



MASSACHUSETTS
GENERAL HOSPITAL

HEART CENTER

Atrial Fibrillation

E. Kevin Heist, MD, PhD

Updates in General Internal Medicine for Specialists
January 27, 2020



A Teaching Affiliate
of Harvard Medical School

Disclosures

<u>Recipient:</u>	<u>Company:</u>	<u>Description:</u>	<u>Content Area:</u>
Self	Abbott	Honorarium, Research Grant	Medical Device
Self	Biotronik	Honorarium	Medical Device
Self	Boston Scientific	Honorarium, Research Grant	Medical Device
Self	Johnson & Johnson	Honorarium	Medical Device
Self	Medtronic	Honorarium	Medical Device
Self	Pfizer	Consulting	Pharmaceutical

Outline

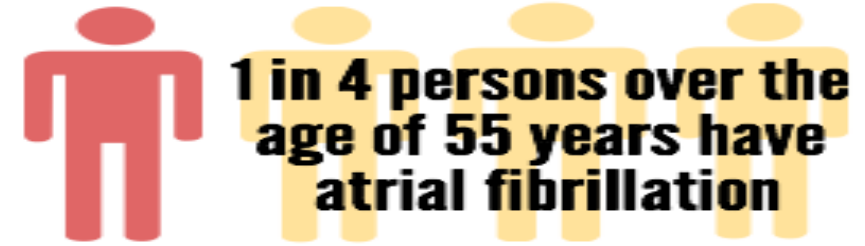
- Rate vs. Rhythm Control
- Methods of Rhythm Control
 - Pharmacologic
 - Ablation
- Stroke Prevention
 - Pharmacologic
 - Devices

Definitions

- Atrial Fibrillation: rapid, chaotic atrial rhythm, typically with irregular and possibly rapid ventricular response.
- Paroxysmal AF: AF episodes < 7 days in duration
- Persistent AF: > 7 days, < 1 year in duration
- Long-standing Persistent (Chronic) AF: AF > 1 year in duration
- Permanent AF: No plan to try to reverse AF

Atrial fibrillation - a growing epidemic

Atrial fibrillation is the most common cardiac arrhythmia causing a fast and irregular heartbeat

