



# New Anticoagulants:

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Are we Ready to Replace Warfarin?

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Stroke Conference 2011

# Warfarin

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- Decreases stroke risk by 60-70%
- Superior to ASA and ASA plus clopidogrel
- Recommended for patients with moderate and above stroke risk (CHADS  $\geq 2$ )
- Prescribed for only 50-65% of appropriate candidates

# Warfarin Challenges

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- Delayed onset of action (72-96 h)
- Drug interactions (CYP2C9,1A2,3A4)
- Diet/food interactions
- Genetic variations
- Requires INR monitoring
- Dose adjustments
- Risk of intracranial hemorrhage

# Learning Objectives

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- Review recommendations for anticoagulation in patients with atrial fibrillation.
- List new oral anticoagulants under investigation for stroke prevention in patients with atrial fibrillation.

# Learning Objectives

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- Describe the mechanism of action, dosing, efficacy, and common side effects of dabigatran and rivaroxaban.
- Compare and contrast oral anticoagulants in terms of cost, convenience, and safety.

# Stroke Risk in Patients with Nonvalvular AF

<b>CHADS<sub>2</sub> Score</b>	<b>Points</b>
Congestive Heart Failure	1
Hypertension	1
Age $\geq$ 75 years	1
Diabetes Mellitus	1
Prior history of Stroke/TIA	2

<b>CHADS<sub>2</sub> Score</b>	<b>Adjusted Stroke Rate %/year</b>
0	1.99
1	2.8
2	4.0
3	5.9
4	8.5
5	12.5
6	18.2

# Recommended Antithrombotic Therapy by Risk Category

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<b>Risk Category</b>	<b>CHADS<sub>2</sub> Score</b>	<b>Recommended Therapy</b>
Moderate Risk and Above	≥2	Oral Anticoagulant (OAC)
Low Risk	1	OAC or ASA OAC Preferred
Very Low Risk	0	ASA or no antithrombotic therapy

# Stroke Risk in Patients with Nonvalvular AF

<b>CHA<sub>2</sub>DS<sub>2</sub> VASc Score</b>	<b>Points</b>
Congestive Heart Failure/ Left Ventricular Dysfunction	1
Hypertension	1
Age ≥ 75 years	2
Diabetes Mellitus	1
Prior Stroke or TIA or Systemic Embolism	2
Vascular Disease	1
Age >65<75	1
Sex-Female	1

<b>CHA<sub>2</sub>DS<sub>2</sub> VASc Score</b>	<b>Stroke Rate %/year</b>
0	0
1	1.3
2	2.2
3	3.2
4	4.0
5	6.7
6	9.8
7	9.6
8	6.7
9	15.2

# Risk of Bleeding

HAS-BLED	Points
Hypertension (SBP > 160 mmHg)	1
Abnormal renal or liver function	1 or 2
Stroke	1
Bleeding	1
Labile INRs	1
Elderly (age > 65)	1
Drugs or alcohol	1 or 2

HAS-BLED Score	Bleeds/100 patient years
0	1.13
1	1.02
2	1.88
3	3.74
4	8.70
5	12.50

