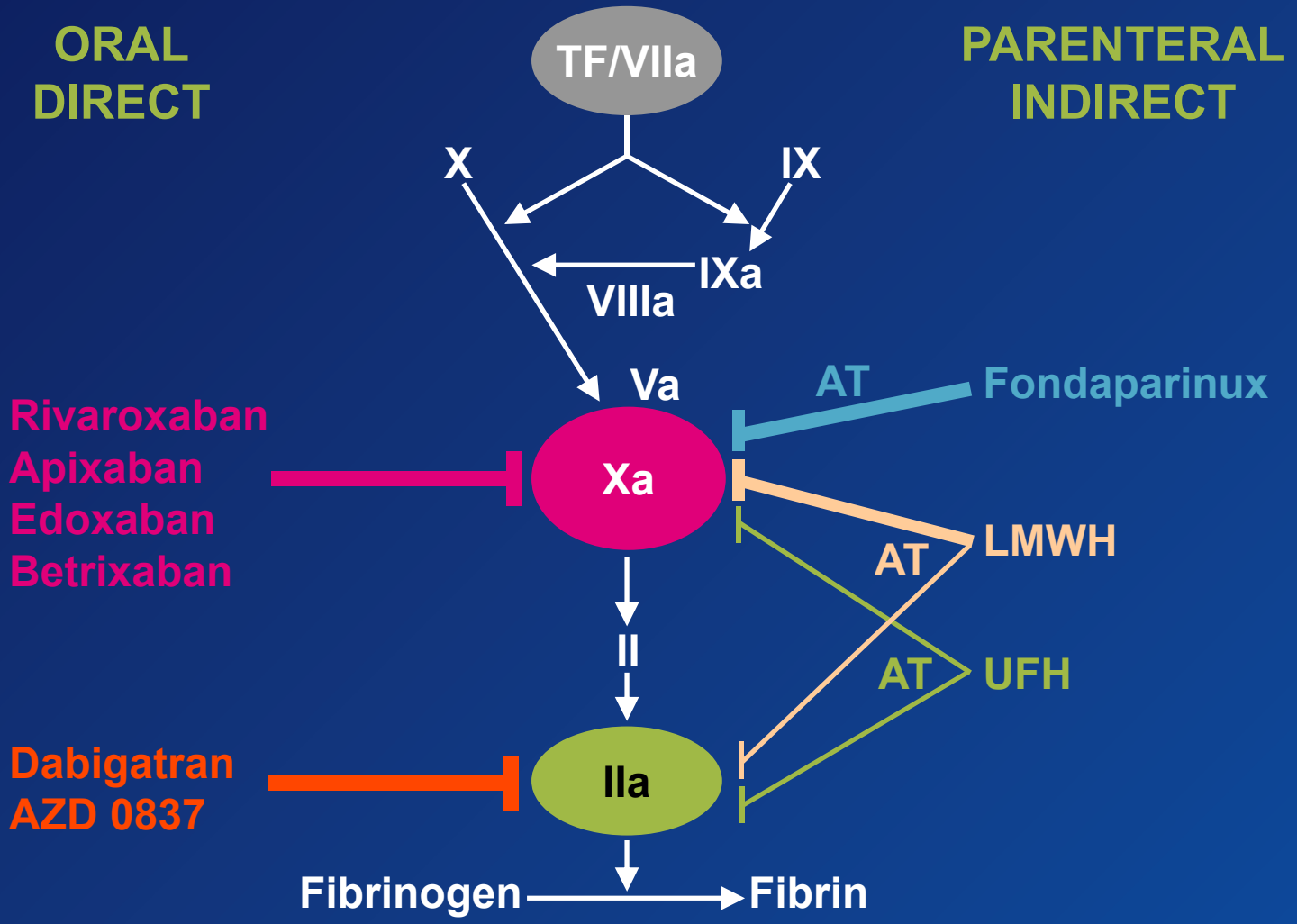
- Regular coagulation monitoring and dose adjustments required