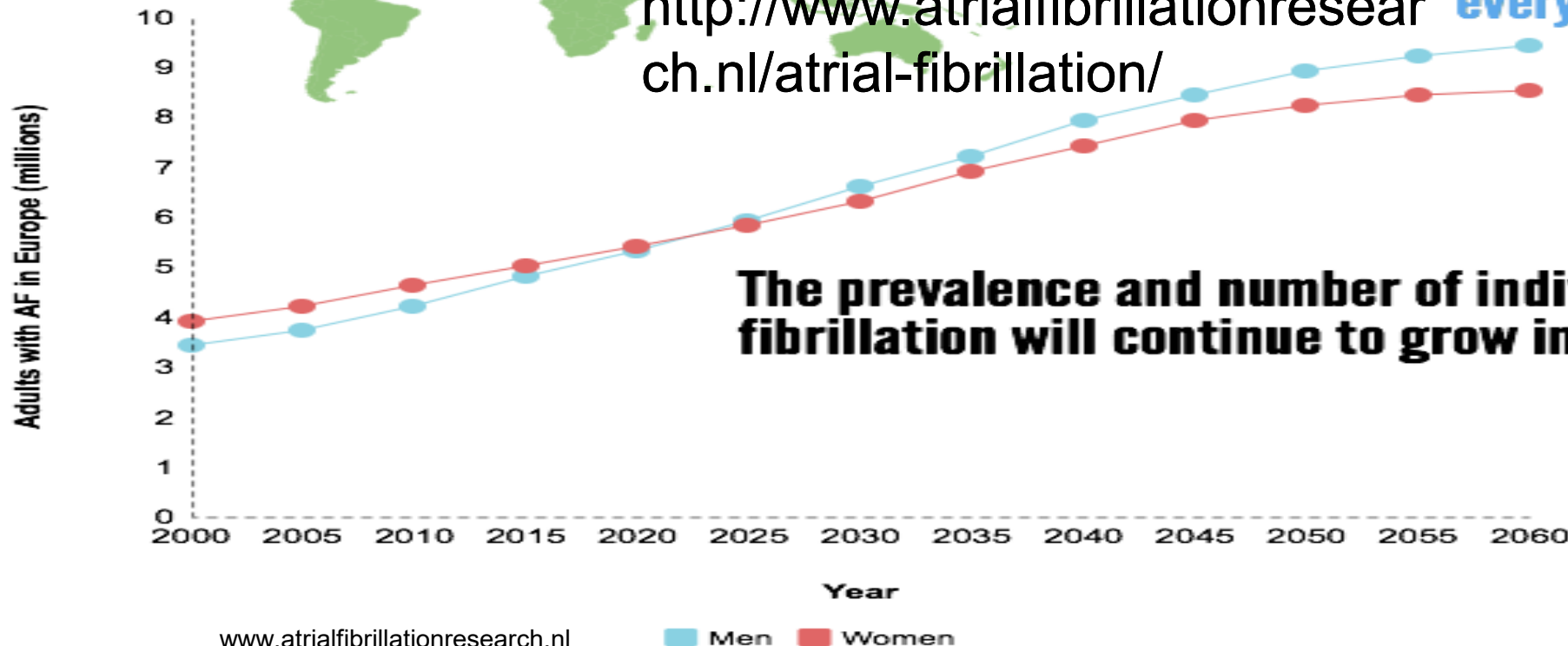


Atrial fibrillation affects 33.5 million people worldwide, 8.8 million in the European Union

Incidence increases with age, doubling each decade after 55

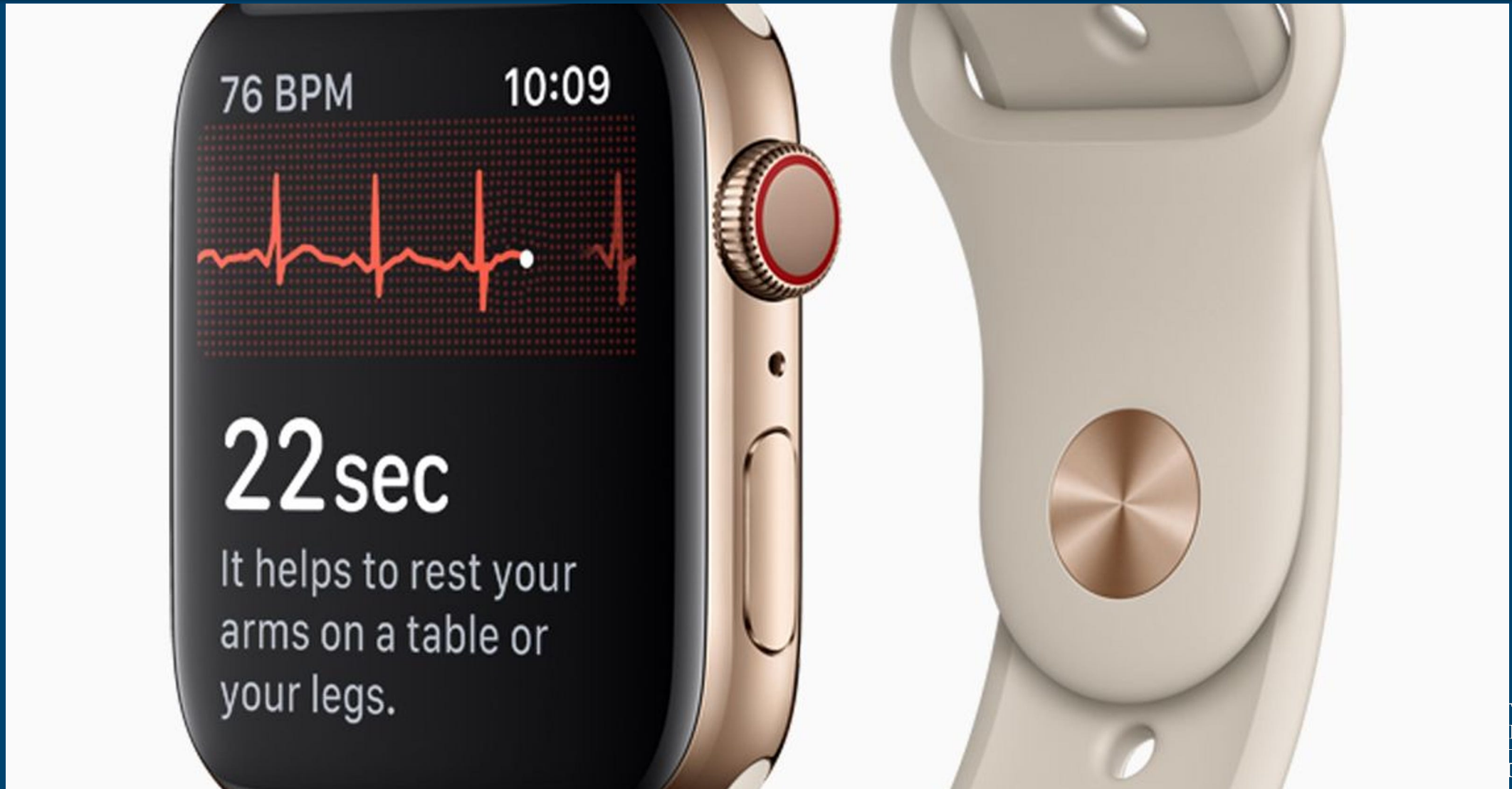
X2
every 10 years

<http://www.atrialfibrillationresearch.nl/atrial-fibrillation/>



The prevalence and number of individuals with atrial fibrillation will continue to grow in the coming years