Score  $\geq 3$  suggests increased bleeding risk

# Oral Anticoagulants in Canada

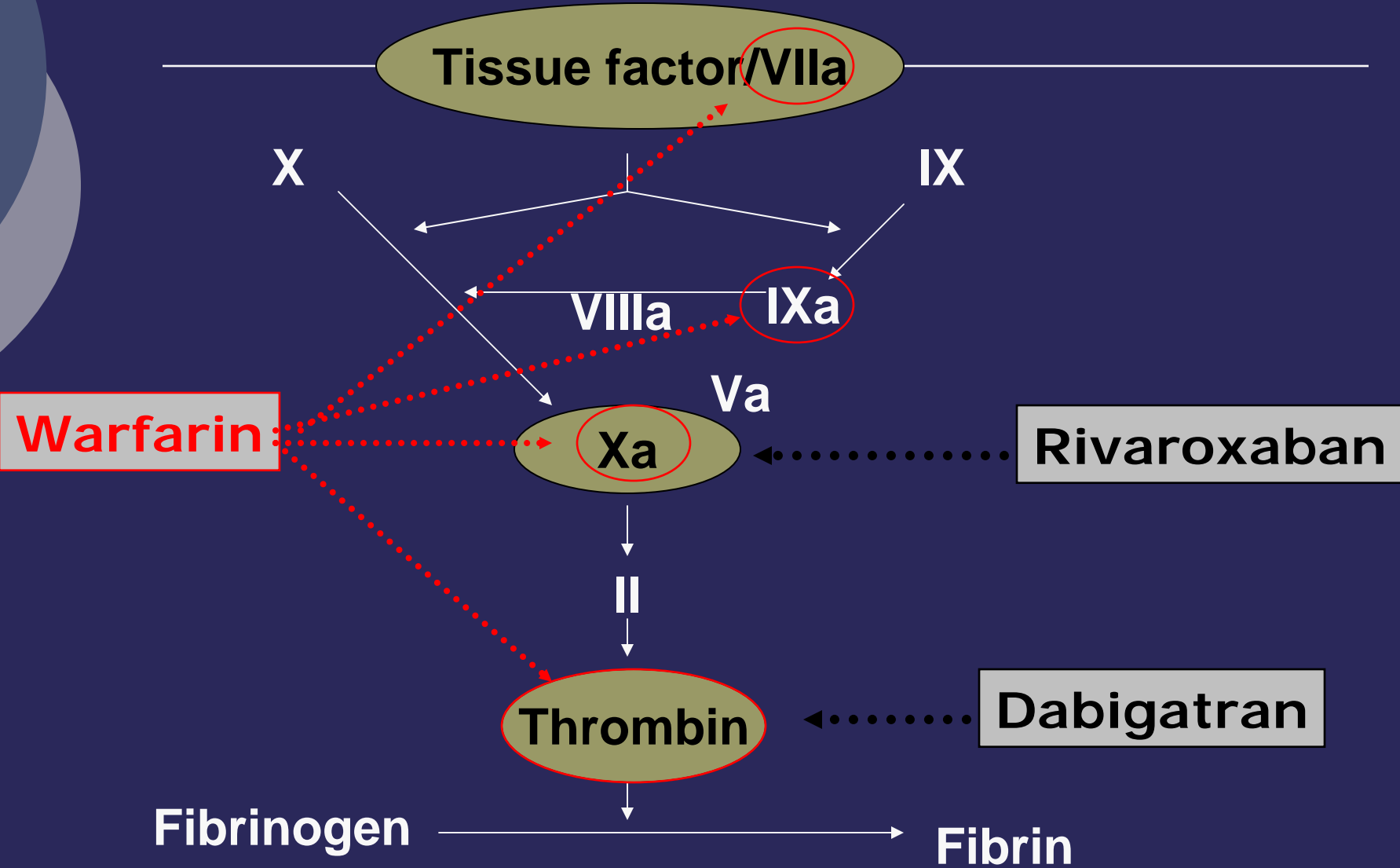
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- Vitamin K antagonists
  - Warfarin
- Direct thrombin inhibitors
  - Dabigatran
- Anti Xa inhibitors
  - Rivaroxaban

**Other agents under investigation include:**

**Tissue Factor inhibitor, Factor VII inhibitor, Factor V inhibitor, Factor IXa inhibitor**

# Coagulation Pathway



# Dabigatran

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- Direct thrombin inhibitor
- Prevents development of thrombi by inhibiting
  - Thrombin-induced platelet aggregation
  - Fibrin bound thrombin
  - Free thrombin



# Dabigatran



- Available as dabigatran etexilate (Pradax) 75, 110 and 150 mg cap
  - A prodrug of dabigatran
  - Converted to dabigatran by plasma esterases in the liver
  - Formulation contains a tartaric acid core
    - Acidic microenvironment
    - Increases drug dissolution and absorption

# Dabigatran Approved Indications

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- Prevention of venous thromboembolic events (VTE) in patients who have undergone elective hip replacement (HR) or total knee replacement (TKR) (NOC June 2008)
  - Dose: dabigatran 220 mg po daily decrease to 150 mg po daily for patient >75 years
- Prevention of stroke and systemic embolism in patients with atrial fibrillation in whom anticoagulation is appropriate (NOC Oct 2010)
  - Dose: dabigatran 150 mg po BID decrease to 110 mg po BID for age > 80 years

# Dabigatran Pharmacokinetics

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<b>Oral bioavailability</b>	<b>~6%</b>
<b>Tmax</b>	<b>2 hours</b>
<b>Half-life (T1/2)</b>	<b>14-17 hours</b>
<b>Renal elimination</b>	<b>80%</b>

# Drug Interactions with Dabigatran

Drug	Effect on Dabigatran	Recommendation
Ketoconazole	increase	Contraindicated
Amiodarone Clarithromycin	increase	No dose adjustment Use with caution
Verapamil Quinine	increase	Give dabigatran 2 hours before
Antacids	decrease	Give dabigatran 2 hours before
PPI	decrease	No dose adjustment
Rifampin	decrease	Avoid

