

Antithrombotic Therapy for Stroke Prevention in Non- valvular Atrial Fibrillation

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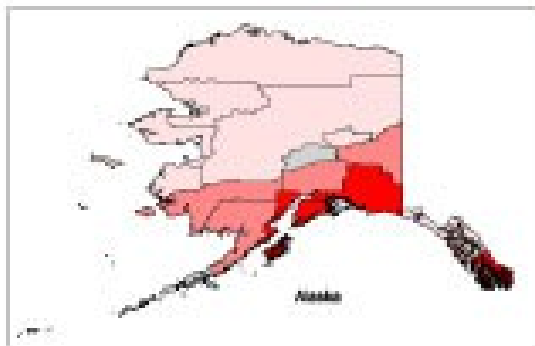
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Why worry about Atrial Fibrillation?



2.66 Million people with AF
461,000 hospital discharges
At 80yo: lifetime risk of 26%M, 23%W
Increases risk of stroke 4 to 5 fold
Accounts for 15% to 20% of strokes



Source: Medicare Provider Analysis and Review (MPAR)



Age-Adjusted Rates per 1,000*	Number of Counties
<11.58-57.48	638
57.47-64.34	638
64.35-70.17	638
70.18-77.07	638
77.08-141.91	638
Insufficient Data	5

* Atrial fibrillation hospitalization rates are spatially smoothed to enhance the stability of rates in counties with small populations.

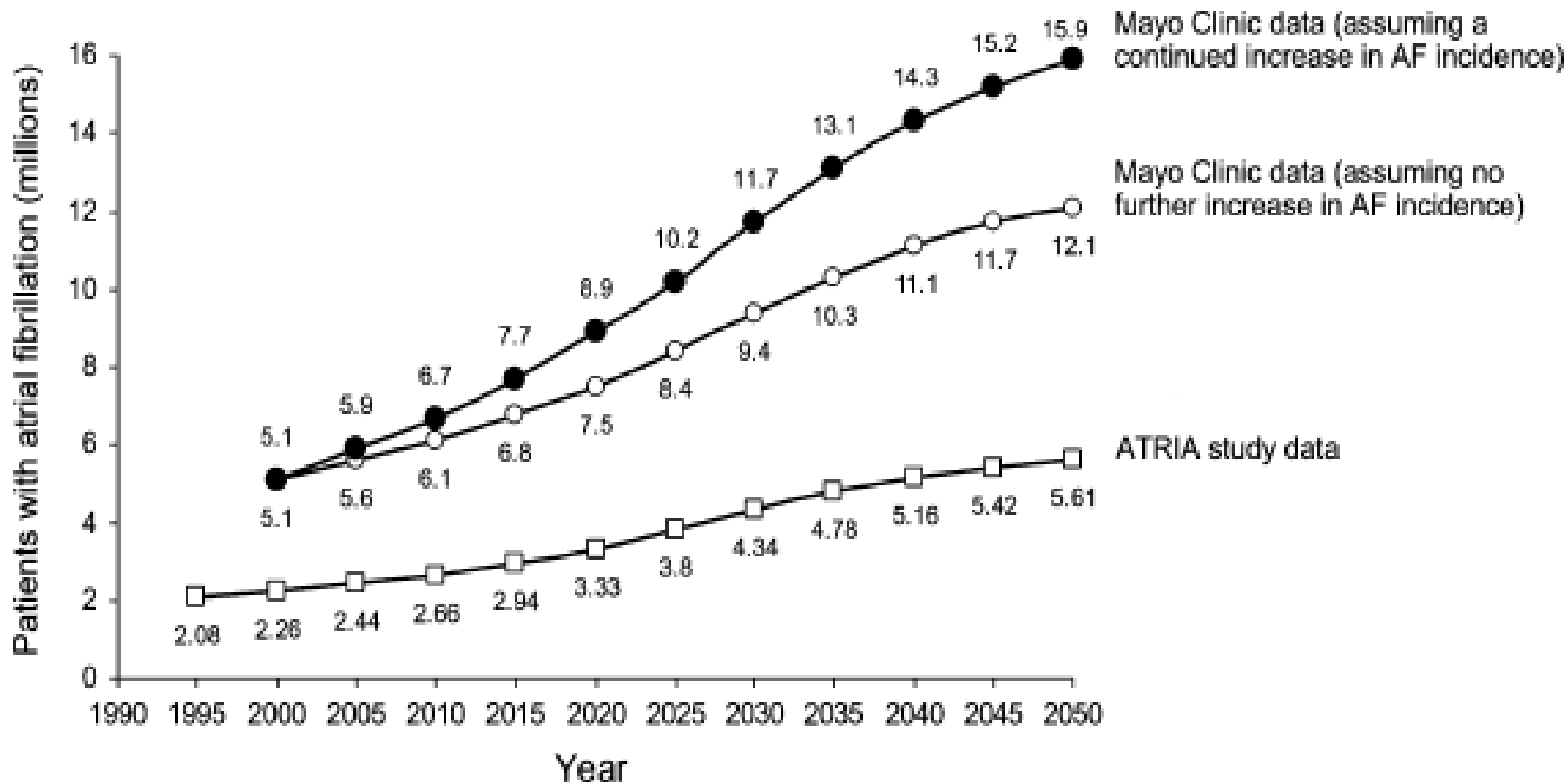
Data includes any mention atrial fibrillation (ICD-9cm 427.3) on the discharge form, not restricted to primary diagnosis.

Cardioembolic Stroke most
common in Atrial Fibrillation

Prevalence of Atrial Fibrillation

New Mayo Clinic Data

Clin. Cardiol. Vol. 31, February 2008



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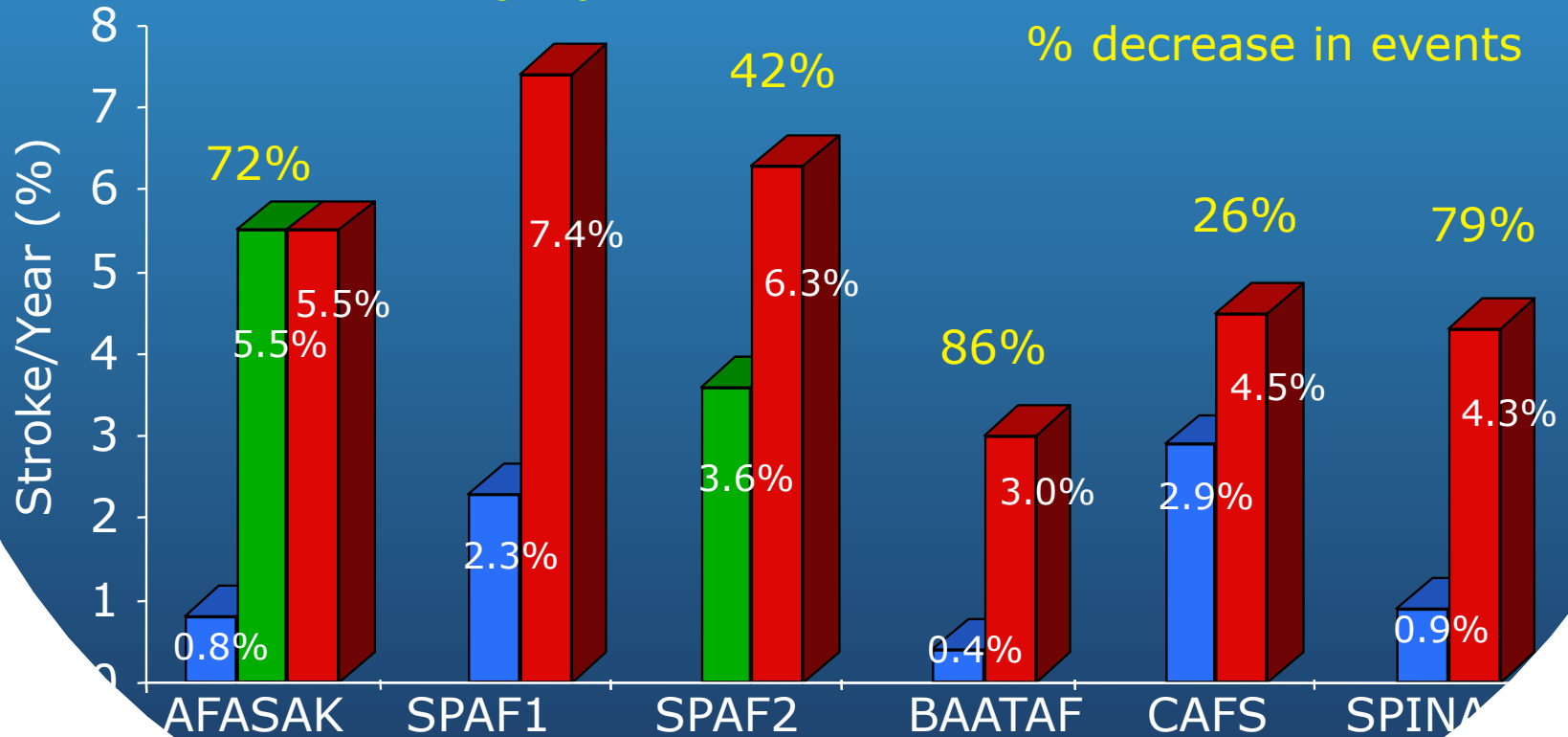
AF - Anticoagulation versus Placebo

Study	Design
AFASAK	Scandinavian: unblinded
SPAF I, II, III	American: unblinded
BAATAF	Boston Area: unblinded
SPINAF	VA: blinded
CAFA	Canada: blinded
EAFT	European: unblinded, post event

Atrial Fibrillation and Stroke: Summary of Randomized Studies



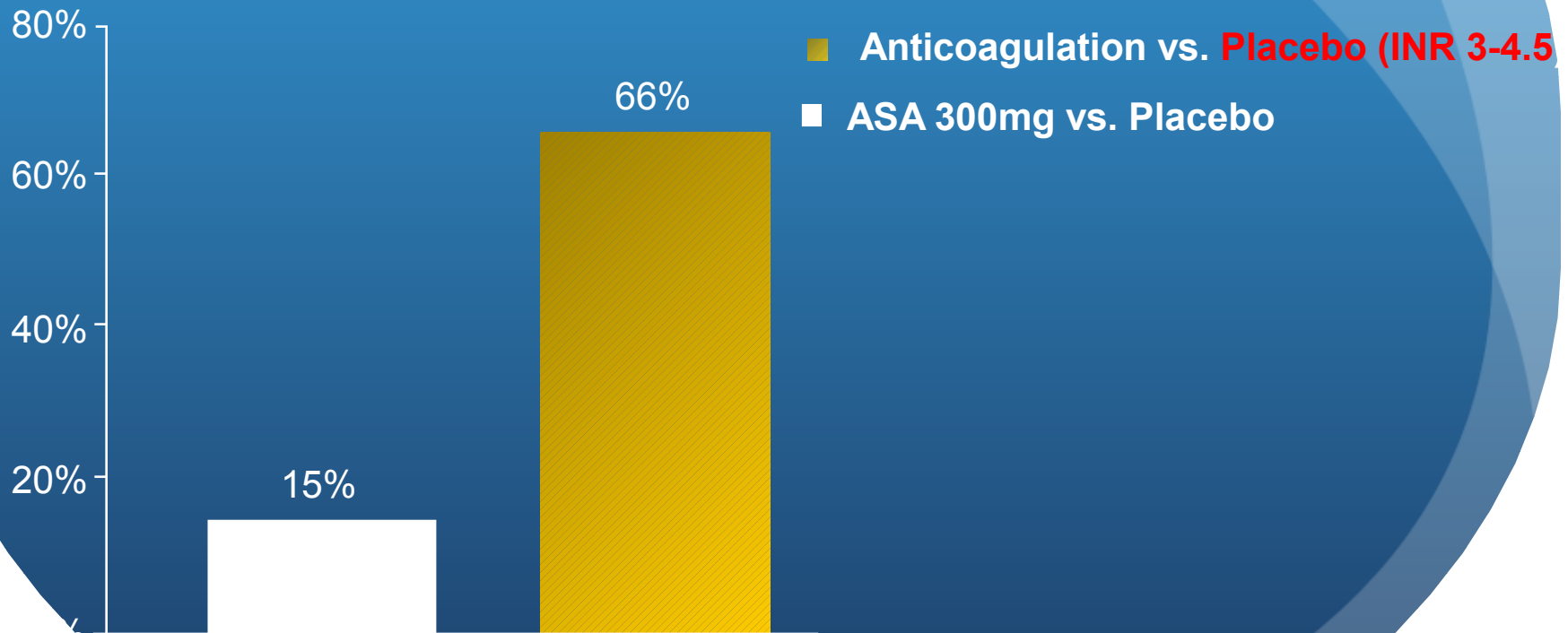
% decrease in events



Antithrombotic Therapy in Secondary Prevention for Patients with Atrial Fibrillation

European Atrial Fibrillation Trial (EAFT)

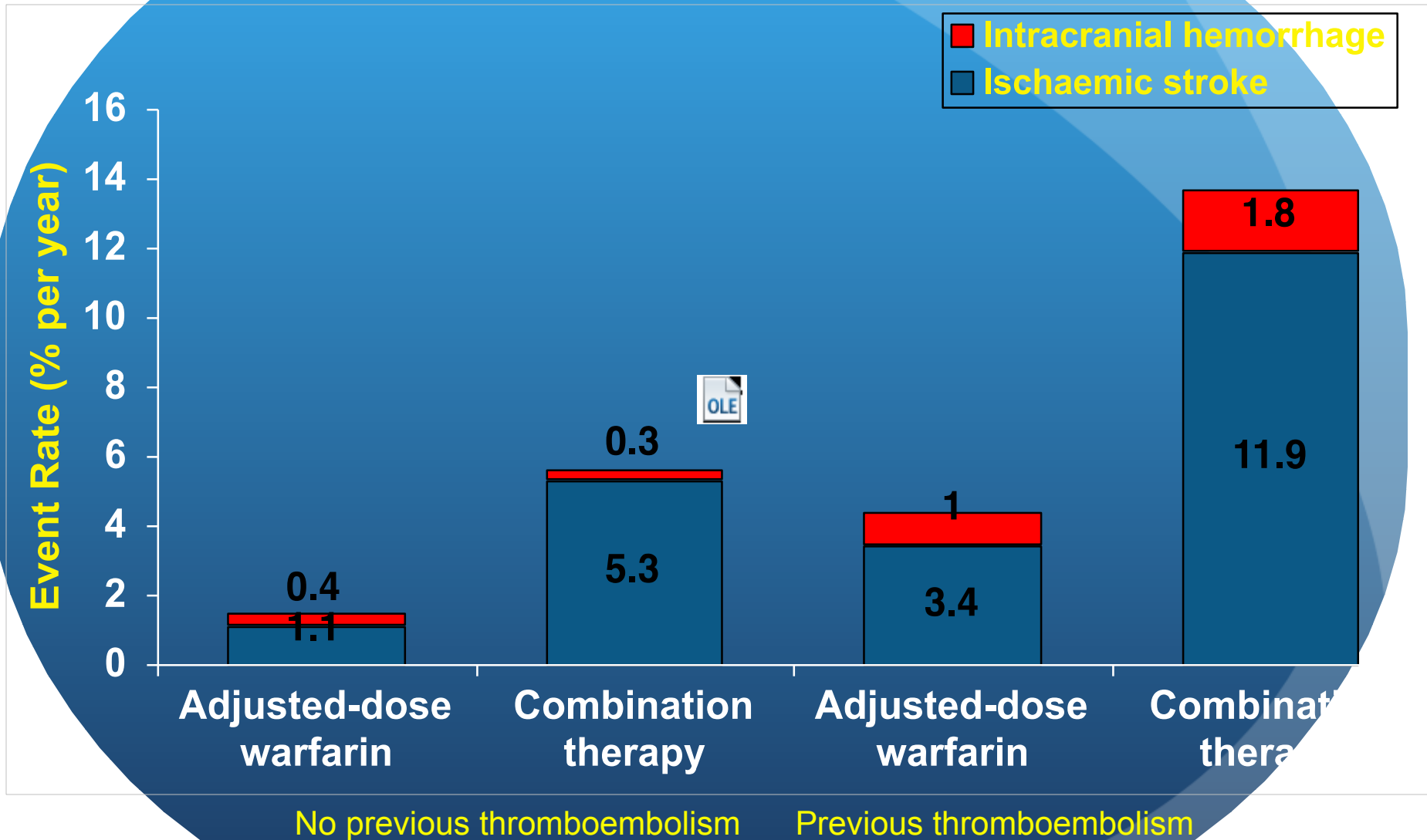
Relative Risk Reduction



Stroke Prevention AF III

- Among NVAF patients who were eligible to take warfarin
- Conventional adjusted dose warfarin aiming for an INR of 2-3
- Combination of mini-warfarin (INR <1.5) plus 325 mg ASA
- Primary Endpoint: Ischemic Stroke or systemic embolism

Stroke Prevention in AF III

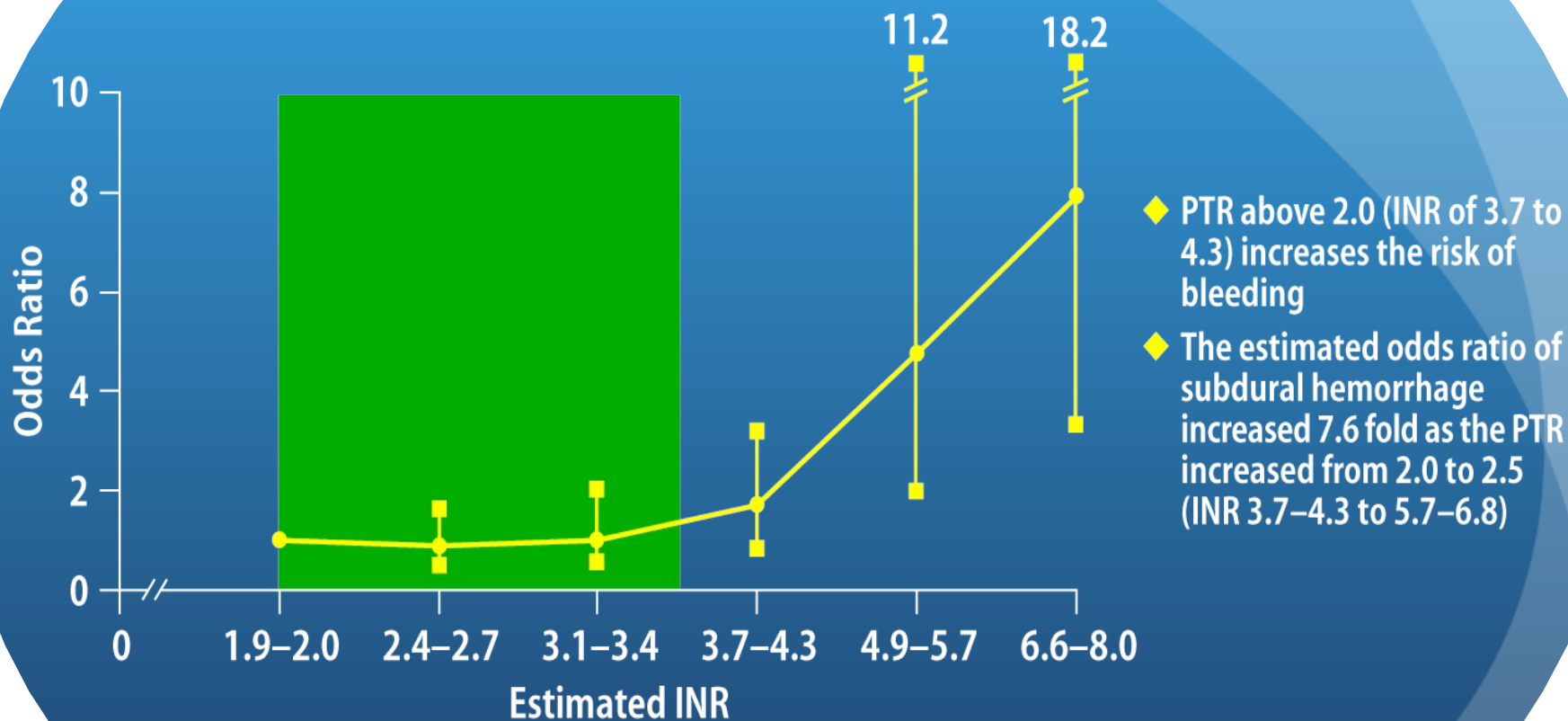


Lowest Effective Intensity for Warfarin Therapy for Stroke Prevention in Atrial Fibrillation



INR below 2.0 results in a higher risk of stroke

Risk of Intracranial Hemorrhage in Outpatients



Adapted from: Hylek EM, Singer DE, *Ann Int Med* 1994;120:897-902

Hylek, et al, studied the risk of intracranial hemorrhage in outpatients with warfarin. They determined that an intensity of anticoagulation corresponding to a prothrombin time ratio (PTR) above 2.0 (roughly corresponding to an INR of 3.7-4.3) resulted in an increase in the risk of bleeding.

Warfarin & Atrial Fibrillation

- Warfarin reduces stroke risk by 68%
- Narrow therapeutic index drug with increased risk of hemorrhagic complications
- Requires monitoring of PT or the INR with Optimal INR: 2.0 - 3.0
- Warfarin is underutilized, prescribed to ~50%
- Major drug and food interactions

How Do We Assess Stroke Risk in Atrial Fibrillation?

- CHADS2
- CHADS2Vasc

CHADS₂ Score

		Score
C	Congestive heart failure	1
H	Hypertension	1
A	Age \geq 75 years	1
D	Diabetes mellitus	1
S	Stroke (or TIA)	2

CHADS₂ and CHA₂DS₂-VASc Scores

		CHADS ₂ Score	CHA ₂ DS ₂ -VASc Score
C	Congestive heart failure	1	1
H	Hypertension	1	1
A	Age ≥ 75 years	1	2
D	Diabetes mellitus	1	1
S	Stroke (or TIA)	2	2
V	Vascular disease*		1
A	Age 66-74 years		1
Sc	Sex category (female)		1

* Prior MI, peripheral artery disease, aortic plaque

Gage BF, et al.^[2]

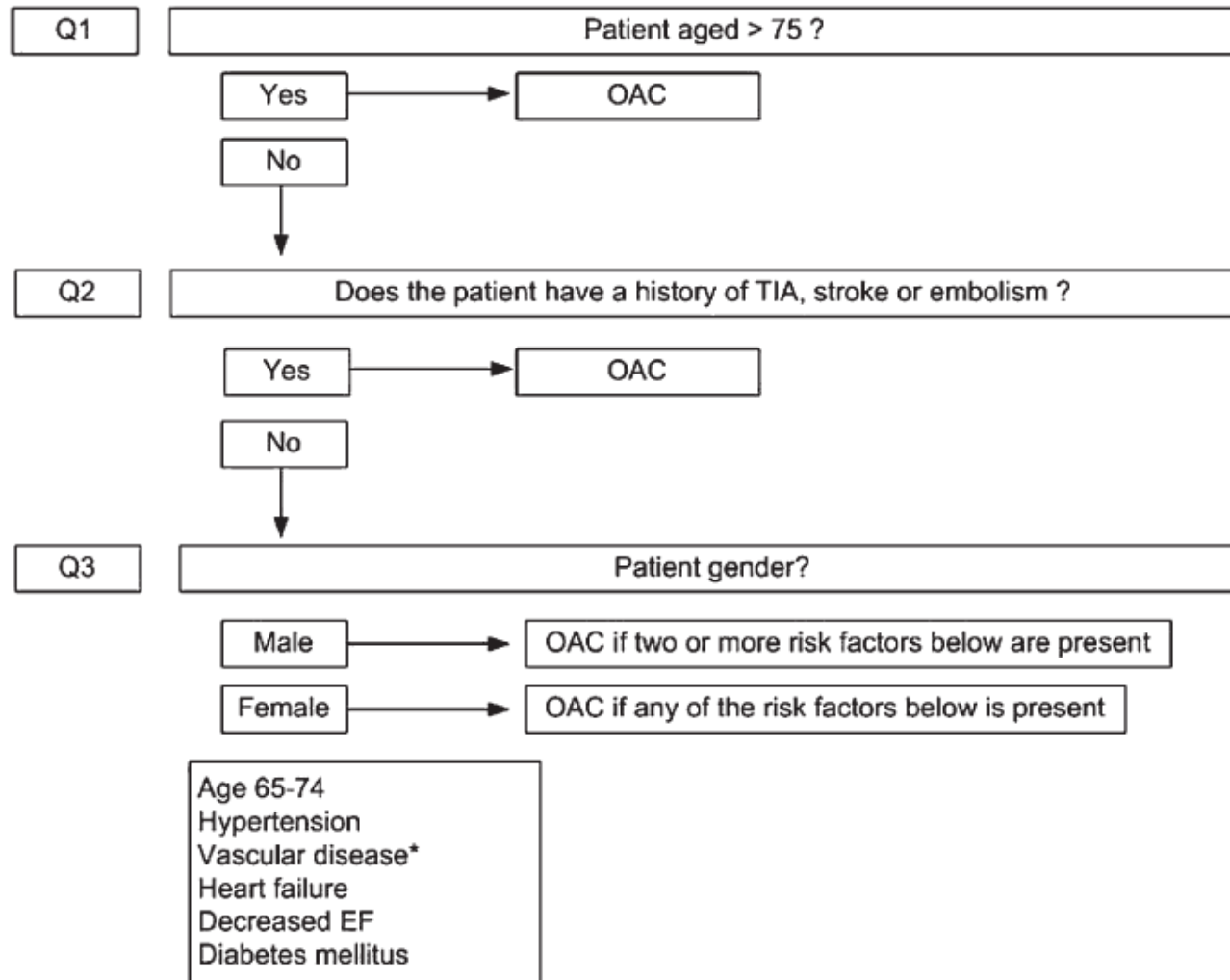
Lip GHY, et al.^[3]

CHADS2 vs. CHA2DS2VASc

- CHADS2 score 0: 1.4% events
- CHA2DS2-VASc 0: 0 events
- CHA2DS2-VASc score 1: 0.6% events
- CHA2DS2-VASc score 2: 1.6% events

Our approach: anticoagulation when
Isch stroke risk > 0.9%/year

CHA2DS2-VASC



*Myocardial infarction, peripheral artery disease or aortic plaque

Who should remain on warfarin?

- Patient already receiving warfarin and stable whose INR is easy to control
- If dabigatran, rivaroxaban, apixaban are not options.
- Cost
- If patient not likely to comply with twice daily dosing (Dabigatran, Apixaban)
- Chronic kidney disease (GFR < 30 ml/min)



New Era in the Management Stroke Prevention in AF

Dabigatran: Pradaxa

Direct Thrombin Inhibitor

FDA approved in October 2010 based on the RELY Trial **Randomized Evaluation of Long-term anticoagulant therapy (RE-LY)** data.

Pharmacologic Characteristics of PRADAXA

Characteristics

- Dabigatran binds rapidly and specifically to both free and clot-bound thrombin
- Dabigatran directly inhibits a single component in the coagulation process
- PRADAXA treatment does not require anticoagulation monitoring
- At recommended therapeutic doses, dabigatran etexilate prolongs the coagulation markers activated partial thromboplastin time (aPTT), ecarin clotting time (ECT), and thrombin time (TT)
- INR is relatively insensitive to the exposure to dabigatran and cannot be interpreted the same way as used for warfarin monitoring
- The aPTT test provides a good approximation of PRADAXA's anticoagulant effect
- The degree of anticoagulant activity can also be assessed by the ECT. This test is a more specific measure of the effect of dabigatran than aPTT

Please see Important Safety Information on slides 12, 16, 20, 23, and 24.

Please see full Prescribing Information and Medication Guide for PRADAXA provided.

The RE-LY[®] trial: PRADAXA vs Warfarin for Stroke Risk Reduction in Patients With Non-valvular AF

Study Parameters

- Multicenter, multinational, randomized, parallel group trial comparing 2 blinded doses of PRADAXA with open-label warfarin
- Blinded adjudication of outcome events
- 50% patients VKA-naïve*
- Primary efficacy outcome: incidence of stroke (ischemic and hemorrhagic) and systemic embolism
- Primary safety outcome: incidence of major bleeds

**18,113
Randomized**

Blinded to dose

*Total lifetime exposure of <2 months.

†PRADAXA 110-mg dose not approved for use.

Connolly SJ, et al. *N Engl J Med*. 2009;361:1139-1151.

Please see Important Safety Information on slides 12, 16, 20, 23, and 24.

Please see full Prescribing Information and Medication Guide for PRADAXA provided.