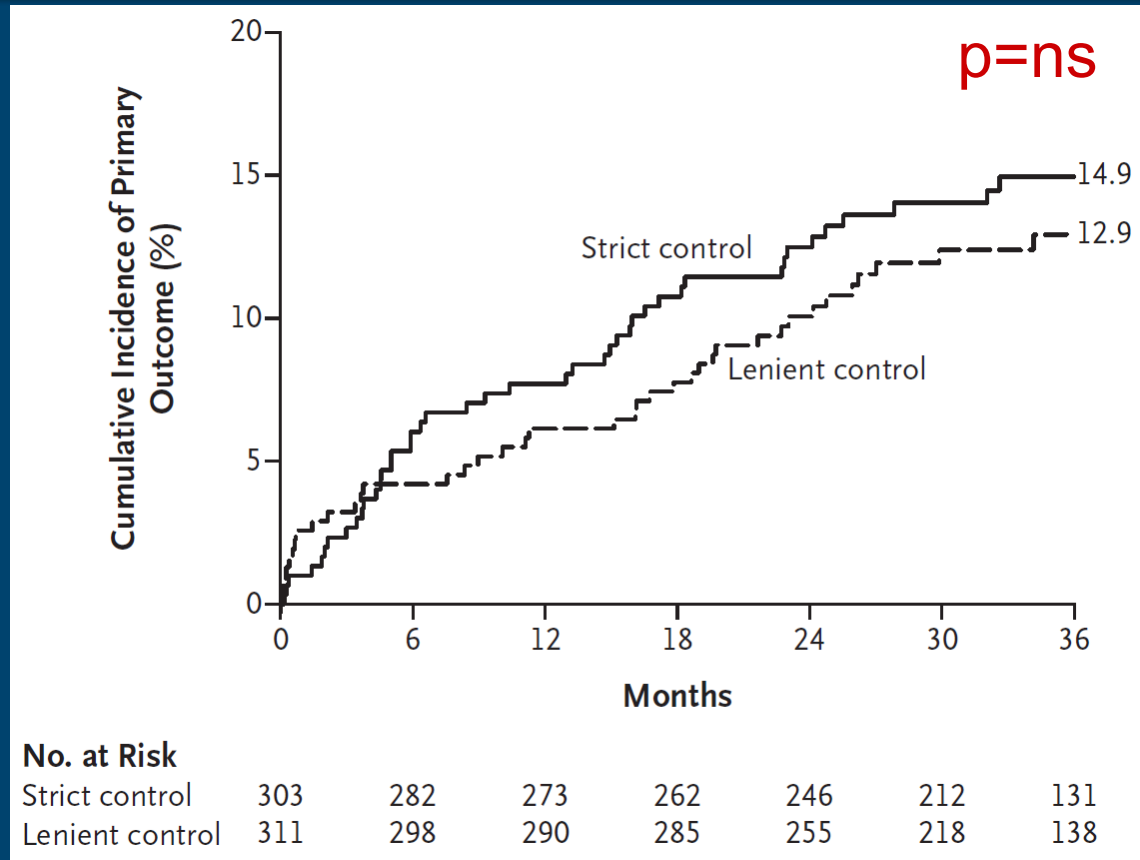
Patient Wearable Monitors to Detect Atrial Fibrillation



Drug Therapy for Rate Control in AF

- Beta Blocker Therapy
- Calcium-Channel Blocker Therapy (Diltiazem, Verapamil)
- Digoxin (increased mortality in some studies)
- Amiodarone (useful in acutely ill patients, chronic use limited by drug toxicity)