# Dabigatran Contraindications

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- Severe renal impairment (CrCl <30 ml/min)
- Haemorrhagic manifestations, bleeding diathesis, impaired haemostasis
- Lesions at risk of clinically significant bleeding
- Concomitant treatment with strong p-glycoprotein inhibitors (ie ketoconazole)

# Efficacy of Dabigatran in Atrial Fibrillation

The NEW ENGLAND  
JOURNAL of MEDICINE

ESTABLISHED IN 1812

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## Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., Michael D. Ezekowitz, M.B., Ch.B., D.Phil., Salim Yusuf, F.R.C.P.C., D.Phil., John Eikelboom, M.D., Jonas Oldgren, M.D., Ph.D., Amit Parekh, M.D., Janice Pogue, M.Sc., Paul A. Reilly, Ph.D., Ellison Themeles, B.A., Jeanne Varrone, M.D., Susan Wang, Ph.D., Marco Alings, M.D., Ph.D., Denis Xavier, M.D., Jun Zhu, M.D., Rafael Diaz, M.D., Basil S. Lewis, M.D., Harald Darius, M.D., Hans-Christoph Diener, M.D., Ph.D., Campbell D. Joyner, M.D., Lars Wallentin, M.D., Ph.D., and the RE-LY Steering Committee and Investigators\*

- Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY)
  - Connolly SJ et al. Dabigatran versus Warfarin in Patients with Atrial Fibrillation. *New Engl J Med.* 2009;361:1139-51.
- Goal
  - Determine efficacy and safety of two fixed doses of dabigatran compared to warfarin in patients with atrial fibrillation at risk of stroke

# RE-LY Design

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- Non-inferiority trial
- PROBE
  - Prospective
  - Randomized
  - Open label warfarin
  - Blinded event adjudication

# RELY Inclusion Criteria

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- Age >18 years
- Atrial fibrillation plus one of
  - Previous stroke, TIA or embolism
  - EF <40%
  - Symptomatic HF class 2 or higher
  - Age  $\geq$ 75 years
  - Age  $\geq$ 65 with DM, CAD or HTN

# RELY Exclusion Criteria

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- History of heart valve disorders
- Severe stroke in past 6 months or any stroke in previous 14 days
- Conditions with increased risk of bleeding
- Contraindication to warfarin
- Reversible AF
- Plan for ablation
- Severe renal impairment
- Active infectious endocarditis
- Active liver disease
- Pregnancy
- Anemia or thrombocytopenia
- Investigational drug in past 30 days
- Unreliably or short life expectancy

# RE-LY Trial

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

Blinded Event Adjudication

R

Open

Blinded

Warfarin Adjusted  
(INR 2-3)  
N=6022

Dabigatran etixilate  
110 mg BID  
N=6015

Dabigatran etixilate  
150 mg BID  
N=6076

# RELY 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 (%)			
2 (%)	32.6	32.2	30.9
3+ (%)	34.7	35.2	37.0
	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

# RELY Outcome Measures

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- Primary outcome
  - Stroke or Systemic embolism
- Secondary outcomes
  - Stroke
  - Systemic embolism
  - Death
- Primary safety outcome
  - Major hemorrhage

# RELY Execution

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- Median follow up of 2 years
- 20 patients lost to follow up
- Mean time in therapeutic range for warfarin was 64%

# RELY Primary Outcome: Stroke or Systemic Embolism

Dabigatran 110 vs. Warfarin



Dabigatran 150 vs. Warfarin



0.50 0.75 1.00 1.25 1.50  
HR (95% CI)

Non-inferiority p-value Superiority p-value

<0.001

0.34

<0.001

<0.001

Margin = 1.46

Dabigatran better

Warfarin better

# RELY Outcomes

	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
Stroke or systemic Embolism	1.5 %	1.1 %	1.7 %	0.91 0.74-1.11	0.34	0.66 0.53-0.82	<0.001
Stroke	1.4 %	1.0 %	1.6 %	0.92 0.74-1.13	0.41	0.64 0.51-0.81	<0.001
Death	3.8 %	3.6 %	4.1 %	0.91 0.80-1.03	0.13	0.88 0.77-1	0.05
MI	0.7 %	0.7 %	0.5 %	1.35 0.98-1.87	0.07	1.38 1-1.91	0.048