Inclusion and Major Exclusion Criteria of the RE-LY[®] Trial

Inclusion Criteria

- Non-valvular persistent, paroxysmal, or permanent atrial fibrillation
- One or more additional risk factors for stroke:
 - Previous stroke, transient ischemic attack, or systemic embolism
 - Left ventricular ejection fraction <40%
 - Symptomatic heart failure, \geq New York Heart Association Class 2
 - Age \geq 75 years
 - Age \geq 65 years and one of the following:
 - Diabetes mellitus
 - Coronary artery disease
 - Hypertension

Major Exclusion Criteria¹

- History of heart valve disorders (ie, prosthetic valve or hemodynamically relevant valve disease)
- 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 (CrCl <30 mL/min)

- Concomitant medications were allowed and included aspirin (\leq 100 mg/day), clopidogrel, proton pump inhibitors (PPIs), antihypertensives, antiarrhythmic agents (eg, amiodarone, verapamil)²

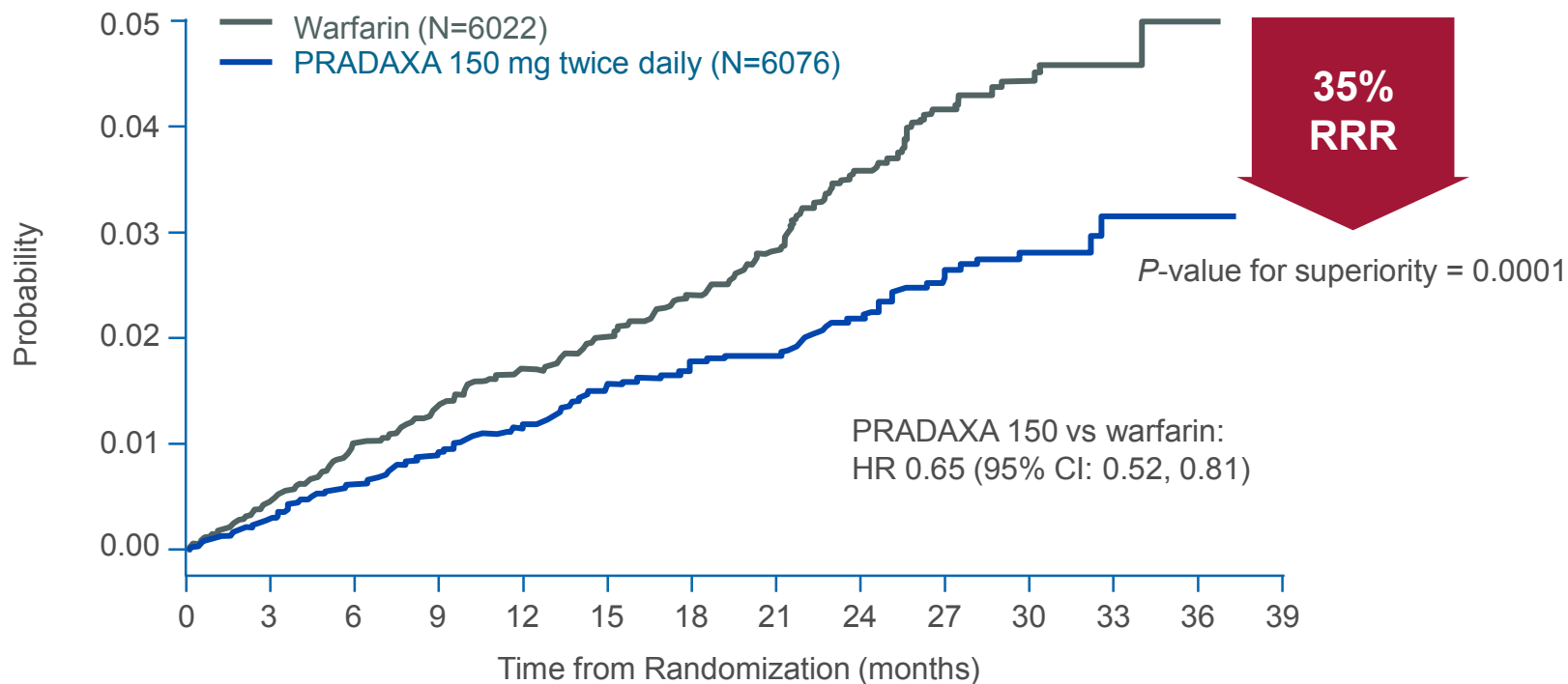
1. Ezekowitz MD, et al. *Am Heart J*. 2009;157:805-810.e2. 2. Connolly SJ, et al. *N Engl J Med*. 2009; 361:1139-1156

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Please see full Prescribing Information and Medication Guide for PRADAXA provided.

In Non-valvular AF, PRADAXA 150 mg Twice Daily Significantly Reduced the Risk of Stroke and Systemic Embolism an Additional 35% vs Warfarin

Estimate of Time to First Stroke or Systemic Embolism

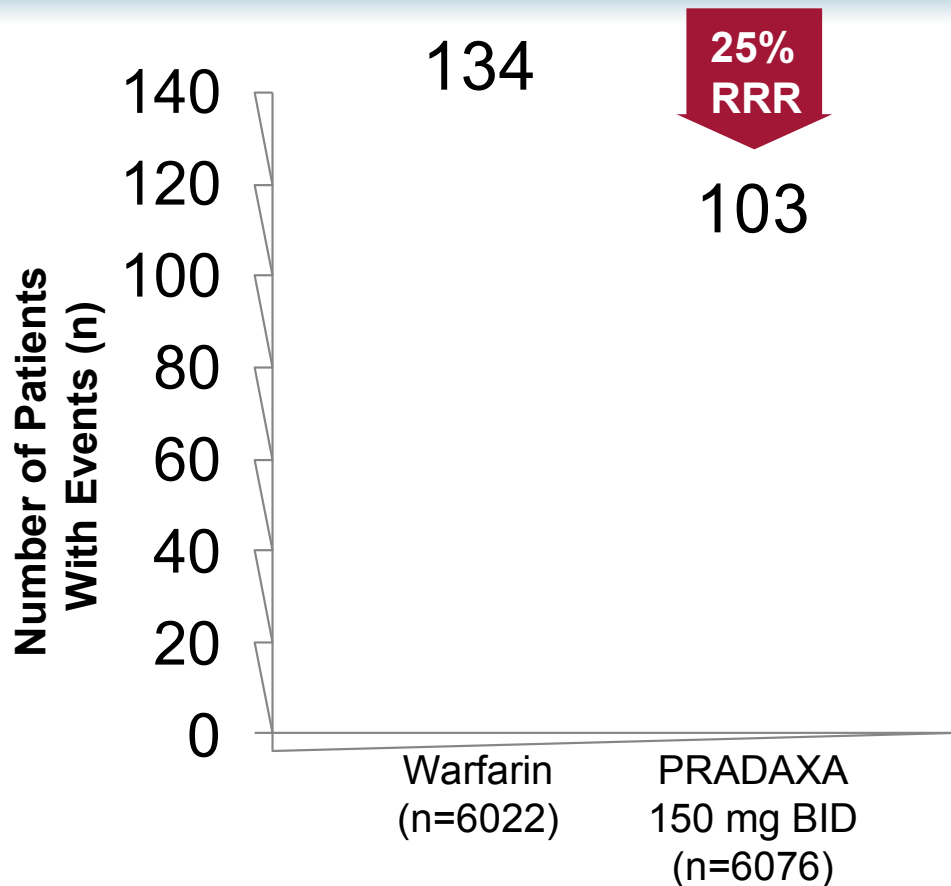


In RE-LY®, a higher rate of clinical myocardial infarction was reported in patients who received PRADAXA (0.7 per 100 patient-years for 150-mg dose) than in those who received warfarin (0.6).

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PRADAXA is the ONLY Oral Anticoagulant to Demonstrate Superior Reduction in Ischemic Stroke vs Warfarin in Non-valvular AF¹⁻³



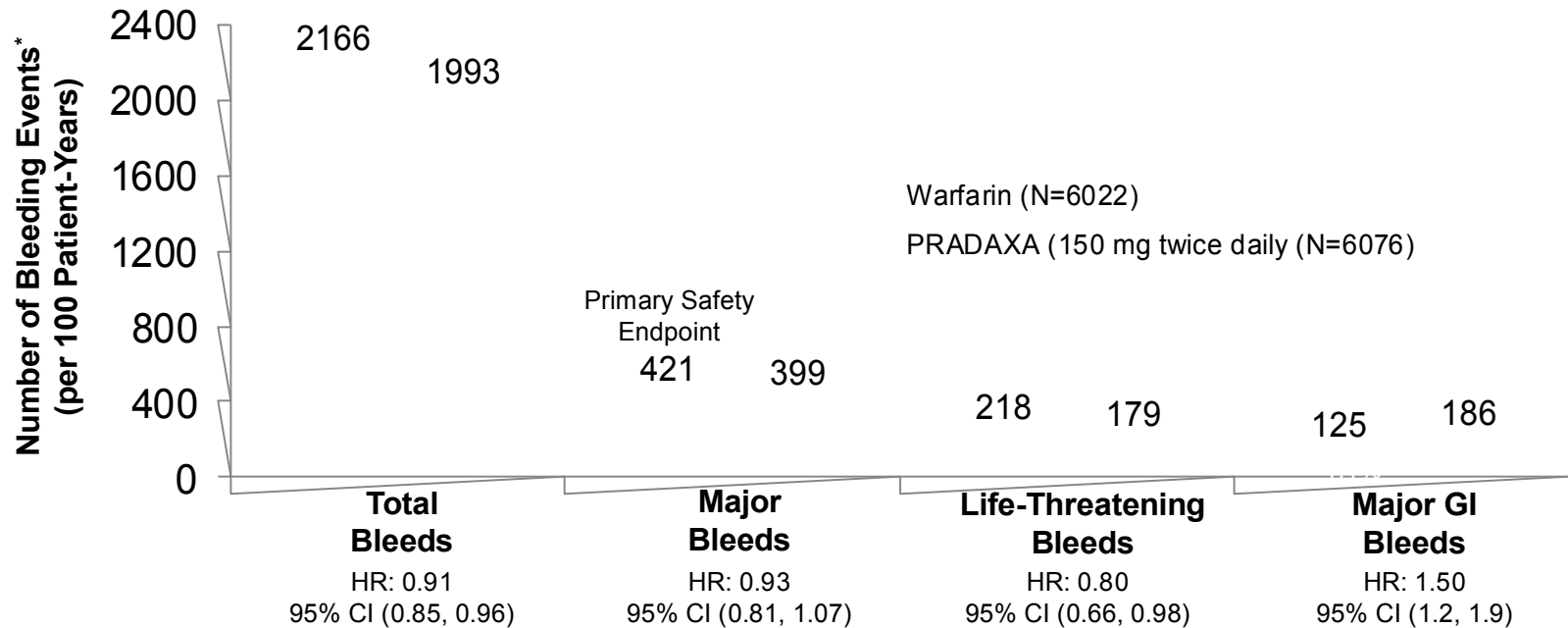
- PRADAXA 150 mg twice daily reduced ischemic stroke by 25% vs warfarin (HR: 0.75; 95% CI, 0.58, 0.97, $P=0.0296$)
- PRADAXA 150 mg twice daily also was superior in reducing hemorrhagic stroke vs warfarin (74% greater reduction, 12 vs 45 events, HR: 0.26; 95% CI, 0.14, 0.49, $P<0.0001$)
- Ischemic and hemorrhagic stroke were part of the primary composite endpoint (stroke and systemic embolism)
- Total strokes: 122 for PRADAXA and 186 for warfarin (HR: 0.64; 95% CI, 0.51, 0.81, $P=0.0001$)

1. Connolly SJ, et al. *N Engl J Med*. 2009;361(12):1139-1151. 2. Connolly SJ, et al. *N Engl J Med*. 2010;363(19):1875-1876.
3. Data on file. Boehringer Ingelheim Pharmaceuticals, Inc.

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Please see full Prescribing Information and Medication Guide for PRADAXA provided.

Rates of Bleeds With PRADAXA 150 mg vs Warfarin per 100 Patient-years^{1,2}



Higher rate of total GI bleeds: 681 (6.1%) vs 452 (4.0%) events, HR: 1.52, (95% CI, 1.35, 1.72)¹⁻³

Number of fatal bleeds 28 (0.23%) for PRADAXA vs 39 (0.33%) for warfarin, HR: 0.70 (95% CI, 0.43, 1.14)^{3,4}

Trend towards a higher incidence of major bleeding on PRADAXA 150 mg for patients ≥75 years of age (HR: 1.2, [95% CI, 1.0, 1.4])

Risk of stroke and bleeding increases with age, but the risk-benefit profile is favorable in all age groups.

*Patients contributed multiple events and events were counted in multiple categories.

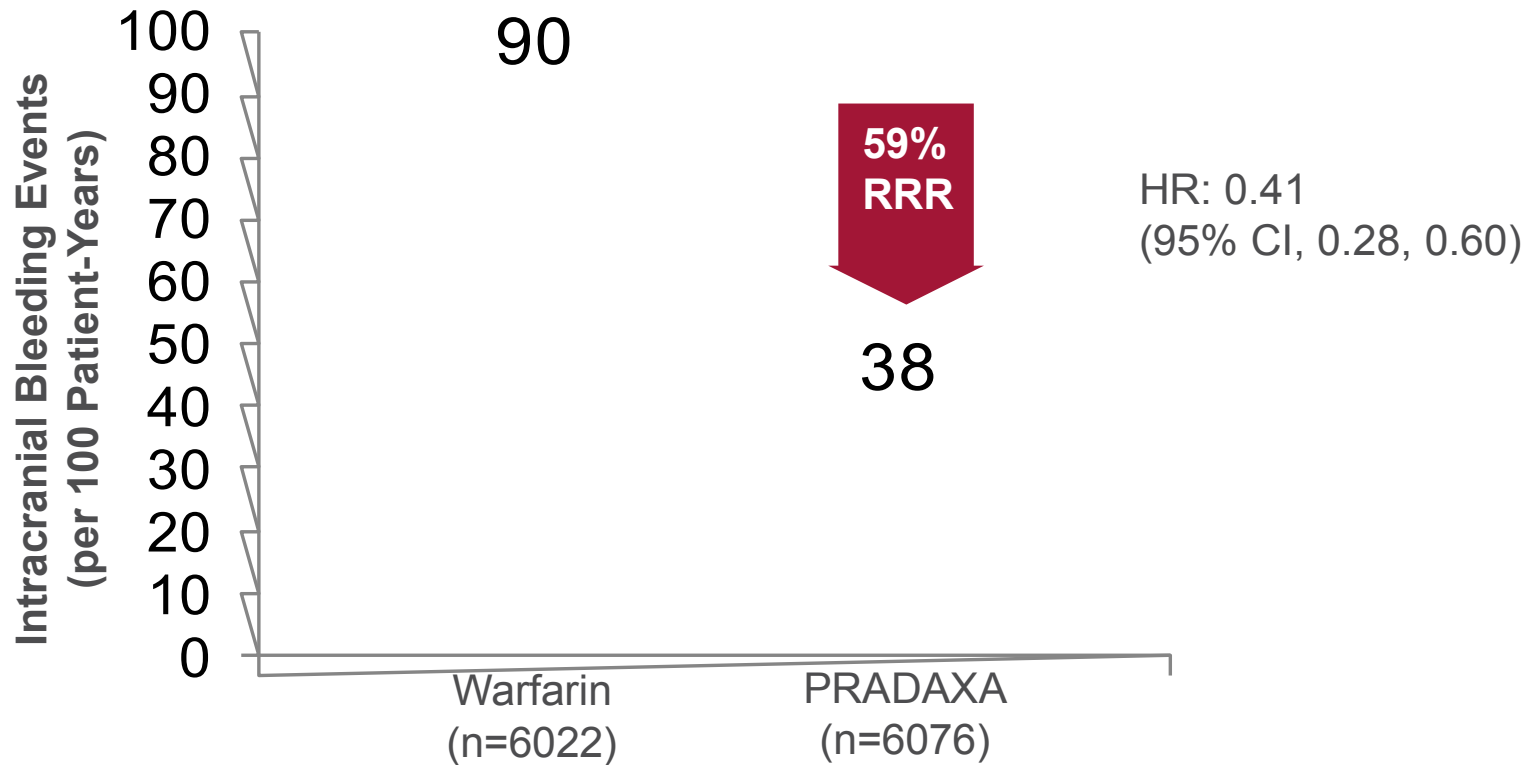
1. Connolly SJ, et al. *N Engl J Med.* 2009;361(12):1139-1151. 2. Connolly SJ, et al. *N Engl J Med.* 2010;363(19):1875-1876.

3. Data on file. Boehringer Ingelheim Pharmaceuticals, Inc. 4. Eikelboom JW, et al. *Circulation.* 2011;123(21):2363-2372.

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Please see full Prescribing Information and Medication Guide for PRADAXA provided.

Lower Rate of Intracranial Bleeding With PRADAXA vs Warfarin^{1,2}



*Per 100 patient-years.

1. Connolly SJ, et al. *N Engl J Med*. 2009;361(12):1139-1151.

2. Connolly SJ, et al. *N Engl J Med*. 2010;363(19):1875-1876.

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Interim Results from RELY-ABLE[®]

- Extension study of RE-LY[®] evaluating safety of PRADAXA 150 mg BID over an additional 2.3 years (4.3 years median treatment with dabigatran)
- 5851 patients were enrolled (2937 PRADAXA 150 mg BID, 2914 dabigatran 110 mg BID)
 - Patients in RELY-ABLE continued same blinded dose of dabigatran
- Considerations specific to RELY-ABLE
 - Outcomes were not adjudicated
 - Warfarin patients were not followed as a comparator group
- During 2.3 years of additional treatment after RE-LY (total mean follow-up 4.3 years)
 - No new safety findings were identified
 - Rates of total bleeding, life-threatening bleeding, and major bleeding were similar to those seen during RE-LY

Connolly SJ, et al. Presented at American Heart Association Scientific Sessions. Los Angeles, CA. November 2012.

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Please see full Prescribing Information and Medication Guide for PRADAXA provided.

FDA Mini-Sentinel Assessment Reinforces Safety Data of PRADAXA

On November 2, 2012, the US Food and Drug Administration (FDA) announced the results of a Mini-Sentinel assessment, evaluating new information about the risk of serious bleeding associated with use of the anticoagulants, PRADAXA and warfarin:

- **Bleeding rates associated with new use of PRADAXA do not appear higher vs new use of warfarin**
- **Results are consistent with observations from the pivotal RE-LY® trial**

FDA investigated the actual rates of gastrointestinal and intracranial bleeding for new users of PRADAXA vs new users of warfarin. This assessment was done using insurance claims and administrative data from the FDA's ongoing Mini-Sentinel pilot of the Sentinel Initiative.

As a result of this assessment, FDA has not changed its recommendations regarding PRADAXA. PRADAXA provides an important health benefit when used as directed. Healthcare professionals who prescribe PRADAXA should carefully follow the dosing recommendations in the drug label, especially for patients with renal impairment to reduce the risk of bleeding.

US FDA. FDA Drug Safety Communication. Update on the risk for serious bleeding events with the anticoagulant Pradaxa. Updated November 2, 2012. Accessed November 7, 2012.

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Starting Patients on PRADAXA

Recommended dose for most patients: 150 mg twice daily, with or without food

Creatinine Clearance	Recommended Dose of PRADAXA
>30 mL/min	150 mg twice daily
15-30 mL/min (severe renal impairment)	75 mg twice daily*
<15 mL/min or dialysis	Dosing recommendations cannot be provided

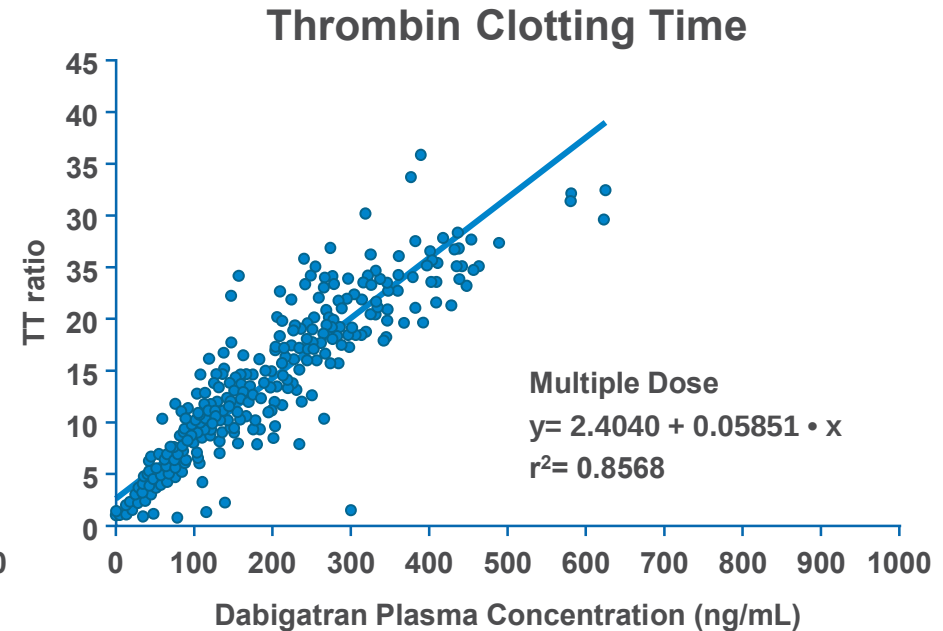
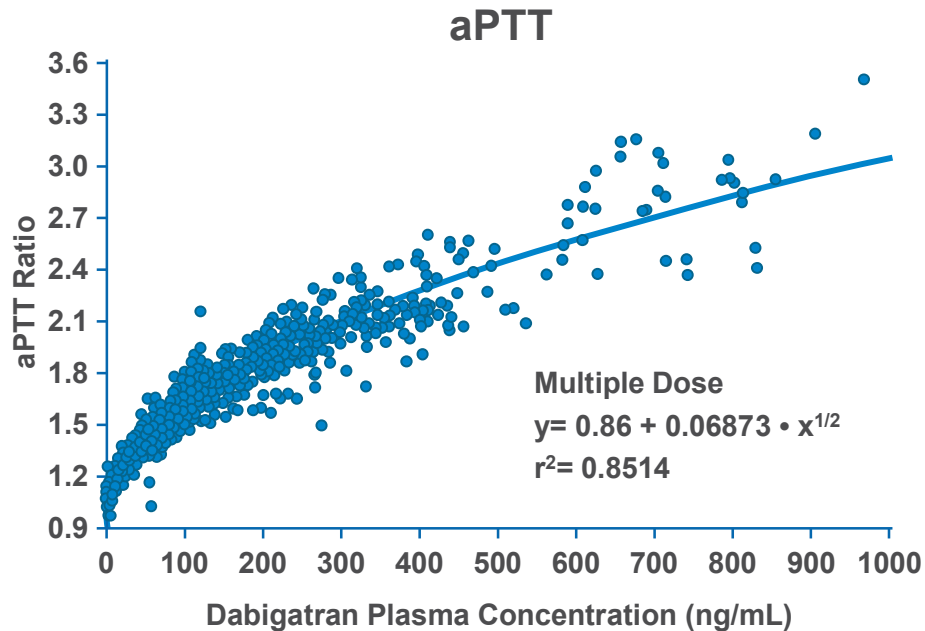
- Assess renal function prior to initiating treatment with PRADAXA
- When converting patients from warfarin therapy to PRADAXA, discontinue warfarin and start PRADAXA when the INR is below 2.0
- Periodically assess renal function as clinically indicated (ie, more frequently in clinical situations that may be associated with a decline in renal function) and adjust therapy accordingly
- Discontinue PRADAXA in patients who develop acute renal failure while on PRADAXA and consider alternative anticoagulant therapy
- PRADAXA is contraindicated in patients with mechanical prosthetic heart valves

*Based on pharmacokinetic modeling, estimated exposure to dabigatran increases with the severity of renal function impairment.

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Coagulation Parameters Correlate With Dabigatran Plasma Concentrations at Steady State



TT = thrombin clotting time.

TT has not been established as a standard anticoagulant test in the clinical setting.

Reprinted with permission from Stangier J. *Clin Pharmacokinet.* 2008;47:285-295.

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Common Concerns with Pradaxa

- No Reversal Agent
- Stopping drug for surgical procedures
- Increased risk of major GI bleeding (best stroke protection)
- GI Upset-Dyspepsia
- TV Ads- “1-800-Bad-Drug”

LATEST ACCP GUIDELINES (cont.)

CHEST. 2012;141(2_suppl):7S-47S. doi:10.1378/chest.1412S3

- 2.1.10. For patients with AF, including those with paroxysmal AF, who are at **high risk** of stroke (eg, CHADS2 score = 2), we recommend oral anticoagulation rather than no therapy (Grade 1A), aspirin (75 mg to 325 mg once daily) (Grade 1B), or combination therapy with aspirin and clopidogrel (Grade 1B). For patients who are unsuitable for or choose not to take an oral anticoagulant (for reasons other than concerns about major bleeding), we recommend combination therapy with aspirin and clopidogrel rather than aspirin (75 mg to 325 mg once daily) (Grade 1B).
- 2.1.11. For patients with AF, including those with paroxysmal AF, for whom we do not have a recommendation in favor of oral anticoagulation, we recommend aspirin (75 mg to 325 mg once daily) (Grade 1B) rather than no therapy (Grade 1B).

Rivaroxaban: Xarelto

- Xa Inhibitor
- Half-life shorter than Dabigatran (5-13 hrs)
- Good GI Tolerance
- ROCKET AF TRIAL led to FDA Approval

Rivaroxaban

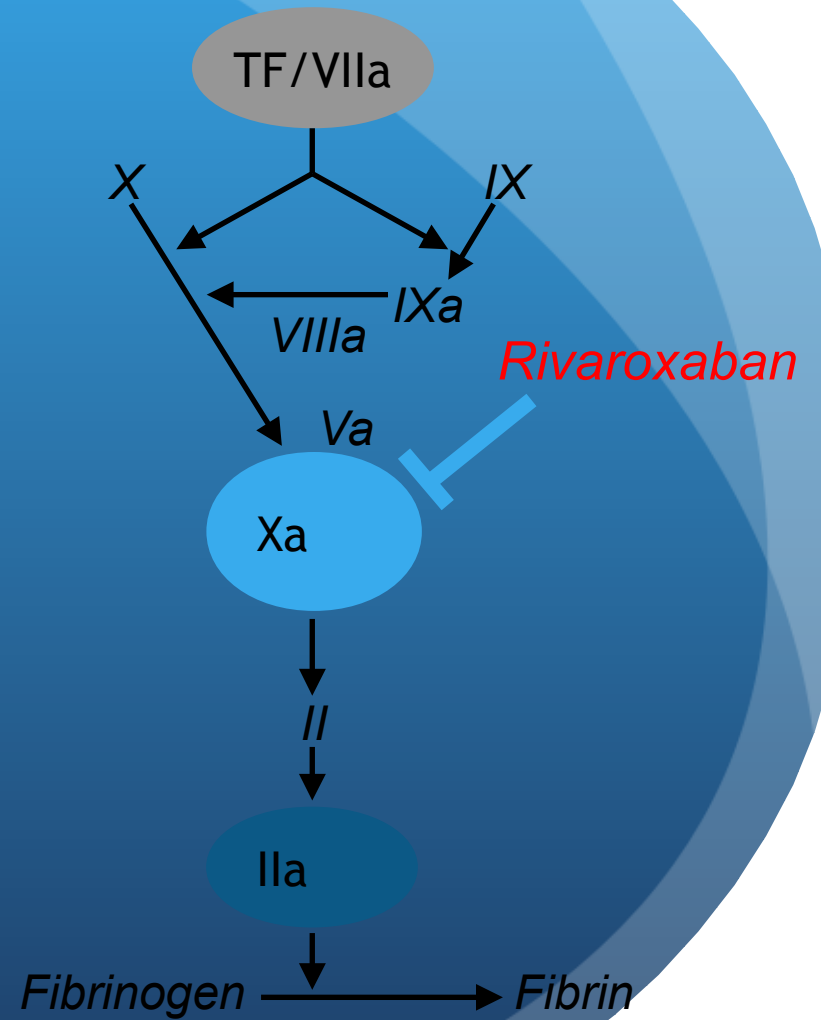
Oral anticoagulant invented and manufactured by Bayer; it is marketed as **Xarelto 20mg**.

- **First available orally active direct factor Xa inhibitor. Absorbed from the gut and maximum inhibition of factor Xa occurs four hours after a dose. The effects lasts 8–12 hours, but factor Xa activity does not return to normal within 24 hours so once-daily dosing is possible.**
- **In September 2008, Health Canada granted marketing authorization for rivaroxaban as one 10 mg tablet taken once daily for the prevention of venous thromboembolism (VTE) in patients who have undergone elective total hip replacement or total knee replacement surgery.**
- **In September 2008, the European Commission granted marketing authorization of rivaroxaban for the prevention of venous thromboembolism in**

Background

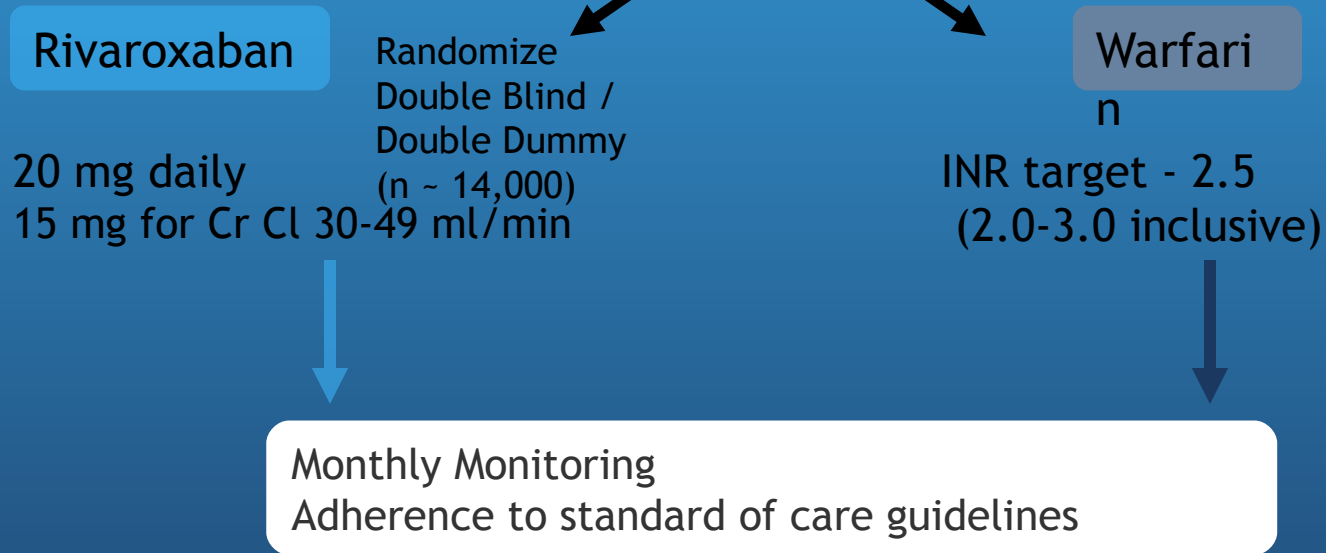
Rivaroxaban

- Direct, specific, competitive factor Xa inhibitor
- Half-life 5-13 hours
- Clearance :
 - 1/3 direct renal excretion
 - 2/3 metabolism via CYP 450 enzymes
- Oral, once daily dosing without need for coagulation monitoring
- Studied in >25,000 patients post-op, DVT, PE and atrial fibrillation patients



Adapted from Weitz et al, 2005; 2008

ROCKET AF Study Design *Atrial Fibrillation*



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%

Summary ROCKET-AF Trial

Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* September 8 2011; 365: 883-891.