RACE II: Intensity of Rate Control



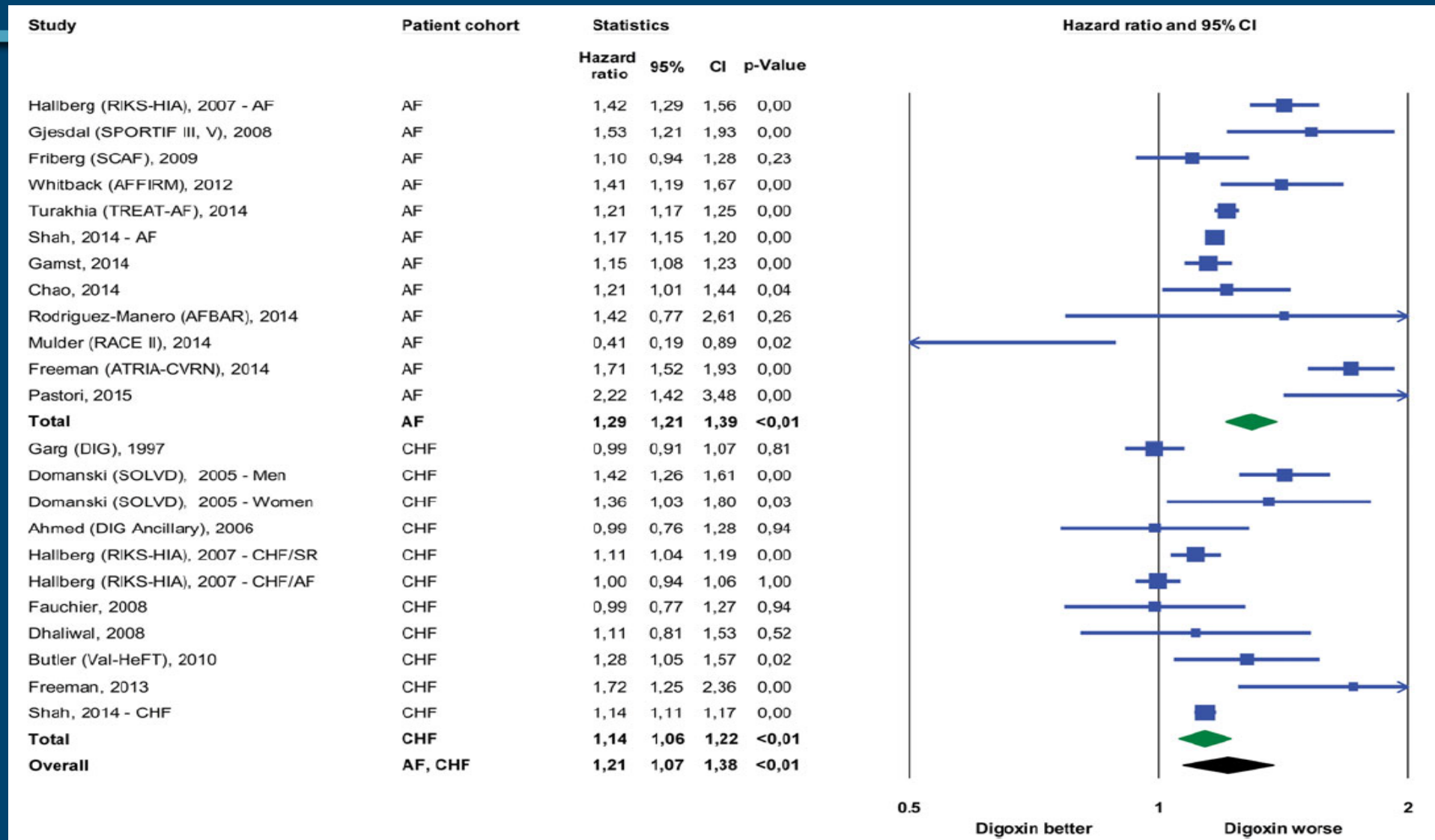
Lenient: resting hr < 110
(rest 93 ± 9 bpm achieved)

Strict: resting hr < 80
hr mod exercise < 110
(rest 76 ± 12 bpm achieved)

