

STROKE PREVENTION IN ATRIAL FIBRILLATION

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OBJECTIVES

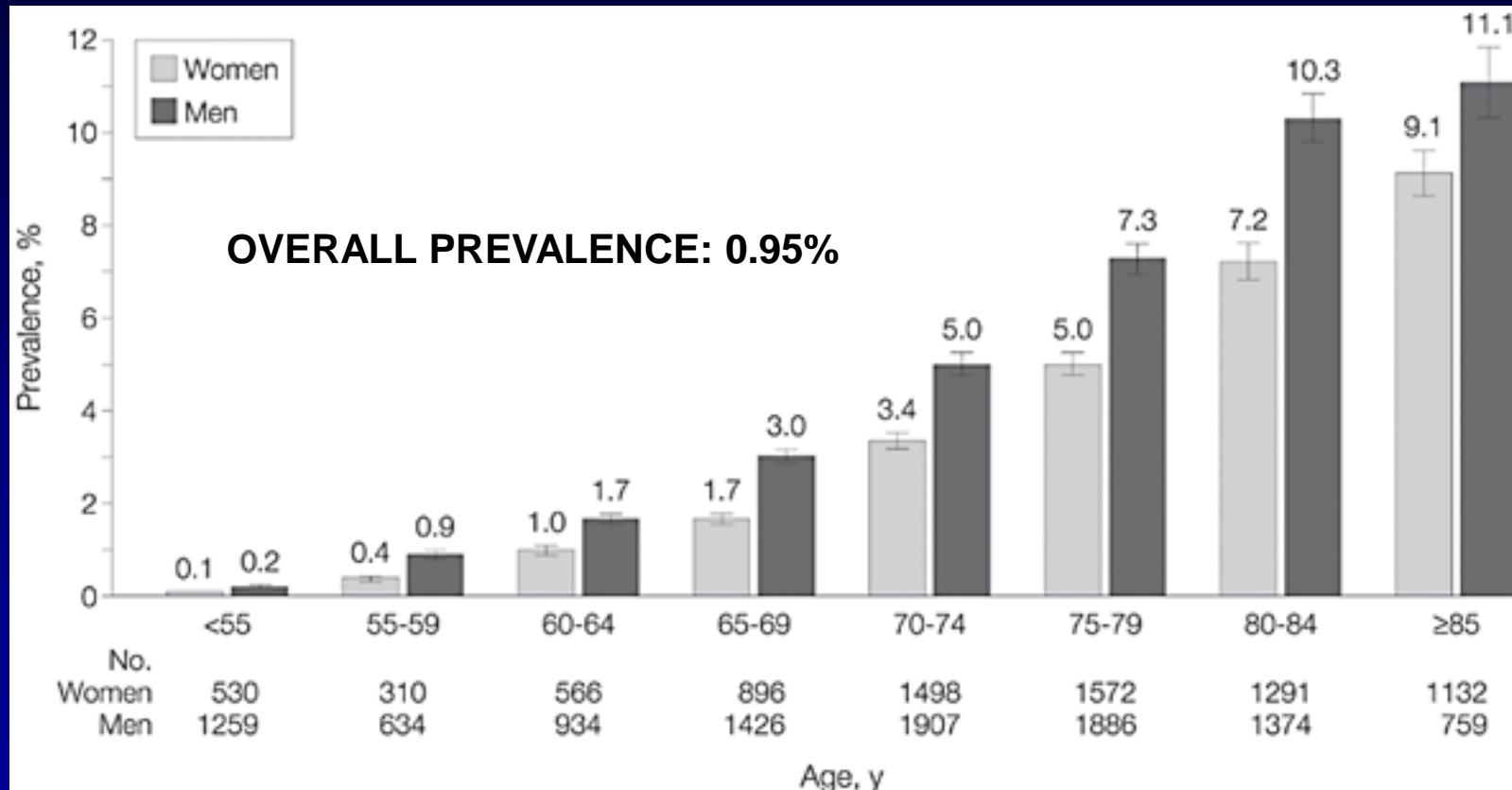
- 1. Review epidemiology, pathophysiology and risk factors for stroke in patients with AF**
- 2. Evaluate the role of antithrombotic therapies for stroke prevention in AF**
- 3. Consider the future of anticoagulant therapy in light of the availability of new drug therapies**

GENERAL EPIDEMIOLOGY OF ATRIAL FIBRILLATION

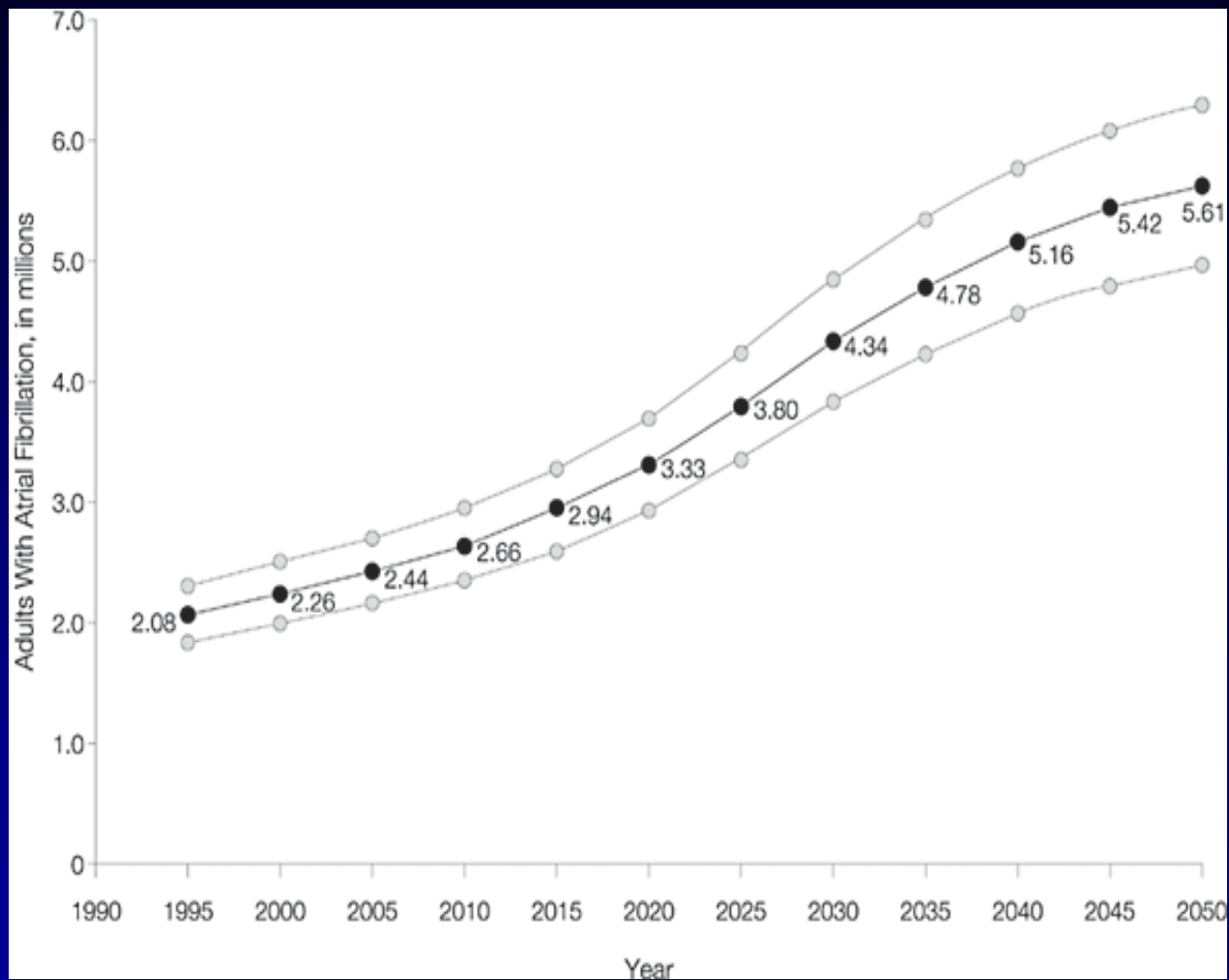
- 0.4% of the general US population has AF
- 2.2 million Americans are affected
- Most common heart rhythm disturbance
- Accounts for 1/3 of all hospital admissions for arrhythmia
- men > women (regardless of age)
- whites > blacks
- incidence and prevalence increase with age

PREVALENCE OF AF STRATIFIED BY AGE AND SEX

N = cohort of 17,974 adults with AF identified during 18 month study period among 1.89 million members of a CA health care plan



PROJECTED US ADULTS WITH AF 1995 - 2050



Go AS et al. ATRIA Study. JAMA 2001; 285: 2370-5.

MULTIVARIABLE RISK FOR DEVELOPING AF

Results from the Framingham Heart Study

ODDS RATIO

	MEN	WOMEN
<i>Congestive heart failure</i>	4.5 ^a	5.9 ^a
<i>Age (per decade)</i>	2.1 ^a	2.2 ^a
<i>Valvular heart disease</i>	1.8 ^c	3.4 ^a
<i>Diabetes</i>	1.4 ^b	1.6 ^c
<i>Hypertension</i>	1.5 ^c	1.4 ^b
<i>Myocardial infarction</i>	1.4 ^b	1.2
<i>LV hypertrophy by echo</i>	1.4	1.3
<i>Smoking</i>	1.1	1.4

a p<0.001
b p<0.05
c p<0.1

ACUTE CAUSES OF ATRIAL FIBRILLATION

- Alcohol intake
- Surgery
- Electrocutation
- Myocardial infarction
- Pericarditis
- Myocarditis
- Pulmonary embolism
- Hyperthyroidism

CLINICAL CLASSIFICATION OF ATRIAL FIBRILLATION

- **Paroxysmal** - Converts spontaneously to sinus rhythm
- **Persistent** - Capable of being converted to sinus rhythm
- **Permanent** - Conversion to sinus rhythm not possible

ATRIAL FIBRILLATION: GOALS OF THERAPY

- **Rate control**
 - Patient remains in AF, but rate is controlled to the point that symptoms are not experienced
 - Heart rate (HR) < 80 beats/min (bpm)
- **Rhythm control**
 - Electrical or pharmacologic cardioversion is used to maintain sinus rhythm
- **Antithrombotic therapy**
 - Prevention of embolic stroke