Increased risk of VKA-induced bleeding

- Particularly in elderly patients

Fear of intracranial haemorrhage, the most devastating bleeding event

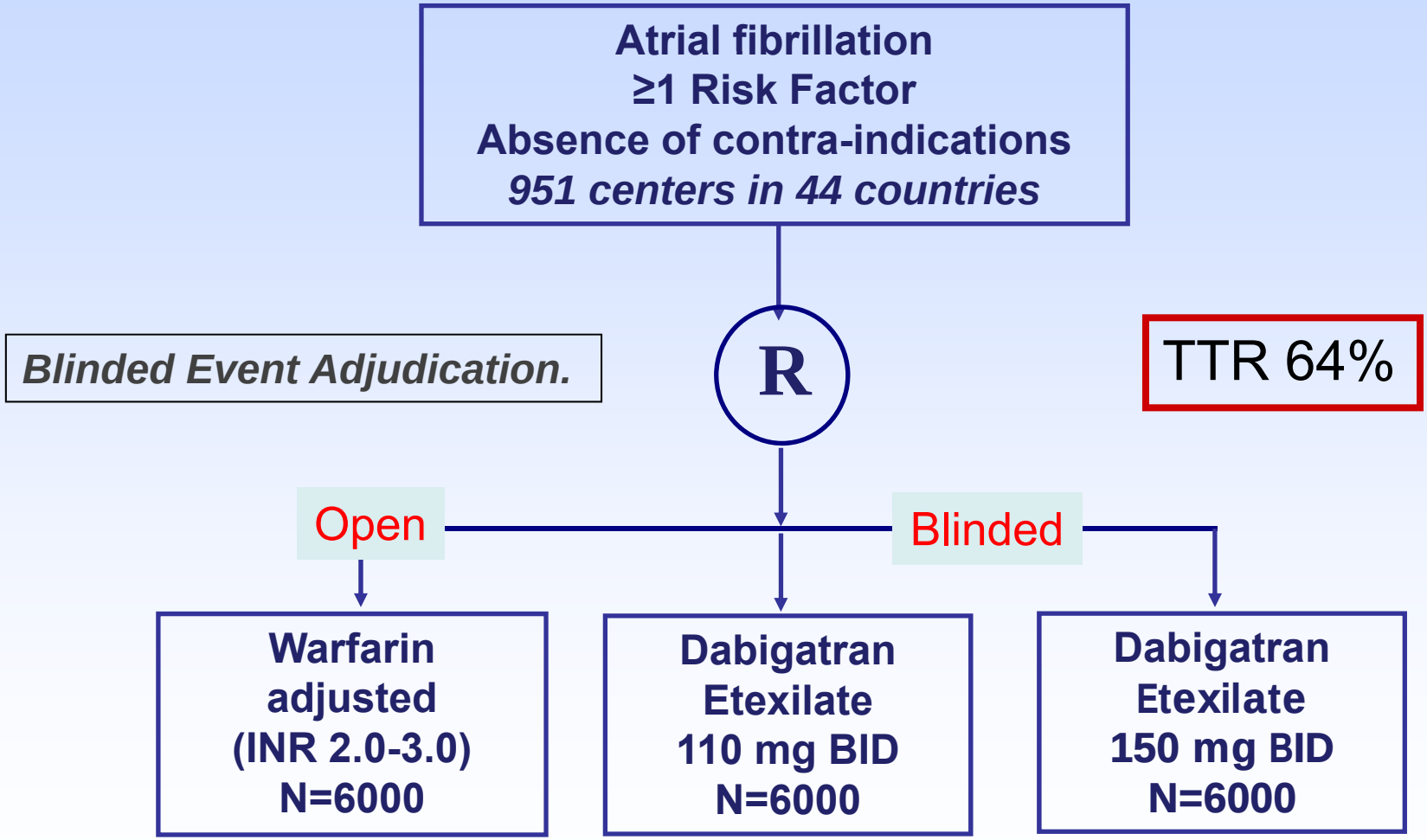
Targets for anticoagulants



Adapted from Weitz *et al*, 2005; 2008

RE-LY: A Non-inferiority Trial

RELY®
Study of stroke prevention in atrial fibrillation



Stroke or Systemic Embolism

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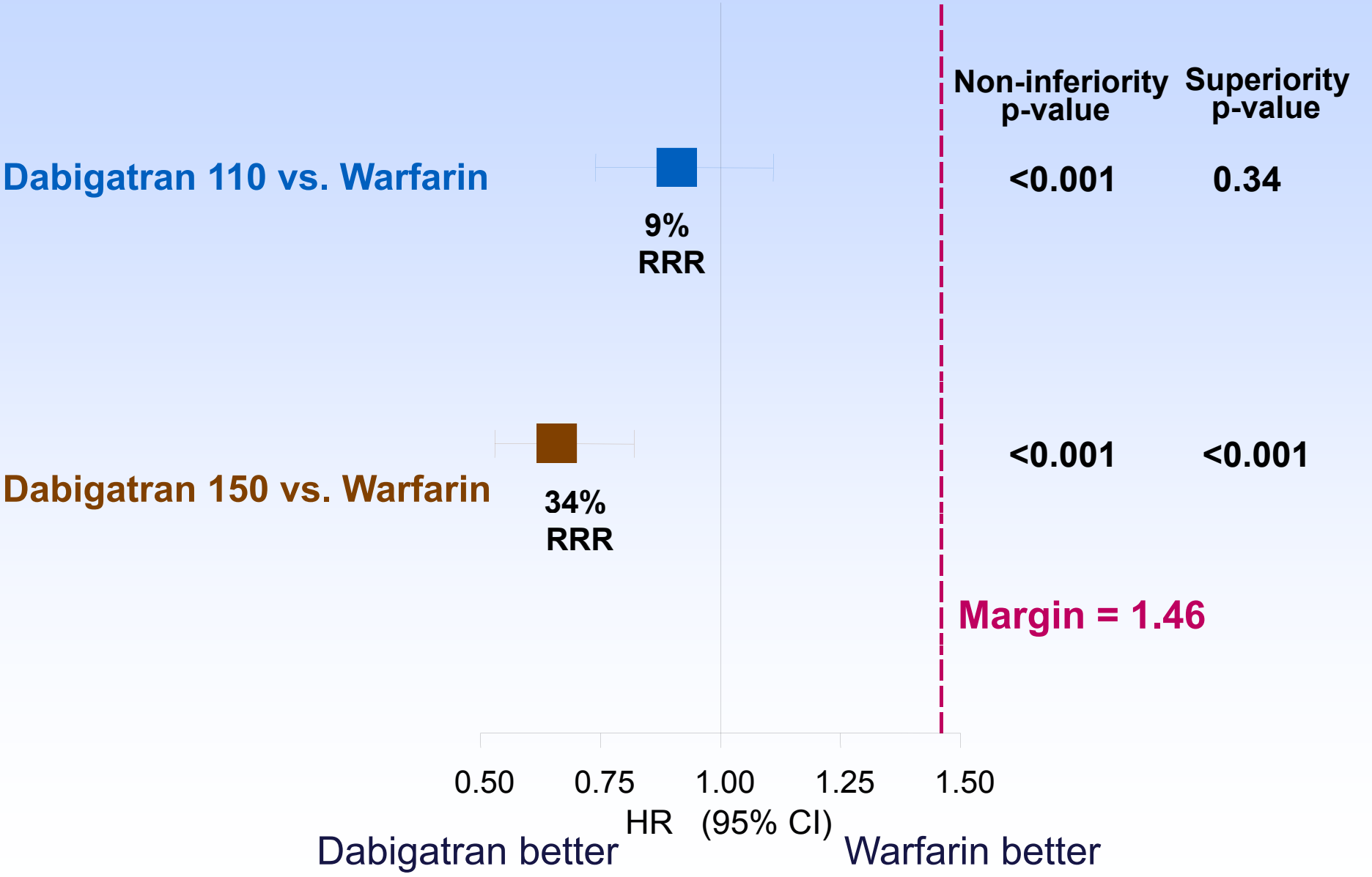