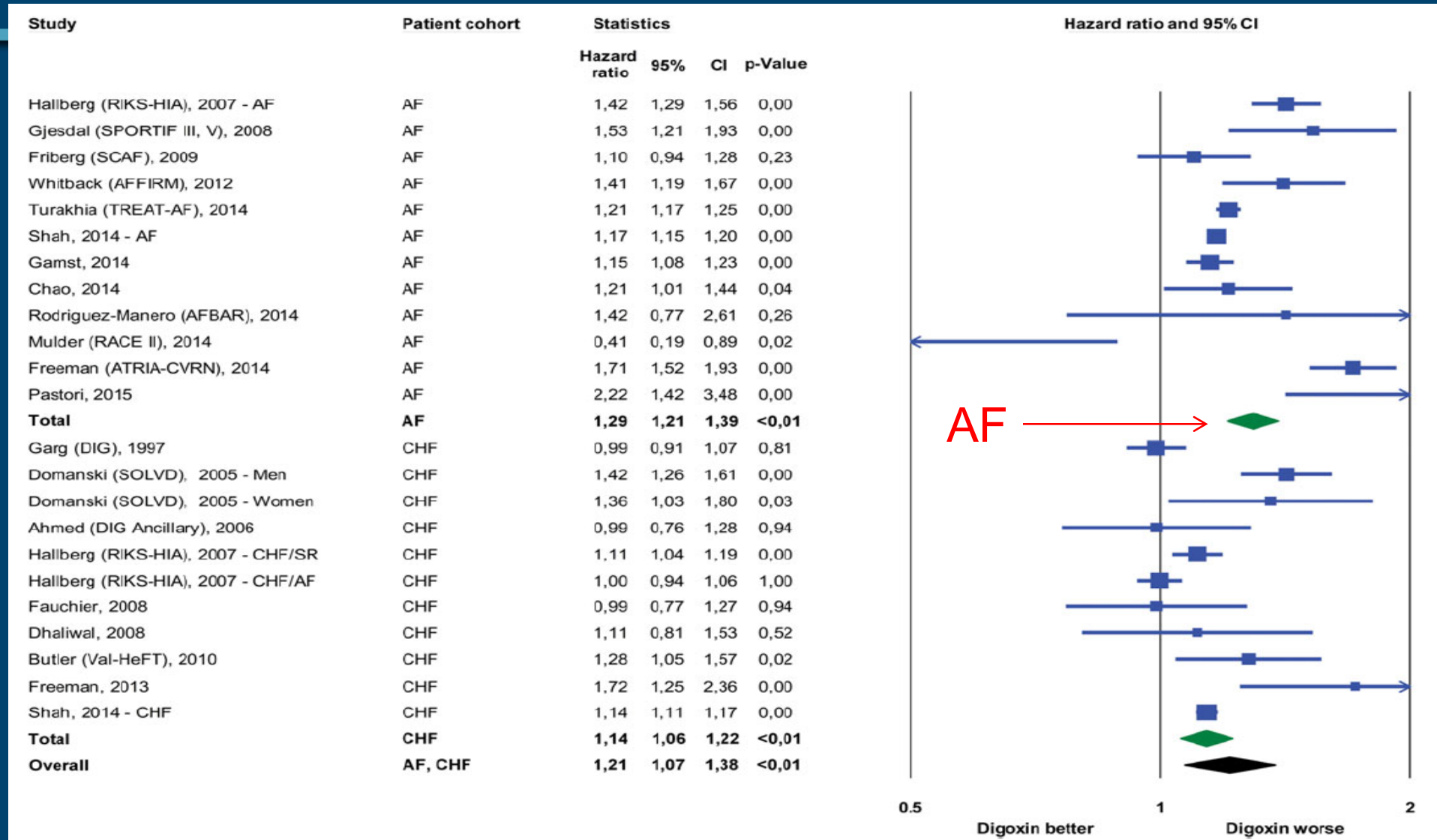
Primary Outcome:

- cardiovascular death
- CHF hospitalization
- stroke
- systemic embolism
- bleeding
- life threatening arrhythmia