ANNUALIZED RISK OF STROKE IN AF

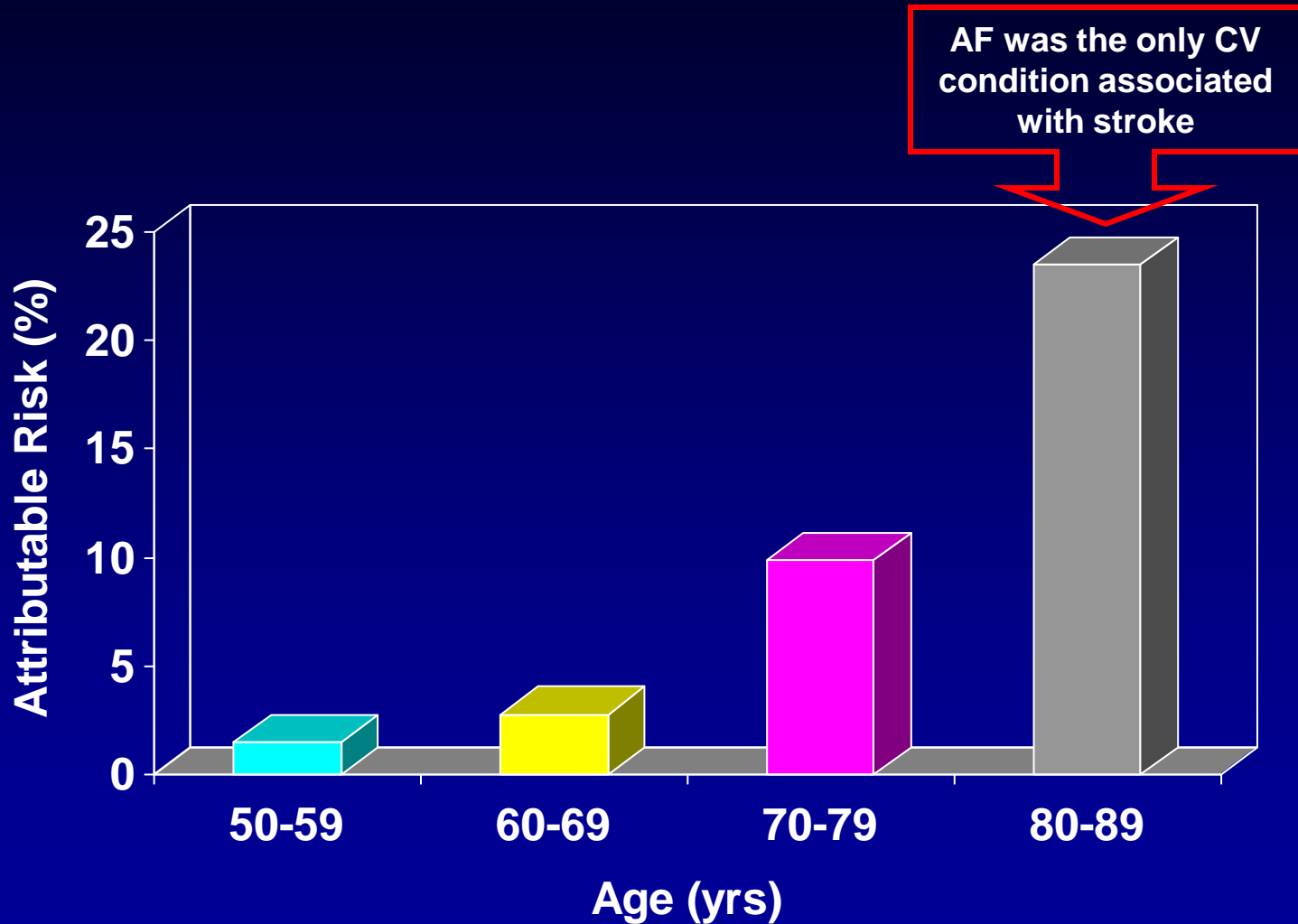
PERMANENT/PERSISTENT AF 3.2%

PAROXYSMAL AF 3.3%

.....
LONE AF < 1%

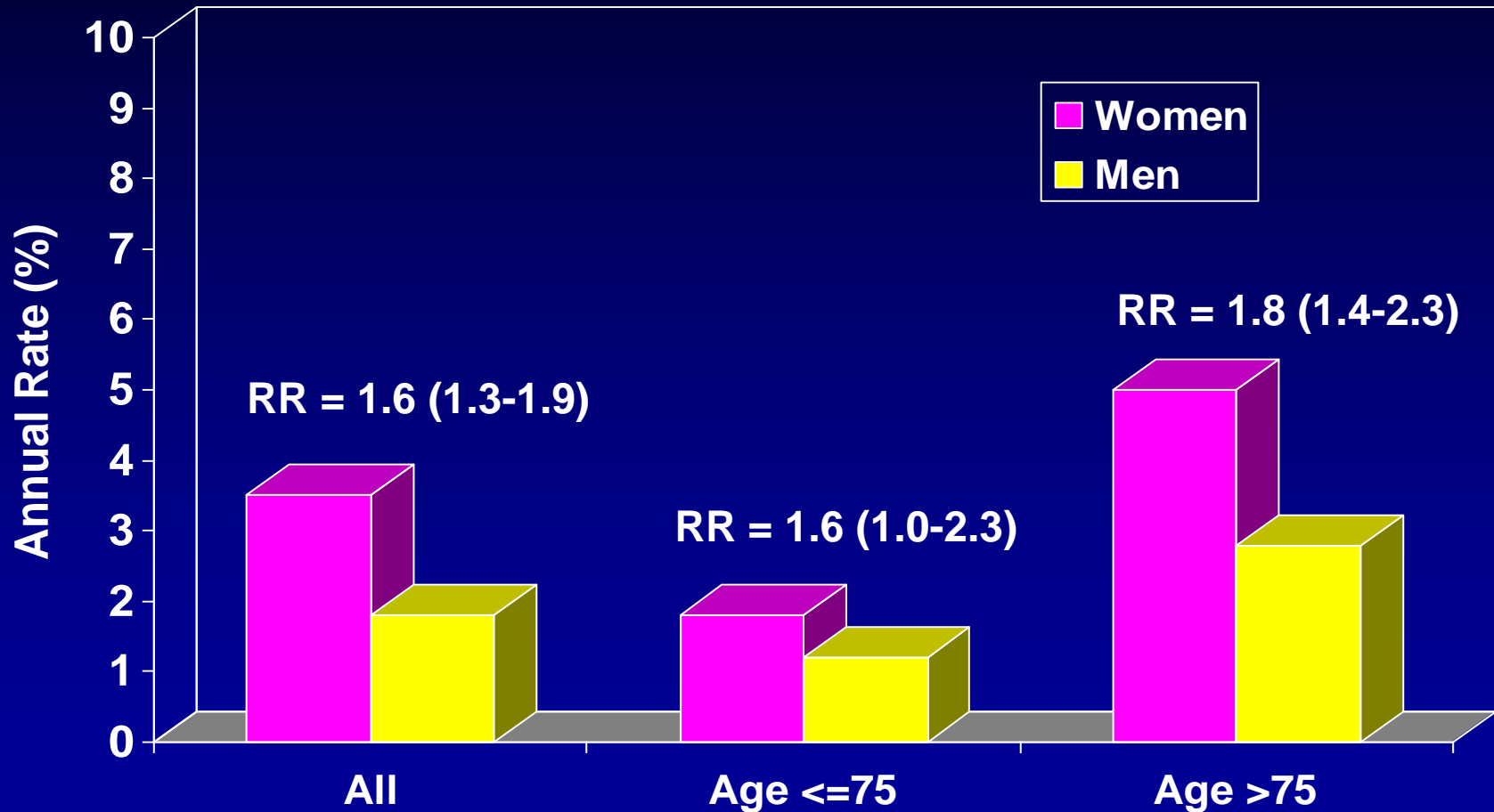
- age < 65
- no prior hx TIA or stroke
- no HTN or DM
- no CHF or LV dysfunction

AGE-RELATED RISK OF STROKE IN AF



GENDER DIFFERENCES IN RISK OF STROKE IN AF

n=13,559 patients with AF

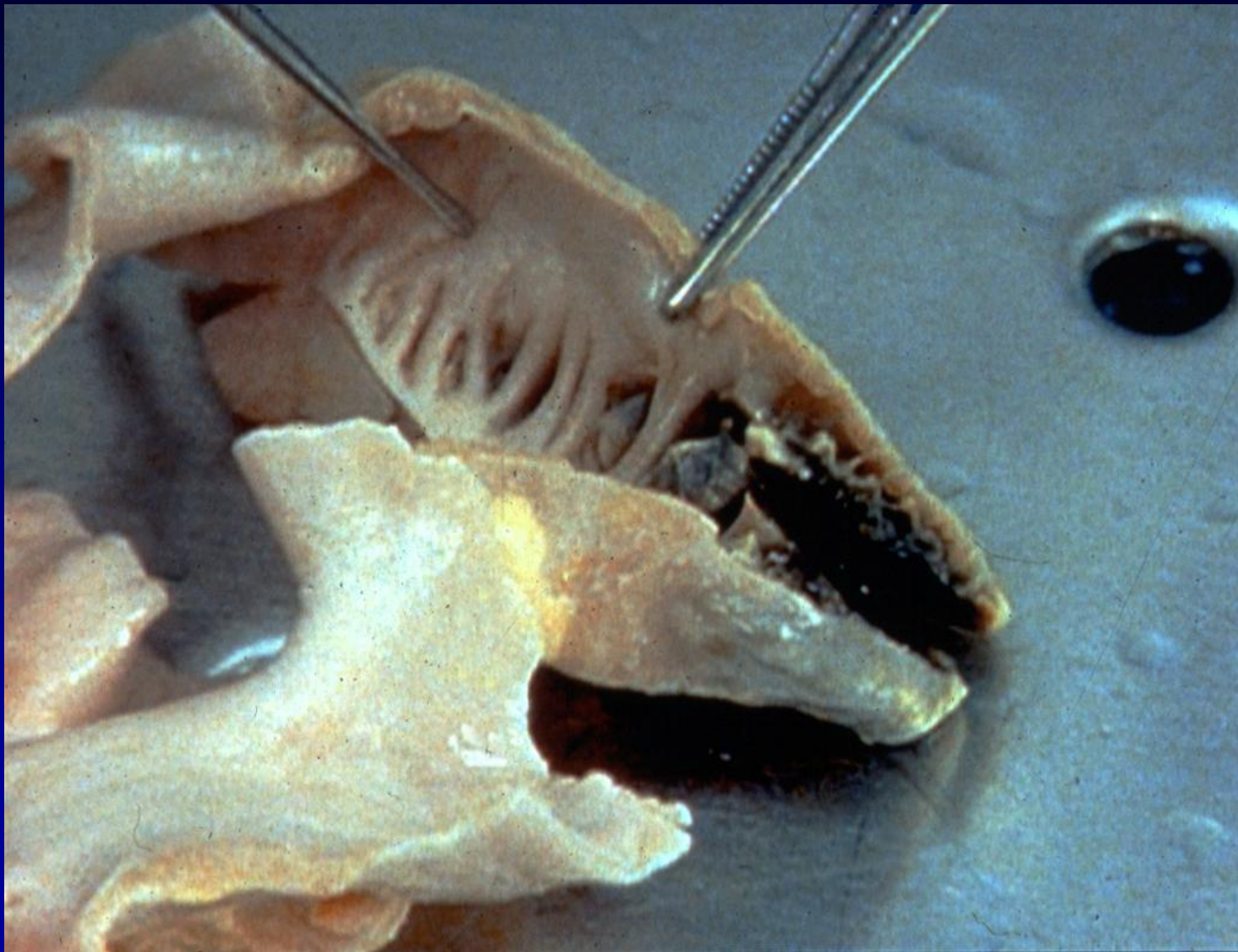


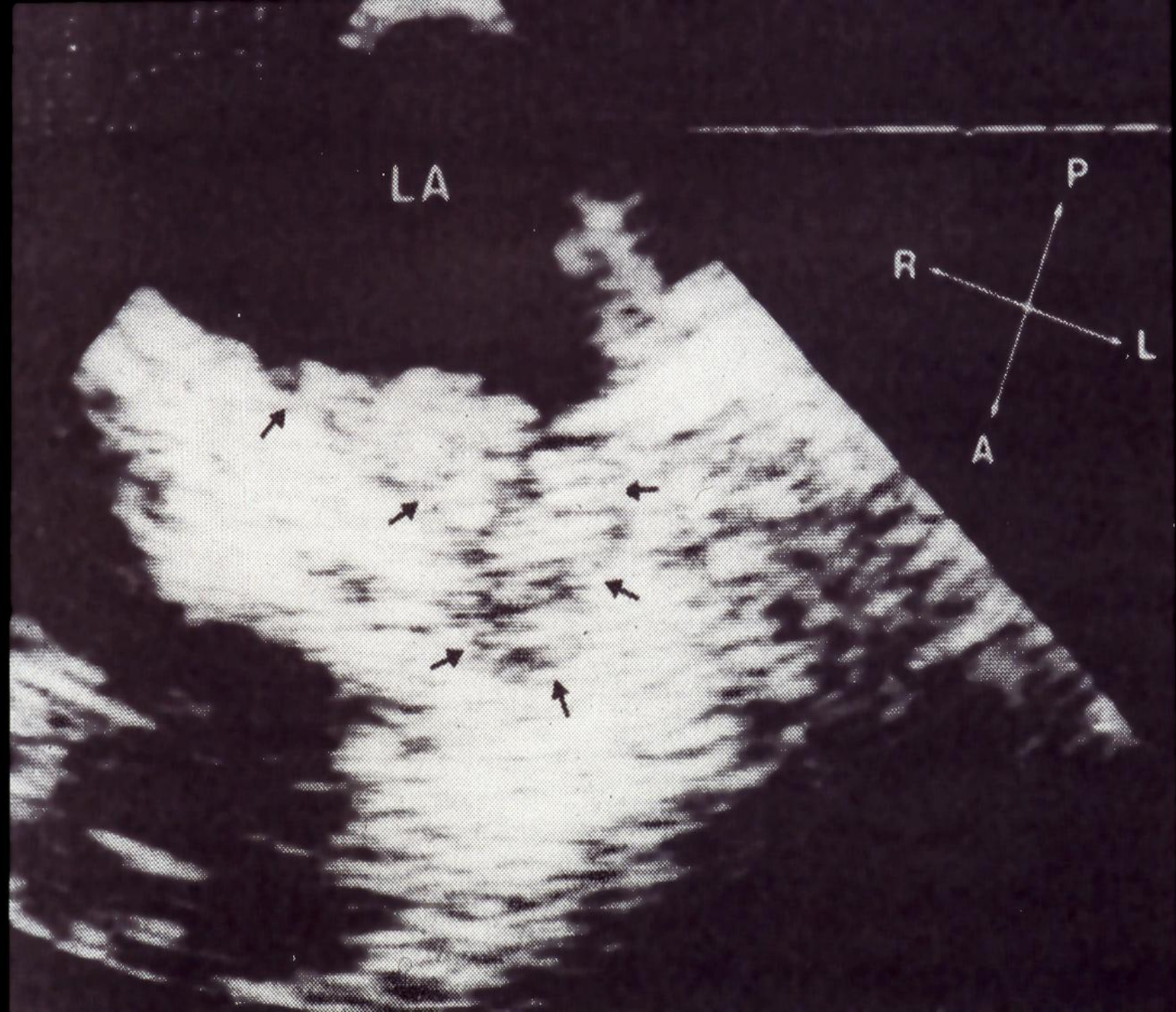
- No significant difference in 30-day mortality between men and women

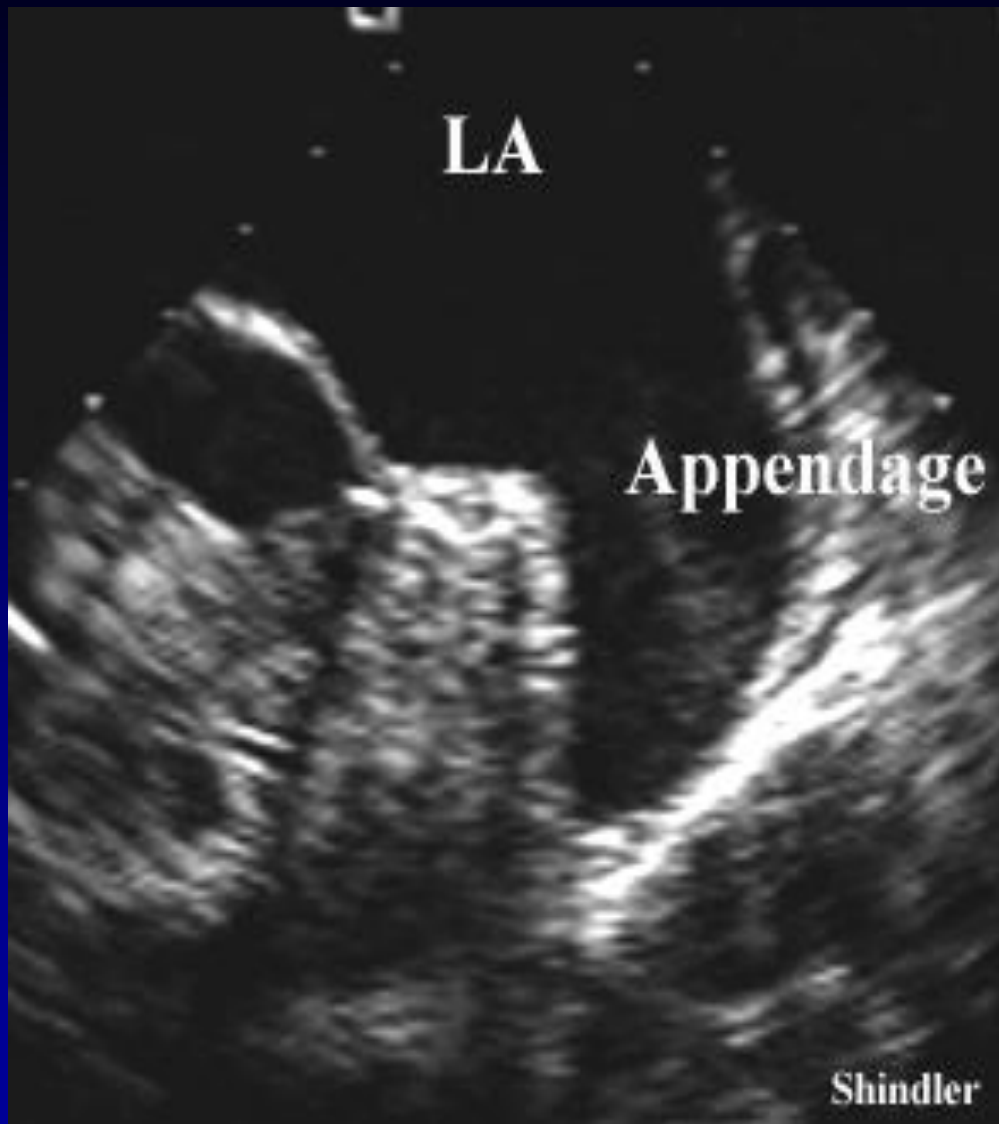
SIMPLISTIC PATHOPHYSIOLOGY OF THROMBOSIS IN AF: STASIS

- **Loss of organized atrial contraction**
- **Progressive atrial dilation**
 - **Left atrial (LA) size is independent risk factor for stroke**
- **Abnormal stasis in LA and left atrial appendage (LAA) can be visualized as spontaneous echocontrast during a transesophageal echocardiogram**
 - **LAA is site of thrombus formation in 70-90% cases of AF**
 - **LA thrombi present in 5-14% of patients if AF duration > 48 hrs**
- **Pooling of blood in atria → Mural thrombi**
- **Thrombi can break off and travel up carotid artery to brain → Thromboembolic stroke**