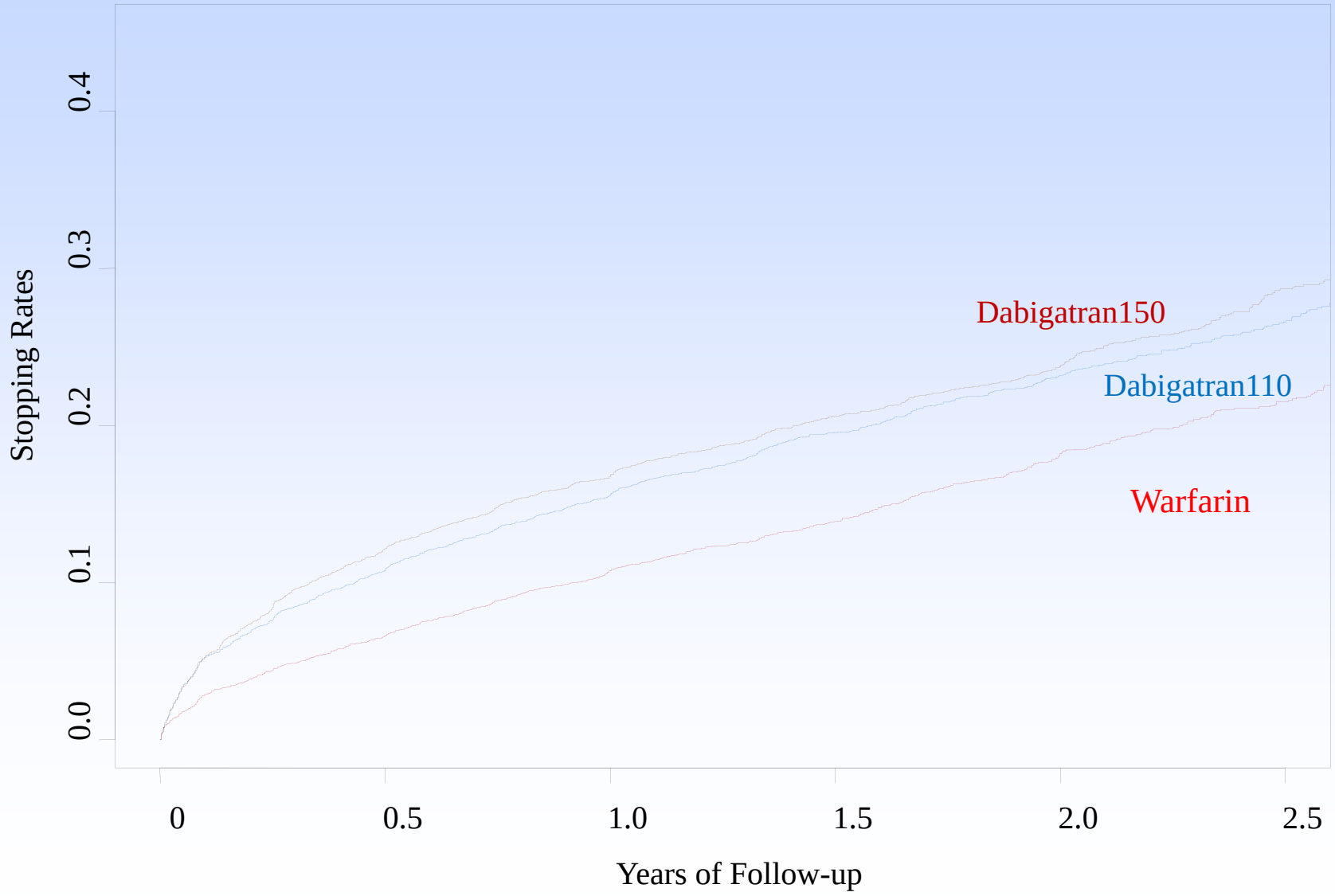
Bleeding

RELY®
Study of stroke prevention in atrial fibrillation

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

Permanent Discontinuation

RELY®
Study of stroke prevention in atrial fibrillation



Conclusions

RELY®
Study of stroke prevention in atrial fibrillation

- Dabigatran 150 mg significantly reduced stoke compared to warfarin with similar risk of major bleeding
- Dabigatran 110 mg had a similar rate of stroke as warfarin with significantly reduced major bleeding
- Both doses markedly reduced intra-cerebral, life-threatening and total bleeding
- Dabigatran had no major toxicity, but did increase dyspepsia and GI bleeding

ROCKET AF Study Design

Risk Factors
- CHF
- Hypertension
- Age ≥ 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)