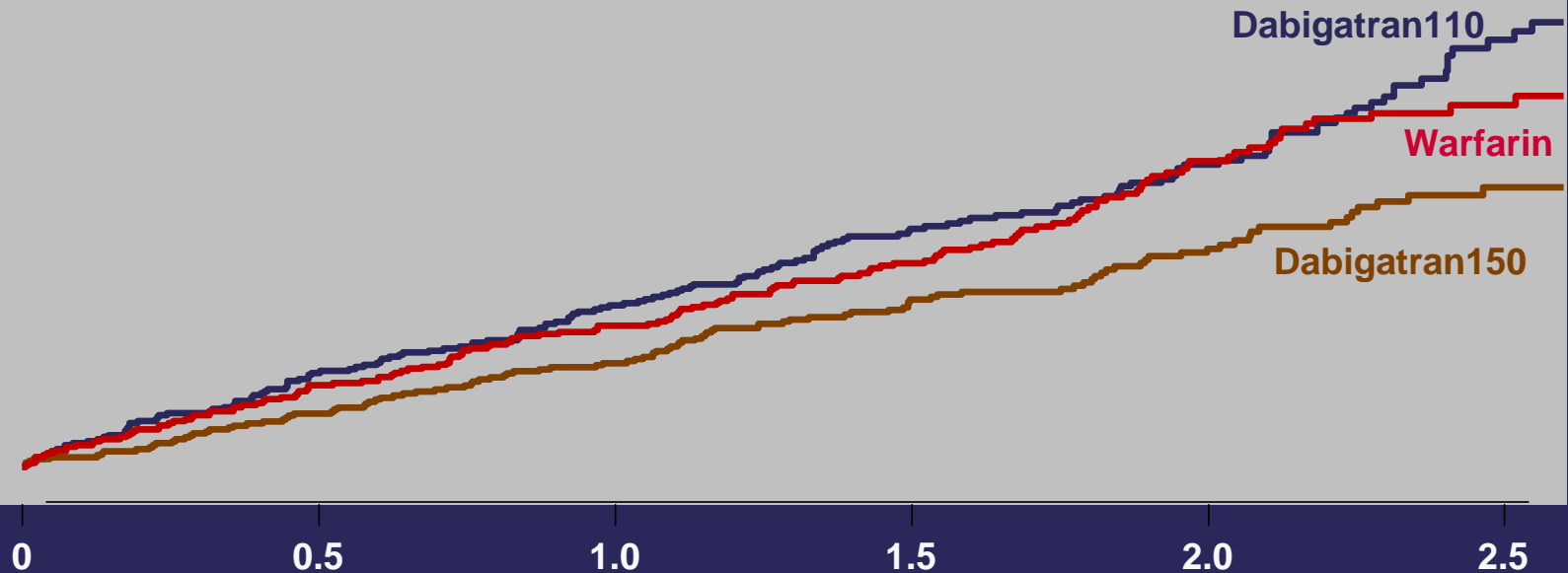
D= dabigatran

# Ischemic/Unspecified Stroke

Cumulative Hazard Rates

0.08  
0.06  
0.04  
0.02  
0.0

D 110 mg vs. Warfarin		D 150 mg vs. Warfarin	
RR	= 1.11	RR	= 0.76
95% CI	= 0.89-1.40	95% CI	= 0.60-0.98
P	= 0.35	P	= 0.03