THROMBUS FORMATION IN THE LEFT ATRIAL APPENDAGE







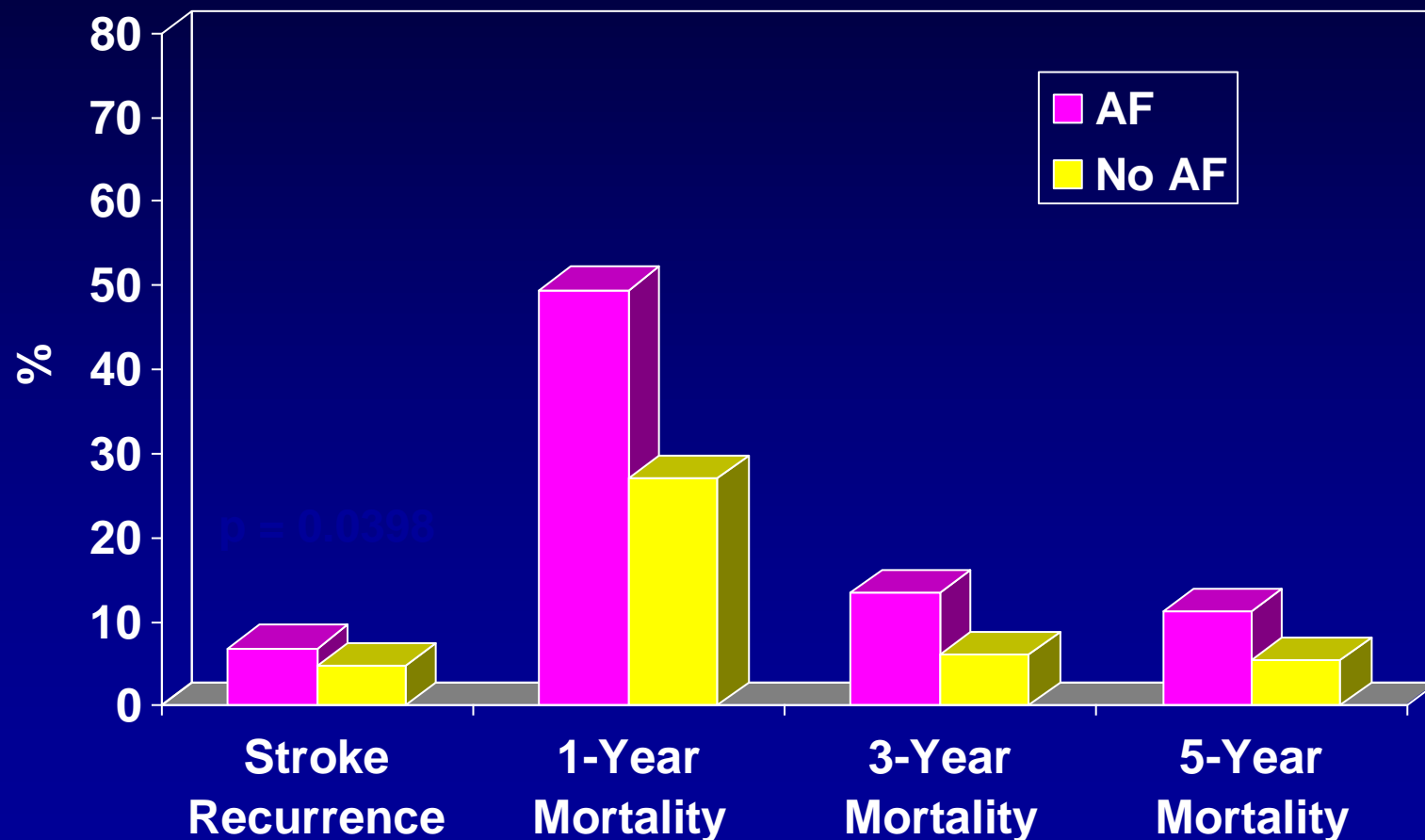
LA

Appendage

Shindler

IMPACT OF AF ON STROKE RECURRENCE AND MORTALITY

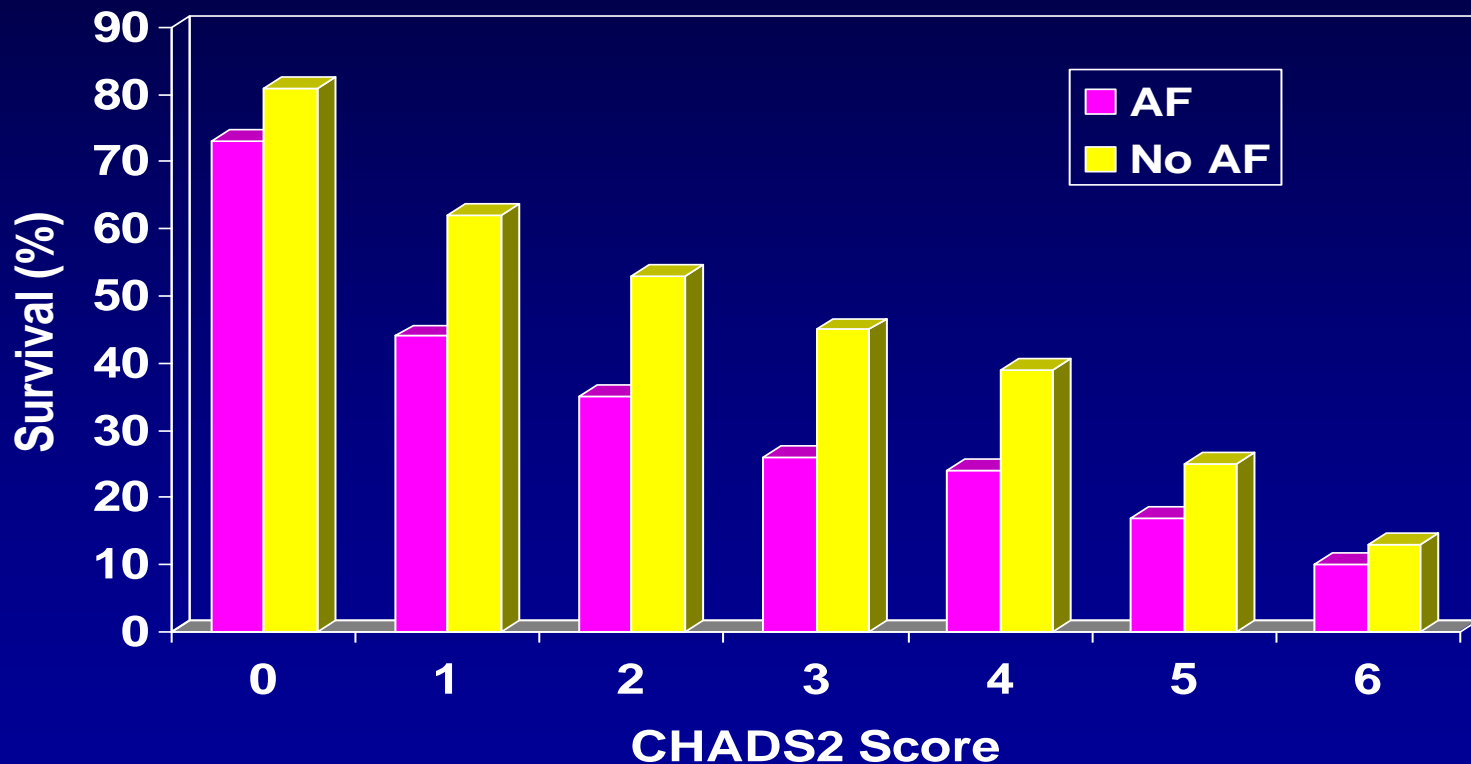
n=3530 patients with first-time ischemic stroke (869 patients with AF)



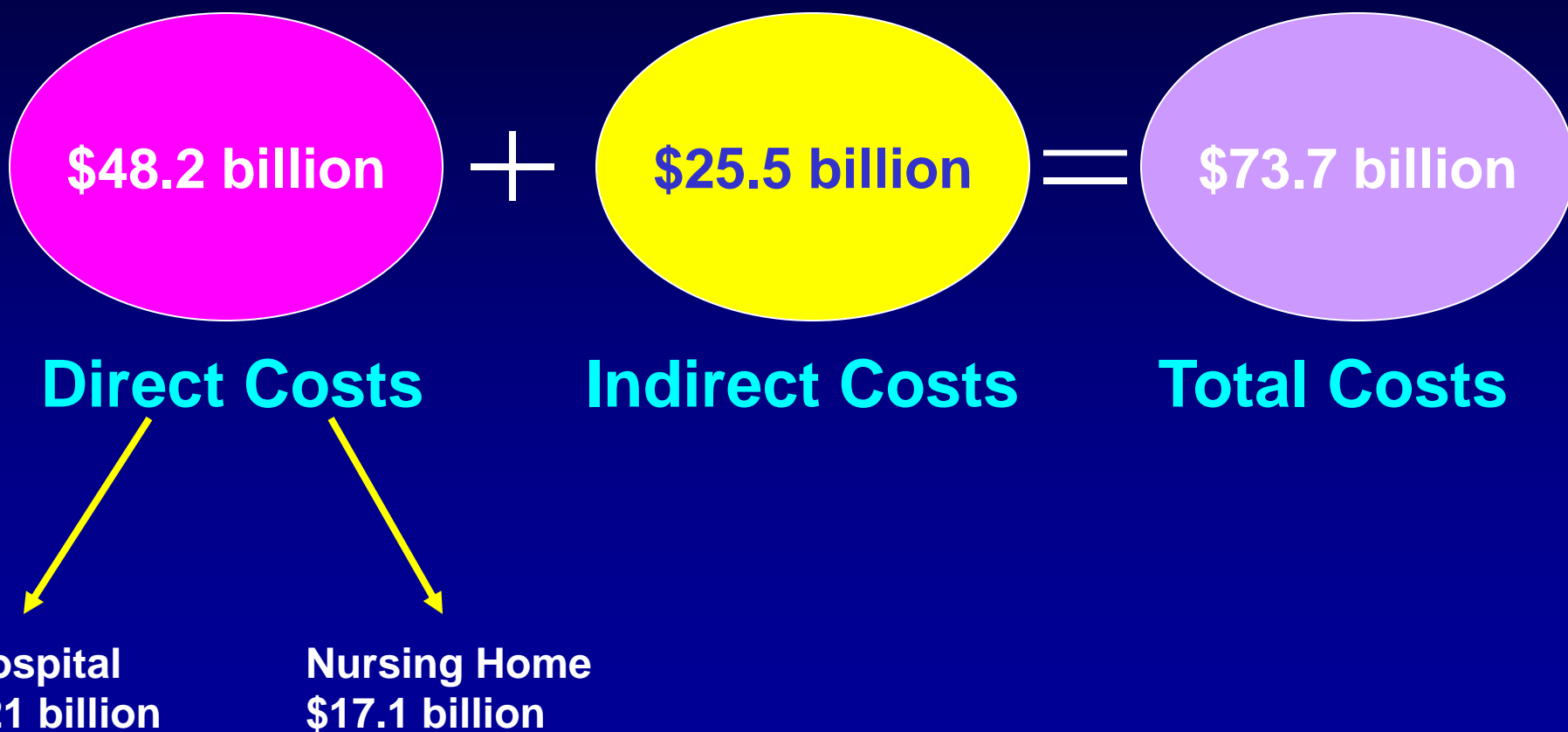
IMPACT OF STROKE ON SURVIVAL

$n = 105,074$ patients with and $73,253$ patients without AF who had a stroke between 2001-2005

5-Year Survival Rates



STROKE-RELATED COSTS IN US



IMPACT OF AF ON COST OF TREATING STROKE

Mean Costs Per Patient

	Patients with AF	Patients without AF
Acute hospitalization	\$7190 ± 4439*	\$5838 ± 3662
Readmission	\$1936 ± 5908	\$1118 ± 4256
Inpatient rehab	\$2058 ± 3637	\$1733 ± 2809
Total direct costs	\$15,575 ± 10,945*	\$11,638 ± 9571

CHADS2 SCORE: ESTIMATING STROKE RISK IN AF

C: recent CHF exacerbation	1 point	0 points:	1.9 %/yr	} LOW MOD
H: hx HTN, even if controlled	1 point	1 point:	2.8 %/yr	
A: age > 75	1 point	2 points:	4.0 %/yr	} HIGH
D: diabetes	1 points	3 points:	5.9 %/yr	
S: hx cerebral ischemia	<u>2 points</u>	4 points:	8.5 %/yr	
TOTAL		5 points:	12.5 %/yr	
		6 points:	18.2%/yr	

ACCP 2008 Evidence-Based Guidelines

STROKE PREVENTION IN ATRIAL FIBRILLATION

No risk factors	Aspirin 75-325mg qd	1B
1 risk factor	Warfarin INR 2.5 (2-3) or	1A
	Aspirin 75-325mg qd	1B
2 risk factors	Warfarin INR 2.5 (2-3)	1A
History of S troke, TIA or systemic embolism	Warfarin INR 2.5 (2-3)	1A
Mitral stenosis or prosthetic heart valve	Warfarin INR 2.5 (2-3) or higher valve-specific INR	1B