- **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.

Apixaban versus Warfarin in Patients with Atrial Fibrillation

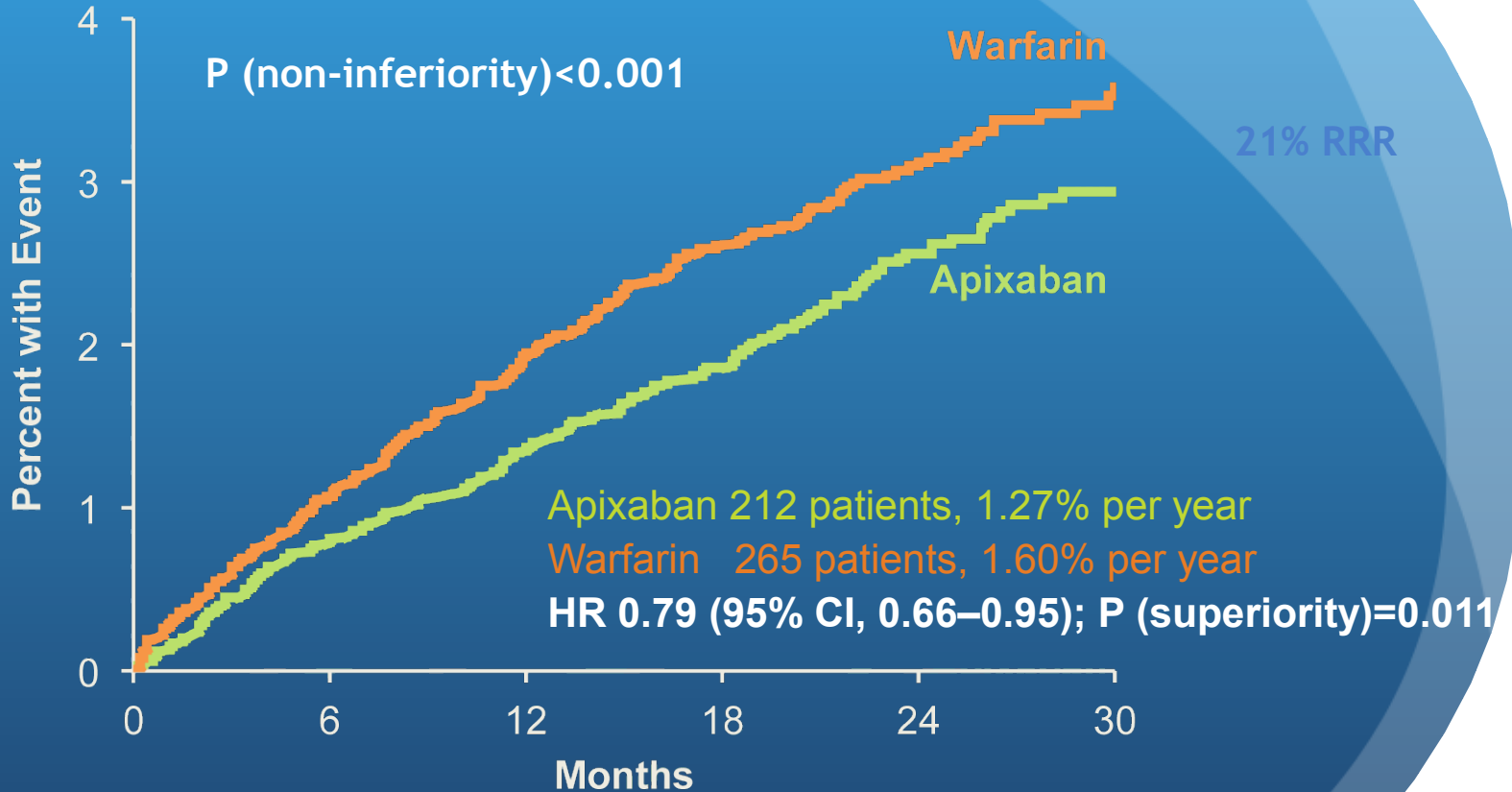
Results of the ARISTOTLE Trial

Presented on behalf of the ARISTOTLE Investigators
and Committees

Sponsored by Bristol-Myers Squibb and Pfizer

Primary Outcome

Stroke (ischemic or hemorrhagic) or systemic embolism

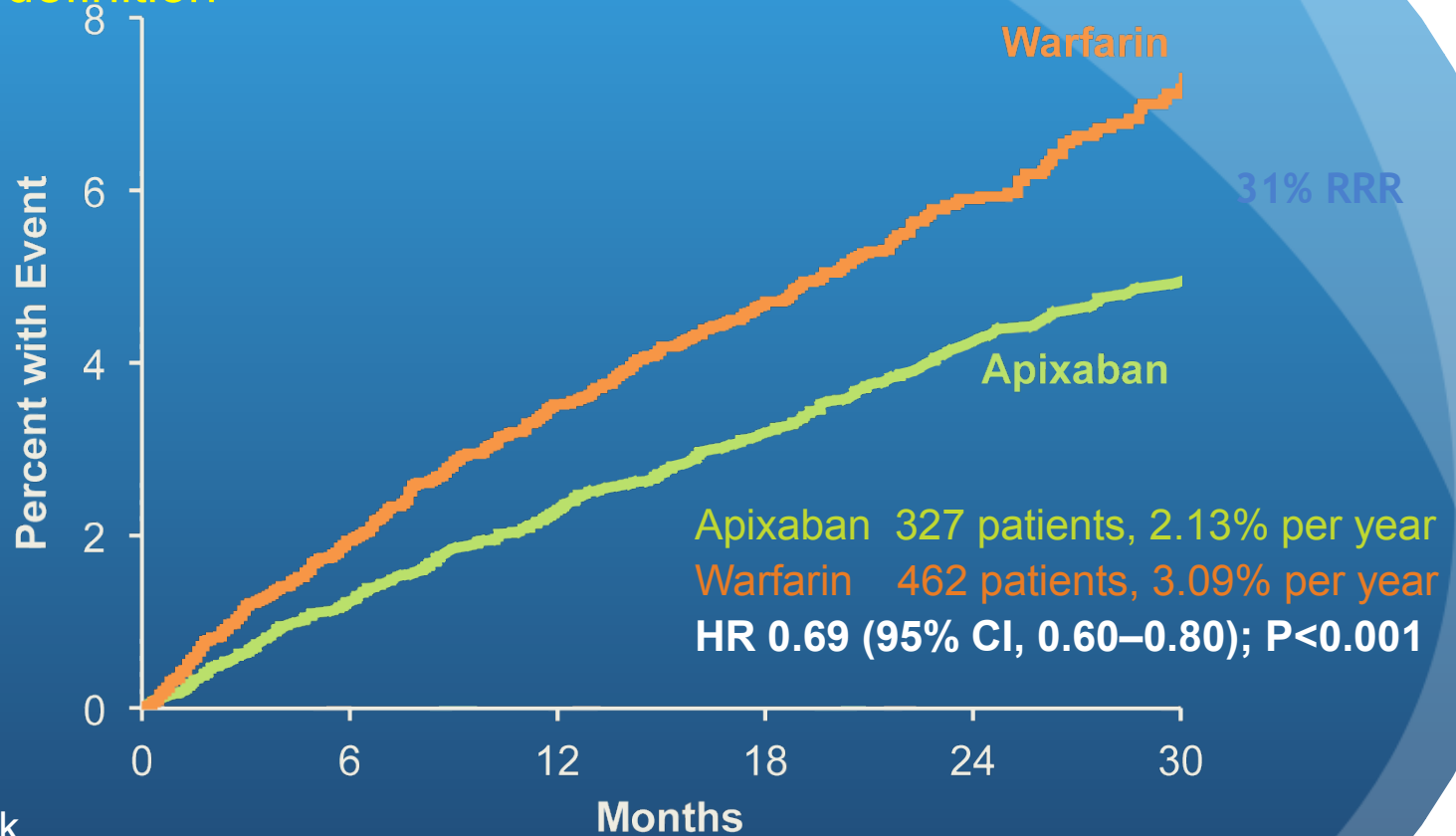


at Risk

Apixaban	9120	8726	8440	6051	3464	1754
Warfarin	9081	8620	8301	5972	3405	1768

Major Bleeding

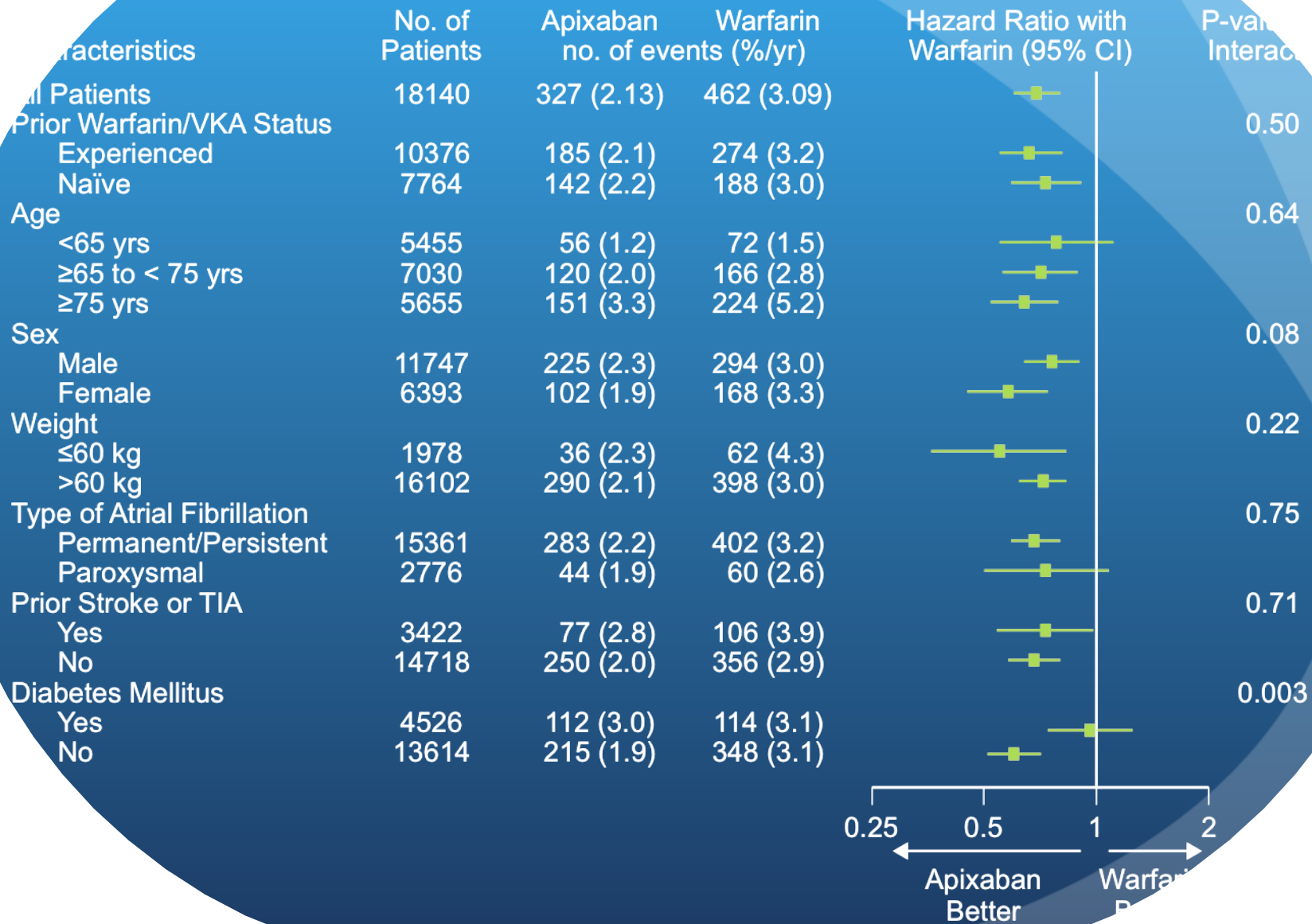
ISTH definition



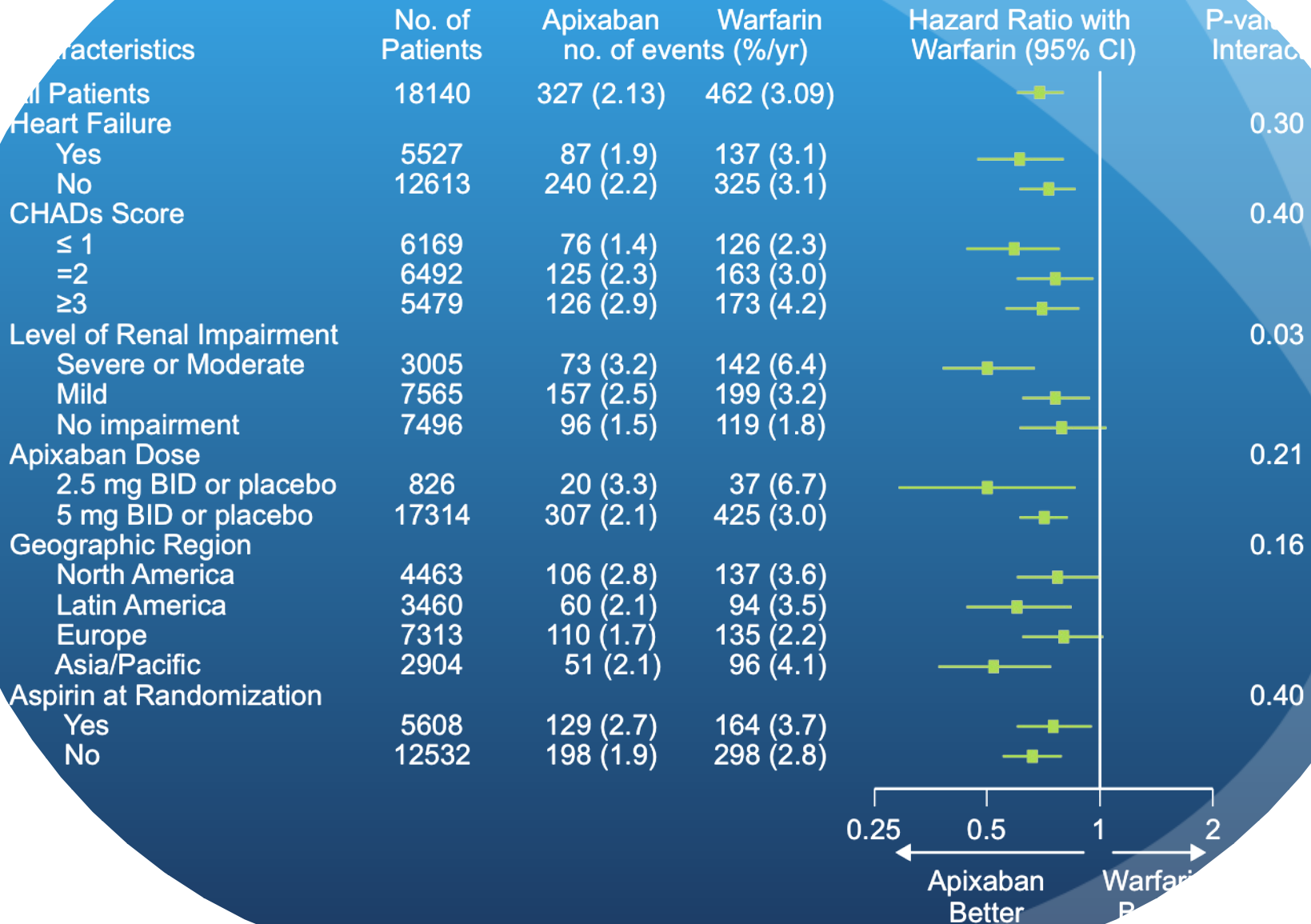
No. at Risk

Apixaban	9088	8103	7564	5365	3048	1515
Warfarin	9052	7910	7335	5196	2956	1491

Subgroups for Major Bleeding (1 of 2)



Subgroups for Major Bleeding (2 of 2)



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.

RELY Ischemic Stroke HR

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

On treatment analysis in Rocket AF Ischemic Stroke rates were 1.34% / yr for rivaroxaban and 1.20% / yr for warfarin, p=0.58. No on treatment analysis is available from RE-LY.

All Cause Mortality

RE-LY

			HR	p-value
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

95% CI 0.89 (0.80, 0.998)

N=448 events planned, 480 in trial

on treatment analysis in Rocket AF mortality rates were 1.87% / yr for rivaroxaban vs 2.14% for warfarin (p=0.073). No on treatment analysis is available from RE-LY.

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 (fatal for Rivaroxaban, major for Apixaban, major at 110 mg for Dabigatran) 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

Comparison of the 3 new OAC's

- Only Dabigatran significantly reduces both ischemic and hemorrhagic stroke whereas the Xa inhibitors superior in reducing hemorrhagic stroke and are non-inferior in reducing ischemic stroke.
- Only Apixaban showed a significant reduction in total mortality and the other 2 agents had near-significant trends.
- Only Apixaban demonstrated a significant reduction in GI bleeding whereas Dabigatran had increase in major GI bleeding (though overall less bleeding) and Rivaroxaban had non-significant reduction in GIB but less fatal bleeding.

Comparison of the 3 new OAC's (cont.)

- All 3 agents had major reductions in intracranial hemorrhage compared to warfarin (major safety benefit)
- Dabigatran has major GI intolerance (15-20%) whereas the other agents did not.
- Summary:

Most efficacious: Dabigatran

Least GI Bleeding: Apixaban

Easiest to comply: Rivaroxaban

THANK YOU

QUESTIONS???

Atrial Fibrillation Issues

1. Rate

control

VS.

Theoretical Benefit of Rhythm Control

- Improved hemodynamics
- Relief of symptoms
- Improved exercise tolerance
- Reduced risk of stroke
- Avoidance of anticoagulants

Amiodarone-overrated

Amiodarone-probably most effective but very toxic
and extremely long half-life

Dofetilide-high cost, hospitalization and high
proarrhythmia risk

The New England Journal of Medicine

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NUMBER 23



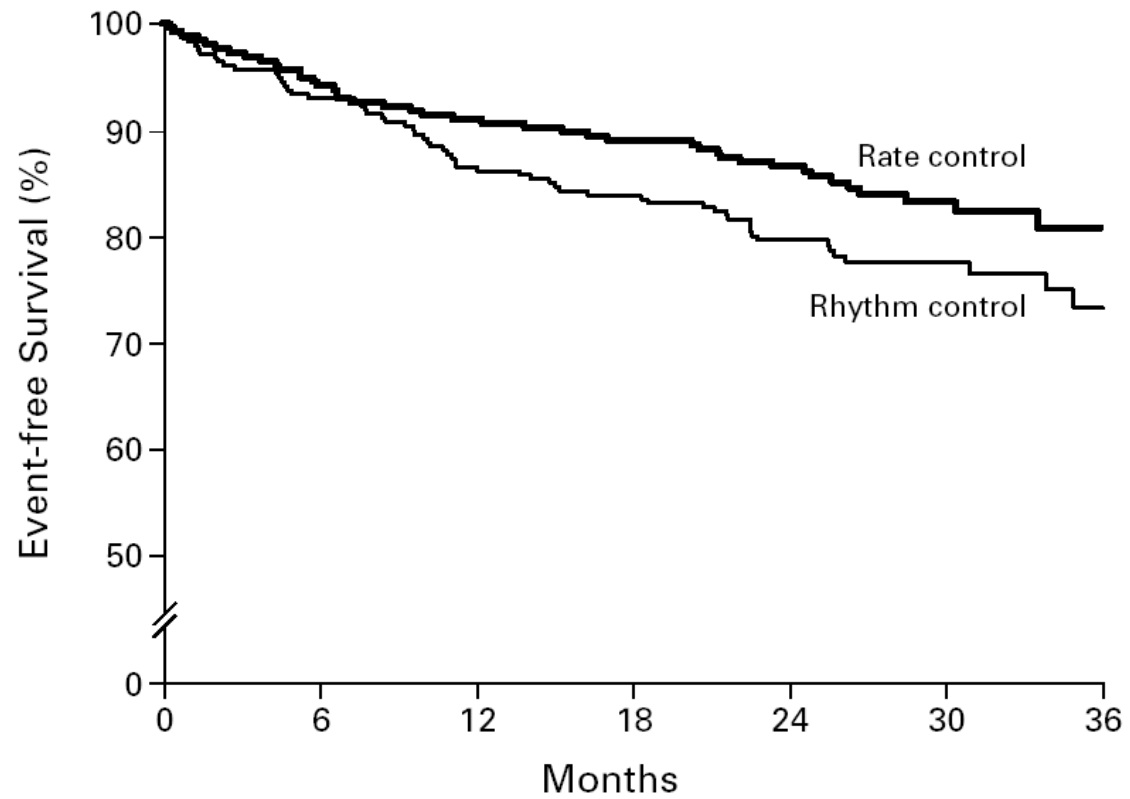
A COMPARISON OF RATE CONTROL AND RHYTHM CONTROL IN PATIENTS WITH ATRIAL FIBRILLATION

THE ATRIAL FIBRILLATION FOLLOW-UP INVESTIGATION OF RHYTHM MANAGEMENT (AFFIRM) INVESTIGATORS*

ABSTRACT

Background There are two approaches to the treatment of atrial fibrillation: one is cardioversion and treatment with antiarrhythmic drugs to maintain sinus rhythm, and the other is the use of rate-controlling drugs, allowing atrial fibrillation to persist. In both approaches, the use of anticoagulant drugs is recommended.

ATRIAL fibrillation is the most common sustained cardiac arrhythmia, yet the optimal strategy for its management remains uncertain.¹⁻⁴ During atrial fibrillation, most symptoms (but perhaps not all) are caused by a poorly controlled or irregular ventricular rate, and the associated risk of death is doubled in patients who have



No. AT RISK

Rate control	256	239	232	222	212	99	25
Rhythm control	266	243	224	218	207	85	24

Figure 2. Kaplan–Meier Curves for Event-free Survival in the Rate-Control and Rhythm-Control Groups.

AFFIRM Trial

- No survival advantage to rhythm control.
- Rhythm control patients were more likely to be hospitalized with adverse drug effects.
- Both groups had similar stroke risk (1% per yr)
 - Majority of strokes when warfarin stopped or INR subtherapeutic
 - Warfarin required long term even if sinus rhythm restored
- Proarrhythmias (Torsades, etc) , bradycardic arrest more common with rhythm control.

Why haven't trials comparing restoration of sinus rhythm (rhythm control) with rate control shown a mortality benefit with rhythm control ?

- Attempts at restoration of sinus rhythm not always successful
 - AFFIRM Trial: only 63% of “rhythm control” group were in sinus rhythm
 - Antiarrhythmics used to maintain sinus rhythm associated with a 25-50% annual failure rate.
- Long term anticoagulation not mandated in the “rhythm control” group
 - Those in afib at risk for stroke
- Medications used to maintain sinus rhythm risk of proarrhythmia and other toxicity

Suggested Approach

- **Rate control as preferred therapy**
 - Age ≥ 70 , less symptomatic, hypertension
 - Recurrent persistent atrial fibrillation
 - Previous antiarrhythmic drug failure
 - Unlikely to maintain sinus rhythm (enlarged LA)

Suggested Approach

- **Rhythm control as preferred therapy**
 - ? First episode afib
 - Reversible cause (alcohol)
 - Symptomatic patient despite rate control
 - Patient unable to take anticoagulant (falls, bleeding, noncompliance)
 - CHF precipitated or worsened by afib
 - ? Young afib patient (to avoid chronic electrical and anatomic remodeling that occurs with afib)

Rate Control

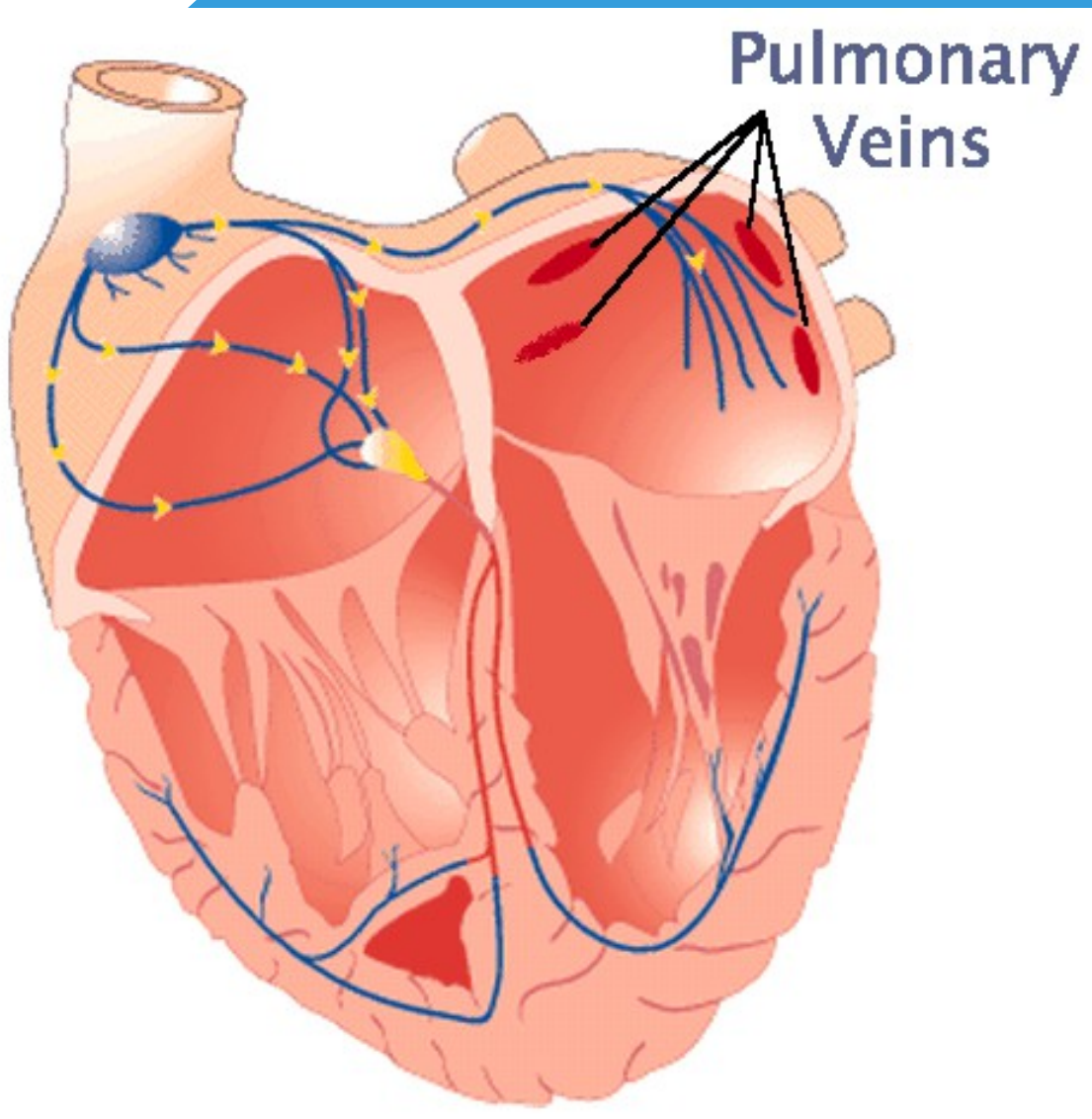
- Beta Blockers
- Calcium Channel Blockers - Diltiazem, Verapamil
- Digoxin

Rhythm Control

- Flecainide, Propafenone-No structural heart disease
- Sotalol-Mild to moderate structural heart disease but not if LVEF is <35%.
- Dofetilide-very selected patients, very expensive, proarrhythmia
- Amiodarone-failure of other agents, severe structural heart disease, frequent side effects, dose should be reduced when able.



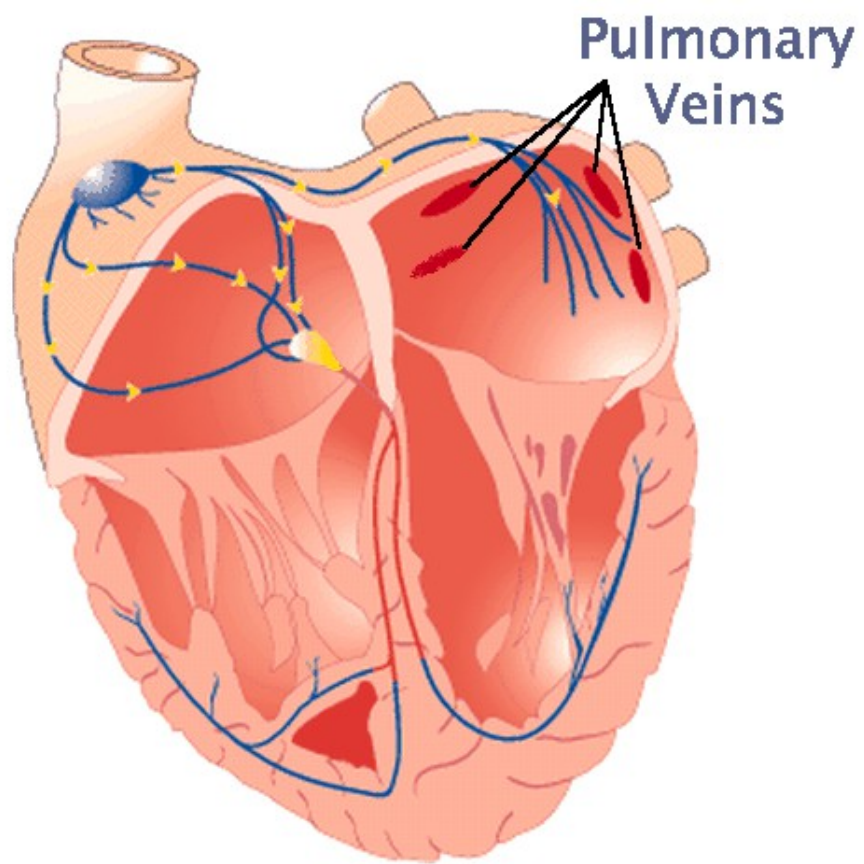
What is atrial fibrillation ablation?