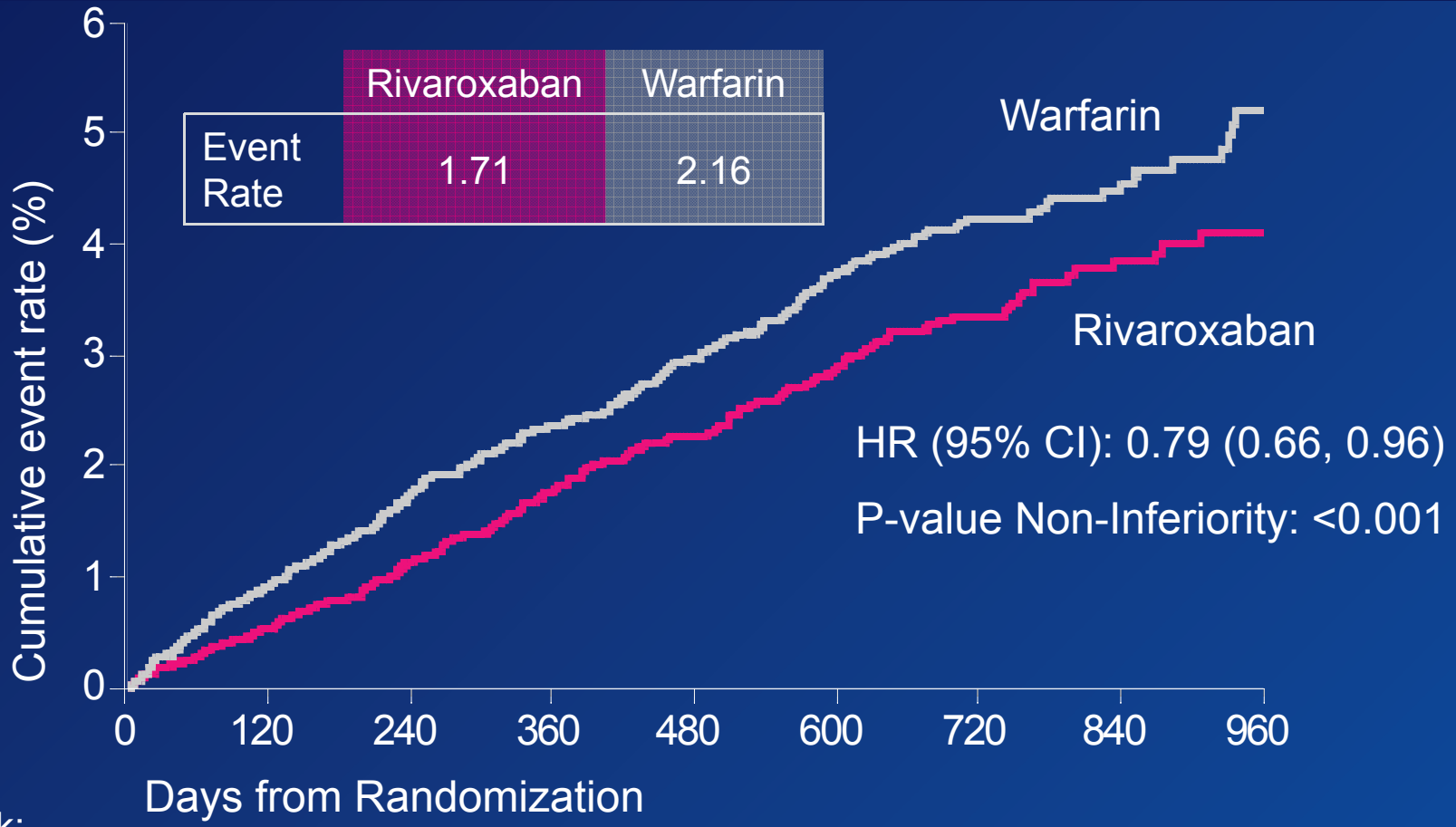
Monthly Monitoring
Adherence to standard of care guidelines

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

Primary Efficacy Outcome
Stroke and non-CNS Embolism



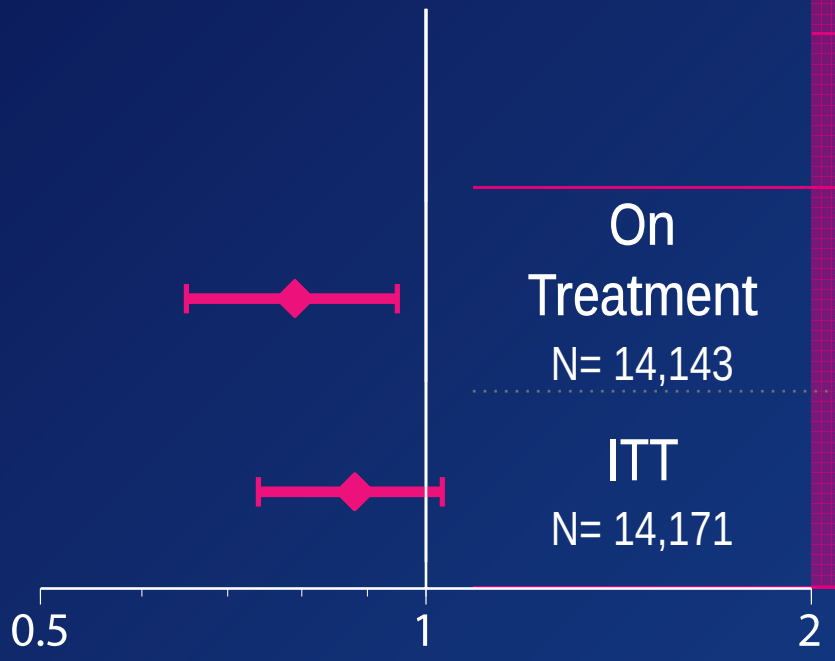
No. at risk:

Rivaroxaban	6958	6211	5786	5468	4406	3407	2472	1496	634
Warfarin	7004	6327	5911	5542	4461	3478	2539	1538	655

Event Rates are per 100 patient-years
Based on Protocol Compliant on Treatment Population

ROCKET AF

Primary Efficacy Outcome
Stroke and non-CNS Embolism



	Rivaroxaban Event Rate	Warfarin Event Rate	HR (95% CI)	P-value
On Treatment N= 14,143	1.70	2.15	0.79 (0.65,0.95)	0.015
ITT N= 14,171	2.12	2.42	0.88 (0.74,1.03)	0.117

Event Rates are per 100 patient-years
Based on Safety on Treatment or Intention-to-Treat thru Site Notification populations