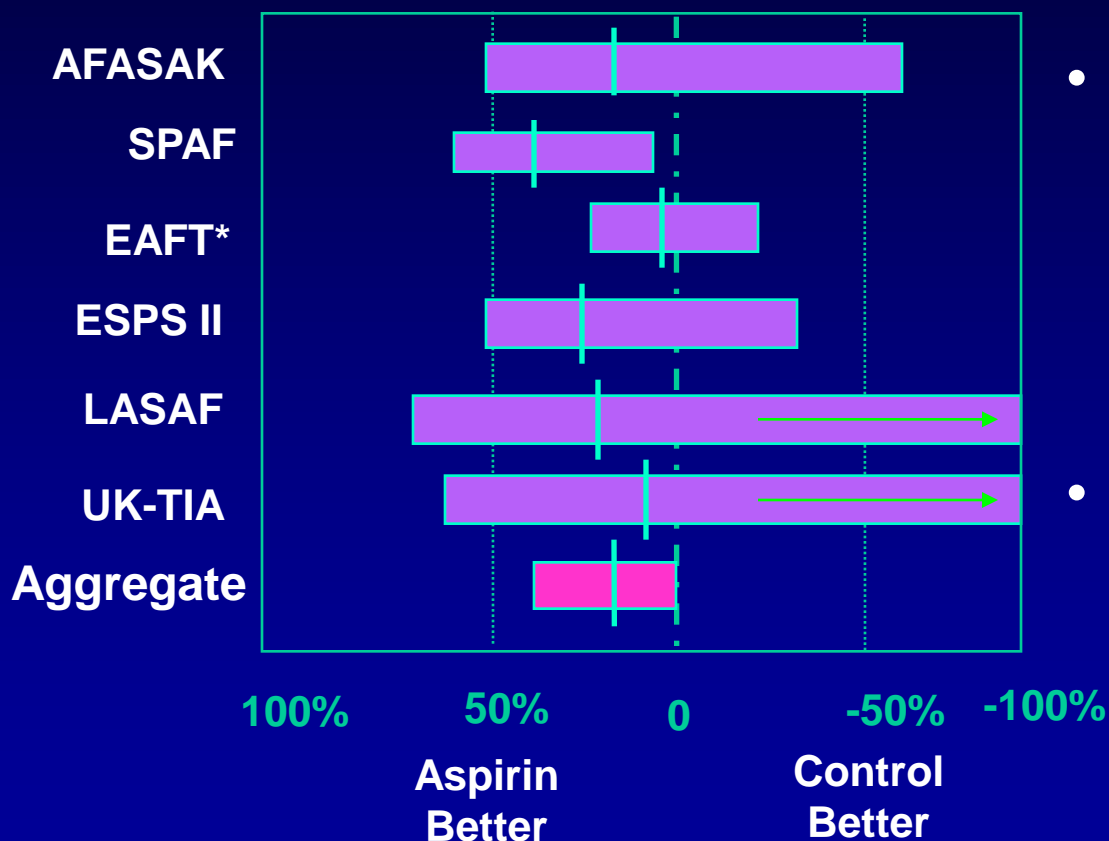
STROKE RISK FACTORS

- Moderate or severe left ventricular dysfunction and/or **C**HF
- History of **H**ypertension
- **A**ge > 75 years
- **D**iabetes mellitus

STROKE PREVENTION IN AF

Risk Reduction With Aspirin

Relative Risk Reduction

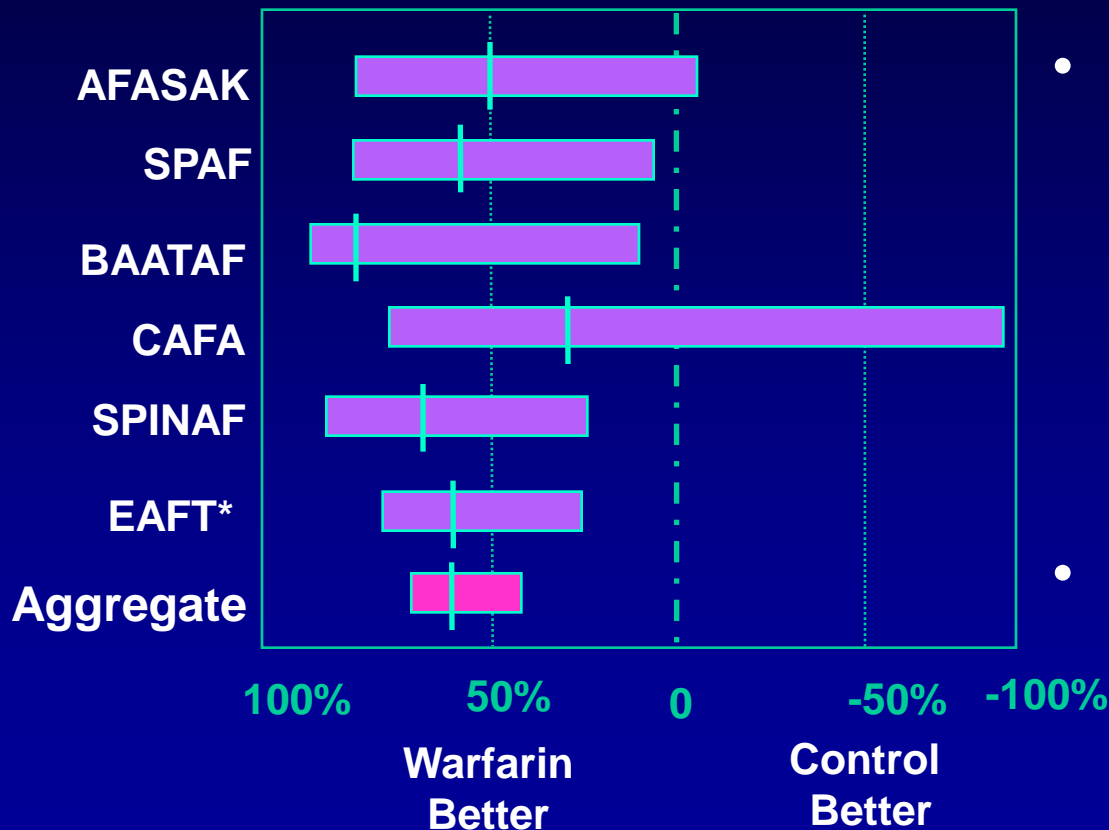


- Aspirin reduced the risk of ischemic stroke by 2%–38% versus control.
- The aggregate relative risk reduction in ischemic stroke was 22%.

STROKE PREVENTION IN AF

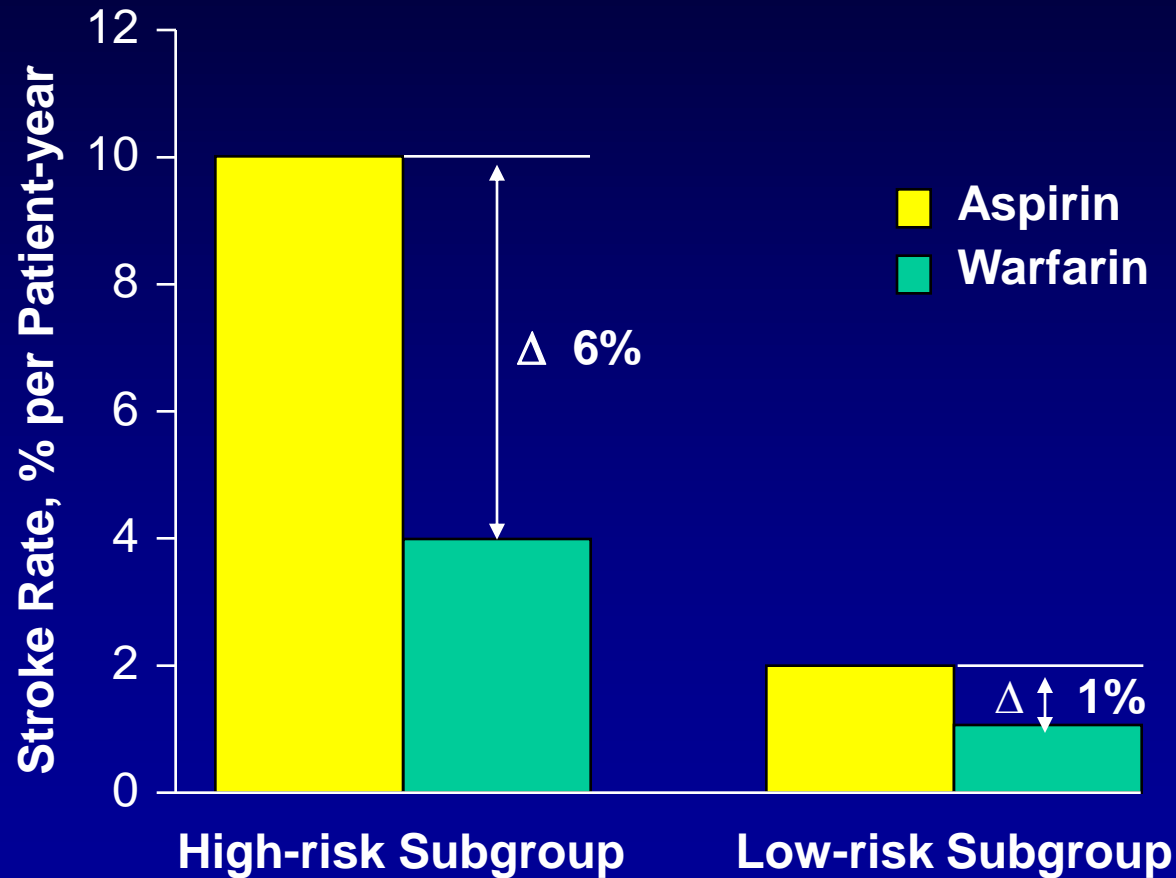
Risk Reduction With Warfarin

Relative Risk Reduction



- Warfarin reduced the risk of ischemic stroke by 33%–86% versus control.
- The aggregate relative risk reduction in ischemic stroke was 68% ($P < 0.001$).

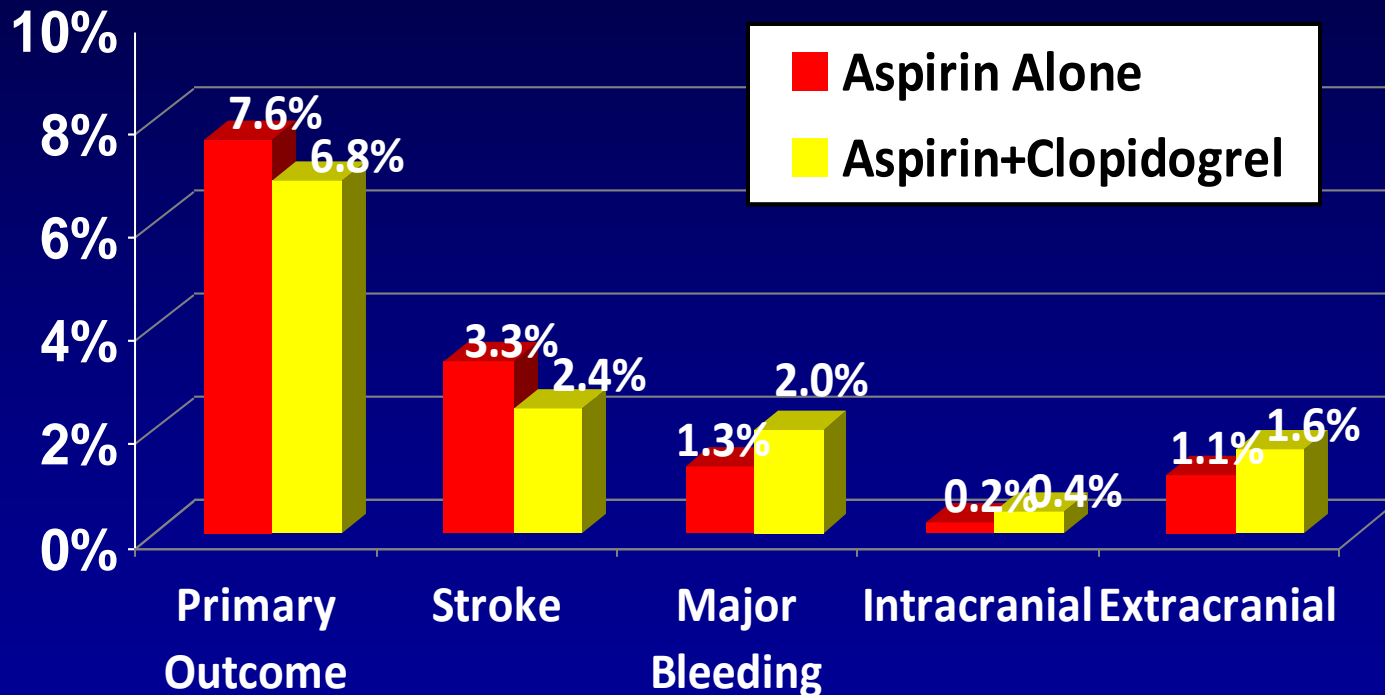
WARFARIN vs ASPIRIN FOR STROKE PREVENTION