Atrial fibrillation

a. Triggers
p. veins

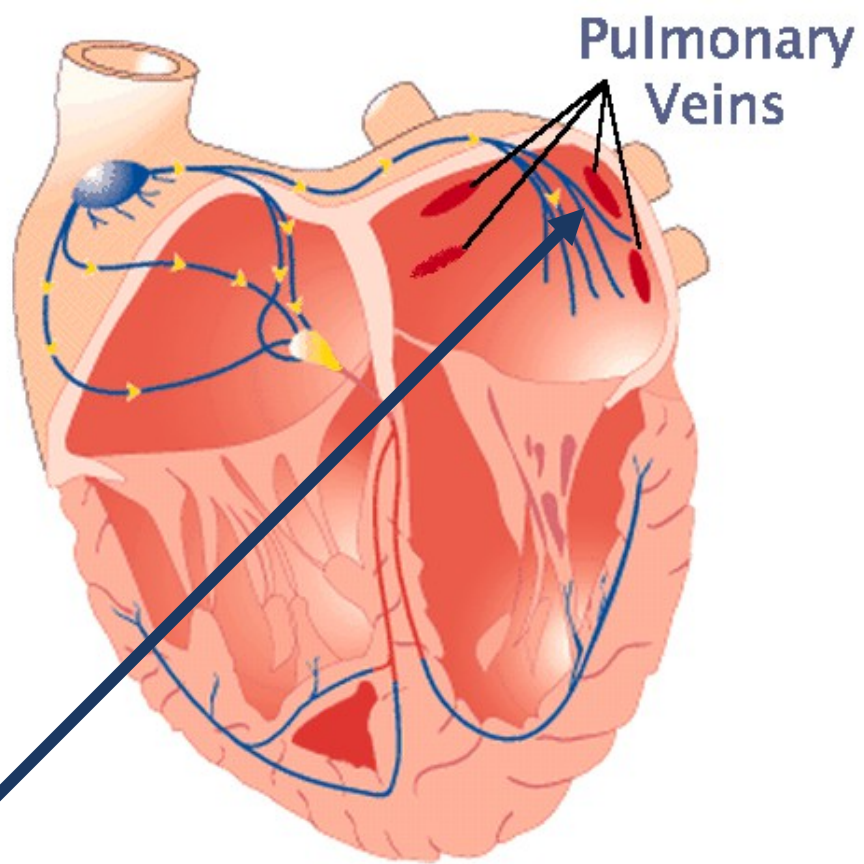
b. Sustainer
left atrium
enlarged
fibrosed



Triggering event

Substrate for perpetuation

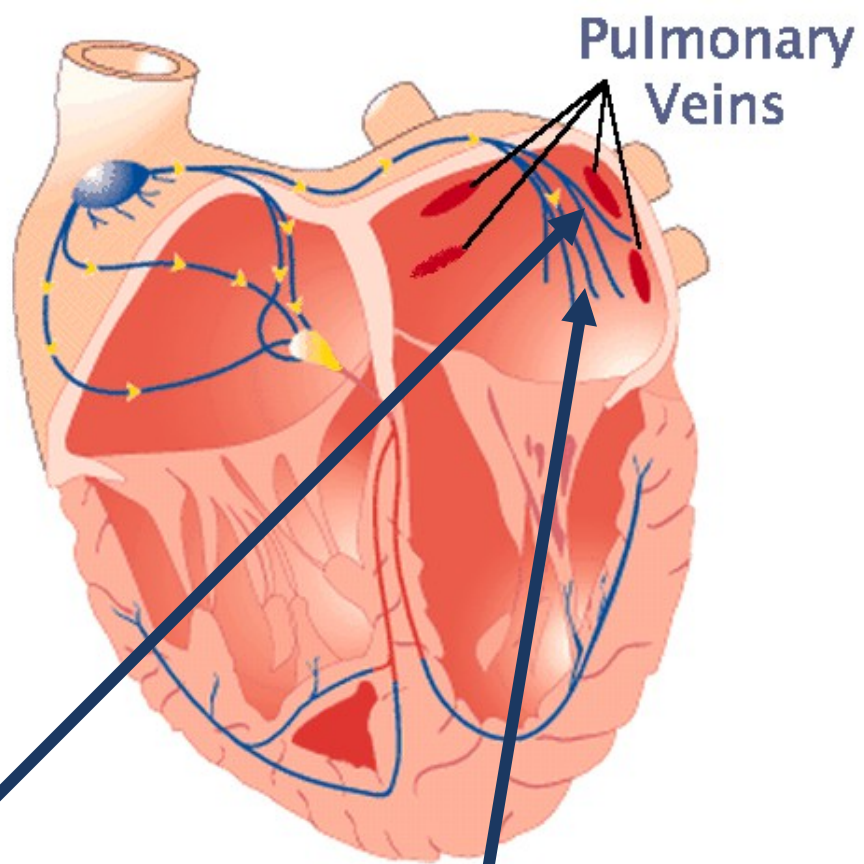




Triggering event

Substrate for perpetuation

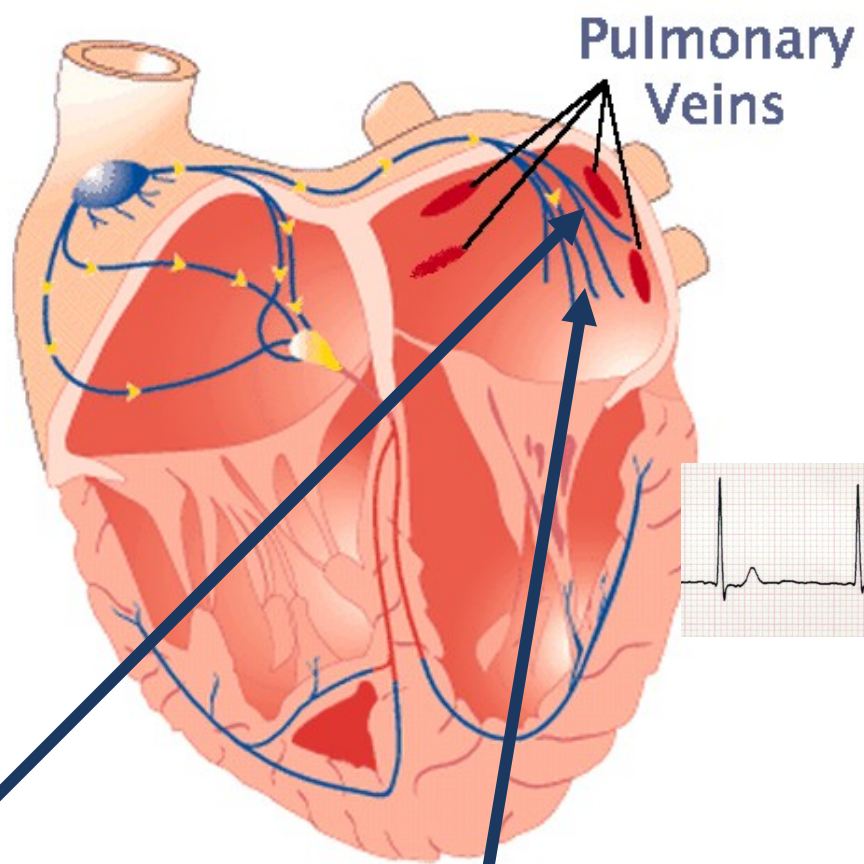




Triggering event

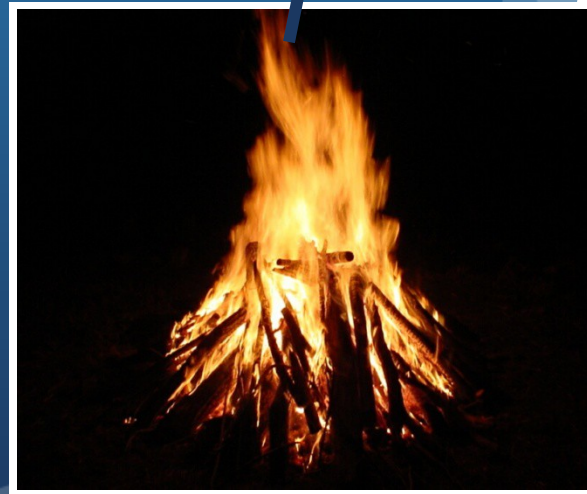
Substrate for perpetuation





Triggering event

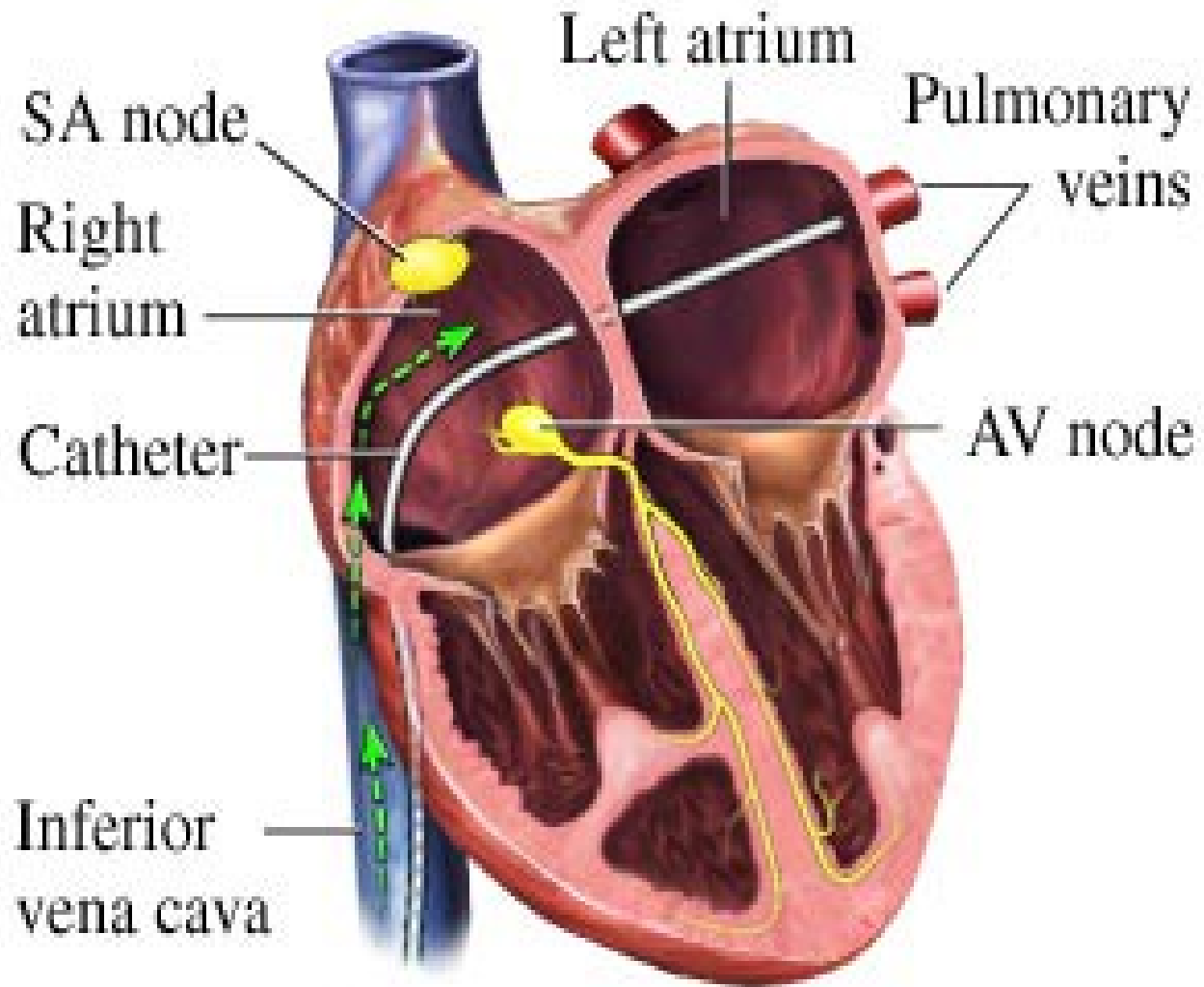
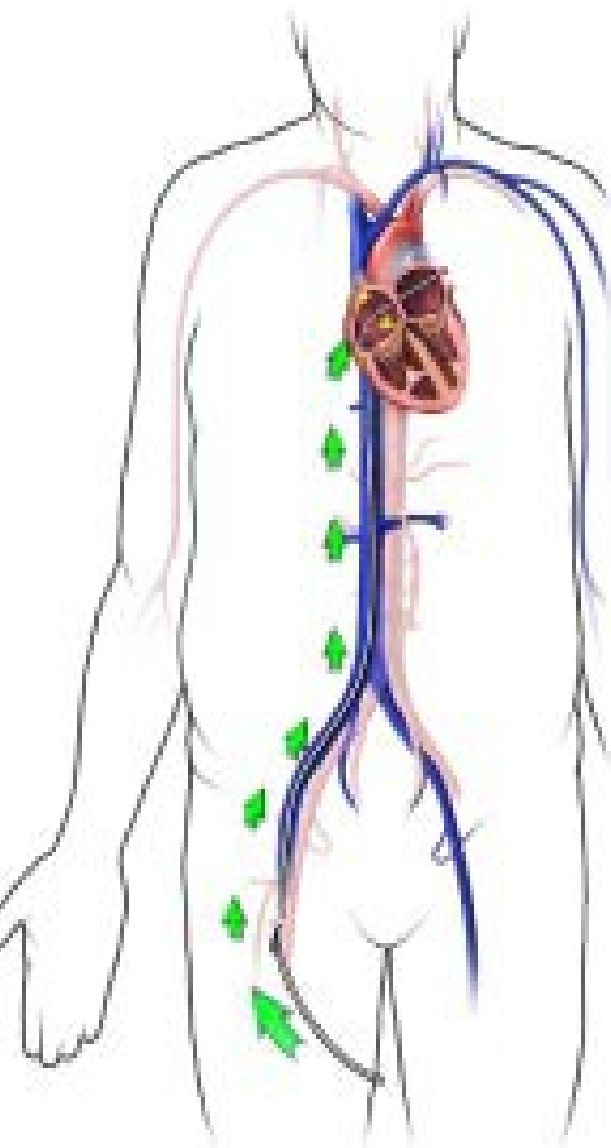
Substrate for perpetuation





Catheter Based Percutaneous Ablation

- Access to left atrium + pulmonary veins
 - Transseptal catheterization
- Localization of the pulmonary veins and left atrial substrate
 - Fluoroscopy
 - Electroanatomical
- Isolation of pulmonary veins and atrial ablation
 - Radiofrequency ablation



When to consider ablation?

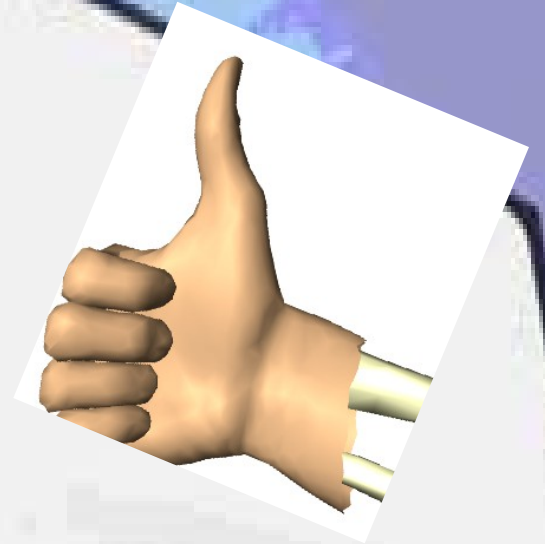
- Antiarrhythmic therapy ineffective
- Antiarrhythmic therapy not tolerated
- Symptomatic afib

Others in whom ablation may be a first strategy

- Patient very symptomatic in AF and refuses antiarrhythmic drug therapy
- Young patient whose only effective antiarrhythmic drug is amiodarone
- Patient with significant bradycardia for whom antiarrhythmic drug therapy will require pacemaker

Who does best ?

- ✓ Paroxysmal AF
- ✓ Younger (<70 years)
- ✓ Minimal structural heart disease
- ✓ Able to tolerate procedure and follow-up



ACTIVE W: Results

Trial was stopped early because of clear evidence of superiority of
OAC

	Clopidogrel + Aspirin % per Year	OAC % per Year	HR (95% CI)	<i>P</i>
Primary end point*	5.6	3.93	1.44 (1.18-1.76)	.0003
• Ischemic stroke	2.15	1.00	2.17 (1.51-3.13)	< .0001
Total mortality	3.8	3.76	1.01 (0.81-1.26)	.91
Hemorrhage (total)	15.4	13.21	1.21 (1.08-1.35)	.001

*Composite of stroke, non-CNS embolus, MI, vascular death

ACTIVE W: Results Stratified by CHADS₂ Score

CHADS ₂ Score	% Patients	Clopidogrel + Aspirin Stroke Rate per 100 Pt-yrs	OAC Stroke Rate per 100 Pt-yrs	RR
0	3	1.9	0.8	3.02
1	36	1.21	0.4	3.11
2	34	1.93	1.86	1.04
3	17	2.79	1.72	1.62
4	7	6.73	3.25	2.07
5	3	11.65	2.69	7.01
6	.4	0	0	N/A

ACTIVE A: Results

	Clopidogrel + Aspirin % per Year	Aspirin % per Year	HR (95% CI)	<i>P</i>
Primary end point*	6.8	7.6	0.89 (0.81-0.98)	.01
• Ischemic stroke	1.9	2.8	0.68 (0.57-0.80)	–
Death (any cause)	6.4	6.6	0.98 (0.89-1.08)	.69
Major bleeding	2.0	1.3	1.57 (1.29-1.92)	< .001

*Composite of stroke, MI, non-CNS embolism, vascular death

CHA₂DS₂-VASc Score

CHA₂DS₂-VASc Score

C	Congestive heart failure	1
H	Hypertension	1
A	Age ≥ 75 years	2
D	Diabetes mellitus	1
S	Stroke (or TIA)	2
V	Vascular disease*	1
A	Age 66-74 years	1
Sc	Sex category (female)	1

* Prior MI, peripheral artery disease, aortic plaque

HAS-BLED Score

	Clinical Characteristic	Score
H	Hypertension	1
A	Abnormal renal or liver function (1 each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INR	1
E	Elderly age	1
D	Drugs or alcohol (1 each)	1 or 2
Maximum Score		9

Hypertension, SBP > 160 mmHg; Abnormal renal function: chronic dialysis, renal transplant, serum creatinine \geq 200 μ mol/L; Abnormal liver function: chronic hepatitis, bilirubin > 2x upper limit of normal (ULN) in association with AST/ALT/ALP > 3 x ULN; Bleeding, previous history, predisposition; Labile INRs, unstable/high INRs in therapeutic range < 60%; Age > 65 years; Drugs/alcohol: concomitant use of antiplatelet agents, NSAIDs, etc.

Rates of Intracranial Bleeding

ARISTOTLE^a	Apixaban (n = 9088)		Warfarin (n = 9052)	P Value
%/y	0.33		0.80	< .001
RE-LY^b	Dabigatran 110 mg (n = 6015)	Dabigatran 150 mg (n = 6076)	Warfarin (n = 6022)	
Rate/y, %	0.2	0.3	0.7	< .001
ROCKET AF^c	Rivaroxaban (n = 7111)		Warfarin (n = 7125)	
%	0.8		1.2	.02

a. Granger CB, et al.^[9]

b. Connolly SJ, et al.^[10]

c. Patel MR, et al.^[11]

AVERROES

Outcome	Apixaban	Aspirin	Apixaban vs Aspirin	
	Annual Rate	Annual Rate	HR (95% CI)	P Value
Stroke or systemic embolism	1.6	3.7	0.45 (0.32-0.62)	< .001
Stroke	1.6	3.4	0.46 (0.33-0.65)	< .001
• Ischemic	1.1	3.0	0.37 (0.25-0.55)	< .001
• Systemic embolism	0.1	0.4	0.15 (0.03-0.69)	.01
Major bleeding	1.4	1.2	1.13 (0.74-1.75)	.57

Cardioembolic Stroke Prevention

- Case Definition
- Impact of atrial fibrillation
- Oral anticoagulation trials
- Risk Stratification schemes
- Evidence-based recommendations for Cardioembolic Stroke Risk Factors

Ischemic Stroke Case

78 yo RH woman with sudden difficulty speaking and R arm drift

rior history of palpitations

Past medical history: hypertension, diabetes

Exam:

- Irregularly irregular heart rate
- Wernicke's type aphasia and mild R hemiparesis

CT

- Wedge-shaped lucency in the L temporal parietal cortex

EKG

- Atrial fibrillation

Cardiac Embolism

Cerebral Infarction

Syndrome • Hemispherical

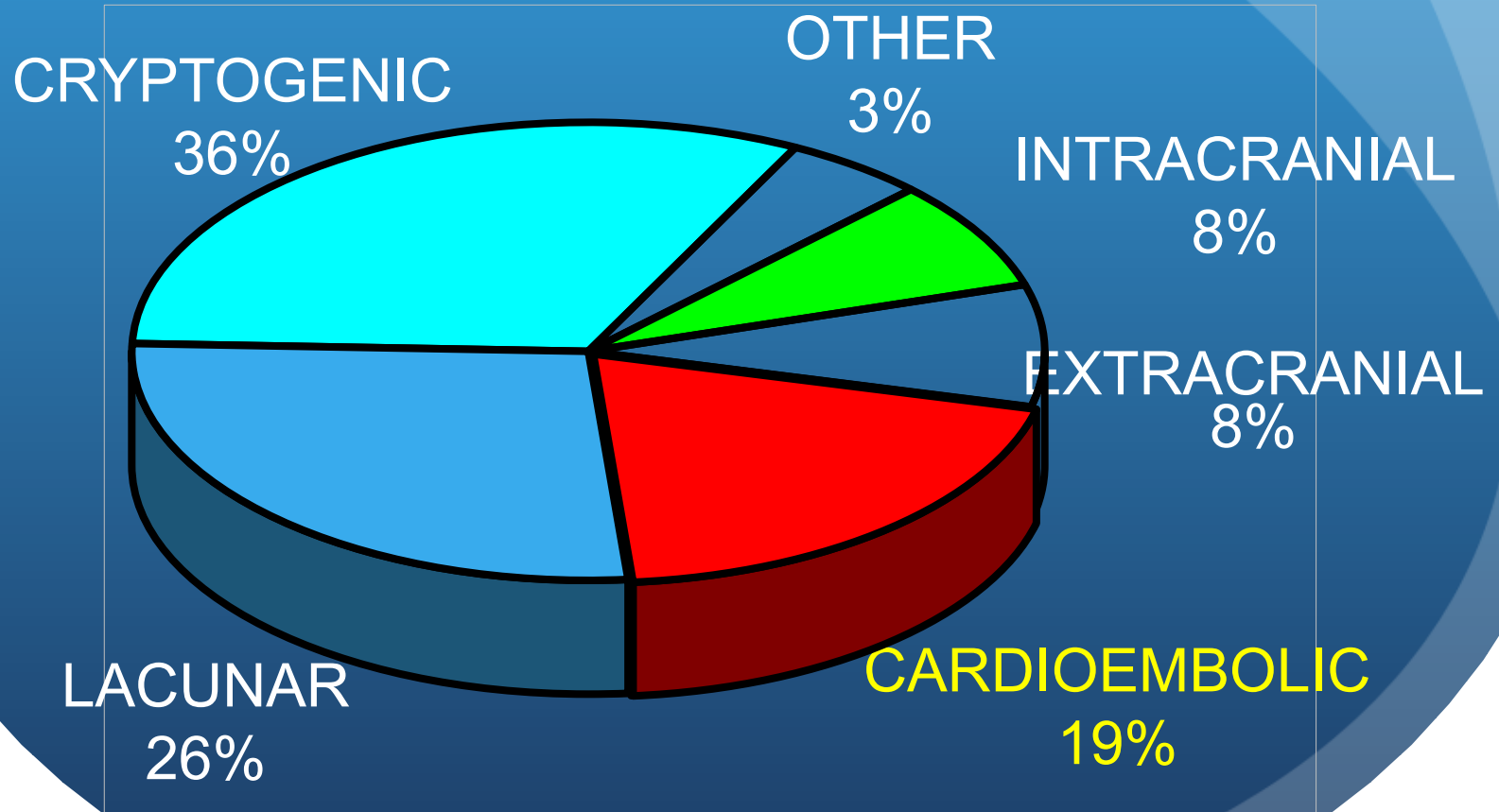
Brain Image • Bland or hemorrhagic infarction of single surface branch or combination

Vascular • Occlusion or retrograde collateral or normal vessel

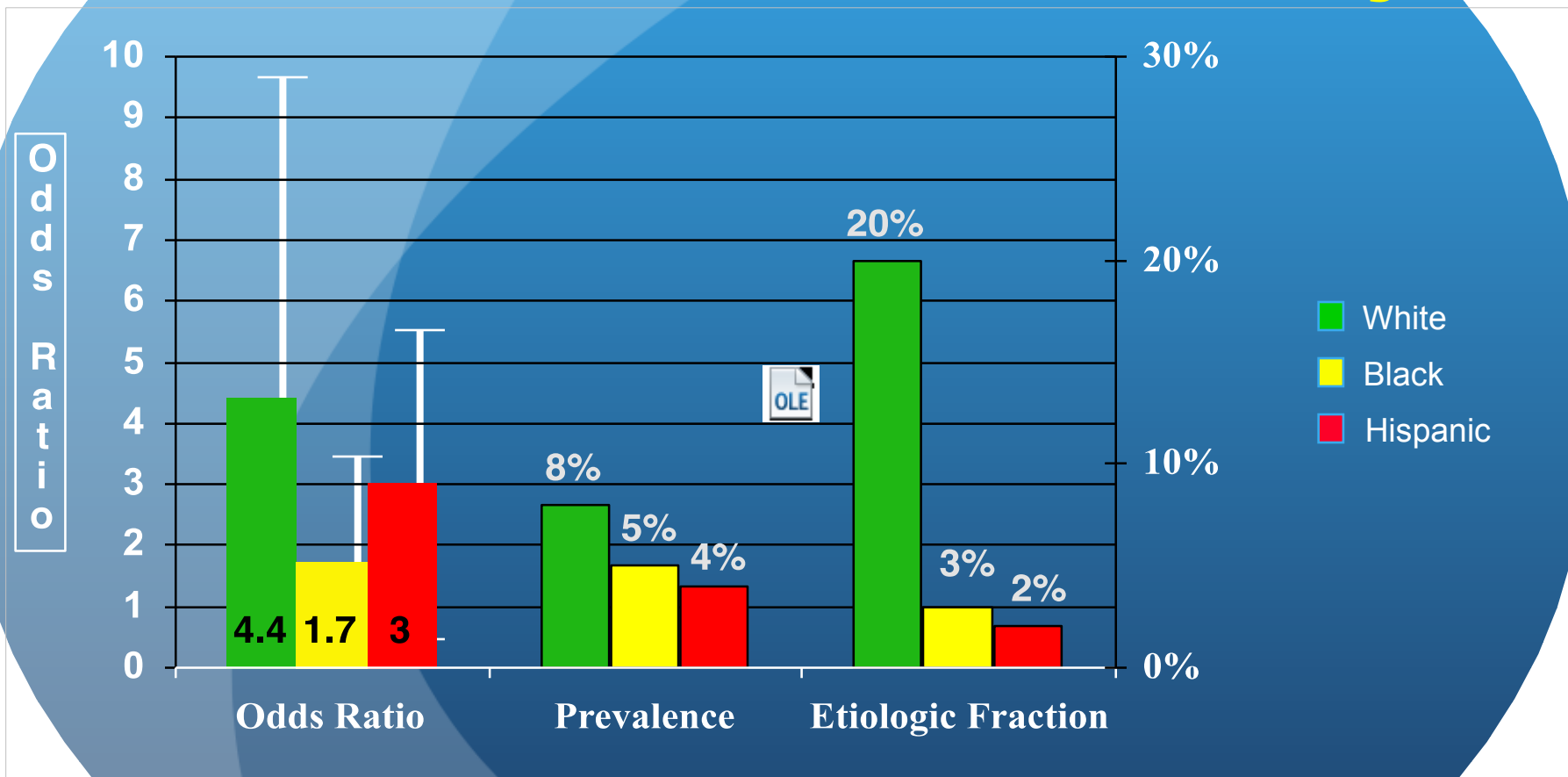
Cardiac

- Atrial fibrillation
- Valvular disease
- Intracardiac thrombus
- Recent MI
- Cardiomyopathy
- Atrial myxoma

MANHATTAN STROKE STUDY
Ischemic Stroke Subtypes (n=992)



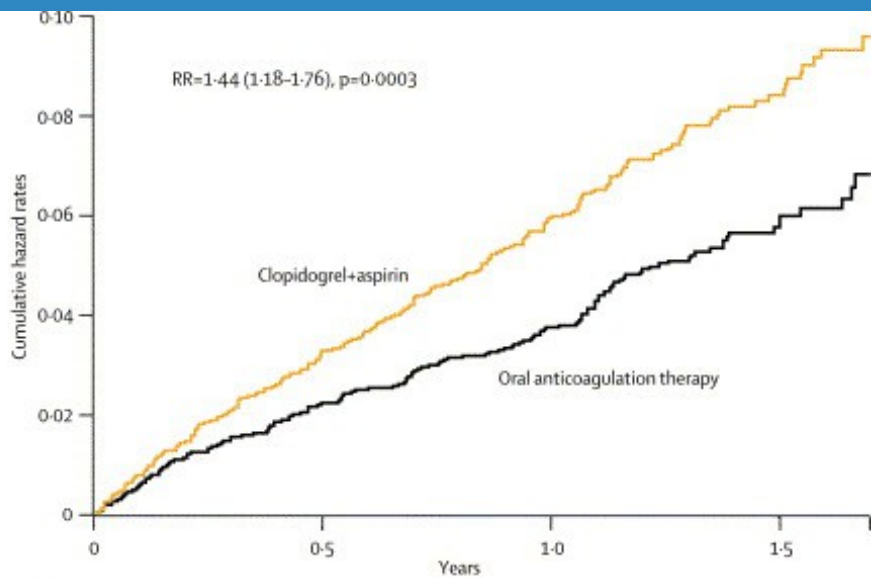
Atrial Fibrillation: Etiologic Fraction Northern Manhattan Stroke Study



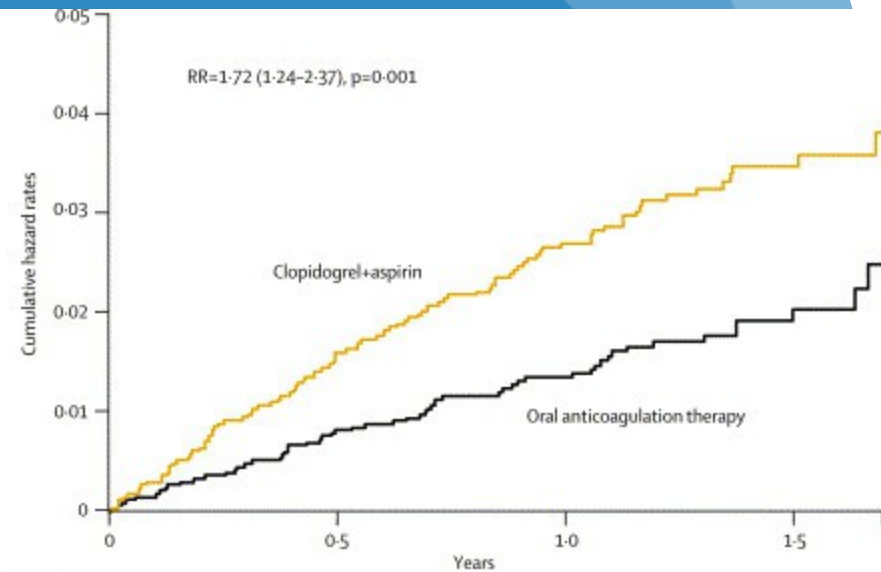
Matched for age and gender and adjusted for HTN, DM, CAD, no physical activity, and education.

Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial

The ACTIVE Writing Group on behalf of the ACTIVE Investigators*



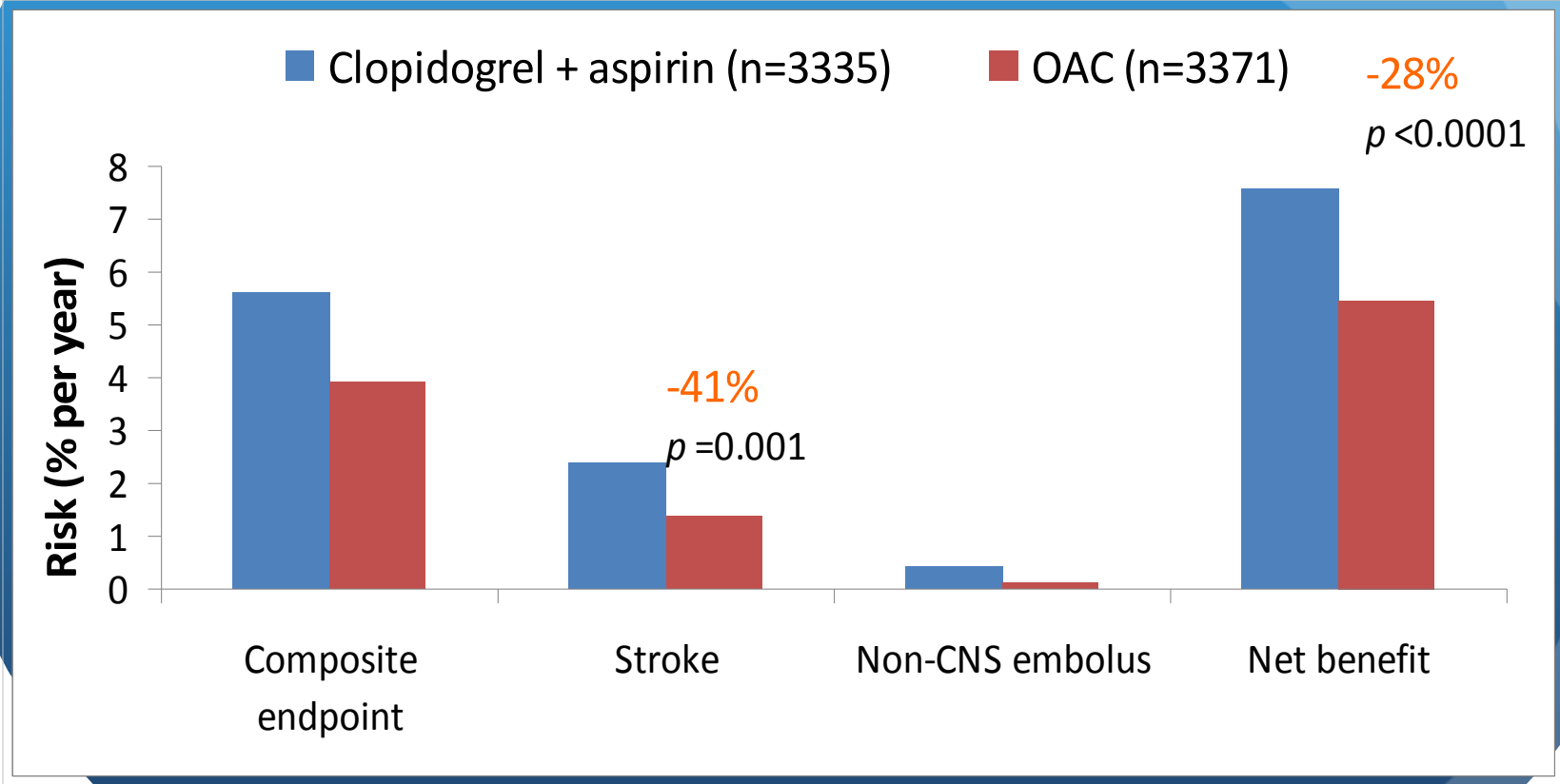
Number at risk	0	0.5	1.0	1.5
Clopidogrel + aspirin	3335	3152	2389	927
Oral anticoagulation therapy	3371	3221	2458	924



Number at risk	0	0.5	1.0	1.5
Clopidogrel + aspirin	3335	3168	2419	941
Oral anticoagulation therapy	3371	3232	2466	930

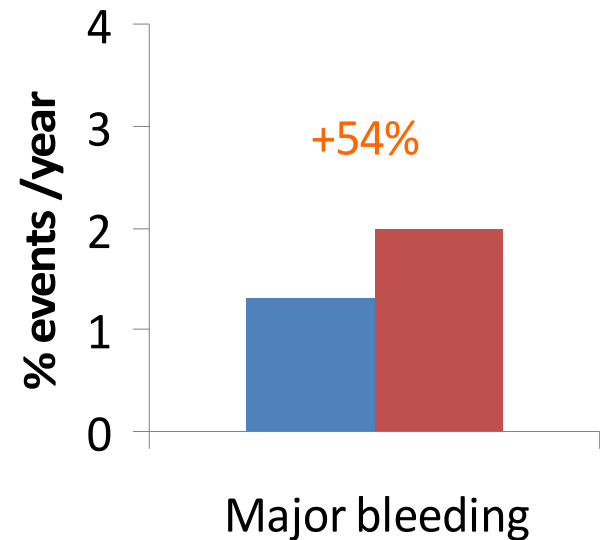
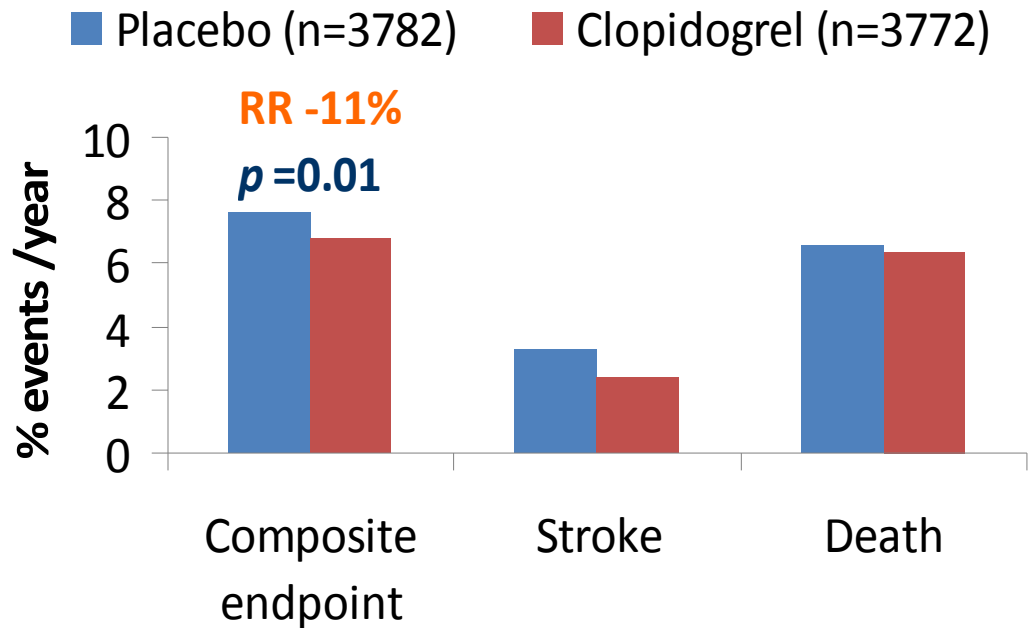
ACTIVE W: Superiority of Warfarin compared to CP+ASA

Stopped early after median follow-up 1.28 years



Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial

ACTIVE-A: Clopidogrel + ASA versus Aspirin in AF patients



Significant reduction by clopidogrel + aspirin versus aspirin alone is primarily due to reduction in stroke (no or only weak differential treatment effects for subgroups)
Median follow-up of 3.6 years

Selection of Antithrombotic Therapy in AF by Risk Strata

Risk Strata

Risk Factors

Very High Any Age + Prior stroke/TIA or embolism

> 75 + HTN or poor LV function

High

> 75

< 75 + HTN or poor LV function

Low-Mod

65-75 yrs, Diabetes,

CAD w preserved LV systolic f

Straus et al. JAMA 2002;288:1388-1395

AHA/ASA Evidence-based Guidelines

AHA/ASA Guideline

EMBARGOED FOR 3 PM CT/4 PM ET, THURSDAY, OCT 21, 2010

Guidelines for the Prevention of Stroke in Patients With Stroke or Transient Ischemic Attack

A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

The American Academy of Neurology Affirms the Value of This Guideline as an Educational Tool for Neurologists

The American Association of Neurological Surgeons and Congress of Neurological Surgeons Have Reviewed This Document and Affirm its Educational Content

Karen L. Furie, MD, MPH, FAHA, Chair; Scott E. Kasner, MD, MSCE, FAHA, Vice Chair; Robert J. Adams, MD, MS, FAHA; Gregory W. Albers, MD; Ruth L. Bush, MD, MPH; Susan C. Fagan, PharmD, FAHA; Jonathan L. Halperin, MD, FAHA; S. Claiborne Johnston, MD, PhD; Irene Katzan, MD, MS, FAHA; Walter N. Kernan, MD; Pamela H. Mitchell, PhD, CNRN, RN, FAAN, FAHA; Bruce Ovbiagele, MD, MS, FAHA; Yuko Y. Palesch, PhD; Ralph L. Sacco, MD, MS, FAHA, FAAN; Lee H. Schwamm, MD, FAHA; Sylvia Wassertheil-Smoller, MD, PhD, FAHA; Tanya N. Turan, MD, FAHA; Deidre Wentworth, MSN, RN; on behalf of the American Heart Association Stroke Council; Council on Cardiovascular Nursing; Council on Clinical Cardiology; and Interdisciplinary Council on Quality of Care and Outcomes Research

Recommendations for Patients With Cardioembolic Stroke Types

Risk Factor – Atrial Fibrillation	Class/ LOE
For patients with ischemic stroke or TIA	
With paroxysmal (intermittent) or permanent AF, anticoagulation with a vitamin K antagonist (target INR 2.5; range, 2.0 to 3.0) is recommended.	Class I; LOE A
Unable to take oral anticoagulants, aspirin alone. The combination of clopidogrel plus aspirin carries a risk of bleeding similar to that of warfarin and therefore is not recommended for patients with a hemorrhagic contraindication to warfarin.	Class I; LOE A Class III; LOE B New Rec
High risk for stroke (stroke/TIA < 3 months, CHADS2 \geq 5, mechanical valve or rheumatic valve disease) who require temporary interruption of oral anticoagulation, bridging therapy with an LMWH administered SQ is reasonable.	Class IIa; LOE C New Rec

MI and LV Thrombus

- In the absence of acute reperfusion therapy, intracardiac thrombi occurs in about 1/3 of patients in the first 2 weeks after anterior MI and in higher rates in those with large infarcts.
- Cerebral infarcts occur in about 10% of patients with LV thrombus in the absence of anticoagulation.
- Ventricular mural thrombi occur in patients with chronic ventricular dysfunction resulting from CAD, hypertension, or other dilated cardiomyopathy.
- These are at persistent risk of stroke and systemic embolism whether or not AF is documented.

Recommendations for Patients With Cardioembolic Stroke Types

Risk Factor – Acute MI and LV thrombus	Class/ LOE
Patients with ischemic stroke or TIA in the setting of acute MI complicated by LV mural thrombus formation identified by echocardiography or another cardiac imaging technique should be treated with oral anticoagulation (target INR 2.5; range 2.0 to 3.0) for at least 3 months	Class I; LOE B

Cardiomyopathy

- 40% of patients with ischemic stroke have an LVEF $\leq 30\%$.
- Optimal stroke prevention in certain conditions is not clear.
- The Warfarin and Antiplatelet Therapy in Chronic Heart Failure trial (WATCH) - terminated without adequate power to define the effect of warfarin compared with aspirin or clopidogrel on stroke.
- The ongoing Warfarin vs. Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) is designed to compare the efficacy of warfarin (INR 2.5-3.0) and aspirin (325mg daily) .
- Composite endpoint of death or stroke (ischemic or hemorrhagic) in patients with LVEF $< 35\%$ without documented AF, mechanical heart valves, or other indications for anticoagulant therapy.

Recommendations for Patients With Cardioembolic Stroke Types

Risk Factor – Cardiomyopathy	Class/ LOE
In patients with prior stroke or TIA in sinus rhythm who have cardiomyopathy characterized by systolic dysfunction (LVEF \leq 35%), the benefit of warfarin has not been established.	Class IIb; LOE B New REC
Warfarin (INR 2.0 to 3.0), aspirin (81 mg daily), clopidogrel (75 mg daily), or the combination of aspirin (25 mg twice daily) plus extended-release dipyridamole (200 mg twice daily) may be considered to prevent recurrent ischemic events in patients with previous ischemic stroke or TIA and cardiomyopathy.	Class IIb; LOE B

Recommendations for Patients With Cardioembolic Stroke Types

Risk Factor – Native Valvular Heart Disease For patients with ischemic stroke or TIA	Class /LOE
Rheumatic mitral valve disease, whether or not AF is present - long-term warfarin therapy is reasonable with an INR target range of 2.5 (range, 2.0 to 3.0).	Class IIa; LOE C
To avoid additional bleeding risk, antiplatelet agents should not be routinely added to warfarin.	Class III; LOE C
Native aortic or nonrheumatic mitral valve disease who do not have AF - antiplatelet therapy may be reasonable.	Class IIb; LOE C
Mitral annular calcification - antiplatelet therapy may be considered.	Class IIb; LOE C
MVP - long-term antiplatelet therapy may be considered.	Class IIb; LOE C

Recommendations for Patients With Cardioembolic Stroke Types

Risk Factor – Prosthetic Heart Valves For patients with ischemic stroke or TIA	Class/ LOE
Mechanical prosthetic heart valves, warfarin is recommended with an INR target of 3.0 (range, 2.5 to 3.5).	Class I; LOE B
Mechanical prosthetic heart valves who have an ischemic stroke or systemic embolism despite adequate therapy with oral anticoagulants, aspirin 75 mg/d to 100 mg/d in addition to oral anticoagulants and maintenance of the INR at a target of 3.0 (range, 2.5 to 3.5) is reasonable if the patient is not at high bleeding risk (e.g., history of hemorrhage, varices, or other known vascular anomalies conveying increased risk of hemorrhage, coagulopathy).	Class IIa; LOE B
Bioprosthetic heart valves with no other source of thromboembolism, anticoagulation with warfarin (INR 2.0 to 3.0) may be considered.	Class IIb; LOE C

...illation; INR, international normalized ratio; LMWH, low-molecular-weight heparin; LV, left ventricular
...: MVP, mitral valve prolapse; and TIA, transient ischemic attack.

... of class and level of evidence

Management of Cardioembolic Stroke

- CEMB stroke patients have a high risk of stroke recurrence and greater mortality
- Warfarin is effective for stroke prevention in patients with AF who have had a stroke or TIA and in high-risk AF patients
- Efficacy of antiplatelets for prevention of cardioembolic stroke is less than warfarin
- Newer and better drugs are available and being tested to reduce stroke risk in AF

Pr Brilliation Update 2035

11.4 million



Philadelphia 1.5 million

San Francisco 700,000

Boston 600,000



Houston 2 million

Los Angeles 3.8 million

Chicago 2.8 million

AFFIRM : 5 Year Outcomes

<u>Survival</u>	<u>Rhythm Control</u>	<u>Rate Control</u>
1 year	96%	96%
3 year	87%	89%
5 year	76%	79%

p = 0.058

NO Difference : death, disabling stroke, major bleed, or cardiac arrest

Sinus rhythm maintained in only 63% of rhythm control group

ACCF/AHA/HRS Focused Update

2011 ACCF/AHA/HRS Focused Update on the Management of Patients With Atrial Fibrillation (Updating the 2006 Guideline) A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

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ORIGINAL ARTICLE

Lenient versus Strict Rate Control in Patients with Atrial Fibrillation

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ABSTRACT

BACKGROUND

Rate control is often the therapy of choice for atrial fibrillation. Guidelines recommend strict rate control, but this is not based on clinical evidence. We hypothesized that lenient rate control is not inferior to strict rate control for preventing cardiovascular morbidity and mortality in patients with permanent atrial fibrillation.

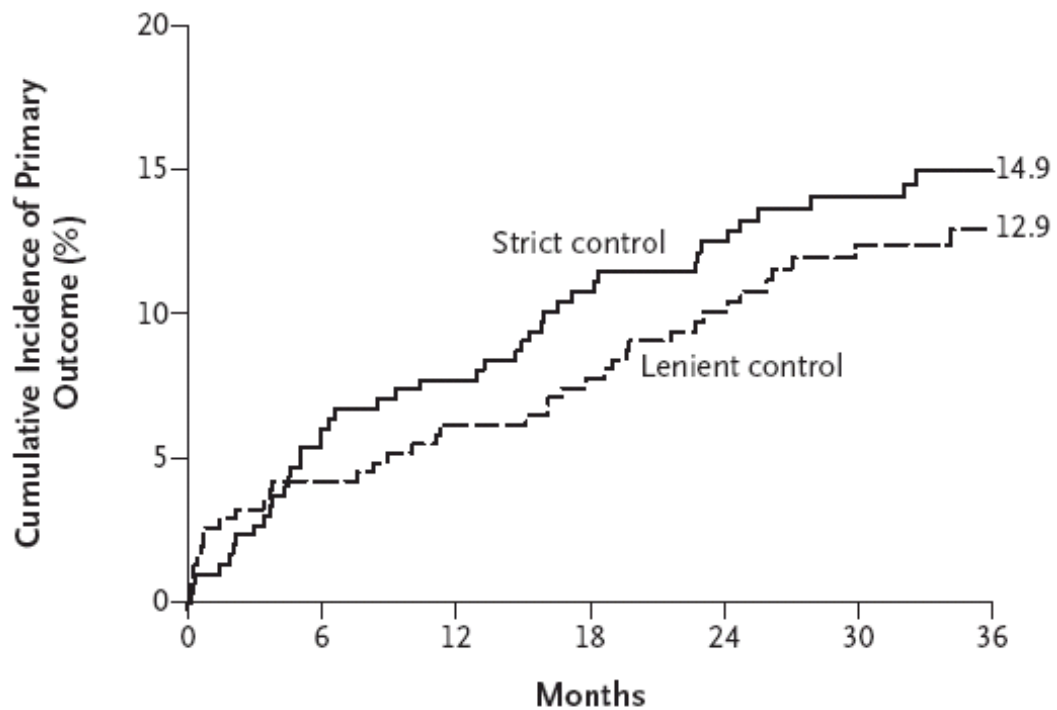
METHODS

We randomly assigned 614 patients with permanent atrial fibrillation to undergo a lenient rate-control strategy (resting heart rate <110 beats per minute) or a strict rate-control strategy (resting heart rate <80 beats per minute and heart rate during moderate exercise <110 beats per minute). The primary outcome was a composite of death from cardiovascular causes, hospitalization for heart failure, and stroke, systemic embolism, bleeding, and life-threatening arrhythmic events. The duration of follow-up was at least 2 years, with a maximum of 3 years.

Lenient
Hr < 110 bpm

Strict
Rest hr < 80
Mod exerc hr < 110

From the Department of Cardiology (I.C.V.G., H.F.G., H.L.H., D.J.V.V., M.P.V.B.) and the Trial Coordination Center, Department of Epidemiology (H.L.H., J.A.B.-K.), University Medical Center Groningen, University of Groningen, Groningen; the Interuniversity Cardiology Institute of the Netherlands, Utrecht (I.C.V.G.); Maastricht University Medical Center, Maastricht (H.J.G.M.C.); Deventer Hospital, Deventer (Y.S.T.); Academic Medical Center, University of Amsterdam (J.G.P.T.), and VU University Medical Center (O.K.) — both in Amsterdam; Amphibia Hospital, Breda (A.M.A.); Medical Center, Alkmaar (J.H.C.); Kennemer Hospital, Haarlem (R.T.); and Rijnstate Hospital, Arnhem (H.A.B.) — all in the Netherlands. Address correspondence to Dr. Van Gelder



No. at Risk							
Strict control	303	282	273	262	246	212	131
Lenient control	311	298	290	285	255	218	138

Figure 2. Kaplan–Meier Estimates of the Cumulative Incidence of the Primary Outcome, According to Treatment Group. The numbers at the end of the Kaplan–Meier curves are the estimated cumulative incidence of the primary outcome at 3 years.

Primary Outcomes

- Cardiac death
- CHF
- Stroke
- Systemic embolism
- Major bleed
- Syncope
- Sust VT
- Cardiac arrest
- Life threat compl of antiarrhythmic
- Pacemaker

Secondary Outcomes

- Symptoms

ORIGINAL ARTICLE

Lenient versus Strict Rate Control in Patients with Atrial Fibrillation

Isabelle C. Van Gelder, M.D., Hessel F. Groenveld, M.D., Harry J.G.M. Crijns, M.D., Ype S. Tuininga, M.D., Jan G.P. Tijssen, Ph.D., A. Marco Alings, M.D., Hans L. Hillege, M.D., Johanna A. Bergsma-Kadijk, M.Sc., Jan H. Cornel, M.D., Otto Kamp, M.D., Raymond Tukkie, M.D., Hans A. Bosker, M.D., Dirk J. Van Veldhuisen, M.D., and Maarten P. Van den Berg, M.D., for the RACE II Investigators*

ABSTRACT

BACKGROUND

Rate control is often the therapy of choice for atrial fibrillation. Guidelines recommend strict rate control, but this is not based on clinical evidence. We hypothesized that lenient rate control is not inferior to strict rate control for preventing cardiovascular morbidity and mortality in patients with permanent atrial fibrillation.

METHODS

We randomly assigned 614 patients with permanent atrial fibrillation to undergo a lenient rate-control strategy (resting heart rate <110 beats per minute) or a strict rate-control strategy (resting heart rate <80 beats per minute and heart rate during moderate exercise <110 beats per minute). The primary outcome was a composite of death from cardiovascular causes, hospitalization for heart failure, and stroke, systemic embolism, bleeding, and life-threatening arrhythmic events. The duration of follow-up was at least 2 years, with a maximum of 3 years.

Lenient
Hr < 110 bpm

Strict
Rest hr < 80
Mod exerc hr < 110

**Most patients in Lenient
HR < 100**

From the Department of Cardiology (I.C.V.G., H.F.G., H.L.H., D.J.V.V., M.P.V.B.) and the Trial Coordination Center, Department of Epidemiology (H.L.H., J.A.B.-K.), University Medical Center Groningen, University of Groningen, Groningen; the Interuniversity Cardiology Institute of the Netherlands, Utrecht (I.C.V.G.); Maastricht University Medical Center, Maastricht (H.J.G.M.C.); Deventer Hospital, Deventer (Y.S.T.); Academic Medical Center, University of Amsterdam (J.G.P.T.), and VU University Medical Center (O.K.) — both in Amsterdam; Amphibia Hospital, Breda (A.M.A.); Medical Center, Alkmaar (J.H.C.); Kennemer Hospital, Haarlem (R.T.); and Rijnstate Hospital, Arnhem (H.A.B.) — all in the Netherlands. Address correspondence to Dr. Van Gelder

Rate Control Options

- Beta blocker
 - Avoid carvedilol-less effective in AV node blockade
 - Calcium channel blocker
 - Verapamil, diltiazem
- Digoxin
 - Not as the sole agent
- Amiodarone
 - In refractory cases when other approaches fail
 - Only when other drugs ineffective
- Dronedarone
 - Less effective than amiodarone
 - Increased mortality in heart failure
- AV junction ablation plus pacemaker

How do we determine stroke risk ?

- **CHADS2 (Gage, et al.: JAMA 2001)**

- Congestive heart failure - 1pt

- Hypertension - 1pt

- Age > 75 - 1 pt

- Diabetes - 1pt

- Stroke or TIA - 2 pts

- 0 points – low risk (1.2-3.0 strokes per 100 patient years)

- 1-2 pts – moderate risk (2.8-4.0 strokes per 100 patient years)

How do we determine stroke risk?

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 - **Congestive heart failure - 1pt**
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 - **Age > 75 - 1 pt**
 - **Diabetes - 1pt**
 - **Stroke or TIA - 2 pts**
- **0 points – low risk** (1.2-3.0 strokes per 100 patient years)
- **1-2 points – moderate risk** (2.8-4.0 strokes per 100 patient years)
- **3 points – high risk** (5.9-18.2 strokes per 100 patient years)

Table 2—The 2009 Birmingham Schema Expressed as a Point-Based Scoring System, With the Acronym CHA_2DS_2-VASc

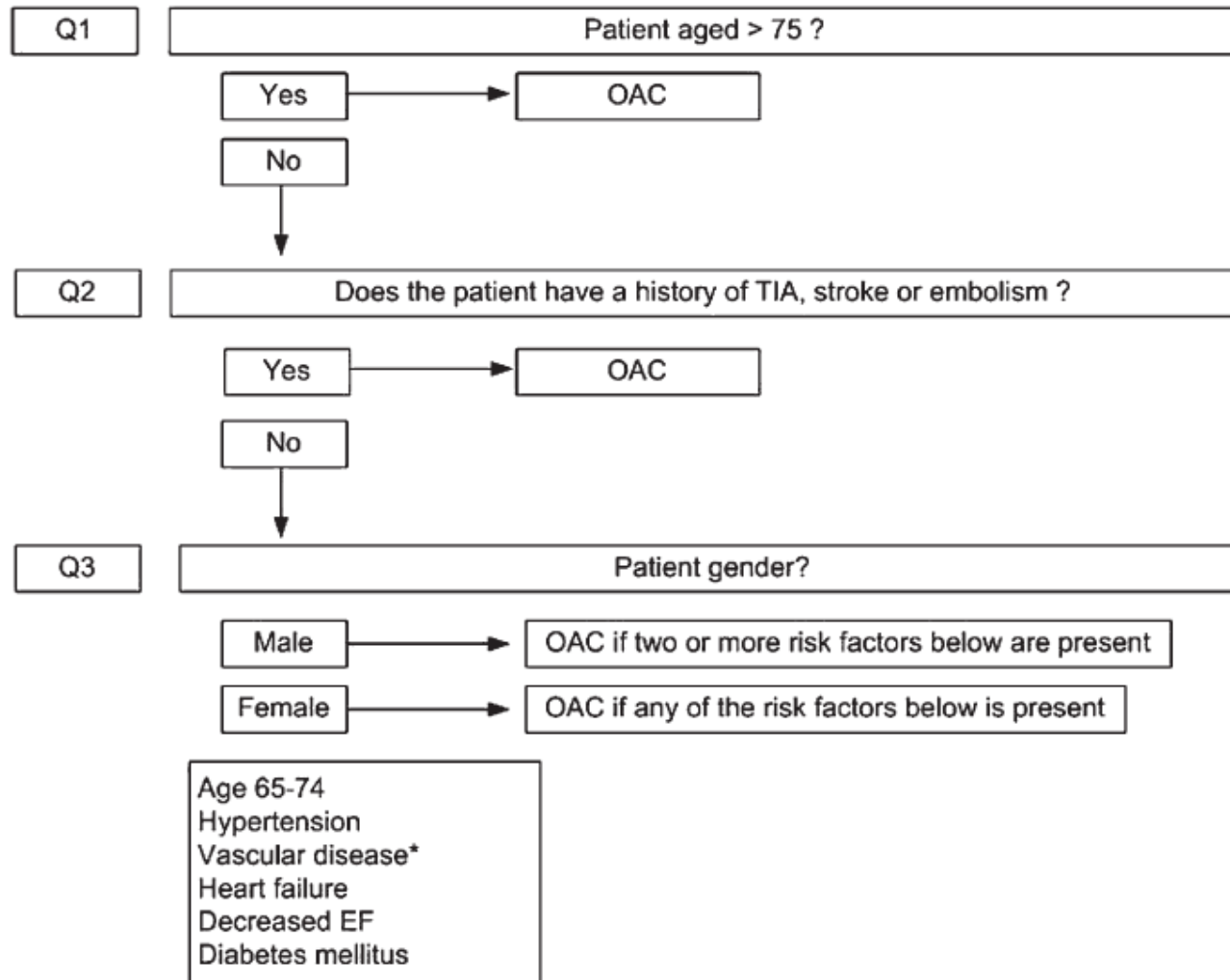
Risk Factor	Score
<u>C</u> ongestive heart failure/LV dysfunction	1
<u>H</u> ypertension	1
<u>A</u> ge ≥ 75 y	2
<u>D</u> iabetes mellitus	1
<u>S</u> troke/TIA/TE	2
<u>V</u> ascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque)	1
<u>A</u> ge 65-74 y	1
<u>S</u> ex category (ie female gender)	1

CHADS2 vs. CHA2DS2VASc

- CHADS2 score 0: 1.4% events
- CHA2DS2-VASc 0: 0 events
- CHA2DS2-VASc score 1: 0.6% events
- CHA2DS2-VASc score 2: 1.6% events

Our approach: anticoagulation when
Isch stroke risk > 0.9%/year

CHA2DS2-VASC



*Myocardial infarction, peripheral artery disease or aortic plaque

in the clinic

However, clinicians should keep in mind that the rate of stroke in patients with nonvalvular atrial fibrillation and at least 1 risk factor exceeds that of hemorrhage from chronic anticoagulation.