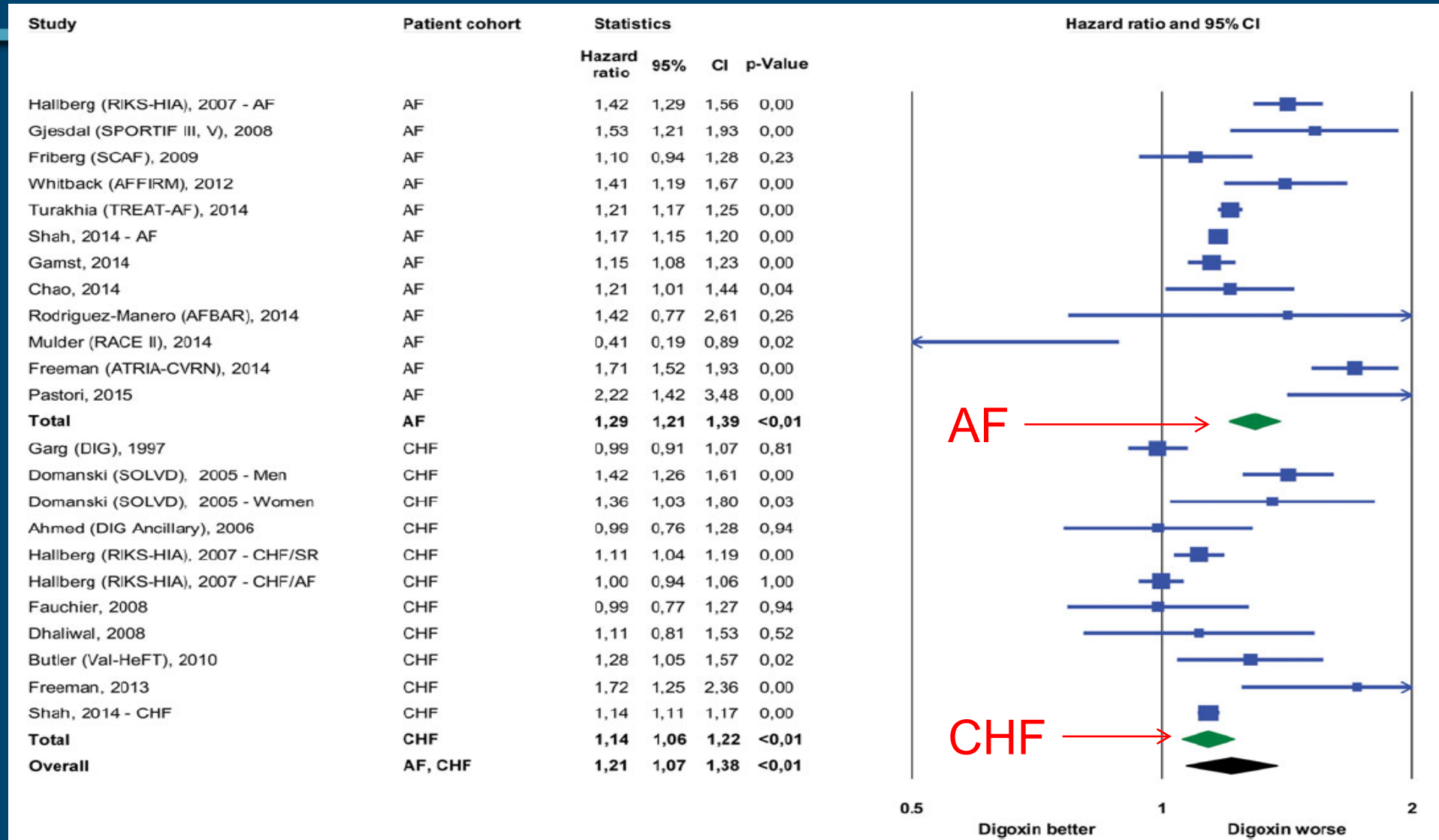
Digoxin Use and Overall Mortality



Digoxin Use and Overall Mortality



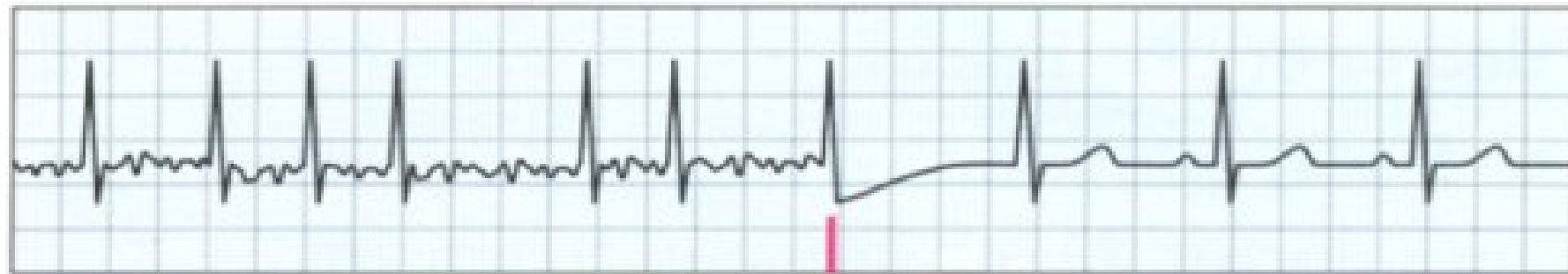
Digoxin Use and Overall Mortality



AV Nodal Ablation/Pacemaker: Definitive Rate Control

- Ablation of the AV node causes complete AV block, makes a patient “pacemaker-dependent”
- Does not prevent atrial fibrillation: the risk of stroke and need for anti-coagulation remains
- Typically reserved for elderly and/or sick patients who can't be acceptably rate controlled with tolerated medications

Electrical Cardioversion is effective, but...