ACTIVE-A

ASA vs ASA + Clopidogrel in AF

N = 7554 AF pts not eligible for OAC



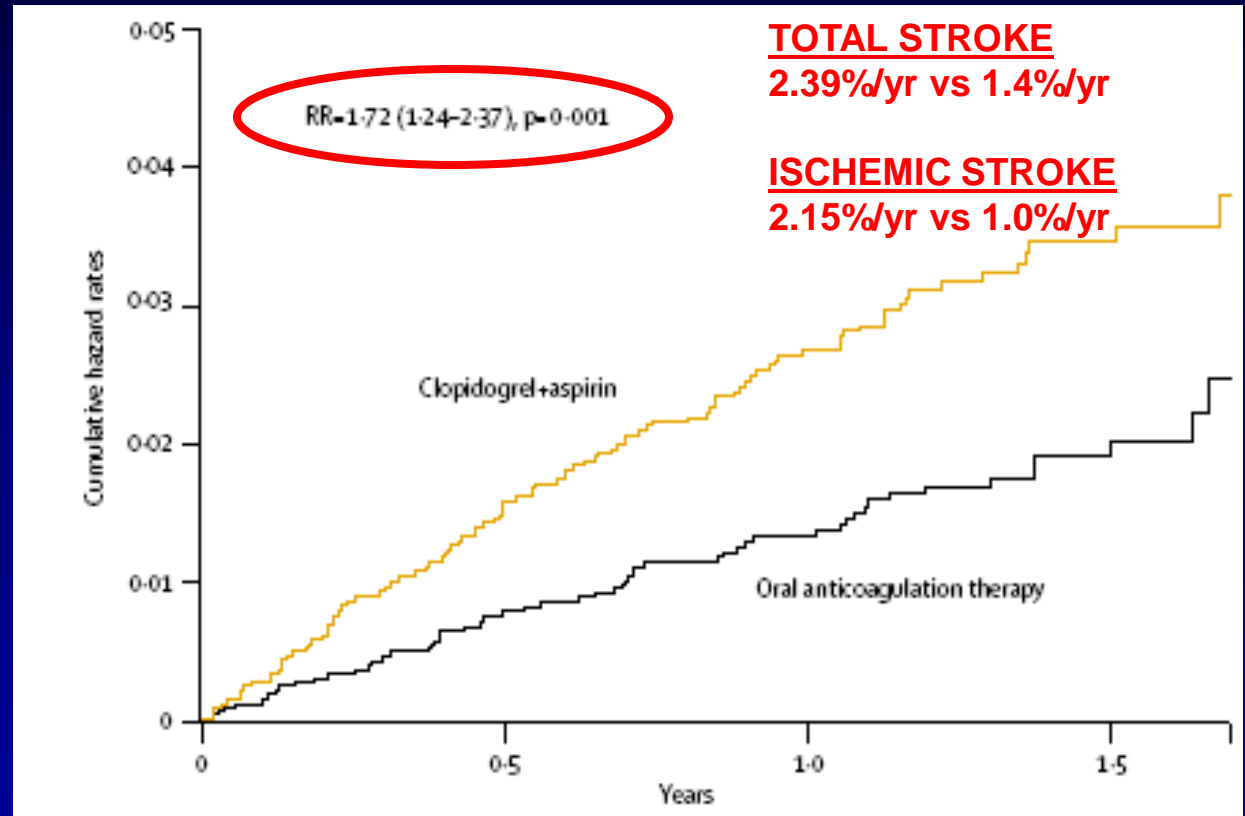
ACTIVE-W

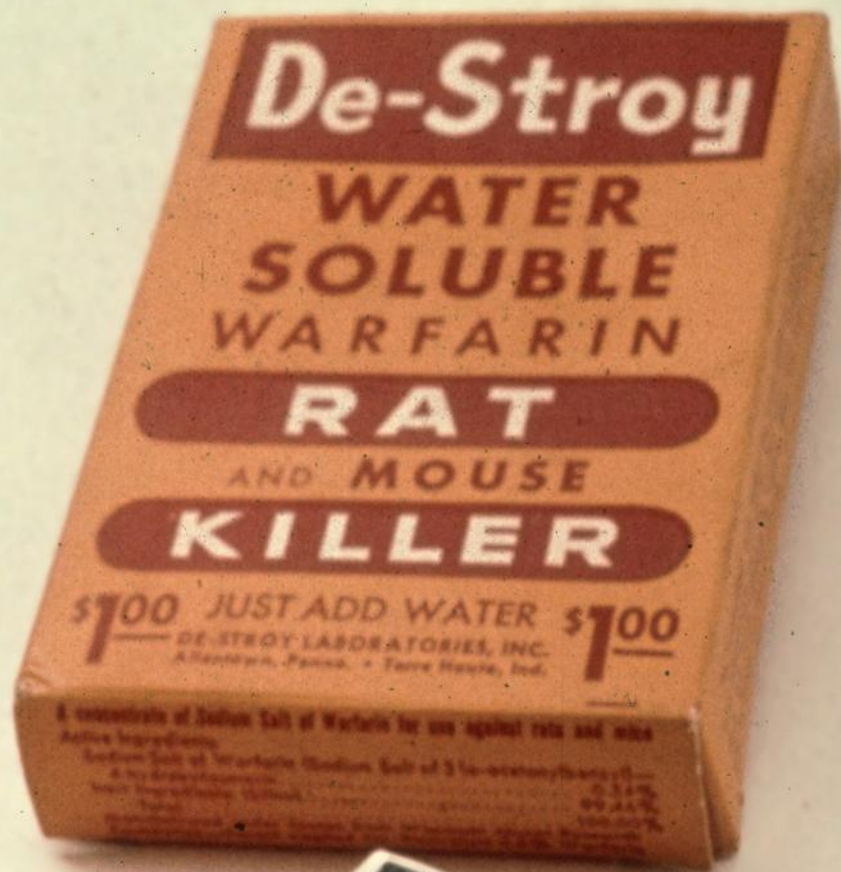
Warfarin vs ASA + Clopidogrel in AF

N = 6706 pts with AF (mean CHADS2 = 2)

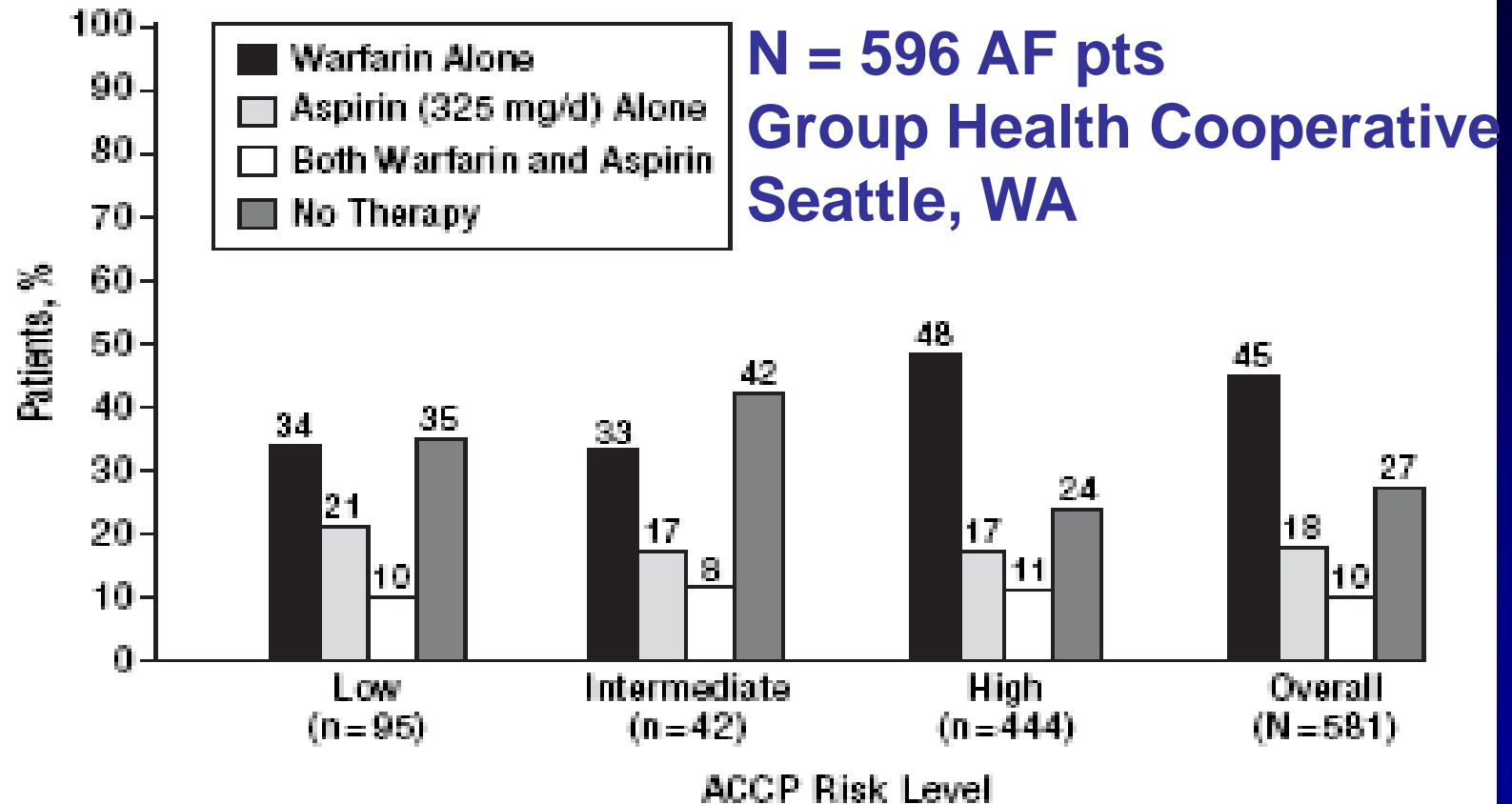
Incidence of Primary Endpoint

(stroke, systemic embolus, MI or vascular death)