Arrhythmia/Electrophysiology

Major Hemorrhage and Tolerability of Warfarin in the First Year of Therapy Among Elderly Patients With Atrial Fibrillation

Elaine M. Hylek, MD, MPH; Carmella Evans-Molina, MD; Carol Shea, RN;
Lori E. Henault, MPH; Susan Regan, PhD

Background—Warfarin is effective in the prevention of stroke in atrial fibrillation but is under used in clinical care. Concerns exist that published rates of hemorrhage may not reflect real-world practice. Few patients ≥ 80 years of age were enrolled in trials, and studies of prevalent use largely reflect a warfarin-tolerant subset. We sought to define the tolerability of warfarin among an elderly inception cohort with atrial fibrillation.

Methods and Results—Consecutive patients who started warfarin were identified from January 2001 to June 2003 and followed for 1 year. Patients had to be ≥ 65 years of age, have established care at the study institution, and have their warfarin managed on-site. Outcomes included major hemorrhage, time to termination of warfarin, and reason for discontinuation. Of 472 patients, 32% were ≥ 80 years of age, and 91% had ≥ 1 stroke risk factor. The cumulative incidence of major hemorrhage for patients ≥ 80 years of age was 13.1 per 100 person-years and 4.7 for those < 80 years of age ($P=0.009$). The first 90 days of warfarin, age ≥ 80 years, and international normalized ratio (INR) ≥ 4.0 were associated with increased risk despite trial-level anticoagulation control. Within the first year, 26% of patients ≥ 80 years of age stopped taking warfarin. Perceived safety issues accounted for 81% of them. Rates of major hemorrhage and warfarin termination were highest among patients with CHADS₂ scores (an acronym for congestive heart failure, hypertension, age ≥ 75 , diabetes mellitus, and prior stroke or transient ischemic attack) of ≥ 3 .

Conclusions—Rates of hemorrhage derived from younger noninception cohorts underestimate the bleeding that occurs in practice. This finding coupled with the short-term tolerability of warfarin likely contributes to its underutilization. Stroke prevention among elderly patients with atrial fibrillation remains a challenging and pressing health concern. (*Circulation*. 2007;115:2689-2696.)

Major Hemorrhage of Thromboembolism

Background—Warfarin

Concerns exist regarding the tolerability of warfarin in elderly patients.

Methods and Results

Patients were followed for major bleeding while on warfarin management. Discontinuation of warfarin was associated with age ($P=0.009$).

Conclusions—Results

practice. This study suggests that prevention among elderly patients with atrial fibrillation remains a challenging and pressing health concern. (*Circulation*. 2007;115:2689-2696.)

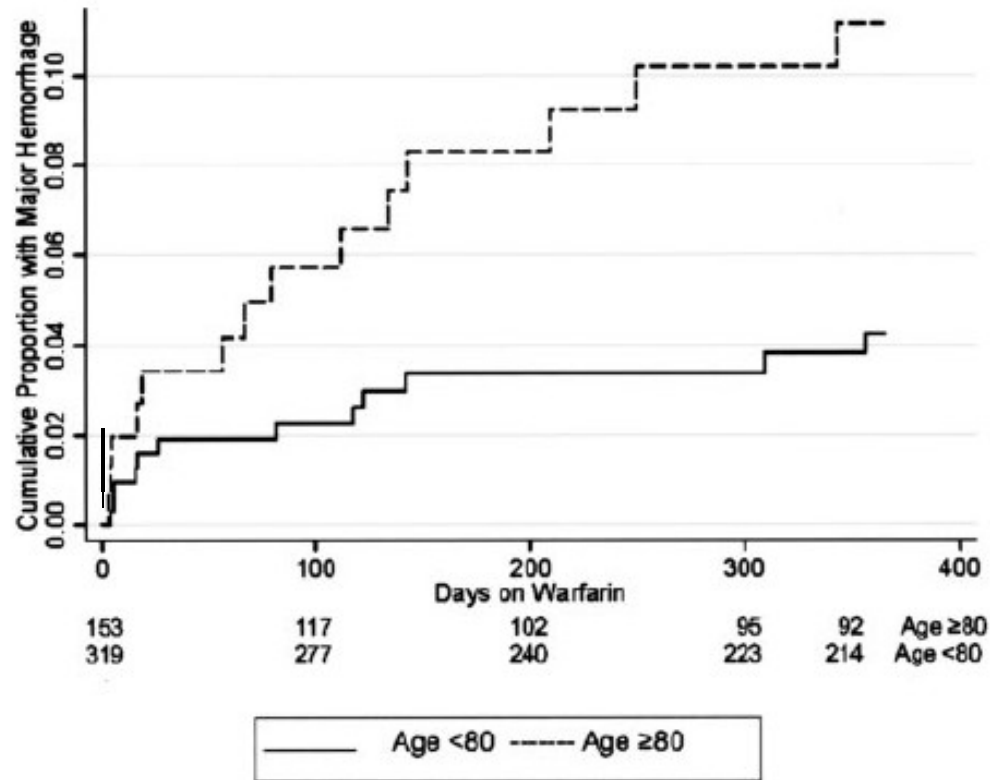


Figure 1. Cumulative incidence of major bleeding among patients aged ≥ 80 years and < 80 years ($n=472$). Numbers below graph are the number of patients without bleeding who continued on warfarin at that time point ($P=0.009$, log-rank test).

First Year of Atrial Fibrillation

ARN;

used in clinical care. Patients ≥ 80 years of age were sought to define the

1 to June 2003 and patients, and have their warfarin, and reason for treatment. The cumulative incidence of major bleeding for those < 80 years of age (INR) ≥ 4.0 were significantly higher than for patients ≥ 80 years of age.

bleeding that occurs in elderly patients.

utilization. Stroke

TABLE 7. Avoiding CNS Bleeding During Antithrombotic Therapy

Elderly patients and those with cerebrovascular disease are at special risk

Keep INRs ≤ 3.0

Warfarin combined with aspirin should be used with special caution in elderly patients and those with cerebrovascular disease

Combination of clopidogrel with aspirin may accentuate ICH risk in stroke patients

Modest blood pressure-lowering profoundly reduces CNS bleeding

ICH indicates intracerebral hemorrhage.

From Hart RG, et al. Stroke. 2005;36:1588

Warfarin

- Effective
- Reversible
- Inexpensive

- Slow onset of action
- Regular monitoring
- Food interaction
- Medication interaction

Dabigatran: Implications for Clinical Practice

- A dose of 150 mg twice daily was approved for patients with a GFR > 30 mL/min.
- A dose of 75mg twice daily was approved for CKD/Stage IV— (GFR 15 to 30 mL/min).
- **Monitoring of renal function is extremely important as**
80 % of dabigatran is excreted through the kidneys.

Dabigatran is contraindicated :

- In patients with a GFR less than 15 mL/min—even on dialysis.
- In patients with severe hepatic dysfunction.

Interim Results from RELY-ABLE®

- Extension study of RE-LY® evaluating safety of PRADAXA 150 mg BID over an additional 2.3 years (4.3 years median treatment with dabigatran)
- 5851 patients were enrolled (2937 PRADAXA 150 mg BID, 2914 dabigatran 110 mg BID)
 - Patients in RELY-ABLE continued same blinded dose of dabigatran
- Considerations specific to RELY-ABLE
 - Outcomes were not adjudicated
 - Warfarin patients were not followed as a comparator group
- During 2.3 years of additional treatment after RE-LY (total mean follow-up 4.3 years)
 - No new safety findings were identified
 - Rates of total bleeding, life-threatening bleeding, and major bleeding were similar to those seen during RE-LY

Connolly SJ, et al. Presented at American Heart Association Scientific Sessions. Los Angeles, CA. November 2012.

Please see Important Safety Information on slides 12, 16, 20, 23, and 24.

Please see full Prescribing Information and Medication Guide for PRADAXA provided.

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Dabigatran versus Warfarin in Patients with Atrial Fibrillation

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ABSTRACT

BACKGROUND

Warfarin reduces the risk of stroke in patients with atrial fibrillation but increases the risk of hemorrhage and is difficult to use. Dabigatran is a new oral direct thrombin inhibitor.

METHODS

In this noninferiority trial, we randomly assigned 18,113 patients who had atrial fibrillation and a risk of stroke to receive, in a blinded fashion, fixed doses of dabigatran — 110 mg or 150 mg twice daily — or, in an unblinded fashion, adjusted-dose warfarin. The median duration of the follow-up period was 2.0 years. The primary outcome was stroke or systemic embolism.

RESULTS

From the Population Health Research Institute, McMaster University and Hamilton Health Sciences, Hamilton, ON, Canada (S.J.C., S.Y., J.E., J.P., E.T.); Lankenau Institute for Medical Research and the Heart Center, Wynnewood, PA (M.D.E., A.P.); Uppsala Clinical Research Center, Uppsala, Sweden (J.O., L.W.); Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT (P.A.R., J.V., S.W.); Working Group on Cardiovascular Research the Netherlands, Utrecht, the Netherlands (M.A.); St. John's National Academy of Health Sciences, Bangalore, India (D.X.); FuWai Hospital, Beijing (J.Z.); Estudios Clínicos Latinoamérica, Rosario, Argentina (R.D.); Lady

RELY

- Dabigatran 110 mg twice daily
 - Equal to warfarin in stroke prevention
 - Warfarin 1.69%/yr – dabigatran (110mg) 1.53%/yr
 - Less bleeding than warfarin
 - Warfarin 3.36%/year – dabigatran (110mg) 2.71%/yr
- Dabigatran 150 mg twice daily
 - More effective than warfarin in stroke prevention
 - Dabigatran (150mg) 1.11%/yr
 - Equivalent bleeding to warfarin

less hemorrhagic stroke than warfarin

ACCF/AHA/HRS FOCUSED UPDATE

2011 ACCF/AHA/HRS Focused Update on the Management of Patients With Atrial Fibrillation (Update on Dabigatran)

A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

2011 WRITING GROUP MEMBERS

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‡ACCF/AHA Task Force on Performance Measures Representative.

§Recused from voting on Section 8.1.4.2.5, Recommendation for Use of Oral Direct Thrombin Inhibitor Anticoagulant Agents.

||ACCF/AHA Task Force on Practice Guidelines Liaison.

March 2011

Wann et al Atrial Fibrillation Focused Update: Dabigatran

Table 2 Recommendation for emerging antithrombotic agents

2011 Focused update recommendation	Comments
Class I	
1. Dabigatran is useful as an alternative to warfarin for the prevention of stroke and systemic thromboembolism in patients with paroxysmal to permanent AF and risk factors for stroke or systemic embolization who do not have a prosthetic heart valve or hemodynamically significant valve disease, severe renal failure (creatinine clearance <15 mL/min) or advanced liver disease (impaired baseline clotting function). ³ (<i>Level of Evidence: B</i>)	New recommendation

ACC AHA HRS Afib Focused Update (Dabigatran), March 2011

- Non-inferior to warfarin re thromboembolism (afib)
- Caution when CrCl < 30ml/min
- Increased dabigatran levels with amiodarone, verapamil
- Half life 12-17 hours
- No reversal re hemorrhage
 - dialysis
- ? shelf life once bottle opened (FDA alert March 30, 2011)
 - Tablets must stay in manufacturer's container
 - Label: discard product 30 days after opening container
- Coagulation testing ??? aPTT, dilute thrombin time

Table 3. Guide to the Discontinuation of Dabigatran Etextilate Before Invasive Procedures Such as Elective Surgery in Patients Receiving Once- or Twice-Daily Dosing With a Standard or High Risk of Bleeding

Renal Function (Creatinine Clearance), mL/min	Half-Life, h*	Timing of Discontinuation After Last Dose of Dabigatran Before Surgery	
		Standard Risk of Bleeding	High Risk of Bleeding†
>80	13 (11–22)	24 h	2–4 d
>50–≤80	15 (12–34)	24 h	2–4 d
>30–≤50	18 (13–23)	≥2 d (48 h)	4 d
≤30	27 (22–35)	2–5 d	>5 d

*Data are from renal impairment study in healthy volunteers,³² geometric mean (range).

†Types of surgery associated with a high risk of bleeding (or major surgery in which complete hemostasis may be required) include but are not limited to cardiac surgery, neurosurgery, abdominal surgery, or surgery involving a major organ. Other procedures such as spinal anesthesia may also require complete hemostatic function. Other important determinants of bleeding risk include advancing age, comorbidities (eg, major cardiac, respiratory, or liver disease), and concomitant use of antiplatelet therapy.

ONLINE FIRST

Dabigatran Association With Higher Risk of Acute Coronary Events

Meta-analysis of Noninferiority Randomized Controlled Trials

Ken Uchino, MD; Adrian V. Hernandez, MD, PhD

Background: The original RE-LY (Randomized Evaluation of Long-term Anticoagulant Therapy) trial suggested a small increased risk of myocardial infarction (MI) with the use of dabigatran etexilate vs warfarin in patients with atrial fibrillation. We systematically evaluated the risk of MI or acute coronary syndrome (ACS) with the use of dabigatran.

Methods: We searched PubMed, Scopus, and the Web of Science for randomized controlled trials of dabigatran that reported on MI or ACS as secondary outcomes. The fixed-effects Mantel-Haenszel (M-H) test was used to evaluate the effect of dabigatran on MI or ACS. We expressed the associations as odds ratios (ORs) and their 95% CIs.

Results: Seven trials were selected (N=30 514), including 2 studies of stroke prophylaxis in atrial fibrillation, 1 in acute venous thromboembolism, 1 in ACS, and 3 of short-term prophylaxis of deep venous thrombosis. Control arms included warfarin, enoxaparin, or placebo ad-

ministration. Dabigatran was significantly associated with a higher risk of MI or ACS than that seen with agents used in the control group (dabigatran, 237 of 20 000 [1.19%] vs control, 83 of 10 514 [0.79%]; OR_{M-H} , 1.33; 95% CI, 1.03-1.71; $P=.03$). The risk of MI or ACS was similar when using revised RE-LY trial results (OR_{M-H} , 1.27; 95% CI, 1.00-1.61; $P=.05$) or after exclusion of short-term trials (OR_{M-H} , 1.33; 95% CI, 1.03-1.72; $P=.03$). Risks were not heterogeneous for all analyses ($I^2=0\%$; $P\geq .30$) and were consistent using different methods and measures of association.

Conclusions: Dabigatran is associated with an increased risk of MI or ACS in a broad spectrum of patients when tested against different controls. Clinicians should consider the potential of these serious harmful cardiovascular effects with use of dabigatran.

Arch Intern Med.

Published online January 9, 2012.

doi:10.1001/archinternmed.2011.1666

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Rivaroxaban

- Once daily
- As effective or better than warfarin
- Less hemorrhagic stroke than warfarin
- Similar reduction in ischemic stroke
- Less bleeding than warfarin
- No routine lab testing
- No reversal
 - Half life 5-9 hours
- Coagulation testing: aPTT

Apixaban

- Twice daily
- As effective or better than warfarin
- Less hemorrhagic stroke than warfarin
- Similar reduction in ischemic stroke
- Less bleeding than warfarin
- Lower overall mortality
- No routine lab testing
- No reversal
 - Half life 8-15 hours

New anticoagulants

- Short half life – less bleeding
 - Subtherapeutic if misses one or two doses
- Lack of need for routine monitoring
 - No standard available test to assess if anticoagulated
- Generally safer than warfarin
 - No antidote
 - ??? Dabigatran
- Cost of medication
 - Overall cost of care

Who should remain on warfarin?

- Patient already receiving warfarin and stable whose INR is easy to control
- If dabigatran, rivaroxaban, apixaban not available
- Cost
- If patient not likely to comply with twice daily dosing (Dabigatran, Apixaban)
- Chronic kidney disease (GFR < 30 ml/min)

How about Clopidogrel + Aspirin ?

ORIGINAL ARTICLE

Effect of Clopidogrel Added to Aspirin in Patients with Atrial Fibrillation

The ACTIVE Investigators*

ABSTRACT

BACKGROUND

Vitamin K antagonists reduce the risk of stroke in patients with atrial fibrillation but are considered unsuitable in many patients, who usually receive aspirin instead. We investigated the hypothesis that the addition of clopidogrel to aspirin would reduce the risk of vascular events in patients with atrial fibrillation.

METHODS

A total of 7554 patients with atrial fibrillation who had an increased risk of stroke and for whom vitamin K-antagonist therapy was unsuitable were randomly assigned to receive clopidogrel (75 mg) or placebo, once daily, in addition to aspirin. The primary outcome was the composite of stroke, myocardial infarction, non-central nervous system systemic embolism, or death from vascular causes.

The members of the writing group (Stuart J. Connolly and Janice Pogue, Population Health Research Institute, Hamilton, ON, Canada; Robert G. Hart, University of Texas Health Center, San Antonio; Stefan H. Hohnloser, Goethe University Hospital, Frankfurt, Germany; Marc Pfeffer, Brigham and Women's Hospital, Boston; and Susan Chrolavicius and Salim Yusuf, Population Health Research Institute, Hamilton, ON, Canada) of Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE) assume responsibility for the overall content and integrity of the article. Address

How about Clopidogrel + Aspirin ?

ORIGINAL ARTICLE

Effect of Clopidogrel Added to Aspirin in Patients with Atrial Fibrillation

The ACTIVE Investigators*

BACKGROUND

Vitamin K a
but are cons
We investig
reduce the r

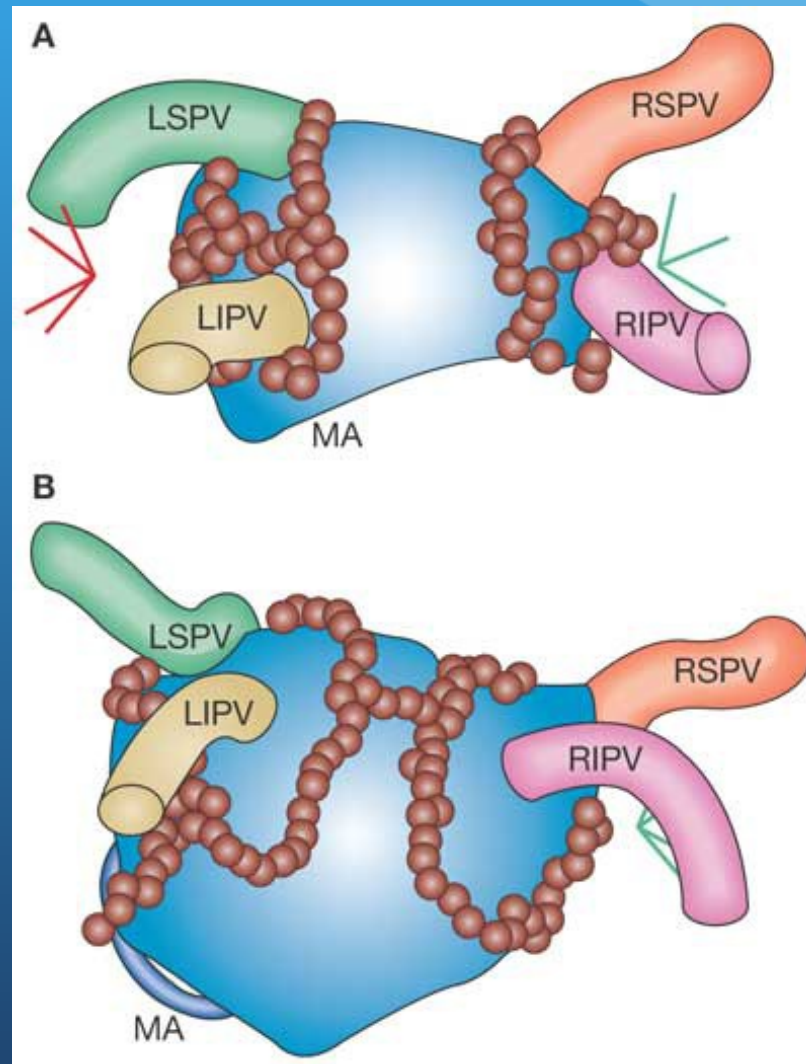
METHODS

A total of 75
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The members of the writing group (Stuart J. Connolly and Janice Pogue, Population Health Research Institute, Hamilton, ON, Canada; Robert G. Hart, University of Texas Health Center, San Antonio; Stefan H. Hohnloser, Goethe University Hospital, Frankfurt, Germany; Marc Pfeffer, Brigham and Women's Hospital, Boston; and Susan Chrolavicius and Salim Yusuf, Population Health Research Institute, Hamilton, ON, Canada) of Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE) assume responsibility for the overall content and integrity of the article. Address



Anatomic Carto Map of Let atrium – ablation points



Warfarin Management Post Ablation

1. Warfarin is recommended for all patients for at least two months following an AF ablation procedure,
2. Decisions regarding the use of warfarin more than two months following ablation should be based on the patient's risk factors for stroke and not on the presence or type of AF.
3. Discontinuation of warfarin therapy post ablation is generally not recommended in patients who have a CHADS score ≥ 2 [REDACTED]

Heart Rhythm Society Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation. Heart Rhythm 4(6) June 2007

Results

- Difficult to interpret
 - Success rate
 - Optimal patient:
 - single procedure 60 - 80%
 - Multiple procedures 80 – 90%
 - Poor patient (eg 3 years persistent afib, sig enlarged LA)
 - Best success with paroxysmal and healthy heart
 - Least success with chronic and diseased left atrium
 - May recur despite initial success
 - May recur without symptoms
 - ??? Warfarin
- Ultimate goal: Rhythm control without toxic antiarrhythmics

Atrial fibrillation ablation issues

- Complication rate 1-5%
 - Tamponade – atrial perforation
 - TIA, stroke
 - Major bleed
 - Creation of atrial flutter (up to 8%)
 - Vascular access complications
 - Pulmonary vein stenosis (lower incidence than initial)
 - Aorto-esophageal fistula
 - Fatal 1/1000
- Cathy procedure

Catheter Ablation for Atrial Fibrillation

Are Results Maintained at 5 Years of Follow-Up?

Rukshen Weerasooriya, BMEDSc(HONS), MBBS,*† Paul Khairy, MD, PhD,‡ Jean Litalien, MD,*
Laurent Macle, MD,‡ Meleze Hocini, MD,* Frederic Sacher, MD,* Nicolas Lellouche, MD,*
Sebastien Knecht, MD,* Matthew Wright, PhD, MD,* Isabelle Nault, MD,* Shinsuke Miyazaki, MD,*
Christophe Scavee, MD,* Jacques Clementy, MD,* Michel Haissaguerre, MD,* Pierre Jais, MD*

Bordeaux-Pessac, France; Crawley, Western Australia; and Montreal, Quebec, Canada

Objectives

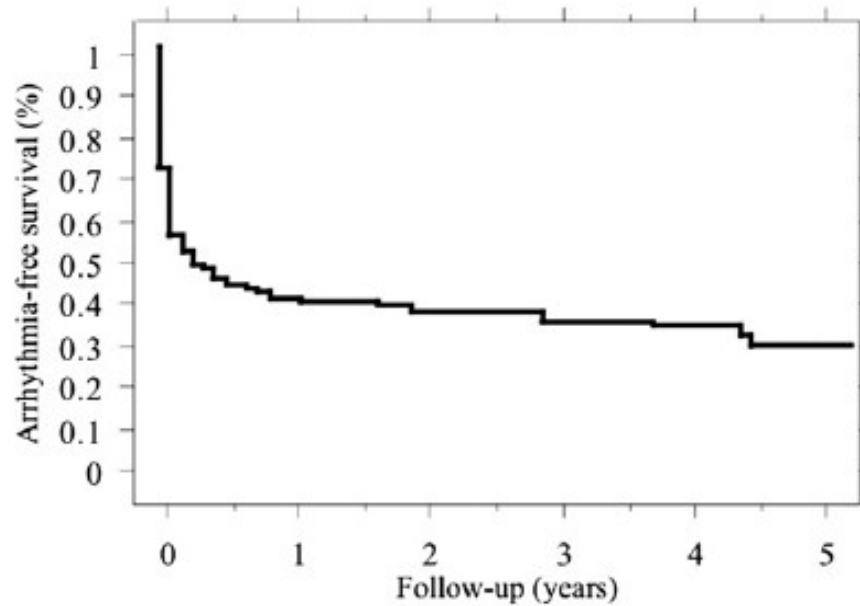
This study describes 5-year follow-up results of catheter ablation for atrial fibrillation (AF).

Background

Long-term efficacy following catheter ablation of AF remains unknown.

Methods

A total of 100 patients (86 men, 14 women), age 55.7 ± 9.6 years, referred to our center for a first AF ablation (63% paroxysmal; 3.5 ± 1.4 prior ineffective antiarrhythmic agents) were followed for 5 years. Complete success was defined as absence of any AF or atrial tachycardia recurrence (clinical or by 24-h Holter monitoring) lasting ≥ 30 s.



Number at risk	100	36	33	31	29	10
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Figure 2 Single Procedure Success

Kaplan-Meier event-free survival curve after a single catheter ablation attempt.

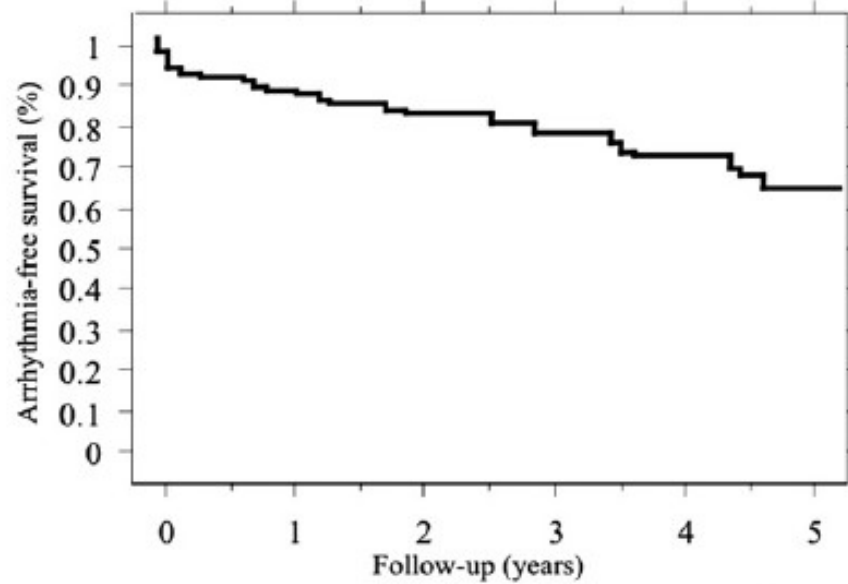


Figure 3 Multiple Procedure Success

Kaplan-Meier event-free survival curve after the last catheter ablation attempt.

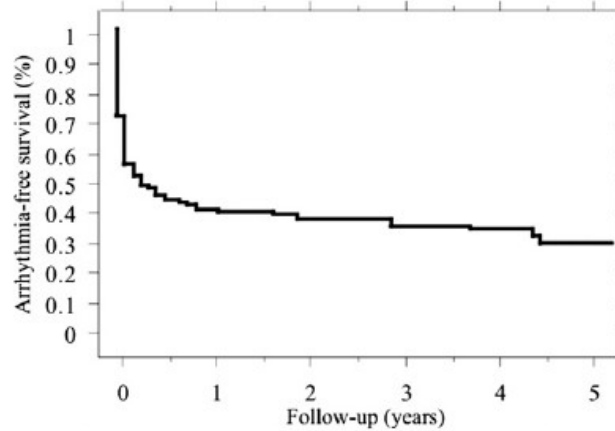


Figure 2 Single Procedure Success

Kaplan-Meier event-free survival curve after a single catheter ablation attempt.

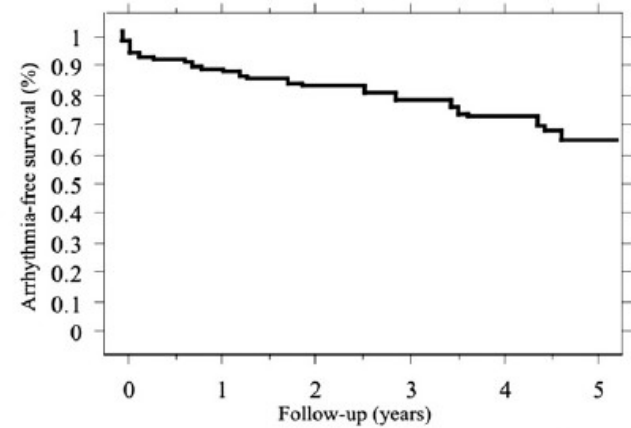


Figure 3 Multiple Procedure Success

Kaplan-Meier event-free survival curve after the last catheter ablation attempt.