ROCKET AF

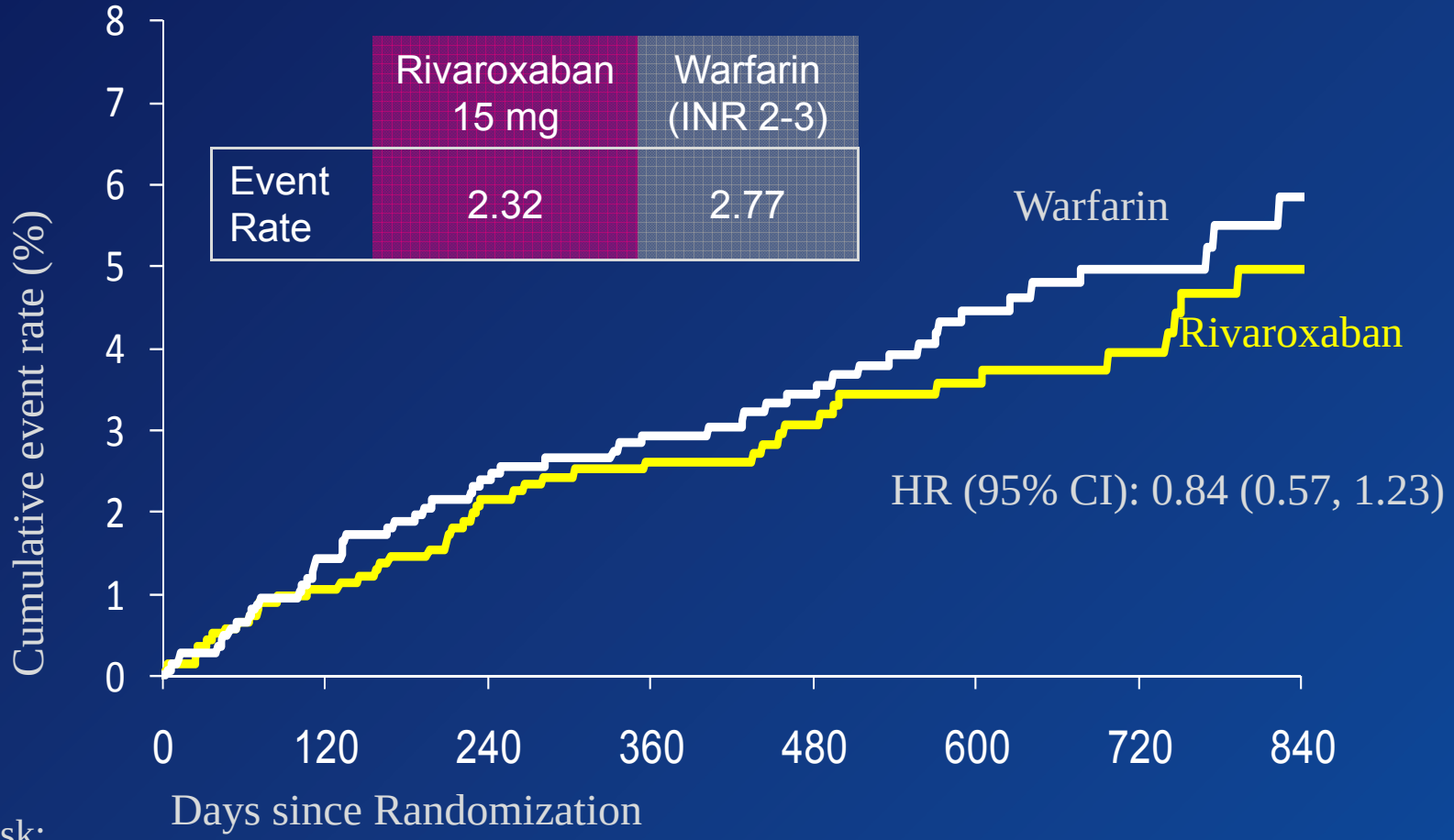
Bleeding Outcomes

	Rivaroxaban	Warfarin		
	Event Rate or N (Rate)	Event Rate or N (Rate)	HR (95% CI)	P-value
Major	3.60	3.45	1.04 (0.90, 1.20)	0.576
≥2 g/dL Hgb drop	2.77	2.26	1.22 (1.03, 1.44)	0.019
Transfusion	1.65	1.32	1.25 (1.01, 1.55)	0.044
Critical organ bleeding	0.82	1.18	0.69 (0.53, 0.91)	0.007
Bleeding causing death	0.24	0.48	0.50 (0.31, 0.79)	0.003
Intracranial Hemorrhage	55 (0.49)	84 (0.74)	0.67 (0.47, 0.94)	0.019
Intraparenchymal	37 (0.33)	56 (0.49)	0.67 (0.44, 1.02)	0.060
Intraventricular	2 (0.02)	4 (0.04)		
Subdural	14 (0.13)	27 (0.27)	0.53 (0.28, 1.00)	0.051
Subarachnoid	4 (0.04)	1 (0.01)		

Event Rates are per 100 patient-years
Based on Safety on Treatment Population

ROCKET AF

Stroke or non-CNS embolism among those with CrCl 30–49 mL/min



No. at risk:

Rivaroxaban	1434	1226	1103	1027	806	621	442	275
Warfarin	1439	1261	1140	1052	832	656	455	272

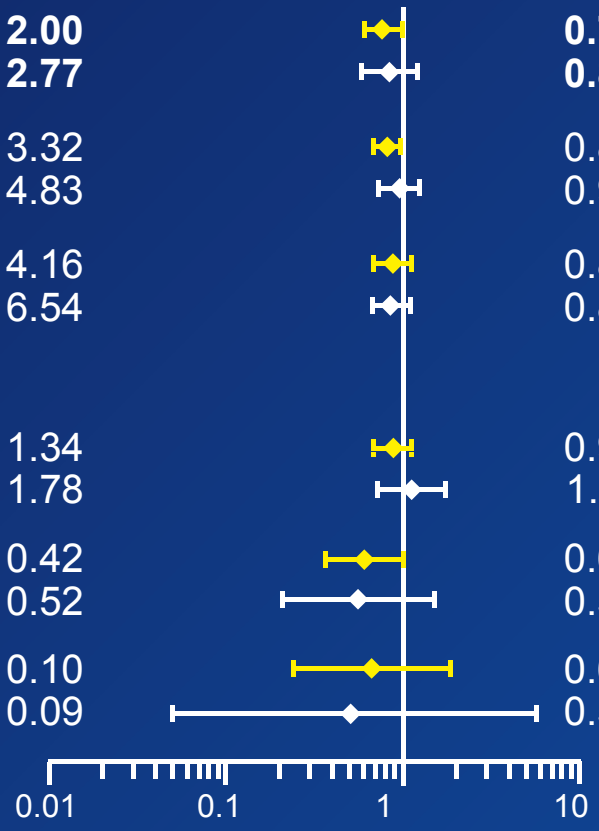
Event rates are % per year

Based on Protocol Compliant on Treatment Population

ROCKET AF

Efficacy endpoints on treatment

Clinical endpoint (% per year)	Rivaroxaban (N=7111)	Warfarin (N=7116)	HR (95% CI) Rivaroxaban vs warfarin	*P* (interaction)
Primary efficacy endpoint*	**1.57** **2.32**	**2.00** **2.77**	**0.78 (0.63–0.98)** **0.84 (0.57–1.23)**	**0.76**
PE + vascular death	2.76 4.64	3.32 4.83	0.83 (0.70–0.98) 0.96 (0.73–1.27)	0.38
PE + MI, vascular death	3.55 5.58	4.16 6.54	0.85 (0.73–0.99) 0.85 (0.67–1.09)	0.98
Stroke				
Ischaemic	1.20 1.98	1.34 1.78	0.90 (0.69–1.16) 1.11 (0.71–1.73)	0.41
Haemorrhagic	0.26 0.29	0.42 0.52	0.62 (0.37–1.03) 0.56 (0.21–1.51)	0.88
Undetermined	0.07 0.05	0.10 0.09	0.68 (0.24–1.90) 0.51 (0.05–5.67)	0.84