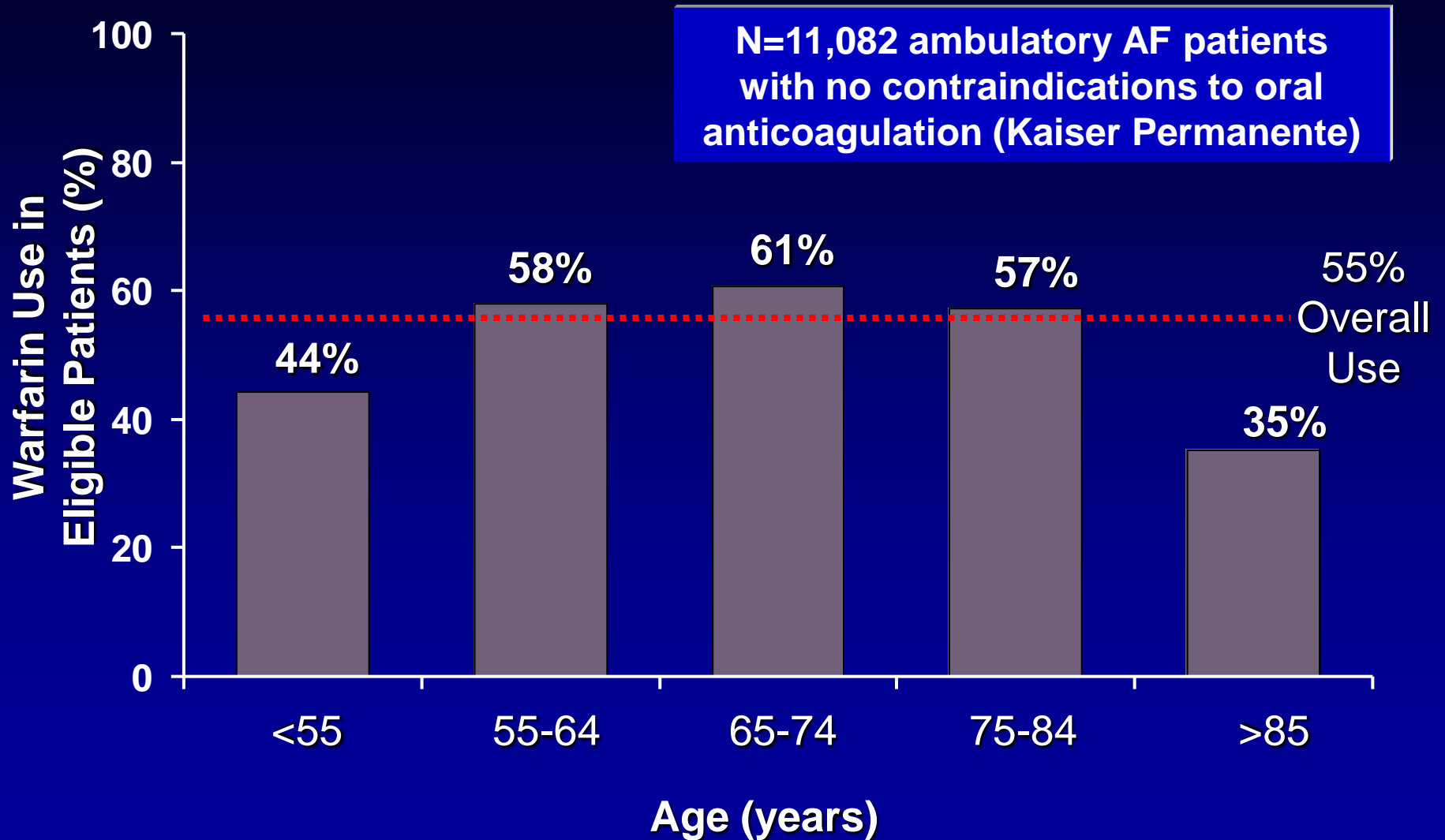




UNDERUSE OF ANTICOAGULATION IN AF

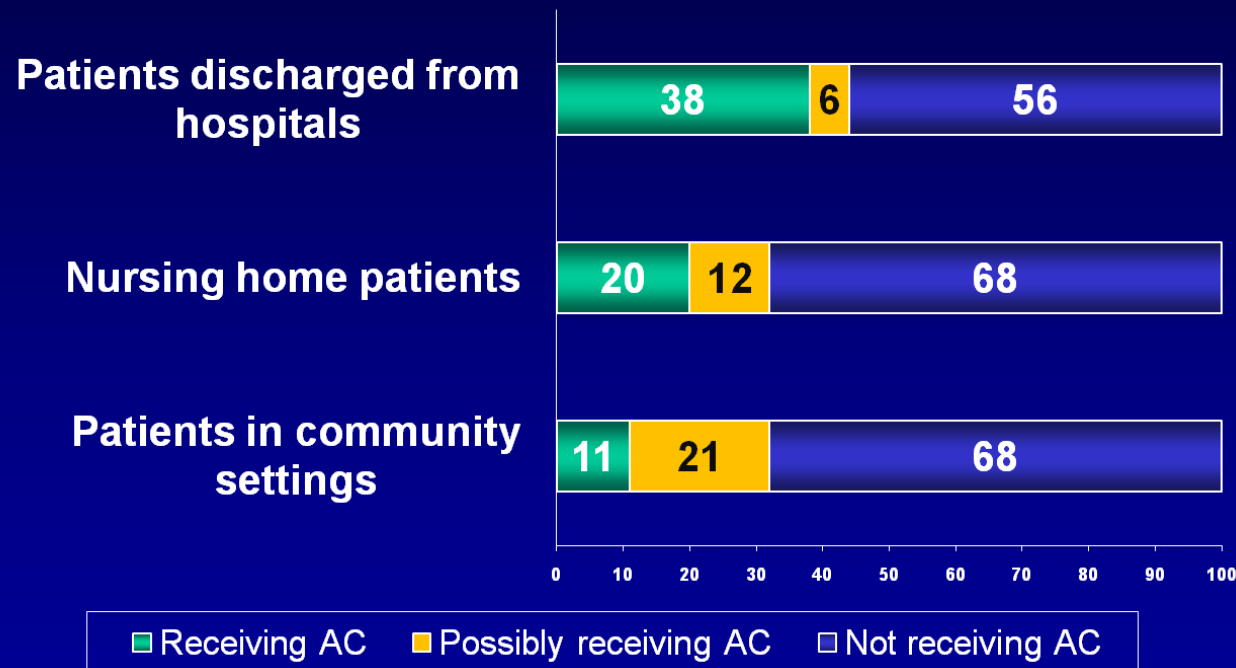


UNDERUSE OF WARFARIN IN AF



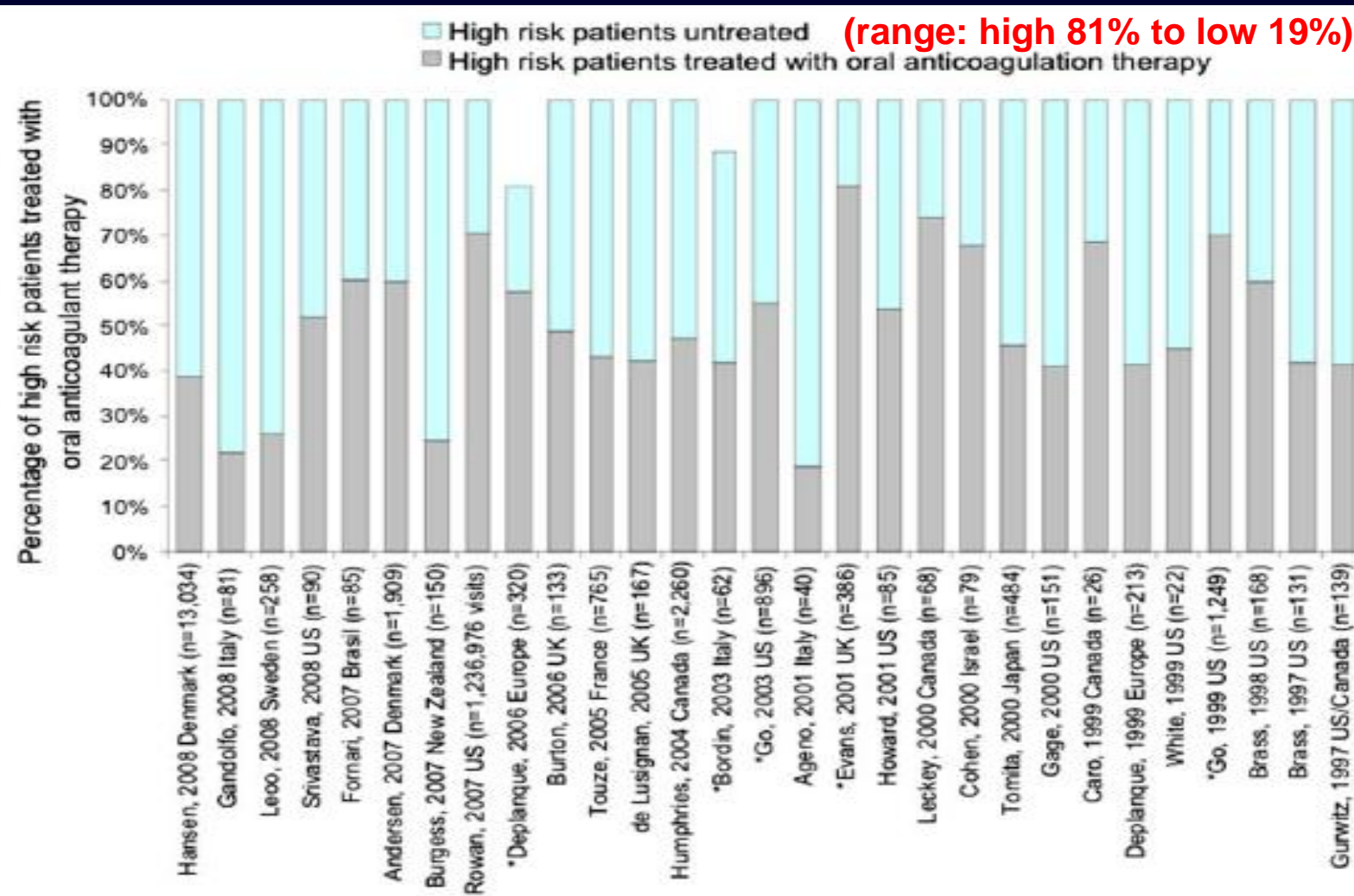
UNDERUSE OF WARFARIN IN AF

N = 1125 office visits by patients with AF and no contraindications to warfarin



Stafford RS, Singer DE. *Circulation*. 1998;97:1231.

UNDERUSE OF WARFARIN IN AF: International Meta-Analysis



< 70%
treated
25 of 29
studies

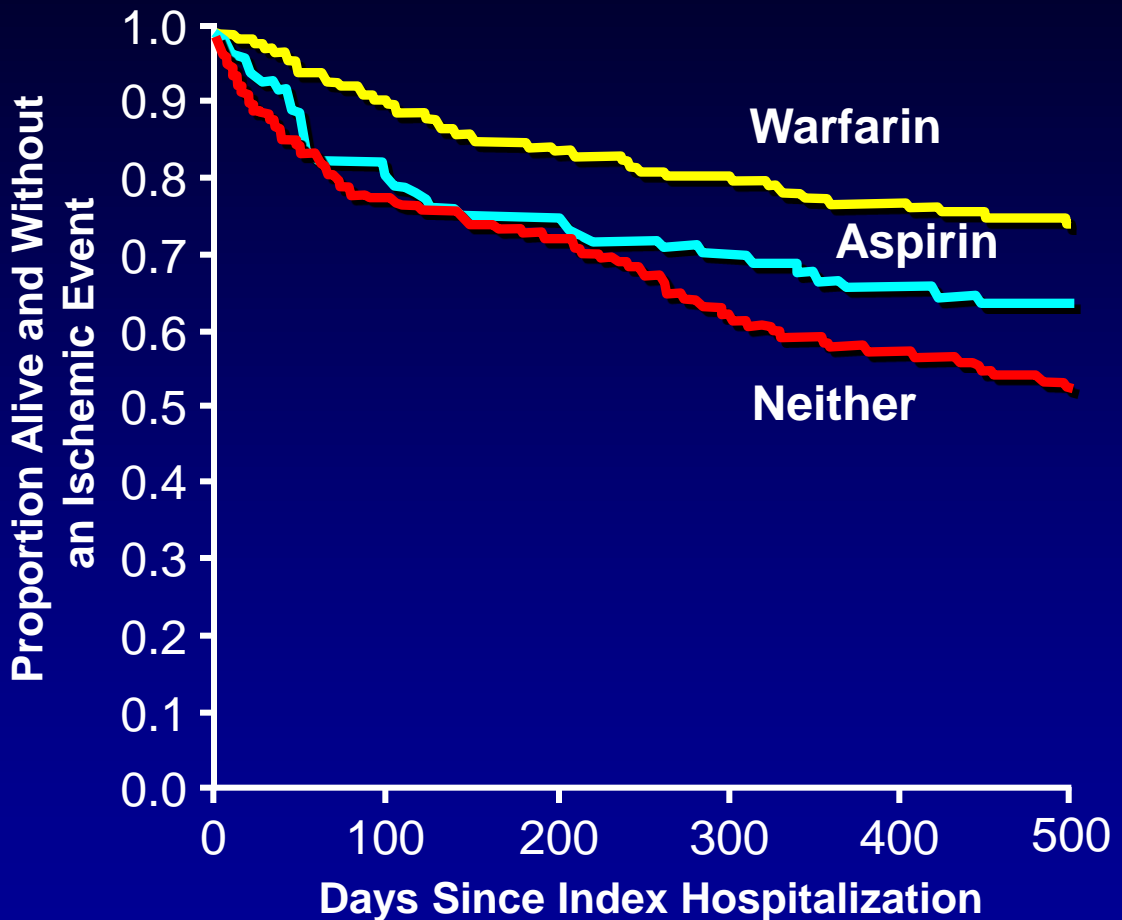
< 60%
treated
21 of 29
studies

< 50%
treated
15 of 29
studies

ADVERSE OUTCOMES ASSOCIATED WITH UNDERUSE OF WARFARIN IN AF

N = 597 Medicare patients with AF
Time of hospital discharge

Death or hospitalization for an ischemic event after discharge from hospital as a function of antithrombotic therapy



BARRIERS TO USE OF WARFARIN IN AF

Literature Review of Physician Surveys 1966-1998

Patient Barriers

advanced age
perceived low embolic risk
perceived high hemorrhagic risk

Physician Barriers

individualized risk vs benefit analysis
clinical uncertainty
difficulty maintaining therapeutic INRs
fear of litigation

Health System Barriers

inconvenience of monitoring
lack of anticoagulation clinic support

2008 ACC/AHA PERFORMANCE MEASURES FOR ATRIAL FIBRILLATION

Performance Measure	Measure Description
Assessment of thromboembolic risk factors	Non-valvular AF patients for whom assessment of thromboembolic risk factors is documented
Chronic anticoagulation therapy	Prescription of warfarin for all patients with any high-risk factor or more than 1 moderate risk factor
Monthly INR measurement	Frequency of monitoring of INR

ADHERENCE TO AF PERFORMANCE MEASURES IN OUTPATIENT MEDICAL PRACTICES

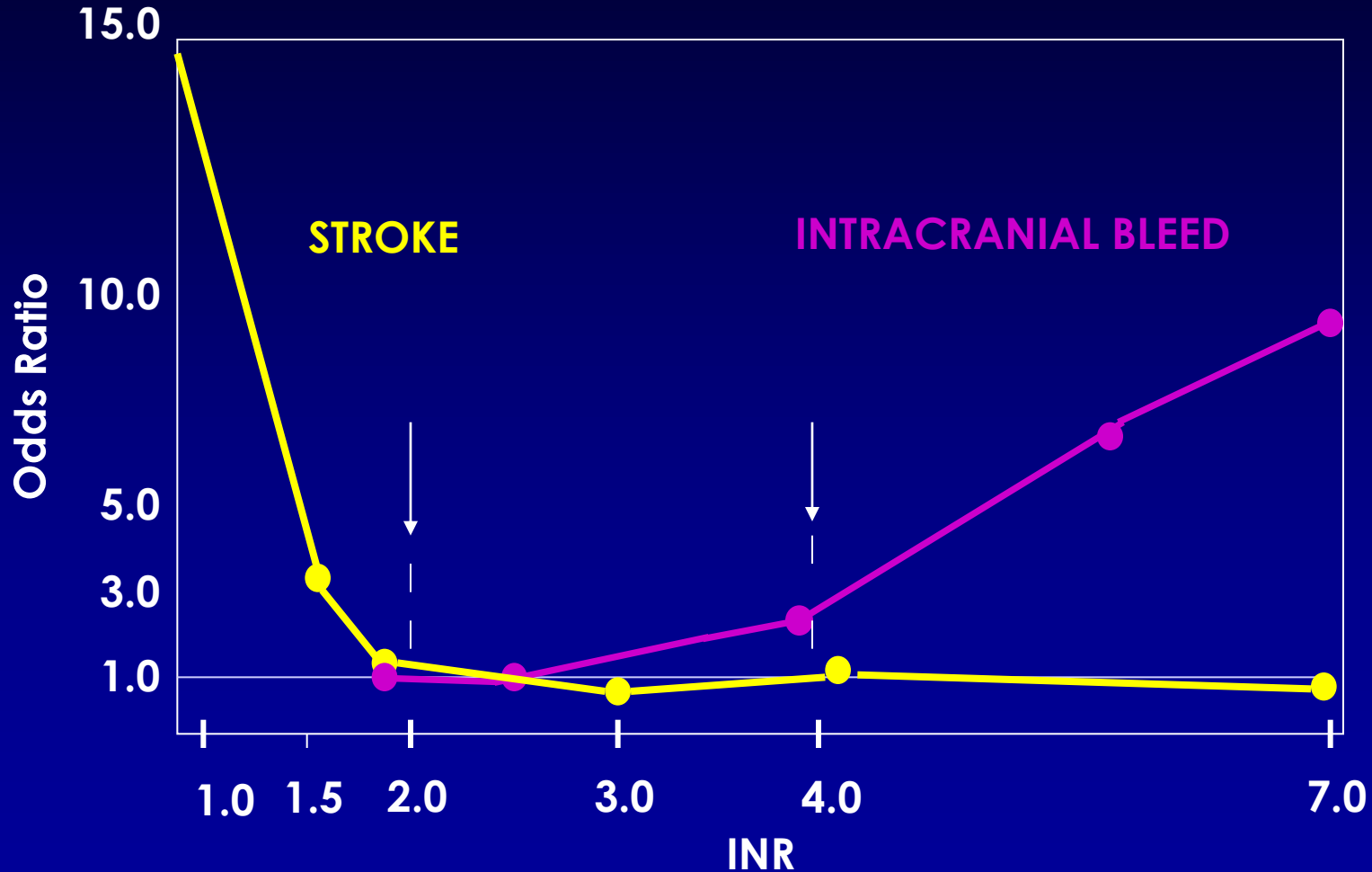
N= 2791 AF patients in 27 US practices enrolled in the ACC/NCDR PINNACLE Program

Performance Measure	Overall Compliance	Compliance in pts < 75	Compliance in pts ≥ 75	Age Group Analysis
Assessment of thromboembolic risk	73.6%	72.0%	75.1%	RR 1.00 p = 0.84
Warfarin prescribed for stroke prevention	79.2%	80.9%	78.4%	RR 0.96 p = 0.15

ACC: American College of Cardiology; NCDR: National Cardiovascular Data Registry; PINNACLE: Practice Innovation and Clinical Excellence

Chan PS et al. *J Am Coll Cardiol.* 2010; 56:8-14.

INR AT TIME OF EVENT PATIENTS WITH AF TAKING WARFARIN



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

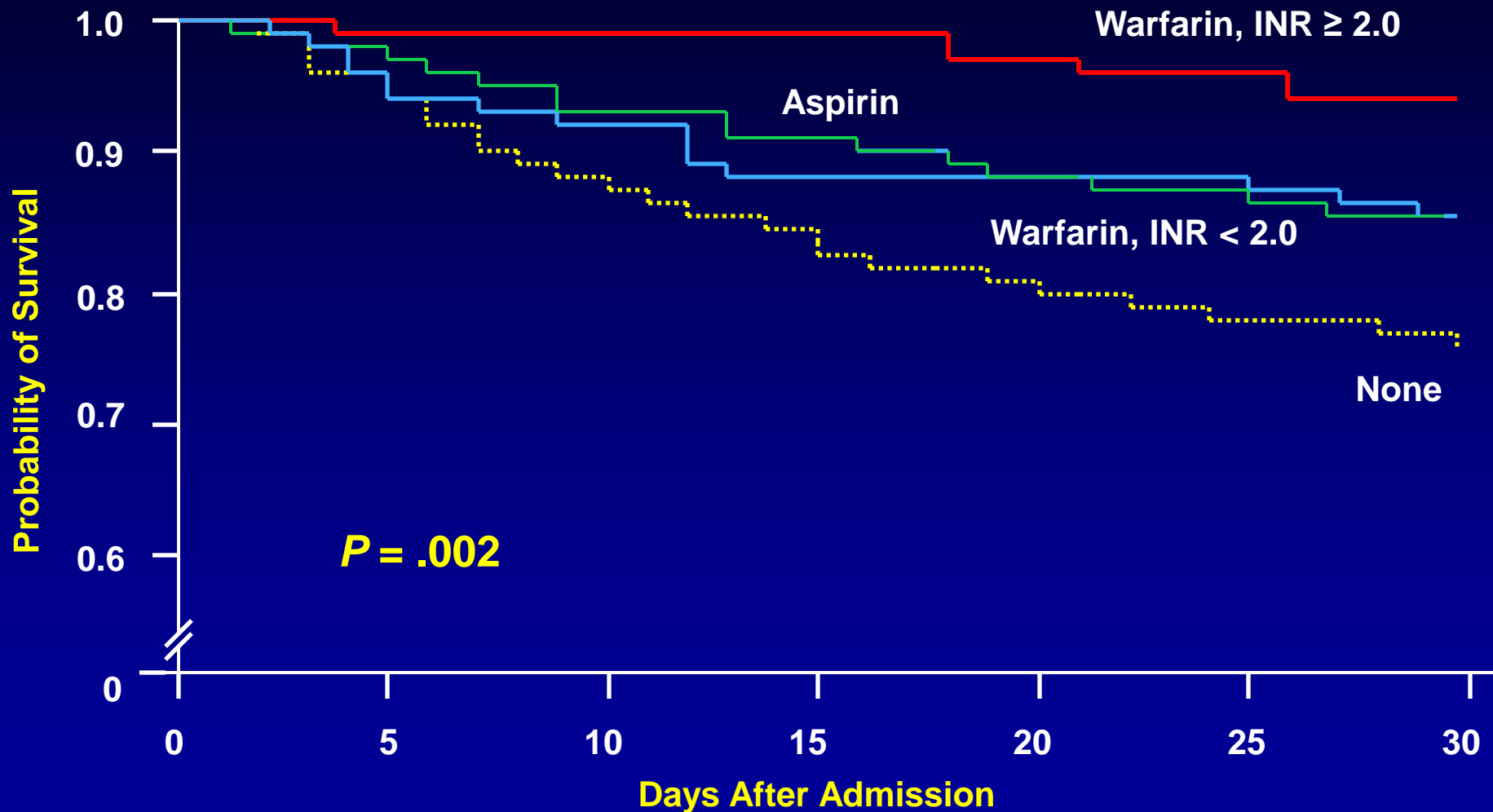
Hylek EM et al. N Eng J Med 1996; 335:540-6.