Risk factors for recurrence of afib

- Long-term persistent afib
- Valvular heart disease
- Dilated cardiomyopathy

	Feel Better	Feel Same	Feel Worse
Live Longer		Anticoagulant	
Live Same	Ablation	Rate Control	
Live Shorter	Antiarrhythmic drugs		

Feel Better

Feel Same

Feel Worse

Live Longer

Anticoagulant

Live Same

Ablation

Rate Control

Live Shorter

Antiarrhythmic drugs

Later's **WARFARIN** BAIT

**KILLS
NORWAY
(SEWER) RATS,
ROOF RATS
& MICE**



**EFFECTIVE CONTROL FOR RATS AND MICE
IN AND AROUND THE HOUSE**

READ THE LABEL BEFORE USING
DOMESTIC USE ONLY - NOT FOR
COMMERCIAL OR INDUSTRIAL USE

500 g
2 x 250 g
SEALED
BAIT BAGS

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1200, Woodbine Way
Brampton, N.Y. 218 001



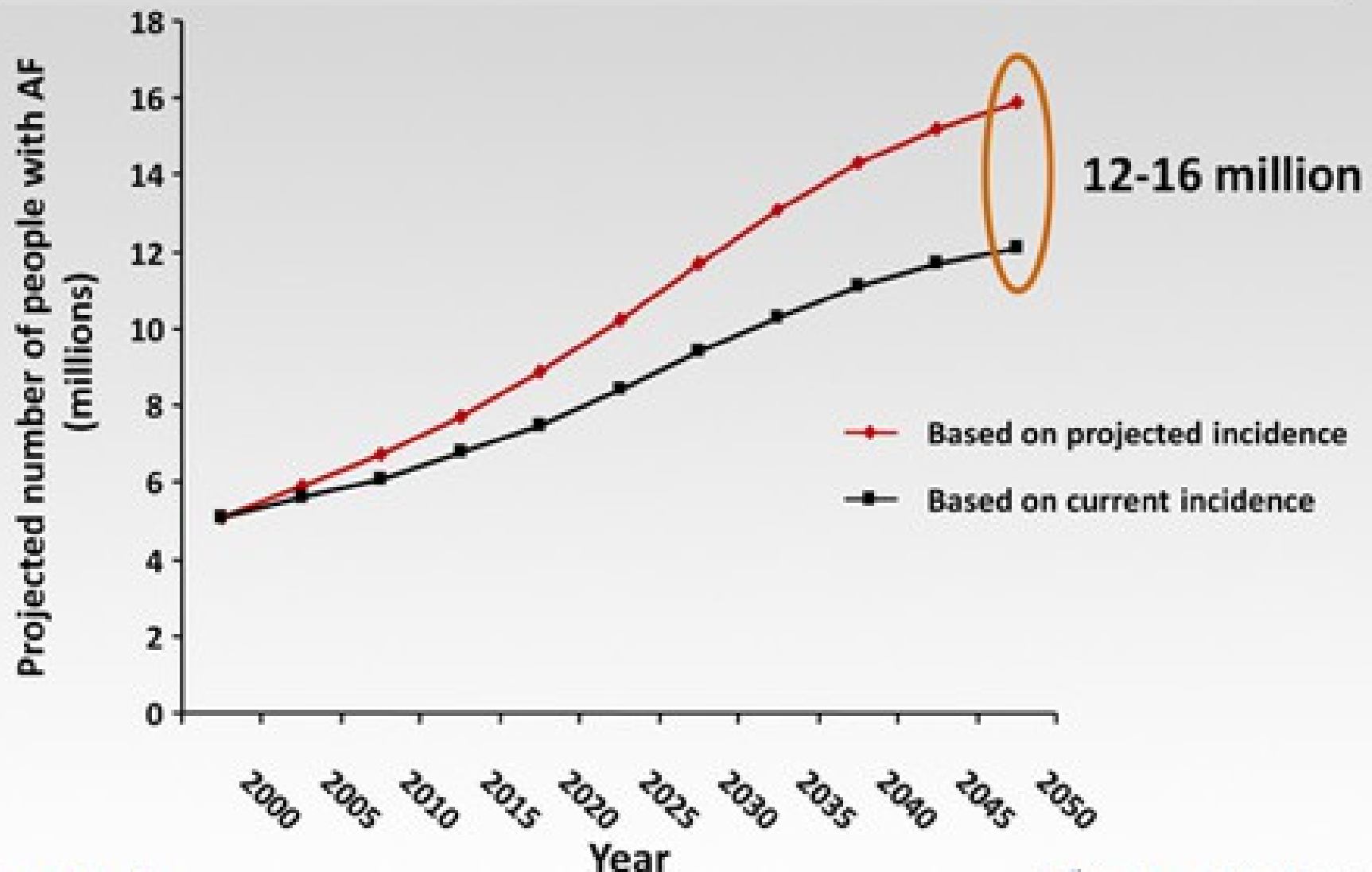
Atrial Fibrillation (AF) Remarkable Evolution in Therapy

➤ Most common arrhythmia in clinical practice.

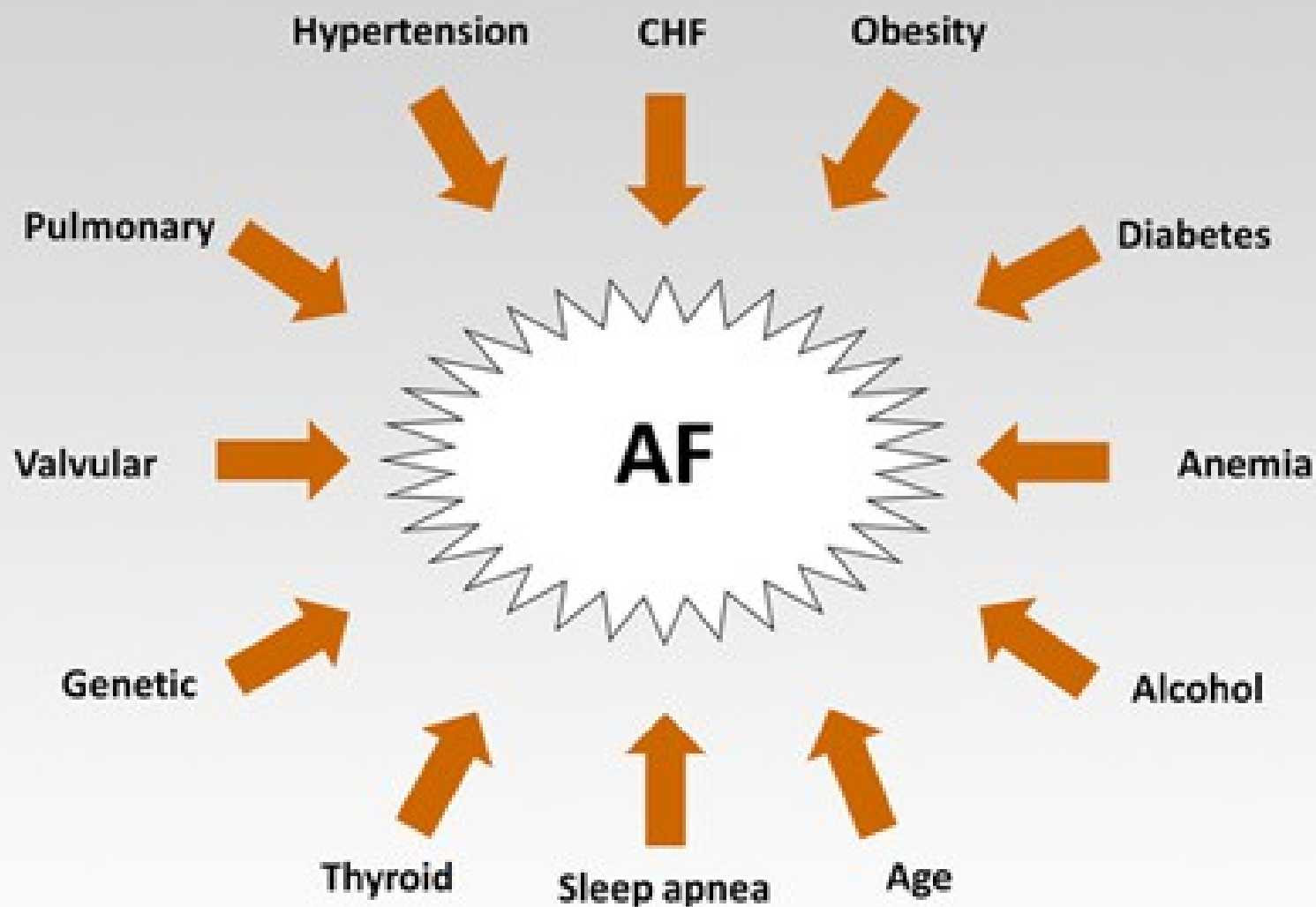
➤ Accounts for more hospitalizations than all other arrhythmia diagnoses combined.

US Prevalence – AF Diagnosis: An Epidemic

1 in 4 lifetime risk in men and women ≥ 40 years old



Causes of AF



CHF = congestive heart failure

European AF Treatment Guidelines

	Class	Level
Antithrombotic therapy to prevent thromboembolism for all patients with AF, except those patients (both male and female) who are at low risk (aged < 65 years and lone AF), or with contraindications.	I	A
The choice of antithrombotic therapy should be based upon the absolute risks of stroke/thromboembolism and bleeding and the net clinical benefit for a given patient.	I	A
The CHA ₂ DS ₂ -VASc score is recommended as a means of assessing stroke risk in non-valvular AF.	I	A
In patients with a CHA ₂ DS ₂ -VASc score of ≥ 2, OAC therapy with adjusted dose VKA (INR 2-3), or a direct thrombin inhibitor (dabigatran), or a oral factor Xa inhibitor (eg, rivaroxaban, apixaban) is recommended unless contraindicated.	I	A
In patients with a CHA ₂ DS ₂ -VASc score of 1, OAC with adjusted dose VKA (INR 2-3), or a direct thrombin inhibitor (dabigatran), or a oral factor Xa inhibitor (eg rivaroxaban, apixaban) should be considered based upon assessment of the risk of bleeding complications and patient preferences.	IIa	A

CHEST ACCP GUIDELINES

CHEST. 2012;141(2_suppl):7S-47S. doi:10.1378/chest.1412S3

- **Patients With Nonrheumatic Atrial Fibrillation (AF)**
- **2.1.8.** For patients with AF, including those with paroxysmal AF, who are at low risk of stroke (eg, CHADS₂ [congestive heart failure, hypertension, age \geq 75 years, diabetes mellitus, prior stroke or transient ischemic attack] score = 0), we suggest no therapy rather than antithrombotic therapy (Grade 2B). For patients who do choose antithrombotic therapy, we suggest aspirin (75 mg to 325 mg once daily) rather than oral anticoagulation (Grade 2B) or combination therapy with aspirin and clopidogrel (Grade 2B).

CHEST ACCP GUIDELINES (cont.)

CHEST. 2012;141(2_suppl):7S-47S. doi:10.1378/chest.1412S3

- **2.1.9. For patients with AF, including those with paroxysmal AF, who are at intermediate risk of stroke (eg, CHADS2 score = 1), we recommend oral anticoagulation rather than no therapy (Grade 1B). We suggest oral anticoagulation rather than aspirin (75 mg to 325 mg once daily) (Grade 2B) or combination therapy with aspirin and clopidogrel (Grade 2B). For patients who are unsuitable for or choose not to take an oral anticoagulant (for reasons other than concerns about major bleeding), we suggest combination therapy with aspirin and clopidogrel rather than aspirin (75 mg to 325 mg once daily) (Grade 2B).**

AF

Important for two reasons

1. It causes severe symptoms that reduce quality of life.
2. It is responsible for stroke.

New AF: Plan of Action

1. Rate and/or rhythm control.
2. Decreasing thromboembolic **stroke** risk.



"Give it to me straight, Doc. How long do I have to ignore your advice?"

Rate vs rhythm control in patients with atrial fibrillation and heart failure: A systematic review and meta-analysis of randomised controlled trials. Eur Journal of Int Med, 09/22/2011.

Evidence Based Medicine Clinical Article

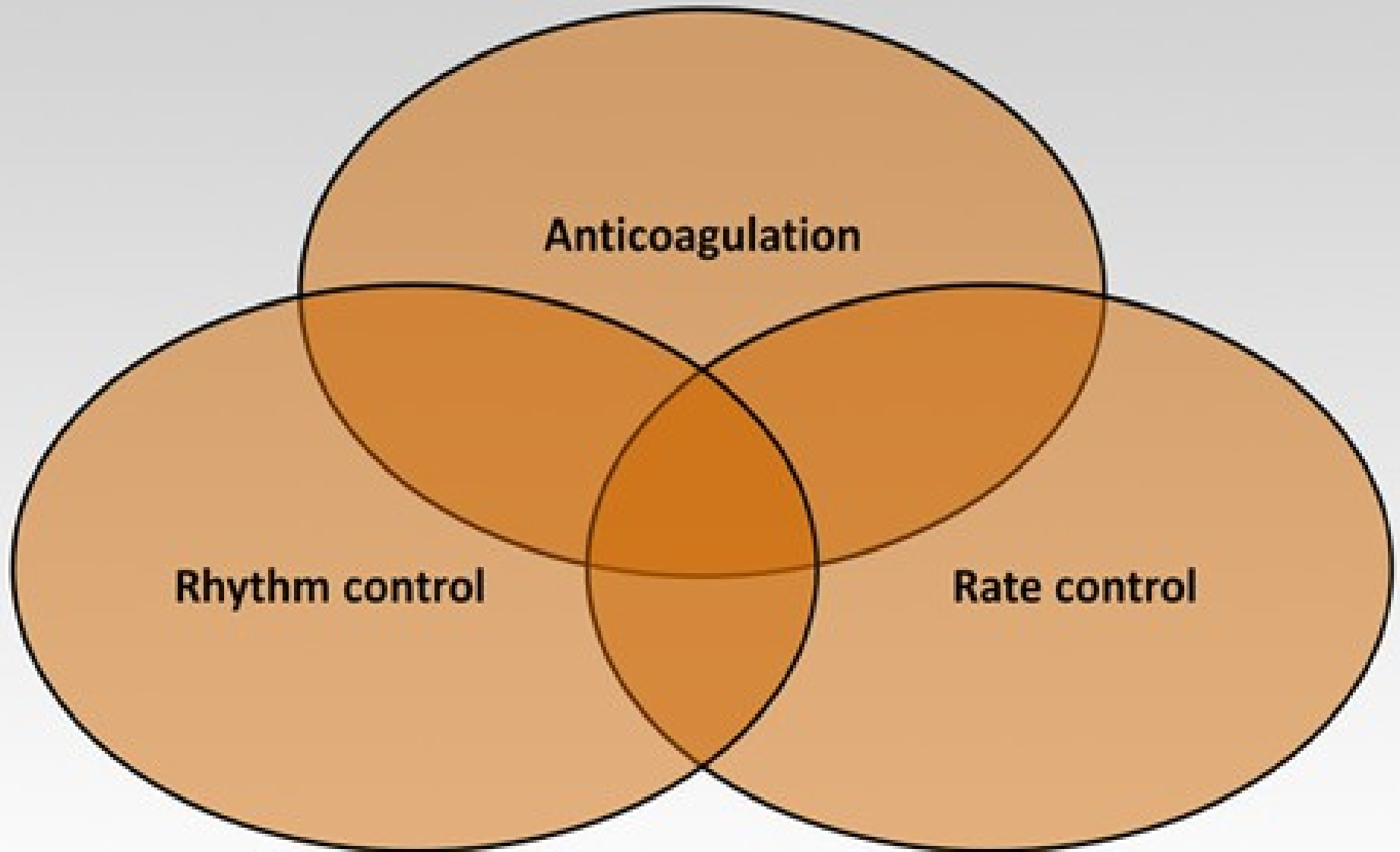
Caldeira D et al. - In patients with Atrial fibrillation (AF) and heart failure (HF), rate control compared with rhythm control showed inferior risk of hospitalization.

Four RCTs with a total of 2486 patients with atrial fibrillation and heart failure were identified.

Results: Mortality and stroke/thromboembolic events were not significantly different in rate and rhythm control arms [RR 1.03; 95% CI: 0.90-1.17] and [RR 1.09; 95% CI: 0.61-1.96]; respectively, hospitalizations were less frequent with rate control than with rhythm control [RR 0.92; 95% CI: 0.86-0.98; p=0.008], in 3 studies involving 2425 patients.

Number needed to treat to prevent one hospitalization was 19 patients.

Treatment of AF



New AF: Plan of Action

1. Rate and/or rhythm control.
2. Decreasing thromboembolic **stroke** risk.

AF

- ▶ Stroke is the leading cause of morbidity and mortality—most common and devastating complication.
- ▶ Patients with AF have a 5-fold higher stroke rate (5%/yr).
- ▶ Proportion of all strokes caused by AF ~ 15%.

Fuster V et al. *Circulation* 2006; 114: e257-354.

Atrial Fibrillation Investigators. *Arch Intern Med* 1994; 154: 1449.

AF

Risk in patients with AF increases with age and continues regardless of whether the AF is intermittent or sustained particularly in the presence of several clinical stroke risk factors.

Stroke Risk CHADS₂ Score

JAMA 2001; 285: 28

	Risk Factor	Points
C	Recent Congestive HF	1
H	Hypertension	1
A	Age ≥ 75	1
D	Diabetes	1
S ₂	Prior Stroke/TIA	2

Practice-Level Variation in Warfarin Use Among Outpatients With Atrial Fibrillation

(From the NCDR PINNACLE Program) Chan PS et al.
Am J Cardiol 2011;Jul 26: [Epub ahead of print].

Conclusions: Almost 50% of outpatients with AF who have a CHADS₂ score >1 and are at moderate to high risk of stroke are not treated with warfarin.

Perspective: Confirms the results of prior studies that have demonstrated widespread underutilization of warfarin.

Inconveniences and risk of hemorrhagic complications associated with warfarin are major factors for underutilization.

ACC/AHA/ESC 2006 Guidelines: Recommended Therapies According to

Risk Category	Recommended Therapy
No risk factors	Aspirin, 81-325 mg daily
One moderate risk factor	Aspirin, 81-325 mg daily, or warfarin (INR 2.0-3.0, target 2.5)
Any high risk factor or ≥ 1 moderate risk factor	Warfarin (INR 2.0-3.0, target 2.5)*

Decreasing Stroke Risk in AF Risk Assessment:

- 2006 ACC/AHA guidelines list less validated risk factors that could potentially modulate risk.
- More recent evidence has supported these additional risk factors should be considered in

Decreasing Stroke Risk in AF

Risk Assessment:

Less Validated/Weaker Risk Factors	Moderate Risk Factors	Score	High Risk Factors	Score
Female gender	Cardiac failure (LVEF < 35%)	C - 1	Previous Stroke, TIA, or emboli	S 2
Age 65-74 yrs	Hypertension	H -1	Mitral stenosis	
Coronary artery disease	Age ≥ 75 yrs	A - 1	Prosthetic heart valve	
Thyrotoxicosis	Diabetes mellitus	D - 1		

Decreasing Stroke Risk in AF Risk Assessment:

Scoring Differences Between CHADS₂ and CHA₂DS₂-VASc

Risk Factor	CHADS ₂	CHA ₂ DS ₂ -VASc
	(Maximum score, 6)	(Maximum score, 9)
Congestive heart failure	1	1
Hypertension	1	1
Diabetes	1	1
Vascular disease	N/A	1
Age 65-74	N/A	1
Age ≥75	1	2
Female sex	N/A	1
Previous stroke/TIA	2	2

Stroke Risk in patients with non-valvular AF not treated with anticoagulation according to CHADS₂ score

*Adjusted stroke rate
Gage BF et al. *JAMA*
EHJ (2010) 31, 2369

CHADS ₂ Score	Patients (n=1730)	Adjusted Stroke Rate* (%/Y)
0	120	1.9 (1.2-3.0)
1	463	2.8 (2.0-3.8)
2	523	4.0 (3.1-5.1)
3	337	5.9 (4.6-7.3)
4	220	8.5 (6.3-11.1)
5	65	12.5 (8.2-17.5)
6	5	18.2 (10.5-27.4)

no ASA

**Stroke
AF not
accord**

Stroke Risk Stratification with CHA₂DS₂-VASc

CHA ₂ DS ₂ -VASc Score	Patients (n-7329)	Adjusted stroke rate (%/Y)
0	1	0
1	422	1.3
2	1230	2.2
3	1730	3.2
4	1718	4.0
5	1159	6.7
6	679	9.8
7	294	9.6
8	82	6.7
9	14	15.2

Guideline References

US AF Guidelines: Wann LS et al. 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (updating the 2006 guideline): A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines.

Circulation Jan 4/11 2011; 123:104.

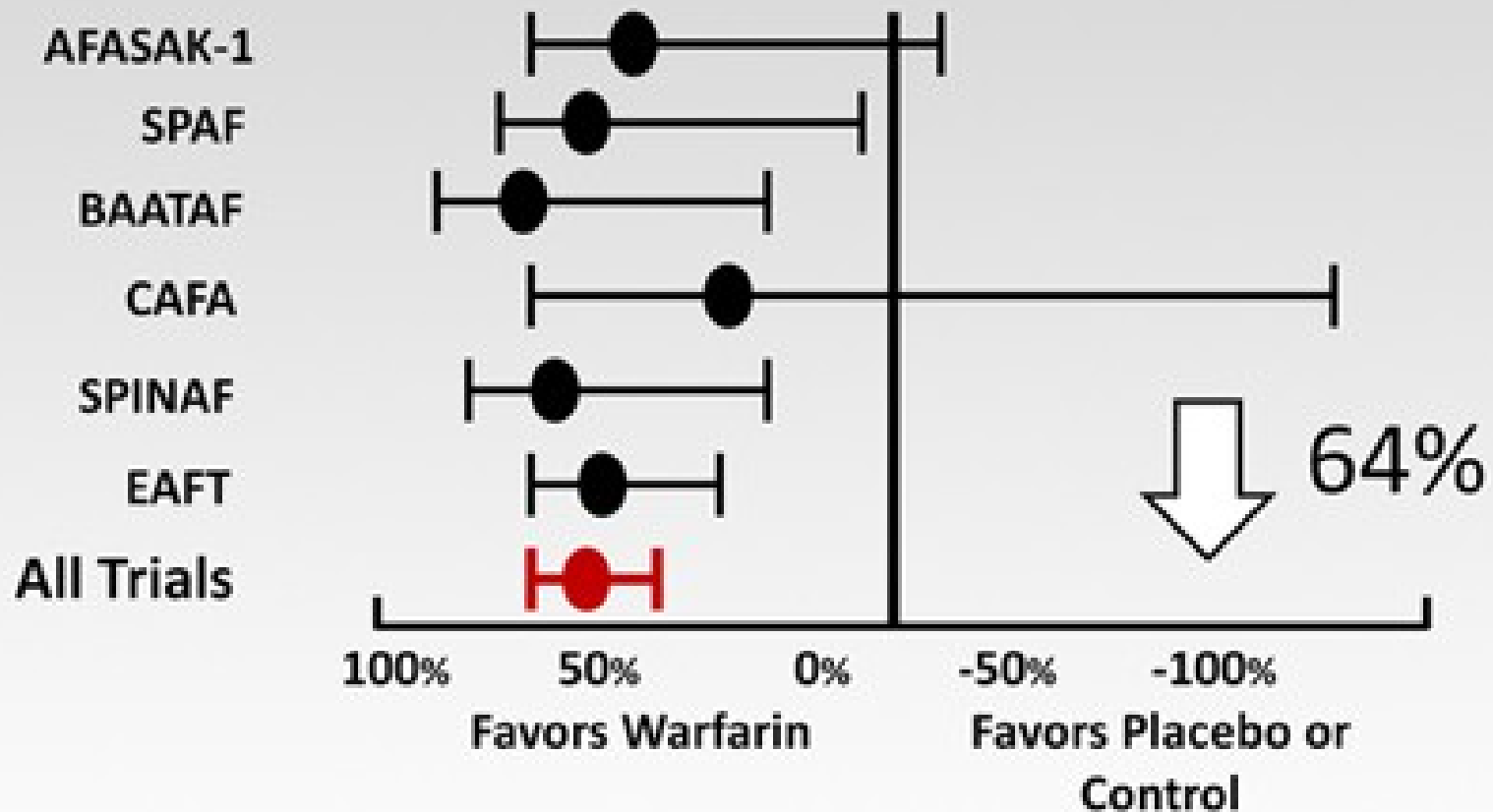
European AF Guidelines: Guidelines for the management of atrial fibrillation: The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC).

Eur Heart J November 2010; 31(19): 2369-2429.

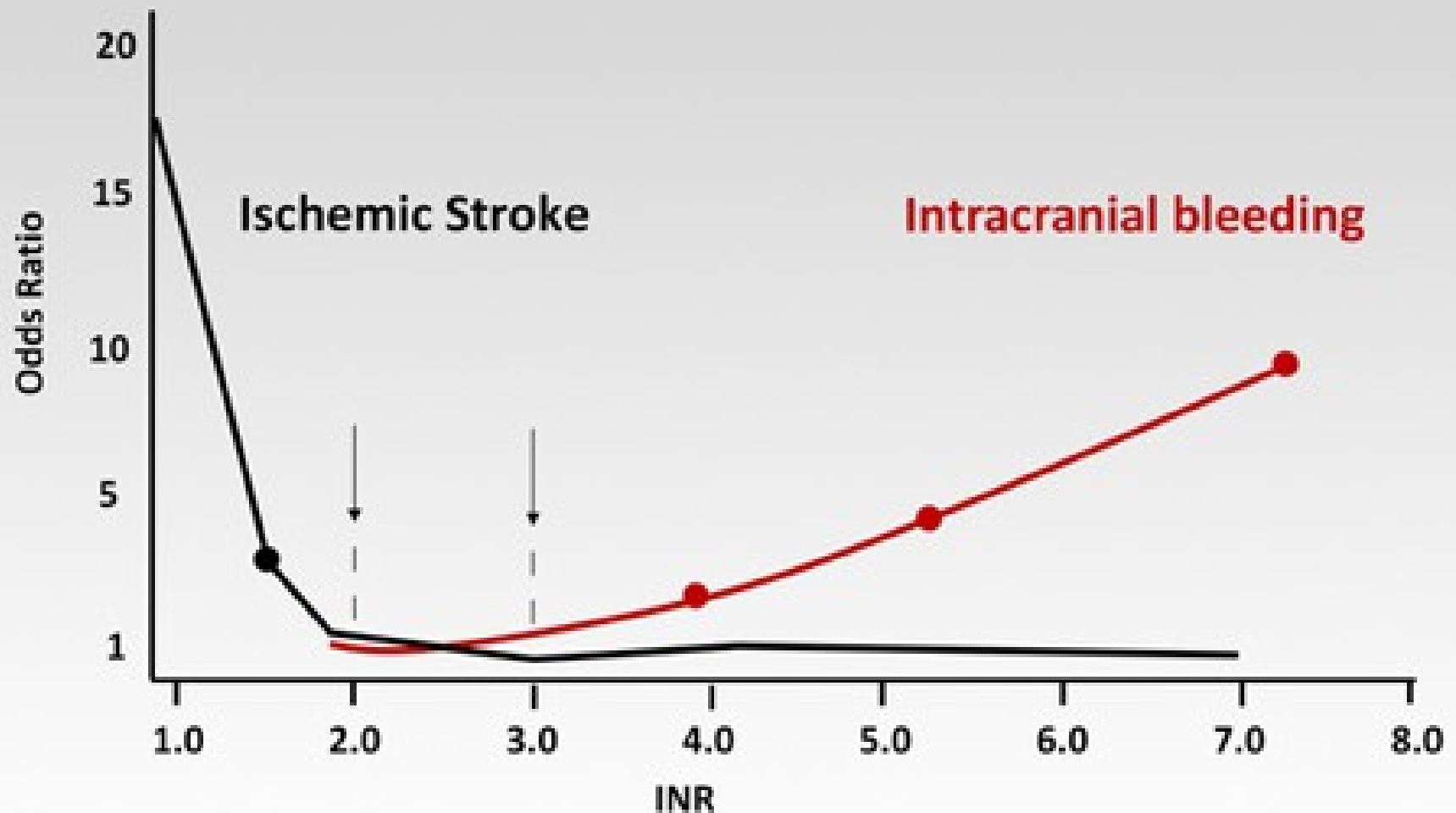
Conclusions:

➤ CHA2DS2-VASc is better than CHADS2 at predicting

Stroke Prevention in AF: Warfarin vs Placebo



Efficacy and Safety of Warfarin



Fang MC, et al. *Ann Intern Med.* 2004;141:745-752.

Hylek EM, et al. *N Engl J Med.* 1996;335:540-546.

Atrial Fibrillation and Stroke

- AF responsible for 1/6 of all strokes
- Warfarin reduces stroke in AF by 64%
 - significant increase in intracranial and other hemorrhage
 - Difficult to use
 - Patients @ appropriate INR only ~ 65% of the time
- Only 50% of eligible patients receive warfarin

Randomized Evaluation of Long-term anticoagulant therapy (RE-LY)

Patients with Atrial Fibrillation at Risk of
Stroke

Connolly SJ, Ezekowitz MD, Yusuf S, et al.
Dabigatran versus warfarin in patients with

atrial fibrillation. (RE-LY) *N Engl J Med* 2009;
361:1139-51.

Dabigatran

- Dabigatran Etexilate, a pro-drug, is rapidly converted to dabigatran—a direct thrombin inhibitor.
- 6.5% bioavailability, 80% excreted by kidney.
- Dabigatran becomes therapeutic within 2 hours of administration.
- Half-life of 12-17 hours.