Based on per-protocol population on treatment
*Stroke and systemic embolism (PE)
†Rivaroxaban 20 mg od. ‡Rivaroxaban 15 mg od

ROCKET AF

Summary

- **Efficacy**:
  - Rivaroxaban was non-inferior to warfarin for prevention of stroke and non-CNS embolism.
  - Rivaroxaban was superior to warfarin while patients were taking study drug.
  - By intention-to-treat, rivaroxaban was non-inferior to warfarin but did not achieve superiority.
- **Safety**:
  - Similar rates of bleeding and adverse events.
  - Less ICH and fatal bleeding with rivaroxaban.
- **Conclusion**:
  - Rivaroxaban is a proven alternative to warfarin for moderate or high risk patients with AF.

ROCKET AF

Atrial Fibrillation with at Least One Additional Risk Factor for Stroke

ARISTOTLE

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

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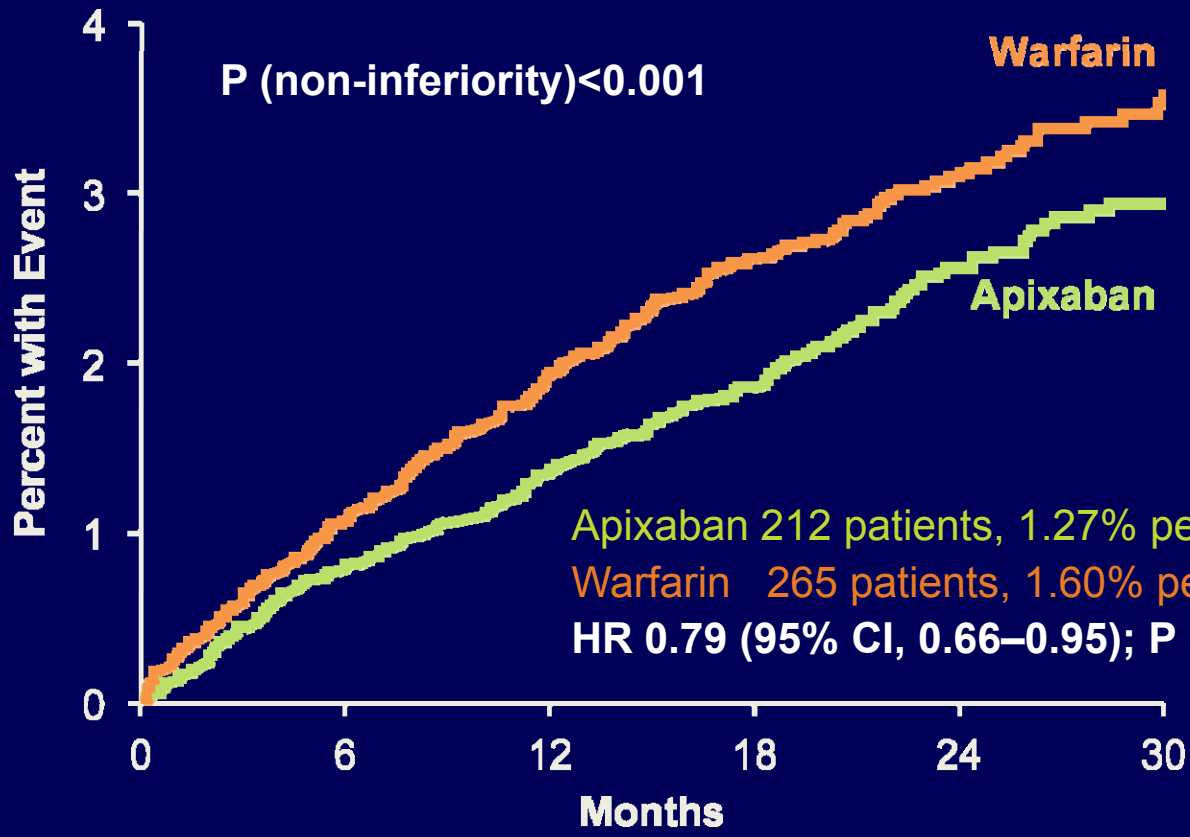
Primary Outcome