EFFECT OF INTENSITY OF ORAL ANTICOAGULATION ON STROKE SEVERITY

N=596 pts with AF and ischemic stroke

	<u>INR < 2</u>	<u>INR > 2</u>
Fatal stroke	9%	1%
Severe (total dependence)	6%	4%
Major (not independent)	<u>44%</u>	<u>38%</u>
TOTAL	59%	43%
Minor (independent)	38%	55%
No neurologic sequelae	<u>3%</u>	<u>2%</u>
TOTAL	41%	57%

EFFECT OF INTENSITY OF ORAL ANTICOAGULATION ON STROKE-RELATED MORTALITY



CAUSES OF OVER- AND UNDER-ANTICOAGULATION

	Out-of-range INRs < 2 <u>(n=2881; 22.3%)</u>	Out-of-range INRs > 4 <u>(n=603; 4.7%)</u>
<i>Dosing Issues</i> ¹	55.2%	22.7%
<i>Interactions</i> ²	15.1%	35.0%
<i>No Explanation</i>	29.7%	42.3%

1. initiation, withholding, noncompliance, dosing adjustments
2. Rx/OTC/herbal meds, diseases, diet, alcohol, activity

NEW ANTITHROMBOTIC AGENTS

IDEAL CHARACTERISTICS

- **Broad therapeutic window**
 - **Low inter- and intra-patient variability**
 - **No need for routine monitoring**
- **Oral administration**
- **No need for parenteral to oral switch**
 - **Use as single agent in acute and chronic indications and in both the hospital and home settings**
- **No drug or diet interactions**
- **Safe with low or no ADRs**
- **Easily reversible with or without an antidote**

WARFARIN REPLACEMENTS ON THE HORIZON

	DABIGATRAN	RIVAROXABAN	APIXABAN
Manufacturer	Boehringer- Ingelheim	Bayer via Ortho McNeil	Pfizer with BMS
Brand Name	Pradaxa (Eur) Pradax (Can)	Xarelto	n/a
Approval Status	Approved in Eur/Can 2008 (VTE px/ortho) 9/14/10: recommended for approval by advisory panel 10/19/10: approved by FDA for stroke prevention in AF	Approved in Eur/Can 2008 (VTE px/ortho) 3/09: FDA advisory panel approval 5/09: additional info requested by FDA 1/11: submitted to FDA for stroke prevention in AF	6/2010: submitted for European approval (EMA)
Mechanism of Action	Direct IIa inhibitor	Direct Xa inhibitor	Direct Xa inhibitor

WHICH TARGET IS BETTER? Xa versus IIa

1. **Claims based on mechanism of action will be made to support the superiority of Xa vs IIa inhibition**
2. **Only comparative clinical trial data will determine the superiority of a particular drug (or target) over another**
3. **“There are many differentiating characteristics between these agents that may matter more than the target itself”**

Bauer KA. *J Thromb Thrombolysis* 2006; 21:67-72.

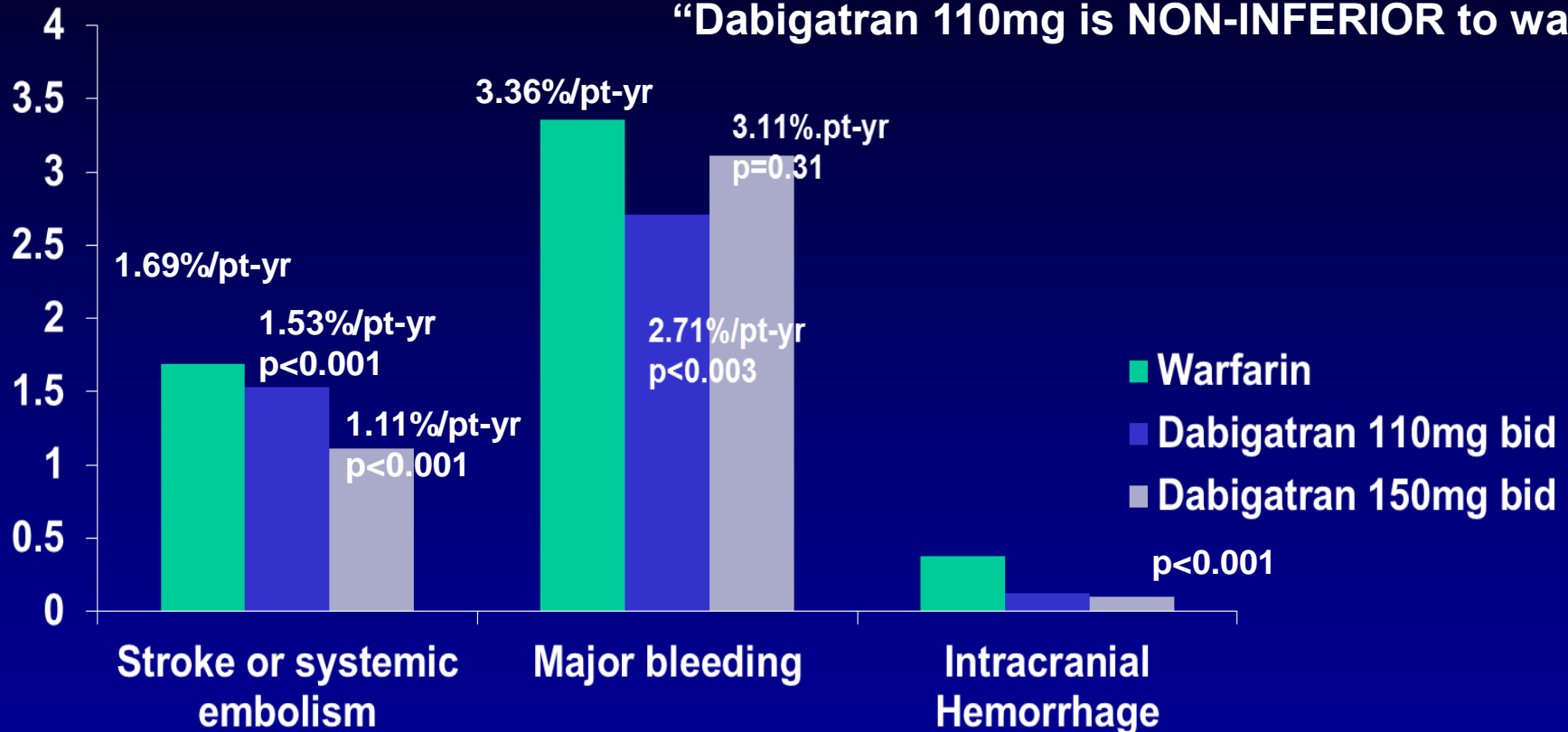
Schulman S. *Semin Thromb Haemost* 2003; 29 (suppl 1):33-36

RE-LY

Dabigatran Etexilate vs Warfarin in AF

“Dabigatran 150mg is SUPERIOR to warfarin”

“Dabigatran 110mg is NON-INFERIOR to warfarin”

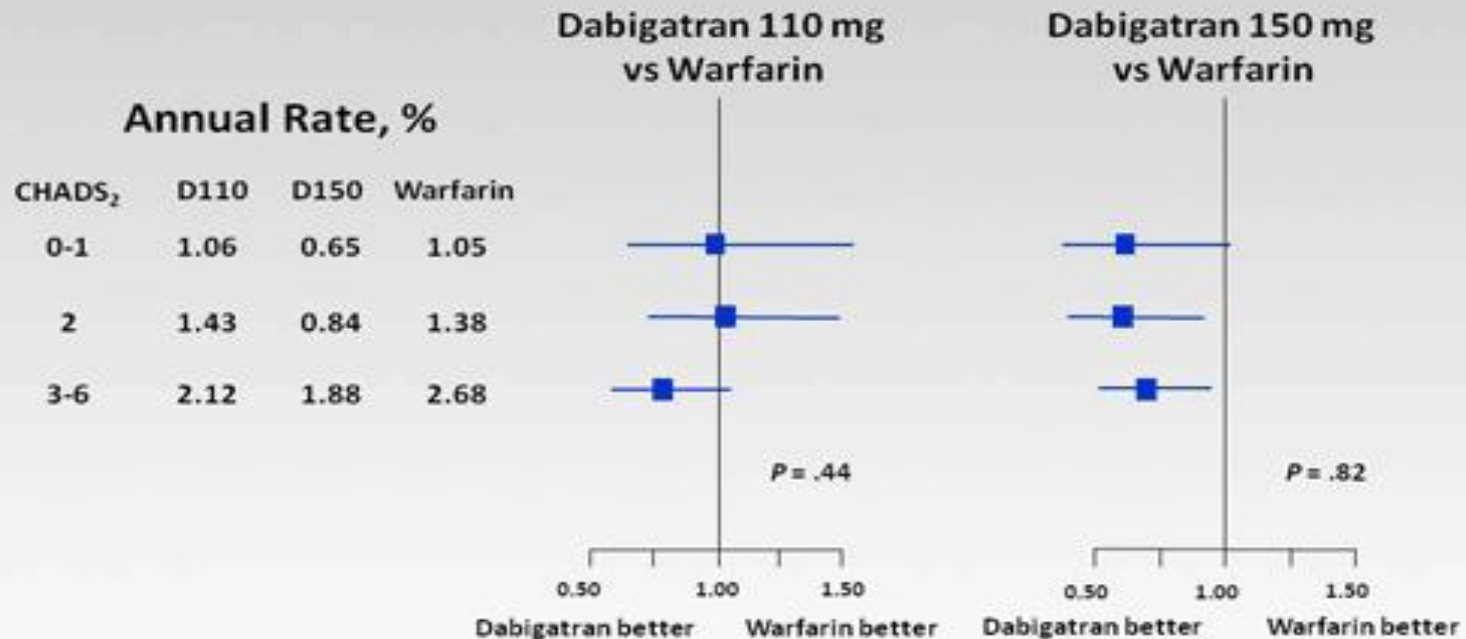


N = 18,113 pts (mean CHADS2 score = 2.1)
Non-inferiority design
Blinded dabigatran dose vs unblinded warfarin
64% Time-in-Range for warfarin
Median followup = 2 years

Characteristic	Dabigatran 110 mg	Dabigatran 150 mg	Warfarin
Randomized	6015	6076	6022
Mean age (years)	71.4	71.5	71.6
Male (%)	64.3	63.2	63.3
CHADS2 score (mean)	2.1	2.2	2.1
0-1 (%)	32.6	32.2	30.9
2 (%)	34.7	35.2	37.0
3+ (%)	32.7	32.6	32.1
Prior stroke/TIA (%)	19.9	20.3	19.8
Prior MI (%)	16.8	16.9	16.1
CHF (%)	32.2	31.8	31.9
Baseline ASA (%)	40.0	38.7	40.6
Warfarin Naïve (%)	49.9	49.8	51.4

RE-LY Subgroup Analysis LOW, INTERMEDIATE, OR HIGH CHADS2 SCORE

Stroke and Systemic Embolism



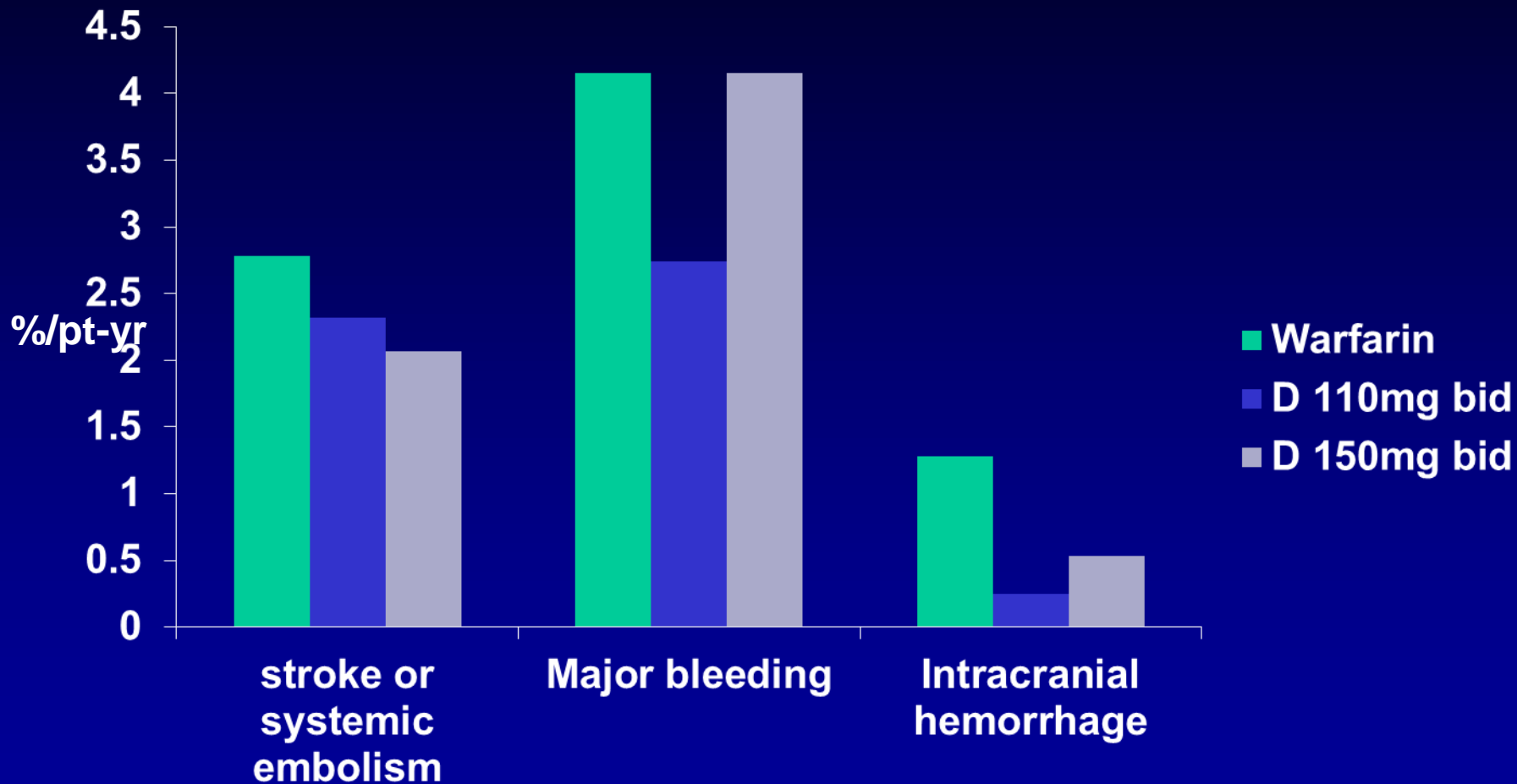
	D 110mg	D 150mg	warfarin	D 110mg vs. Warfarin		D 150mg vs. Warfarin	
	Annual rate	Annual rate	Annual rate	RR 95% CI	p	RR 95% CI	p
Total	14.6%	16.4%	18.2%	0.78 0.74-0.83	<0.001	0.91 0.86-0.97	0.002
Major	2.7 %	3.1 %	3.4 %	0.80 0.69-0.93	0.003	0.93 0.81-1.07	0.31
Life- Threatening major	1.2 %	1.5 %	1.8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