RE-LY: A Non-inferiority Trial

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

Blinded Event Adjudication.

R

Open

Blinded

Warfarin
adjusted
(INR 2.0-3.0)
N=6000

Dabigatran
Etexilate
110 mg BID
N=6000

Dabigatran
Etexilate
150 mg BID
N=6000

Conclusions

- Dabigatran 150 mg significantly reduced stroke 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.

2-LY Conclusions

- Both Dabigatran doses offer advantages over warfarin.
- Dabigatran 150 is more effective and dabigatran 110 has a better safety profile.
- There is potential to tailor therapy to individual patient characteristics.

Dabigatran: Implications for Clinical Practice

- Approved by the FDA in October of 2010.
- Marketed as Pradaxa by Boehringer-

Dabigatran: Implications for Clinical Practice

- Rates for the primary outcome of all stroke (ischemic or hemorrhagic) or systemic embolism were 1.71% per year in the warfarin group.
- Dabigatran etexilate, (Pradaxa 150 mg twice daily)—the available dosage reduced the rate by 35% (to 1.11% per year; P value 0.001 for superiority; RR: 0.65; 95% CI: 0.52 to 0.81), and at this dose there was no increase in major bleeding.
- Major bleeding was 3.36% per year in the warfarin group, as compared with 3.11% per year in the 150 mg dabigatran group (reduced intra-cerebral bleeding with a slight increase in GI bleeds).

Dabigatran: Implications for Clinical Practice

The authors conclude that, “In patients with AF, dabigatran, given at a dose of 150 mg Bid, as compared with warfarin, was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage.”

These results of RE-LY are fantastic as *overall **this is the only trial where warfarin has been beaten....until***

Dabigatran: Implications for Clinical Practice

- *No routine anti-coagulation monitoring is necessary and in fact is unreliable. If an INR was 4 or 5 in a stable patient, it would mean nothing.*
- **no specific antidote for dabigatran related bleeding, which has a half-life of 12 to 17 hours.**
- **General supportive care and “tincture of time” usually work.**

Dabigatran: Implications for Clinical Practice

Dabigatran, with its lower stroke rate and lower intracranial bleeding rate compared with warfarin, will lower the threshold for anticoagulation to prevent stroke in AF patients.

The decision to put a patient with AF on warfarin or dabigatran should be based upon whether the patient can adhere to twice-daily dosing, patient preference, **cost**, and whether an anticoagulation management program is available for routine INR monitoring. Dabigatran will be used primarily in patients who have problems with warfarin such as low rates of INR control, or who are at high-risk for bleeding or for poor compliance to treatment. Based on expert consensus, the authors say that patients taking warfarin who have sufficient INR control might not benefit by switching to dabigatran.

FDA: Dabigatran Should Only Be Stored in Original Containers

Dabigatran (Pradaxa) should only be dispensed and stored in its original manufacturer bottle or blister pack, *not in organizers or pill boxes. Nor should it be cut.*

Lower Threshold for Anticoagulation

- There are many borderline cases that can go “either way” with respect to anticoagulation (**CHADS2 score of 1 plus**)—*this is where CHA2DS2-VASc comes into play.*
- The efficacy and safety of dabigatran will ultimately increase the proportion of AF patients who receive indefinite duration anticoagulation (a little better and safer).

AF

Please remember if the patient has a CHADS2 Score of ≥ 2

Dabigatran: Implications for Clinical Practice

The major question about dabigatran has now shifted from efficacy to cost.

Hopefully with the approval of other efficacious similar agents, cost will go down and usage will expand.

In the future, hopefully, we can transfer all of our

PK/PD of 5 Novel Oral Agents

	Dabigatran	Apixaban	Rivaroxaban	Edoxaban (DU-176b)	Betrixaban (PRT054021)
Target	Ila (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%	40%	33%	35%	<5%

CYP = cytochrome P450; NR = not reported

Phase III AF Trials

	Re-LY	ROCKET-AF	ARISTOTLE	ENGAGE AF-TIMI 48
Drug	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Dose (mg)	150, 110	20 (15*)	5 (2.5*)	60*, 30*
Freq	BID	QD	BID	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 AFI x 2 <12 mths	AF x 1 < 12 mths
% VKA naive	50%	38%	43%	40% goal

*Patients with ↓ drug clearance. **Max of 10% with CHADS-2 score = 2 and no stroke

randomized, open-label, blinded end point evaluation

VKA = Vit

RELY	Dabigatran 110 mg	Dabigatran 150 mg	Warfarin
CHADS2 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
CHADS2 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
CHADS2 Mean	2.1	2.1
0-1 (%)	34	34
2 (%)	35.8	35.8
3+ (%)	30.2	30.2

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%	Mean 62% Median 66%

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

Non Inferiority
p vs warfarin

RE-LY

Dabigatran 110 mg	1.53% per year	HR = 0.91	ITT Analysis p<0.001
Dabigatran 150 mg	1.11% per year	HR = 0.66	p<0.001
Warfarin	1.69% per year		

ROCKET AF

Rivaroxaban 20mg	1.7% per year	HR = 0.79	Modified ITT p<0.001
Warfarin	2.2% per year		

ARISTOTLE

Apixaban 5 mg	1.27% per year	HR = 0.79	ITT Analysis p<0.001
Warfarin	1.60% per year		

Analysis is available for non-inferiority in Rocket AF. An on treatment or per-protocol analysis is generally preferred for the assessment of non-inferiority. If numerous patients come off of study drug, this biases the results towards an inferior result in an ITT analysis. This is the basis for performing a per-protocol analysis in this event.

Hemorrhagic Stroke

RELY

			HR	P-value
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

On treatment analysis in Rocket AF Hemorrhagic Stroke rates were 0.26% / yr for rivaroxaban vs warfarin, p=0.024. No on treatment analysis is available from RE-LY.





Comparison of the 3 new OAC's (cont.)

- All 3 agents had major reductions in intracranial hemorrhage compared to warfarin (major safety benefit)
- Dabigatran has major GI intolerance (15-20%) whereas the other agents did not.
- Summary:

Most efficacious: Dabigatran

Least GI Bleeding: Apixaban

Easiest to comply: Rivaroxaban

**Following Study Drug Discontinuation:
Are There “Rebound” Events or
a “Resumption” of Events?**

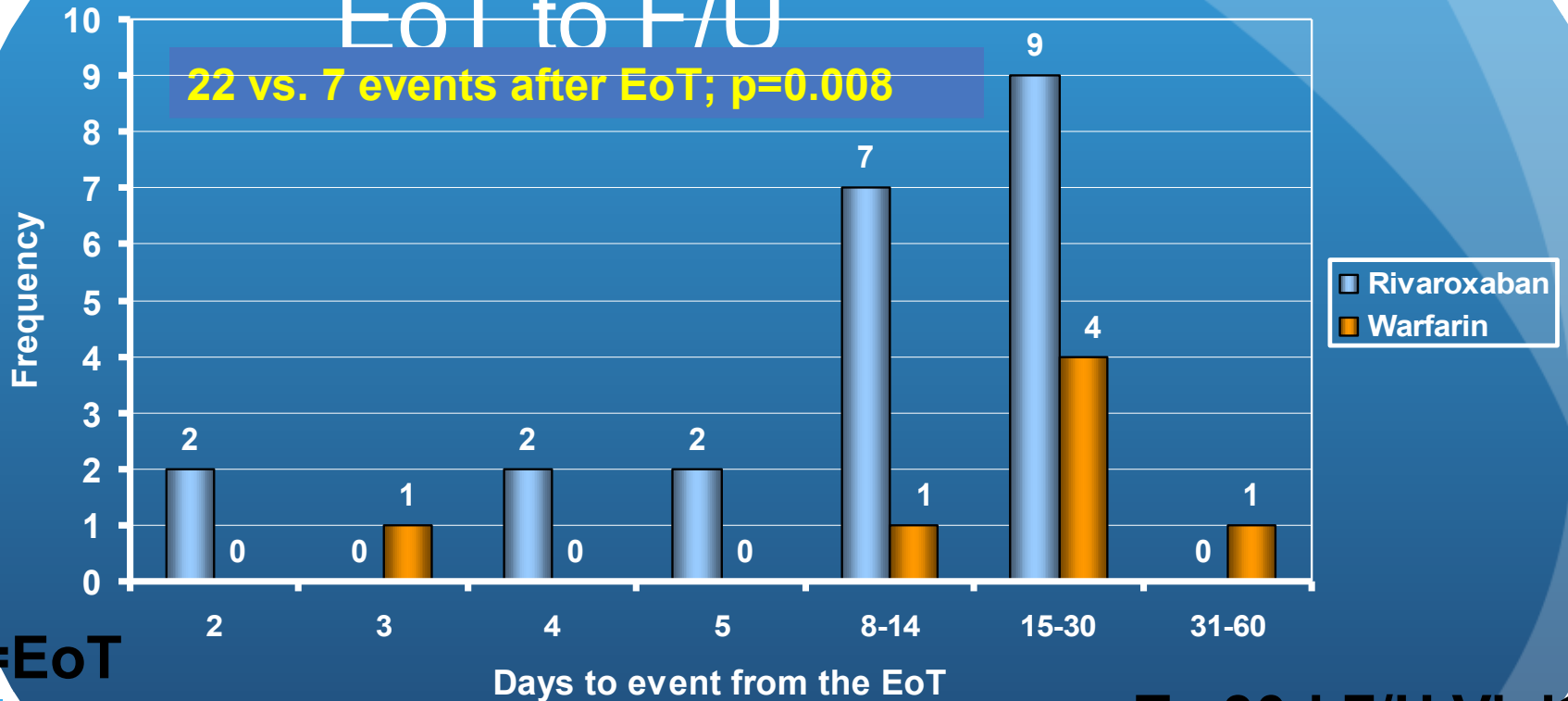
Differential Event Rates

INR for the 60d Transition and

First Primary Event During Transition Period for Patients after EoT

EoT to F/U

22 vs. 7 events after EoT; p=0.008



T=EoT

T= 30d F/U Visit

R Median time to TTR INR 13d / 365 d x avg. annual risk 8.5% x 7131 = 21.6

W Median time to TTR INR 3 / 365 d x avg. annual risk 8.5% x 7133 = 4.98

New Options in Anticoagulation for AF

Del Zopp GJ et al. N Engl J Med

September 8 2011; 365: 952-953.

ARISTOTLE: Another Competitor Beats Warfarin

- **Warfarin** reduces the risk for stroke or systemic embolism in patients with atrial fibrillation (AF). However, warfarin has a narrow therapeutic window and requires frequent blood draws and dietary restrictions, so only about 50% of patients eligible for the drug receive it.

ARISTOTLE—another home run

- In the manufacturer-sponsored ARISTOTLE trial, 18,201 patients with AF and one additional risk factor for stroke (mean CHADS2 score, 2) were randomized to **apixaban** (Eliquis)—(Pfizer/Bristol-Myers Squibb)—another Xa direct thrombin inhibitor—at (5 mg twice daily) or warfarin (dose-adjusted to a target INR ratio of 2 to 3).
- During a mean follow-up of 1.8 years, apixaban was associated with a small but significant reduction in stroke or systemic embolism compared with warfarin (1.27% vs. 1.60% per year)—a relative 21%.
- Apixaban was also associated with significant

- Results are consistent with those of the three prior warfarin-competitor trials, it appears that **Beats Warfarin** will soon have another alternative to

Granger CB et al. Apixaban versus warfarin in patients with atrial fibrillation.

N Engl J Med September 15 2011; 365: 981-992.

Mega JL. A new era for anticoagulation in atrial fibrillation. *N Engl J Med* September 15 2011; 365: 1052-1054.

- Unfortunately, which drug is the best choice for individual patients cannot be definitively determined without direct head-to-head comparison trials, none of which are yet under way.

- Thus, at least for now, prescribing decisions

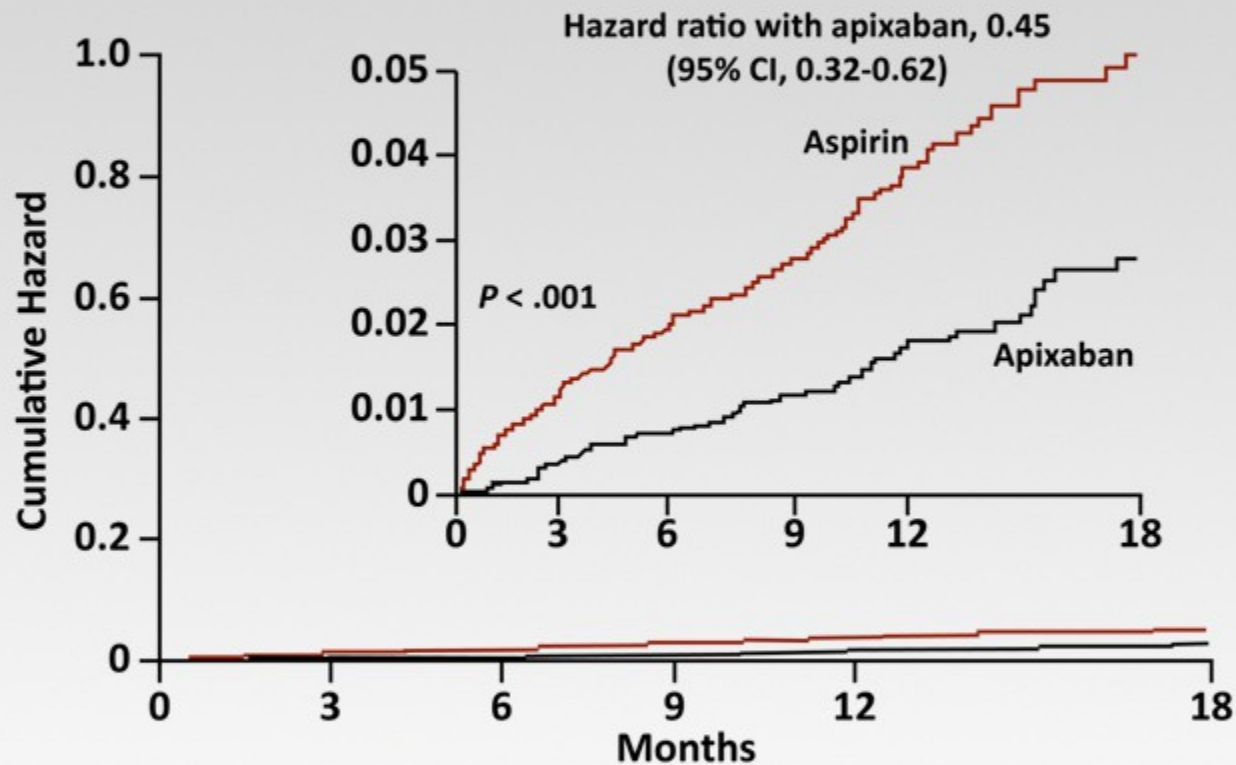
Apixaban-Advantage

Connolly SJ et al. *N Engl J Med* March 3, 2011; 364: 806-817.

- Has another major stroke prevention trial under its belt.
- **AVERROES**: randomization of 5,599 pts. To apixaban vs aspirin in patients not suitable for warfarin.
- Conclusion: the bleeding risk with apixaban was the same as with low dose aspirin with obvious reduction of events.

AVERROES: Apixaban in Patients With AF

Stroke or Systemic Embolism

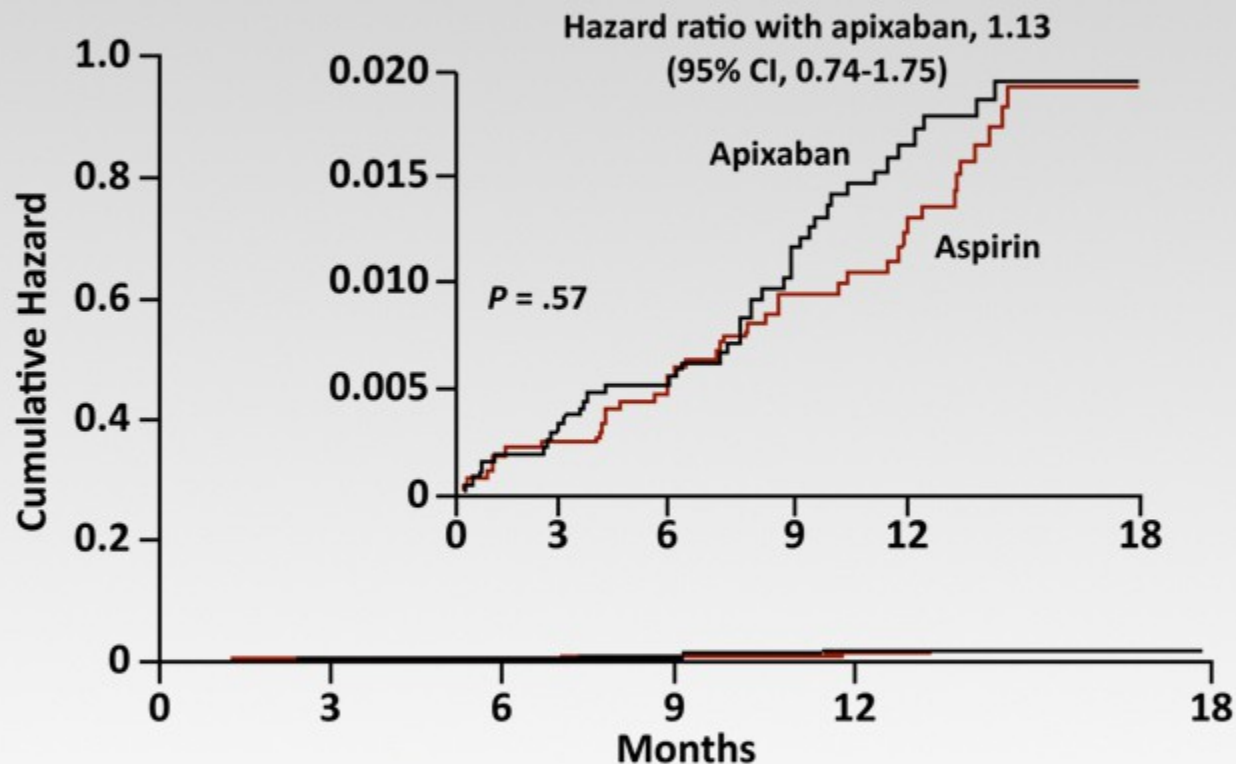


Number at Risk

Aspirin	2791	2716	2530	2112	1543	628
Apixaban	2808	2758	2566	2125	1522	615

AVERROES: Risk for Major Bleeding With Apixaban vs Aspirin

Major Bleeding



Number at Risk

Aspirin	2791	2738	2557	2140	1571	642
Apixaban	2808	2759	2566	2120	1521	622

At 2 years, the rates of permanent discontinuations were 17.9% per year with apixaban and 20.5% per year with aspirin (hazard ratio with apixaban, 0.88; 95% CI, 0.78-0.99; $P = .03$).

ACTIVE-W trial

Connolly et al. *Lancet*, 2006; 367: 1903.

- Compared clopidogrel plus aspirin with warfarin for prevention of vascular events in AF patients.
- Warfarin was found superior for reduction of events.
- Clopidogrel plus aspirin was associated with similar bleeding risk.

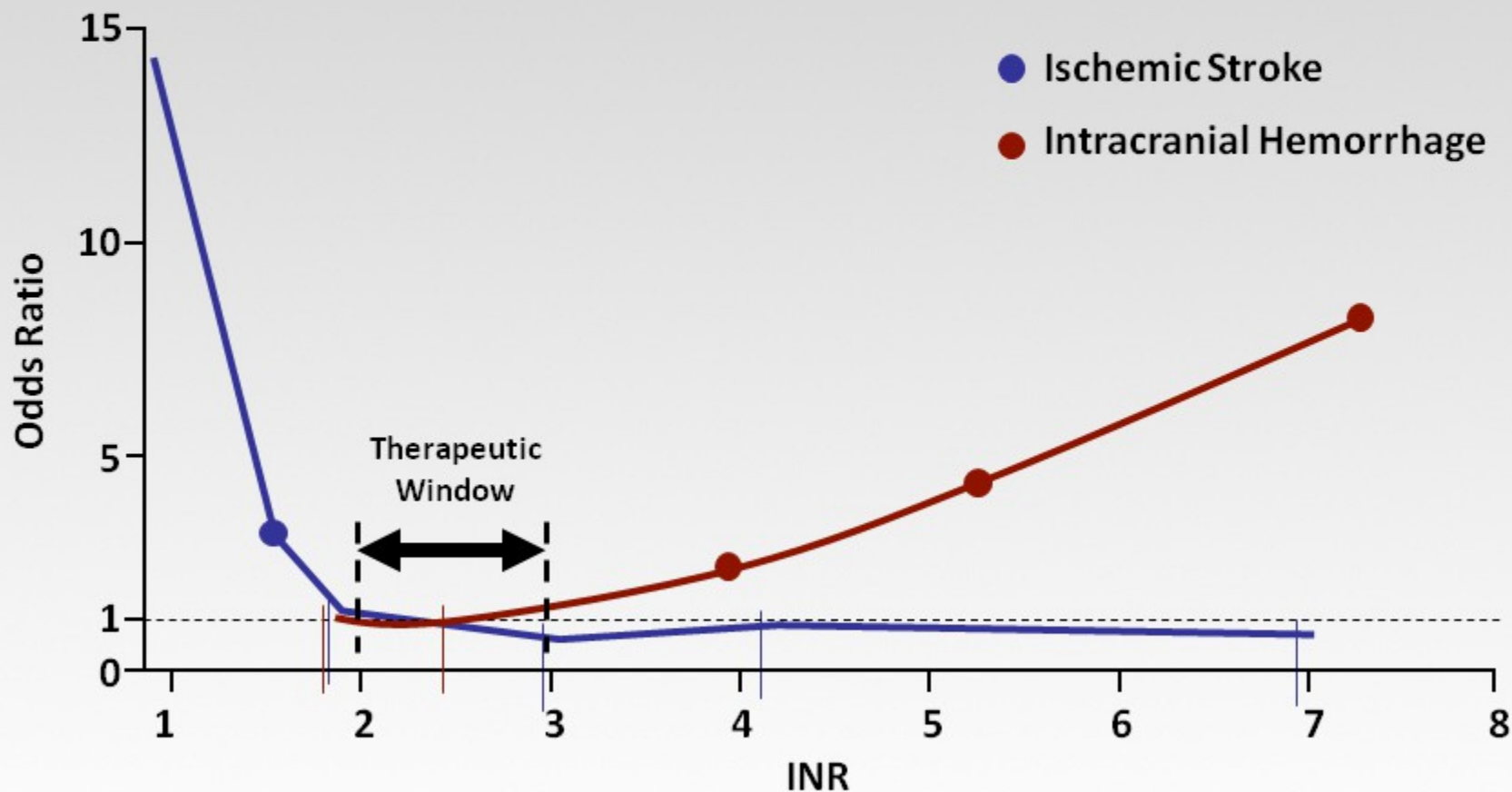
Conclusion: Warfarin is preferable in the absence of contraindications.

ACTIVE-A trial

Connolly SJ et al. N Engl J Med 2009; 360:2066.

- Examined whether the clopidogrel plus aspirin combination would reduce vascular events in AF patients unsuitable for warfarin.
- The combination was found to reduce the risk of major vascular events, especially stroke compared to aspirin.
- The combination was associated with an increased risk of major bleeding compared with aspirin alone.

Warfarin Has a Narrow Therapeutic Window: Relationship Between Clinical Events and INR



Hylek EM, et al. *Ann Intern Med.* 1994;120:897-902.

Hylek EM, et al. *N Engl J Med.* 1996;335:540-546.

Alternatives to Warfarin

Apixaban

Rivaroxaban

Dabigatran

Target

Xa

Xa

Thrombin

Dosing interval

Twice daily

Once daily

Twice daily

Half-life

9-14 hours

5-9 hours
Longer in elderly

8-17 hours

Renal
metabolism

33%

25%

80%

Hepatic
metabolism

67%

75%

20%

None of the alternative anticoagulants listed above has a reversing agent.

Comparison of Features of New Anticoagulants With Those of Warfarin

Features	Warfarin	New Agents
Onset	Slow	Rapid
Dosing	Variable	Fixed
Food effect	Yes	No
Drug interactions	Many	Few
Monitoring	Yes	No
Half-life	Long	Short
Antidote	Yes	No

So, What's the plan?

- There's an old maxim in medicine that one shouldn't be the first to prescribe a new drug, nor the last.
- We have to concede the superiority of the NOACs, now supported as safer and more effective in three clinical trials: RE-LY, ROCKET-AF and ARISTOTLE.

So, What's the plan?

- How, then, could a cardiologist not rush to the electronic prescription pad and immediately take most patients off warfarin and prescribe NOACs?
- Well, for one thing, there's the cost.
- The current lack of a specific drug antidote to the NOACs is of some concern.

Take home Point:

Availability of newer agents and better risk stratification should improve utilization of appropriate treatment and decrease stroke risk.

Aspirin Should Not Be Used for Stroke Prevention in AF

[Hyperlink to Medscape article](#)

Risk of Hemorrhage on Warfarin

- Stratification Score

Risk factor	Points
Severe renal Dx	3
Anemia	3
Age > 75	2
Prior hemorrhage	1
Hypertension	1

- Event Rates/100 patient yrs

Score	Event rates
0 to 3 (low)	0.76
4 (intermediate)	2.62
5 to 10 (high)	5.76

Risk of Bleeding with Multiple Antithrombotic/Antiplatelet Drugs

FIGURE 1

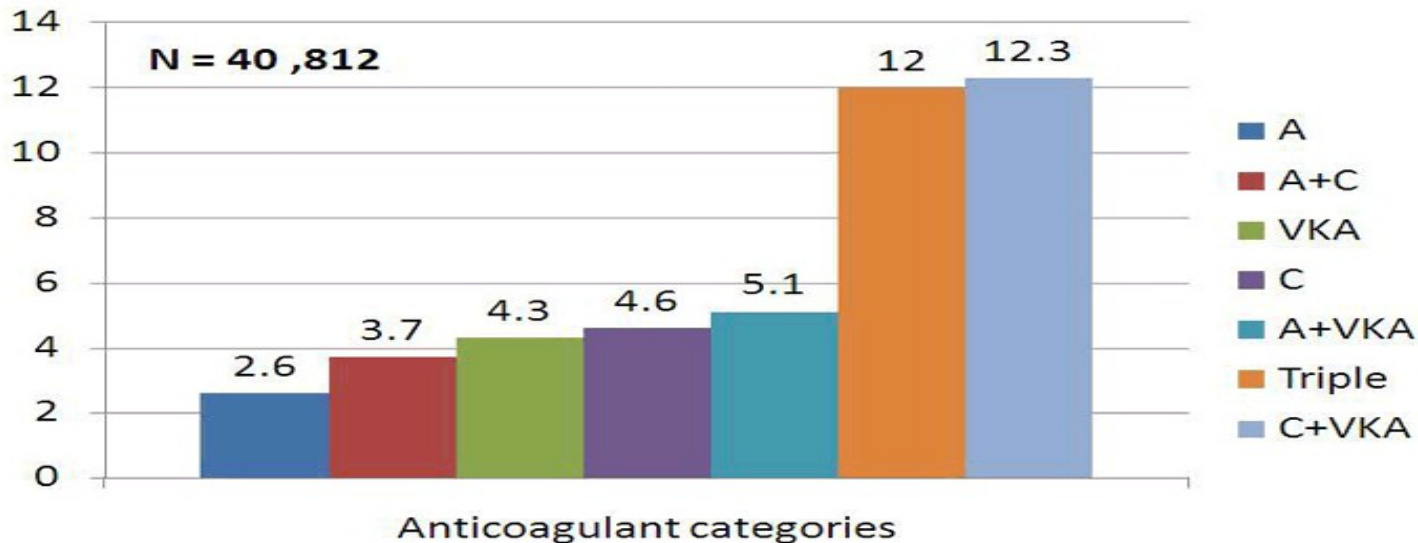


Figure 1. Risk of bleeding requiring hospitalization associated with various antithrombotic regimens post-myocardial infarction. In 40,812 patients, ≥ 30 years of age, admitted from 2000-2005 with first-time AMI to Danish hospitals, shown above are reported rates of bleeding requiring hospitalization, by choice of antithrombotic regimen. On average, 4.6% of patients were admitted for bleeding during a mean follow-up of 476.5 days.

A – aspirin; C – clopidogrel; VKA – Vitamin K antagonists; Triple – triple antithrombotic therapy

Sørensen R, et al. *Lancet* 2009; 374: 1967–1974.

Case Study 1 : New Onset AF

- 70 yr old women with HBP (BP 120/70)—presents with fatigue.
- ECG: AF with VR 120 and LVH.
- Echo: LVH, NL LV size, 2+ MR with LVEF 40-45%.
- ETT Echo negative for ischemia.
- Meds: lisinopril 20mg, ASA 81mg and metoprolol ER 25mg.

Case Study 2: Chronic AF on warfarin

- 65 yr old male-CHADS2 score 3.
- Recurrent GI Bleed.
- Angiodysplasia.
- Plan: ?

Atrial Fibrillation and Dementia

- There is increasing evidence of a link between atrial fibrillation and cognitive impairment irrespective of clinical or imaging evidence of stroke.
- March 5, 2013 *Annals Internal Medicine* (Kalantarian, S., et al) found RR ratio of 1.4 overall incidence of dementia in all patients with AF regardless of stroke history
- Multiple mechanism postulated: Silent microembolic events, occult inflammation, many associated concomitant comorbidities

Shadi Kalantarian, MD, MPH; Theodore A. Stern, MD; Moussa Mansour, MD; and Jeremy N. Ruskin, MD *Ann Intern Med.* 5 March 2013;158(5_Part_1):338-346

Other Options for Stroke
Prevention in Atrial Fibrillation:

LEFT ATRIAL OCCLUSION DEVICES

Left Atrial Appendage Occlusion Devices

Watchman™ Left Atrial Occluder Device

“Watchman” Left Atrial Occluder Device

Watchman™ Left Atrial Occluder Device