Stroke (ischemic or hemorrhagic) or systemic embolism



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

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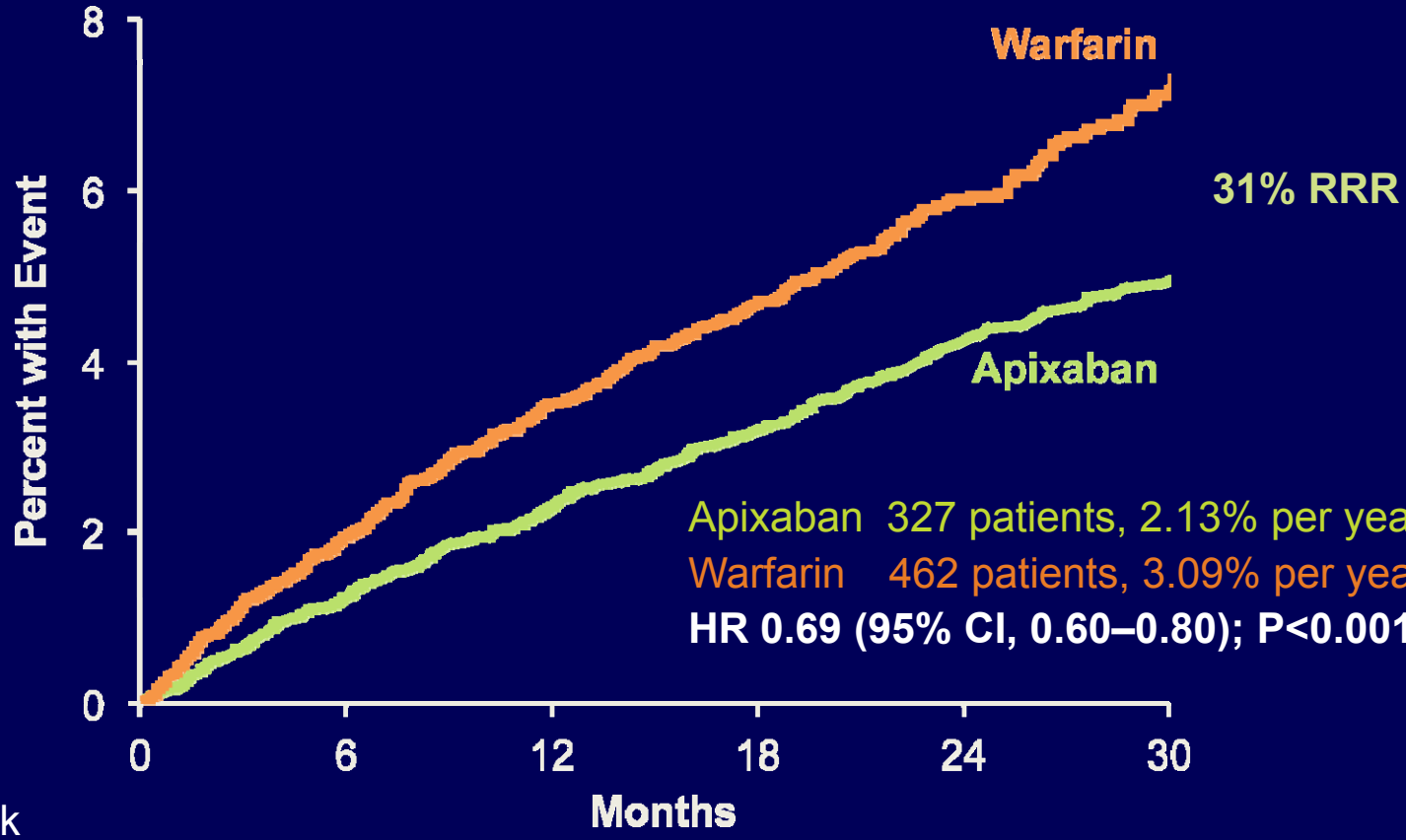
Major Bleeding

ISTH definition



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

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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.

Atrial Fibrillation in Context of Ongoing and Recent Trials

Phase III AF Trials

	Re-LY	ROCKET-AF	ARISTOTLE	ENGAGE AF-TIMI 48
Drug	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Dose (mg) Freq	150, 110 BID	20 (15*) QD	5 (2.5*) BID	60*, 30* QD
N	18,113	14,266	18,206	>21,000
Design	PROBE	2x blind	2x blind	2x blind
AF criteria	AF x 1 < 6 mths	AF x 2 (≥1 in <30d)	AF or AFl x 2 <12 mths	AF x 1 < 12 mths
% VKA naive	50%	38%	43%	40% goal

*Dose adjusted in patients with ↓drug clearance. **Max of 10% with CHADS-2 score = 2 and no stroke/TIA/SEE

PROBE = prospective, randomized, open-label, blinded end point evaluation VKA = Vitamin K antagonist

RELY	Dabigatran 110 mg	Dabigatran 150 mg	Warfarin
$CHADS_2$ 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

ROCKET AF	Rivaroxaban	Warfarin
$CHADS_2$ Mean	3.5	3.5
2 (%)	13	13
3 (%)	43	44
4 (%)	29	28
5 (%)	13	12
6 (%)	2	2

3+ 87%

ARISTOTLE	Rivaroxaban	Warfarin
$CHADS_2$ Mean	2.1	2.1
0-1 (%)	34	34
2 (%)	35.8	35.8
3+ (%)	30.2	30.2

Patel MR et al, NEJM 2011; Connolly SJ, et al. N Engl J Med. 2009;361:1139-1151; Granger C et al, N Eng J Med; 2011

Primary Endpoint of Stroke or Systemic Embolism: Non-inferiority Analysis

			Non Inferiorirty p vs warfarin
RE-LY			ITT Analysis
Dabigatran 110 mg	1.53% per year	HR = 0.91	p<0.001
Dabigatran 150 mg	1.11% per year	HR = 0.66	p<0.001
Warfarin	1.69% per year		
ROCKET AF			Modified ITT
Rivaroxaban 20mg	1.7% per year	HR = 0.79	p<0.001
Warfarin	2.2% per year		
ARISTOTLE			ITT Analysis
Apixaban 5 mg	1.27% per year	HR = 0.79	p<0.001
Warfarin	1.60% per year		

No ITT analysis is available for non-inferiority in Rocket AF. An on treatment or per-protocol analysis is generally performed in the assessment of non-inferiority. If numerous patients come off of study drug, this biases the trial towards a non-inferior result in an ITT analysis. This is the basis for performing a per-protocol analysis in a non-inferiority assessment.

Patel MR et al, NEJM 2011; Connolly SJ, et al. N Engl J Med. 2009;361:1139-1151; Granger C et al, N Eng J Med; 2011

Hemorrhagic Stroke

		ITT HR	ITT P-value
RELY			
Dabigatran 110 mg	0.12% / yr	0.31	<0.001
Dabigatran 150 mg	0.10% / yr	0.26	<0.001
Warfarin	0.38% / yr		
ROCKET			
Rivaroxaban 20 mg	0.26% / yr	0.59	0.012*
Warfarin	0.44% / yr		
ARISTOTLE			
Apixaban 5 mg	0.24% / yr	0.51	<0.001
Warfarin	0.47% / yr		

*In an on treatment analysis in Rocket AF Hemorrhagic Stoke rates were 0.26% / yr for rivaroxaban and 0.44% / yr for warfarin, p=0.024. No on treatment analysis is available from RE-LY.