Adverse events occurring in >5% of any group	Dabigatran 110 mg %	Dabigatran 150 mg %	Warfarin %
Dyspepsia *	11.8	11.3	5.8
Dyspnea	9.3	9.5	9.7
Dizziness	8.1	8.3	9.4
Peripheral edema	7.9	7.9	7.8
Fatigue	6.6	6.6	6.2
Cough	5.7	5.7	6.0
Chest pain	5.2	6.2	5.9
Arthralgia	4.5	5.5	5.7
Back pain	5.3	5.2	5.6
Nasopharyngitis	5.6	5.4	5.6
Diarrhea	6.3	6.5	5.7
Atrial fibrillation	5.5	5.9	5.8
Urinary tract infection	4.5	4.8	5.6
Upper respiratory tract infection	4.8	4.7	5.2

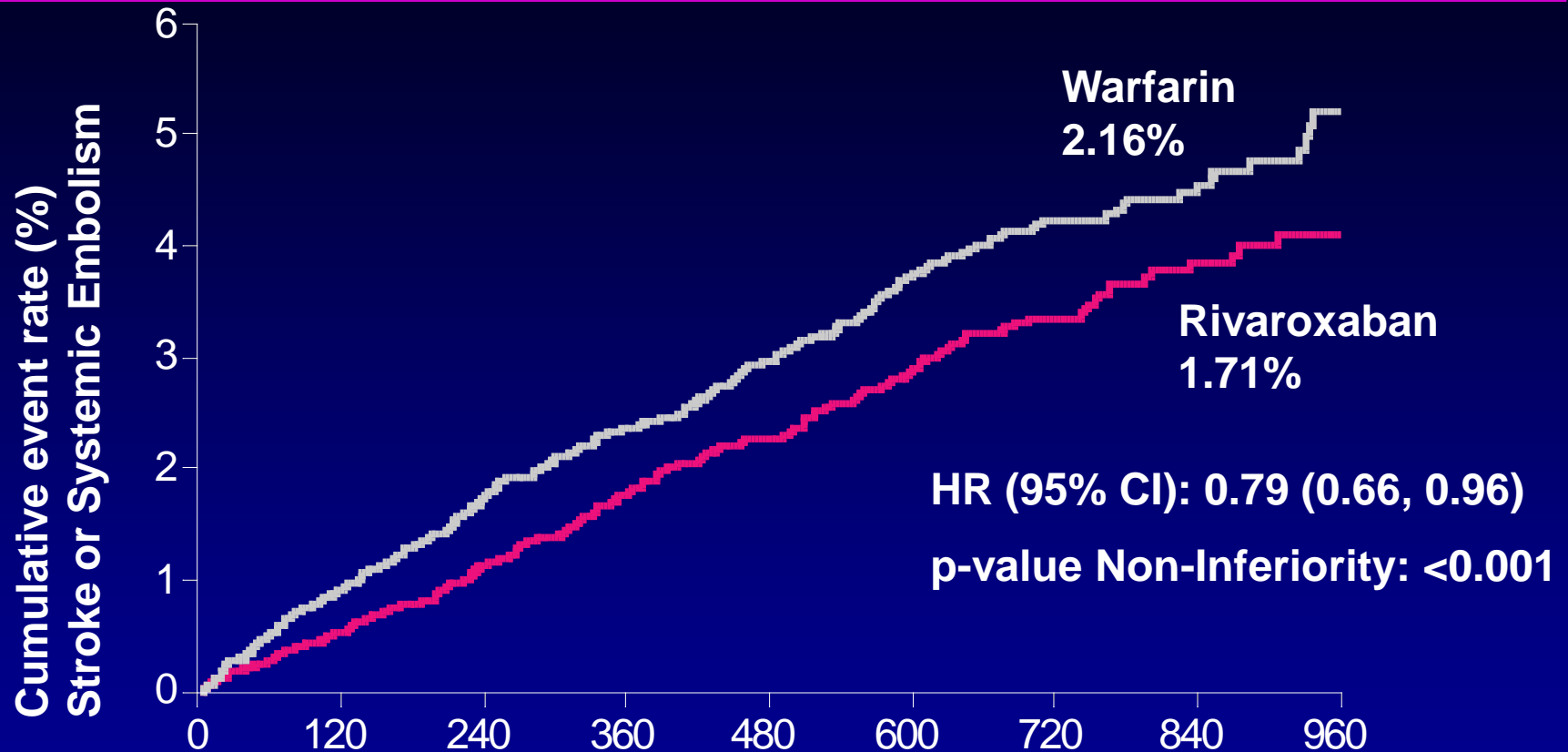
***Occurred more commonly on dabigatran (p<0.001)**

RE-LY Subgroup Analysis

Pts with History of Stroke or TIA

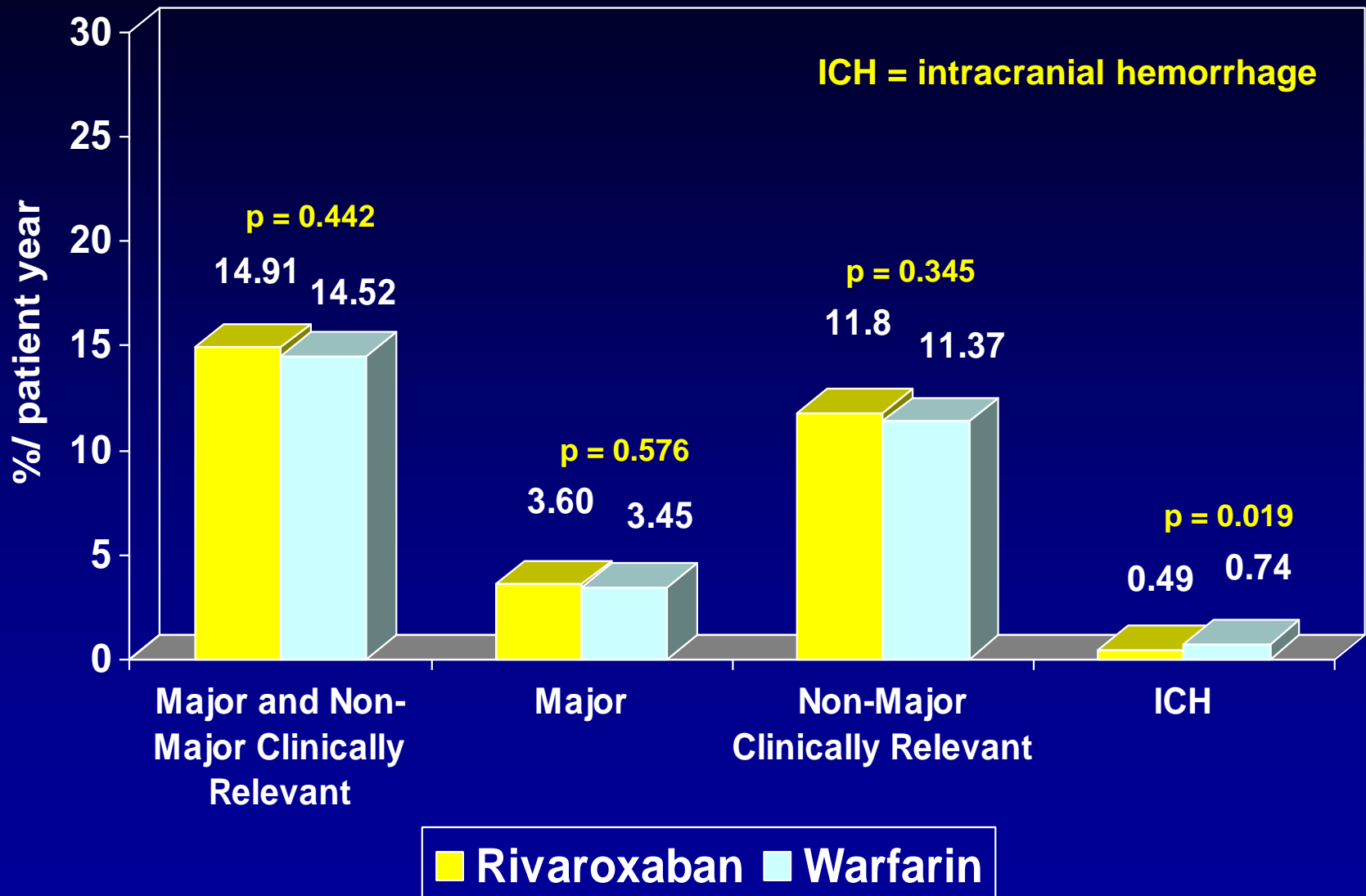


ROCKET AF: *Rivaroxaban vs Warfarin in AF*



N = 14,171pts (mean CHADS2 score = 3.5)
Non-inferiority design
58% Time-in-Range for warfarin

ROCKET AF: Bleeding



APIXABAN TRIALS IN AF

ARISTOTLE¹

warfarin (INR 2-3) vs apixaban 5mg bid
randomized, double-blind, placebo controlled
noninferiority design
CHADS2 score of 1 or greater
n > 18,000 patients

AVERROES²

ASA 81-324mg qd vs apixaban 5mg bid
randomized, double blind, placebo controlled
superiority design
CHADS2 score of 1 or greater
Failed or unsuitable for warfarin therapy
n > 5,600 patients

1. Lopes RD et al. *Am Heart J* 2010; 159:331-9
2. Connolly S, et al. *New Engl J Med* 2011; 364: Feb 17: published online ahead of print.

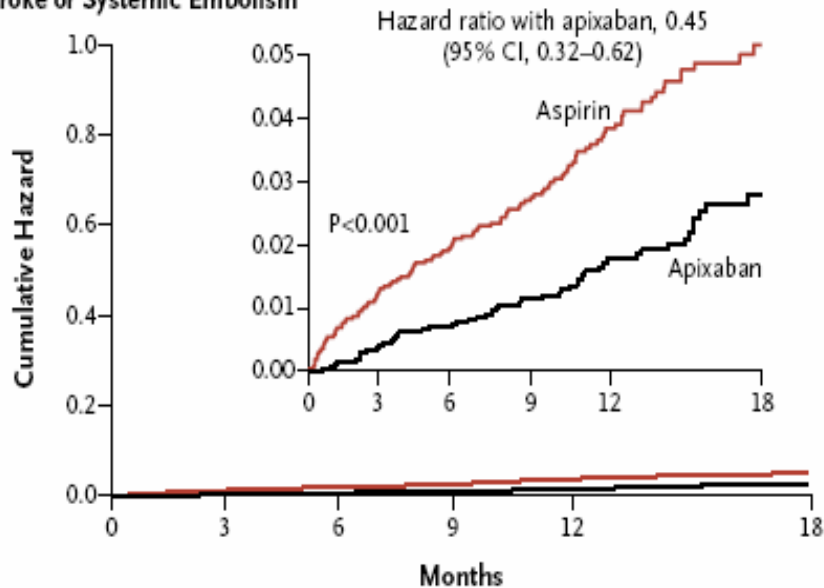
AVERROES Trial

Reasons for Unsuitability of Warfarin Therapy

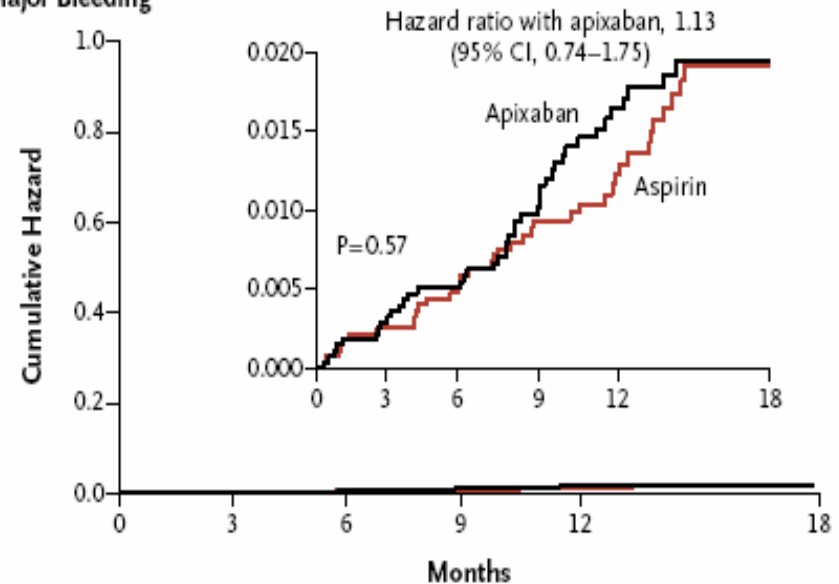
	Apixiban (n=2808)	Aspirin (n=2791)
INR could not be properly monitored	43%	43%
Patient refusal to take warfarin	38%	37%
CHADS2 score of 1 (warfarin not recommended by MD)	21%	22%
Therapeutic INR could not be maintained	17%	17%
Drug adherence issues	16%	15%
Difficulty to contact patient to adjust warfarin dose	11%	12%

AVERROES TRIAL RESULTS

A Stroke or Systemic Embolism



B Major Bleeding



New Anticoagulants

REMAINING QUESTIONS

- **drug interactions**
- **use in hepatic failure and renal insufficiency**
- **use in obesity and underweight patients**
- **role of monitoring and appropriate tests**
- **bridging prior to and following procedures**
- **duplicate therapy**
- **cardioversion/ablation**
- **stroke protocols involving thrombolytic therapy**

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 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

“Because of the twice-daily dosing and greater risk of nonhemorrhagic side effects with dabigatran, patients already taking warfarin with excellent INR control may have little to gain by switching to dabigatran.”

“Selection of patients with AF and at least 1 additional risk factor for stroke who could benefit from treatment with dabigatran as opposed to warfarin should be based on individual clinical features, including the ability to comply with twice-daily dosing, availability of an anticoagulation management program to sustain routine monitoring of INR, patient preferences, cost, and other factors.”