NEJM 2009361:1139-51

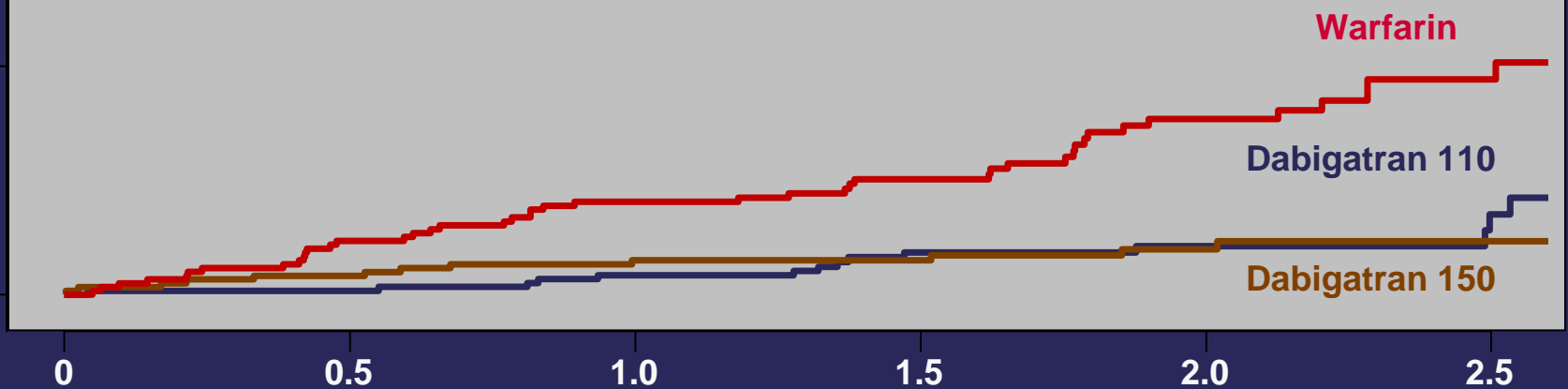
Years of Follow-up

# RELY Outcome: Hemorrhagic Stroke

Cumulative Hazard Rates

0.03  
0.02  
0.01  
0.0

D 110 mg vs. Warfarin		D 150 mg vs. Warfarin	
RR	= 0.31	RR	= 0.26
95% CI	= 0.17-0.56	95% CI	= 0.14-0.49
P	<0.001	P	<0.001



Years of Follow-up

# RELY Bleeding

	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
ICH	0.23 %	0.30 %	0.74 %	0.31 0.20-0.47	<0.001	0.4 0.27-0.6	<0.001

# RELY Common Adverse Events

Adverse events occurring in >5% of any group	Dabigatran 110 mg %	Dabigatran 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 on dabigatran p<0.001

NEJM 2009;361:1139-51

# RELY Conclusions

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- Compared to adjusted dose warfarin
  - Dabigatran 110 mg BID
    - Similar rate of stroke & systemic embolism
    - Lower rates of major bleeding
  - Dabigatran 150 mg BID
    - Decreased rate of stroke & systemic embolism
    - Similar rate of major bleeding
  - Dabigatran increased
    - Dyspepsia
    - GI bleeding

# RELY Study

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## ○ Strengths

- Large study
- Extremely low loss to follow up

## ○ Limitations

- Open label design introduces the potential for reporting bias

# Dabigatran

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## ○ Advantages

- Lower incidence of intracranial hemorrhage
- Does not require INR monitoring
- Fewer drug interactions
- No dietary interactions

## ○ Disadvantages

- Twice daily dosing
- High cost
- Lack of long term safety data
- Lack of antidote
- Dosing in patients with chronic kidney disease
- No readily available measure of activity

# 2010 Canadian Best Practice Recommendations for Stroke Care

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- Patients with atrial fibrillation at *moderate to high risk* of stroke (CHADS2  $\geq 2$ ) should receive either warfarin or dabigatran [Evidence Level A]
- Patients with atrial fibrillation who are already well-controlled on warfarin with a stable therapeutic International Normalized ratio (INR) may continue on warfarin, and may not need to switch to dabigatran [Evidence Level C]

# 2010 Canadian Best Practice Recommendations for Stroke Care

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- Dabigatran is preferred over warfarin for patients with atrial fibrillation who meet the inclusion criteria for the RE-LY trial [Evidence Level A]
- For patients treated with dabigatran, a dose of 150 mg twice daily is appropriate for most individuals; 110 mg twice daily is recommended for patients aged 80 or more years and for patients at risk of bleeding [Evidence Level B]

# Rivaroxaban

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- Oral direct factor Xa inhibitor
- Available as Xarelto 10 mg tablets
- Health Canada approved indication
  - Prevention of venous thromboembolism in patients who have undergone elective total hip replacement or total knee replacement
  - Dose: rivaroxaban 10 mg daily
- Under investigation
  - Prevention of stroke and embolism in atrial fibrillation
  - Treatment of VTE
  - Acute Coronary Syndrome

# Rivaroxaban Pharmacokinetics

<b>Bioavailability</b>	<b>60-80%</b>
<b>Tmax</b>	<b>2.5-4 hours</b>
<b>Half-life</b>	<b>9-13 hours</b>
<b>Renal excretion</b>	<b>33%</b> <b>(active drug)</b>

# Rivaroxaban Contraindications

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- Hepatic disease
- Active bleeding
- Lesions at risk of significant bleeding
- Concomitant treatment with strong inhibitors of CYP3A4 or P-gp
- Pregnancy or nursing
- Hypersensitivity

# Drug Interactions with Rivaroxaban

Drug	Effect on Rivaroxaban	Recommendation
Ketoconazole Ritonavir	increase	Contraindicated
Rifampin	decrease	No dose adjustment Use with caution
Phenytoin Carbamazepine Phenobarbital	decrease	No dose adjustment Use with caution