Patel MR et al, NEJM 2011; Connolly SJ, et al. N Engl J Med. 2009;361:1139-1151; Granger C et al, N Eng J Med; 2011

Major Bleeding

RE-LY

		HR	ITT P-value
Dabigatran 110 mg	2.71% / yr	0.8	0.003
Dabigatran 150 mg	3.11% / yr	0.93	0.31
Warfarin	3.36%/ yr		

150 mg Dabigatran vs 110 mg Dabigatran = HR of 1.16 (1.00–1.34) p = 0.052

ROCKET

			On Treatment P-value
Rivaroxaban 20 mg	3.60% / yr	0.92	0.58*
Warfarin	3.45% / yr		

*There is no ITT analysis of safety in Rocket AF. There is no on treatment analysis of safety from RE-LY.

ARISTOTLE

			P-value
Apixaban 5 mg	2.13% / yr	0.69	<0.001
Warfarin	3.09% / yr		

Patel MR et al, NEJM 2011; Connolly SJ, et al. N Engl J Med. 2009;361:1139-1151; Granger C et al, N Eng J Med; 2011

All Cause Mortality

		HR	ITT p-value
RELY			
Dabigatran 110 mg	3.75% / yr	0.91	0.35
Dabigatran 150 mg	3.64% / yr	0.88	0.051
Warfarin	4.13% / yr		
ROCKET			
Rivaroxaban 20 mg	4.52% / yr	0.92	0.152*
Warfarin	4.91% / yr		
ARISTOTLE			
Apixaban 5 mg	3.52% / yr	0.89	0.01
Warfarin	3.94% / yr		

***In an on treatment analysis in Rocket AF mortality rates were 1.87% / yr for rivaroxaban and 2.21% / yr for warfarin, p=0.073. No on treatment analysis is available from RE-LY.**

Patel MR et al, NEJM 2011; Connolly SJ, et al. N Engl J Med. 2009;361:1139-1151; Granger C et al, N Eng J Med; 2011

Conclusions

Class Effects:

- All three novel anticoagulants are non-inferior to warfarin in reducing the risk of stroke and systemic embolization.
- All three agents reduce the risk of bleeding and intracranial hemorrhage.
- The directionality and magnitude of the mortality reduction is consistent and approximates a RRR of 10% / year

Differentiators:

- Dabigatran at a dose of 150 mg was associated with a reduction in ischemic stroke
- Rivaroxaban is a once a day drug associated with a lower rate of fatal bleeding
- Apixaban was associated with a reduction in all cause but not CV mortality

Conclusions

First Time in > 40 years we will have options for our patients with atrial fibrillation

Decisions about therapy for patients should focus on 3 key factors:

- Efficacy
- Safety
- Tolerability

"The art of medicine is applying the available evidence to patient you are caring for…"

Conclusions

Most Patients at Risk for Stroke with AF are not treated

Choices should be based on Patient Risk

Chads 0-2 - Apixiban > Dabigatran

Chads >2 - Rivaroxaban

Renal Insufficiency / Prior Stroke - Rivaroxaban

Thank You

PK/PD of 5 Novel Oral Agents

	Dabigatran	Apixaban	Rivaroxaban	Edoxaban (DU-176b)	Betrixaban (PRT054021)
Target	IIa (thrombin)	Xa	Xa	Xa	Xa
Hrs to Cmax	2	1-3	2-4	1-2	NR
CYP Metabolism	None	15%	32%	NR	None
Half-Life	12-14h	8-15h	9-13h	8-10h	19-20h
Renal Elimination	80%	33%	33%	35%	<5%

CYP = cytochrome P450; NR = not reported

Ruff CR and Giugliano RP. Hot Topics in Cardiology 2010;4:7-14
Ericksson BI et al. Clin Pharmacokinet 2009; 48: 1-22
Ruff CR et al. Am Heart J 2010; 160:635-41

Protocol Schema

N = 16,500

AF on Electrical Recording ≤ 12 mo
Intended oral A/C
$CHADS_2$ ≥ 2

R

Low Exposure Strategy Edoxaban 30 mg QD (n=5500)

High Exposure Strategy Edoxaban 60 mg QD (n=5500)

Active Control Warfarin (n=5500)

Median duration of follow up 24-months

Primary Objective
Edoxaban: Therapeutically as good as warfarin

1º EP = Stroke or SEE (Non inferiority Boundary HR 1.38)
2º EP = Stroke or SEE or All-Cause Mortality
Safety EPs = Major Bleeding, Hepatic Function

SEE = systemic embolic event

From Giugliani TIMI

Comparison of Trial Metrics

	RE-LY	ROCKET AF	ARISTOTLE
Time in Therapeutic Range (TTR)	64% **67% warfarin-experienced** 61% warfarin-naïve	Mean 55% Median 58%	62%

Patel MR et al, NEJM 2011; Connolly SJ, et al. N Engl J Med. 2009;361:1139-1151; Granger C et al, N Eng J Med; 2011

Ischemic Stroke

		HR	ITT P-value
RELY			
Dabigatran 110 mg	1.34% / yr	1.20	0.35
Dabigatran 150 mg	0.92% / yr	0.76	0.03
Warfarin	1.20% / yr		
ROCKET			
Rivaroxaban 20 mg	1.62% / yr	0.99	0.92*
Warfarin	1.64% / yr		
ARISTOTLE			
Aoixaban 5 mg	0.97% / yr	0.92	0.42
Warfarin	1.05% / yr		

*In an on treatment analysis in Rocket AF Ischemic Stoke rates were 1.34% / yr for rivaroxaban and 1.42% / yr for warfarin, p=0.58. No on treatment analysis is available from RE-LY.

Patel MR et al, NEJM 2011; Connolly SJ, et al. N Engl J Med. 2009;361:1139-1151; Granger C et al, N Eng J Med; 2011