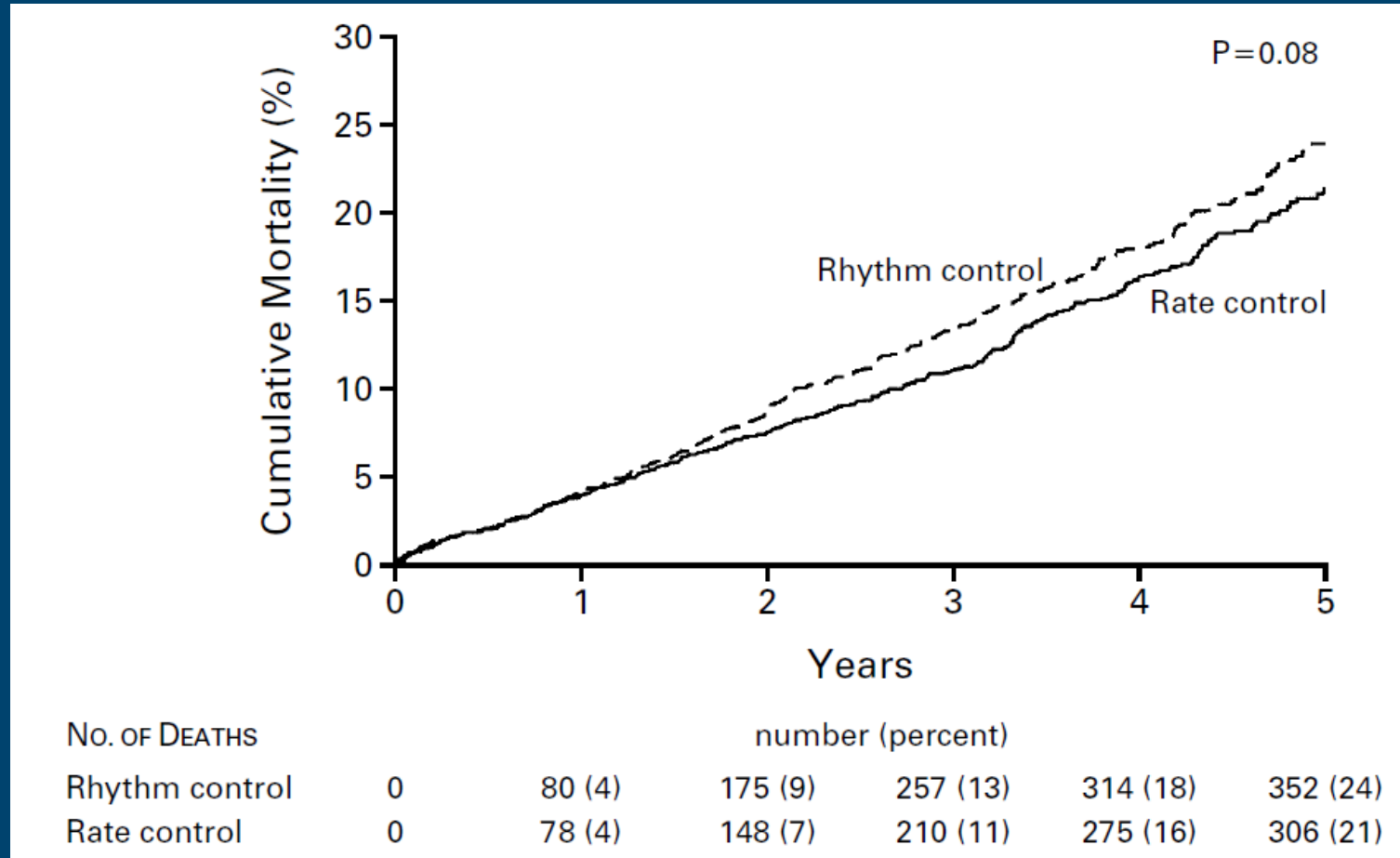
Heart rhythm
in atrial fibrillation

Cardioversion
shock

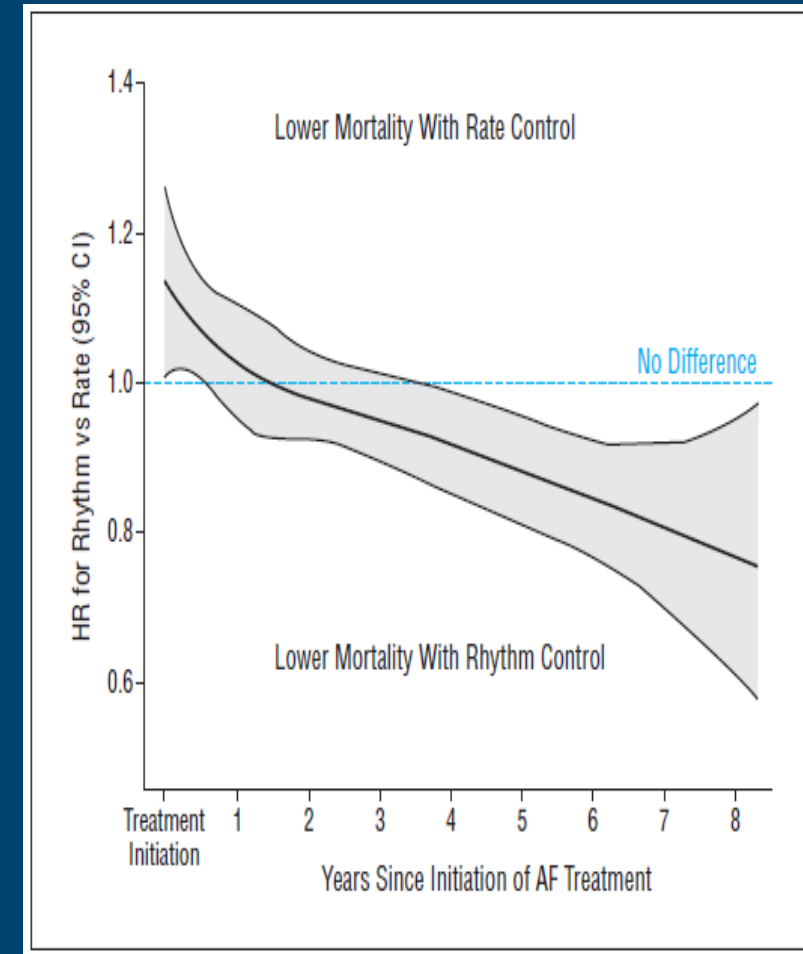