# Rivaroxaban

## Efficacy in Atrial Fibrillation

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- ROCKET-AF

- Rivaroxaban-Once daily, oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation

- Abstract presented at AHA 2010

# ROCKET-AF Study Design

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- Prospective
- Randomized
- Double-blind
- Double dummy
- Parallel group
- Active control

# Rocket AF Study Design

## Non valvular Atrial Fibrillation

### Risk Factors

- CHF
  - Hypertension
  - Age  $\geq$  75
  - Diabetes
- OR
- Stroke, TIA or Systemic embolus

At least 2  
or 3  
required\*

*Randomize  
Double Blind  
Double Dummy  
n = 14,269*

**Rivaroxaban**

20 mg daily  
(15 mg daily if Cr Cl 30-49 ml/min)

**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 Exclusion Criteria

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- Significant mitral stenosis
- Reversible AF
- Severe disabling stroke
- History of intracranial bleeding
- Hemorrhagic disorders

# ROCKET-AF Outcome Measures

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## ○ Primary

- Composite of stroke and non-CNS systemic embolism

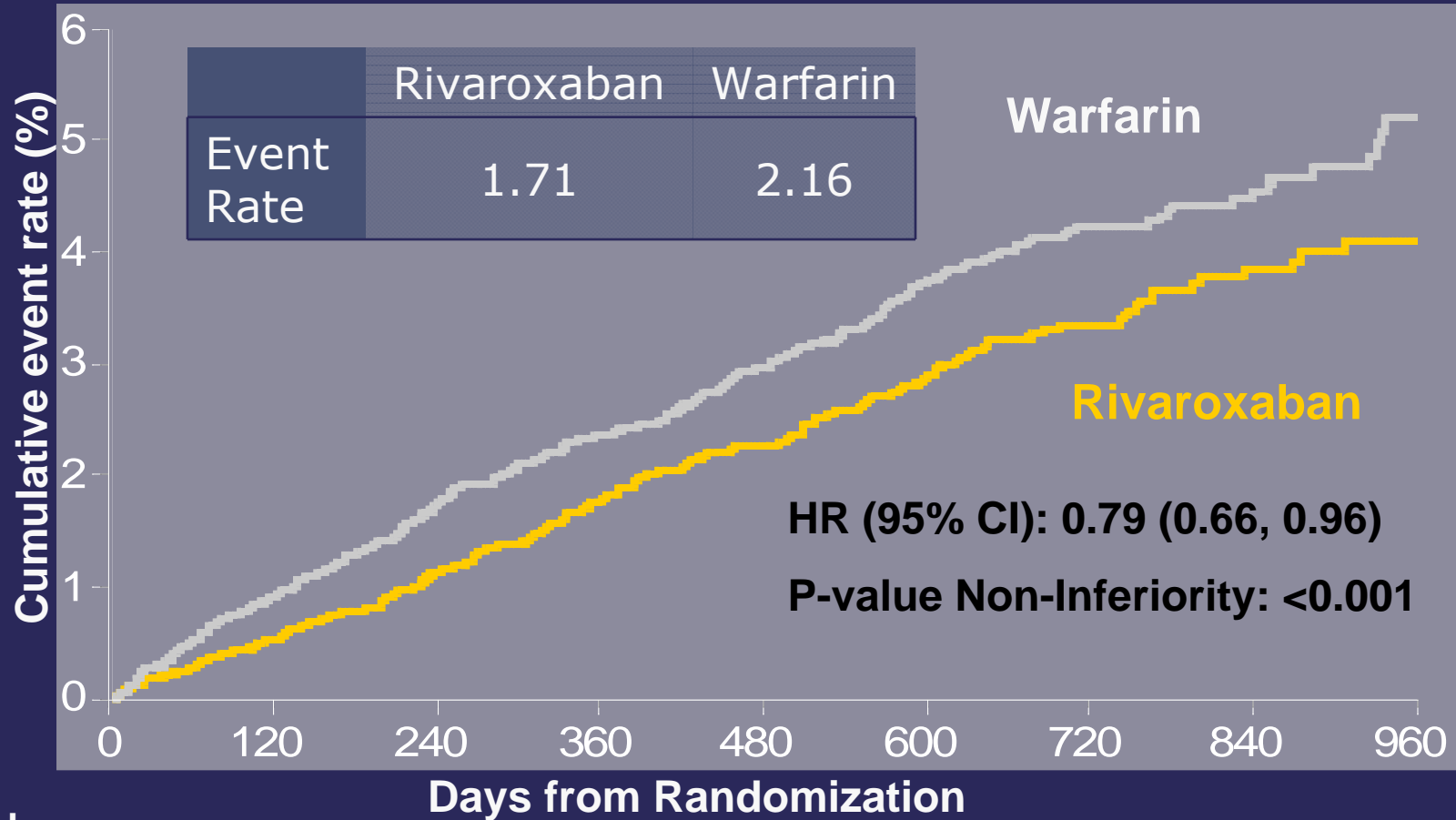
## ○ Secondary

- Composite of stroke, non-CNS systemic embolism and vascular death

## ○ Safety

- Major or non major clinically relevant bleeding

# ROCKET-AF: Primary Efficacy Outcome Stroke and non-CNS Embolism

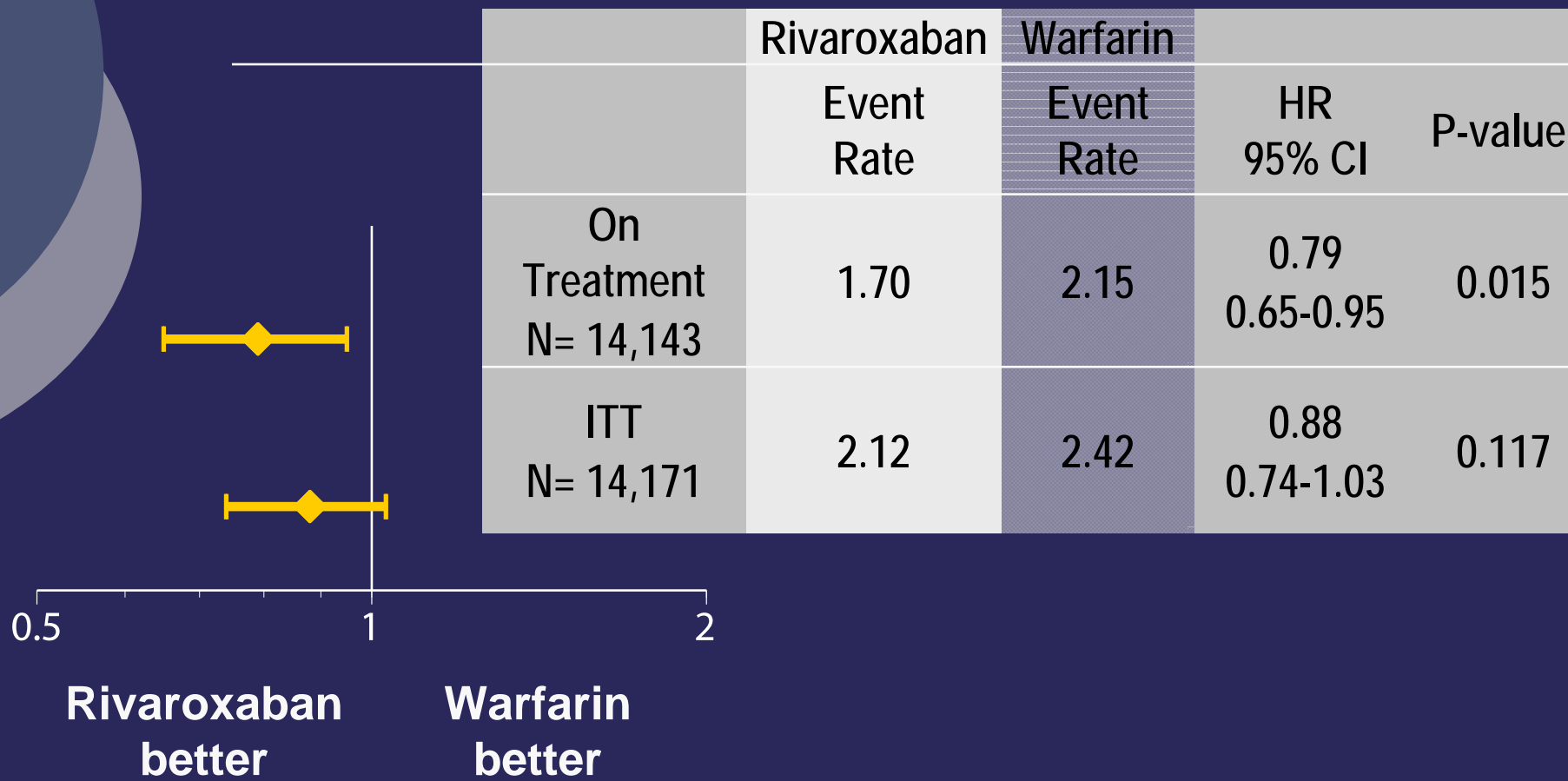


## No. at risk:

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



Event Rates are per 100 patient-years

Based on Safety on Treatment or Intention-to-Treat thru Site Notification populations

# ROCKET-AF: Key Secondary Efficacy Outcomes

	Rivaroxaban	Warfarin		
	Event Rate	Event Rate	HR (95% CI)	P- value
<b>Vascular Death, Stroke, Embolism</b>	3.11	3.63	0.86 (0.74-0.99)	0.034
<b>Stroke Type</b>				
Hemorrhagic	0.26	0.44	0.59 (0.37-0.93)	0.024
Ischemic	1.34	1.42	0.94 (0.75-1.17)	0.581
Unknown Type	0.06	0.10	0.65 (0.25-1.67)	0.366
<b>Non-CNS Embolism</b>	0.04	0.19	0.23 (0.09-0.61)	0.003
<b>Myocardial Infarction</b>	0.91	1.12	0.81 (0.63-1.06)	0.121
<b>All Cause Mortality</b>	1.87	2.21	0.85 (0.70-1.02)	0.073
Vascular	1.53	1.71	0.89 (0.73-1.10)	0.289
Non-vascular	0.19	0.30	0.63 (0.36-1.08)	0.094
Unknown Cause	0.15	0.20	0.75 (0.40-1.41)	0.370

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

Rocket AF Investigators, AHA 2010

# ROCKET-AF: Safety Outcomes for Bleeding

	Rivaroxaban	Warfarin		
	Event Rate	Event Rate	HR (95% CI)	P- value
Major and non-major Clinically Relevant	14.91	14.52	1.03 0.96-1.11	0.442
Major	3.60	3.45	1.04 0.90-1.20	0.576
Non-major Clinically Relevant	11.80	11.37	1.04 0.96-1.13	0.345
ICH	0.49	0.74	0.67 0.47-0.94	0.019

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

Rocket AF Investigators, AHA 2010

# ROCKET-AF Conclusions

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- Rivaroxaban was non-inferior to warfarin for prevention of stroke and non-CNS embolism
- Similar rates of bleeding and adverse events
- Less ICH and fatal bleeding with rivaroxaban

# Cost Comparison for A Fib

Agent	Average Monthly cost
Warfarin INR 2-3	\$10-15
Dabigatran 110 or 150 mg po BID	\$130
*Rivaroxaban 20 mg po daily	Unknown (rivaroxaban 10 MG tabs are currently ~\$9.30/tab)

**\*Rivaroxaban is NOT currently approved for stroke prophylaxis**

# Anticoagulant Comparison

	Warfarin	Dabigatran	Rivaroxaban
<b>Target</b>	<b>Vitamin K epoxide reductase</b>	<b>Thrombin</b>	<b>Factor Xa</b>
<b>Tmax</b>	<b>72-96 h</b>	<b>2 h</b>	<b>2.5-4 h</b>
<b>T1/2</b>	<b>40 h</b>	<b>14-17 hrs</b>	<b>9-13 hrs</b>
<b>Monitoring</b>	<b>Yes</b>	<b>No</b>	<b>No</b>
<b>Bioavailability</b>	<b>&gt;95%</b>	<b>5-6%</b>	<b>60-80%</b>
<b>Renal excretion</b>	<b>none</b>	<b>80%</b>	<b>33%</b>

# Anticoagulant Comparison

	Warfarin	Dabigatran	Rivaroxaban
<b>HC Indication</b>	-prophylaxis and treatment of VTE -stroke prevention for A fib -prophylaxis of systemic embolism post MI	-VTE prevention post HR or TKR -stroke prevention for A Fib	-VTE prevention post HR or TKR
<b>Administration</b>	Once daily	Twice a day	Once daily
<b>Common Adverse Effects</b>	Bleeding	Bleeding* Dyspepsia	Bleeding*
<b>Drug interactions</b>	Many	P-gp inducers and inhibitors	Potent CYP3A4 and P-gp inhibitors

\*less ICH than warfarin

# Conclusions

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- Advantages of new oral anticoagulants
  - More rapid onset of action
  - More rapid elimination
  - Lower potential for drug interactions
  - Predictable response
  - No need for routine lab monitoring
- Disadvantages of new oral anticoagulants
  - Lack of an antidote
  - Potential to increase bleeding in patients with renal dysfunction
  - High cost

# Conclusions

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- Dabigatran is an effective alternative to warfarin for stroke prophylaxis in patients with non-valvular atrial fibrillation
- Evidence for rivaroxaban in stroke prevention is expected to be published soon
- Other agents are undergoing investigation and review