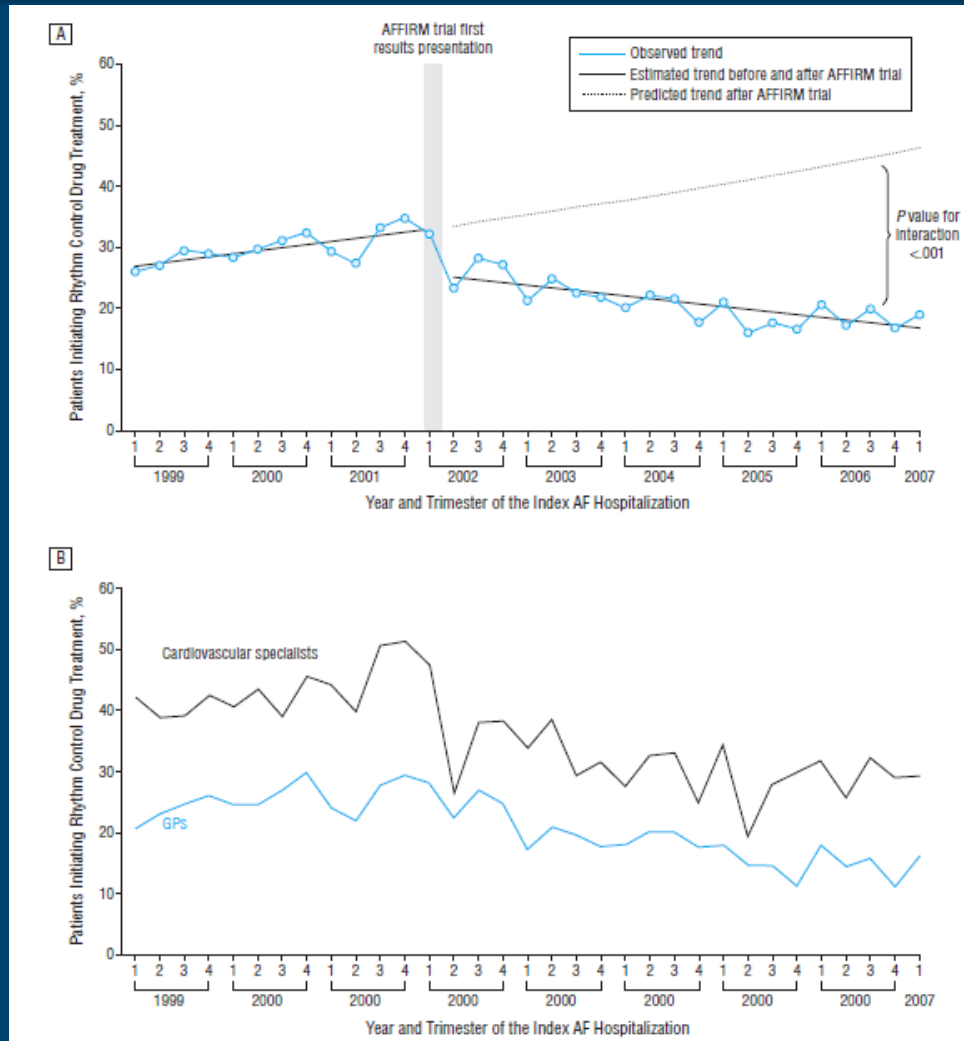
Normal heart
rhythm

...Atrial fibrillation often recurs

Medical Rate vs. Rhythm Control: AFFIRM



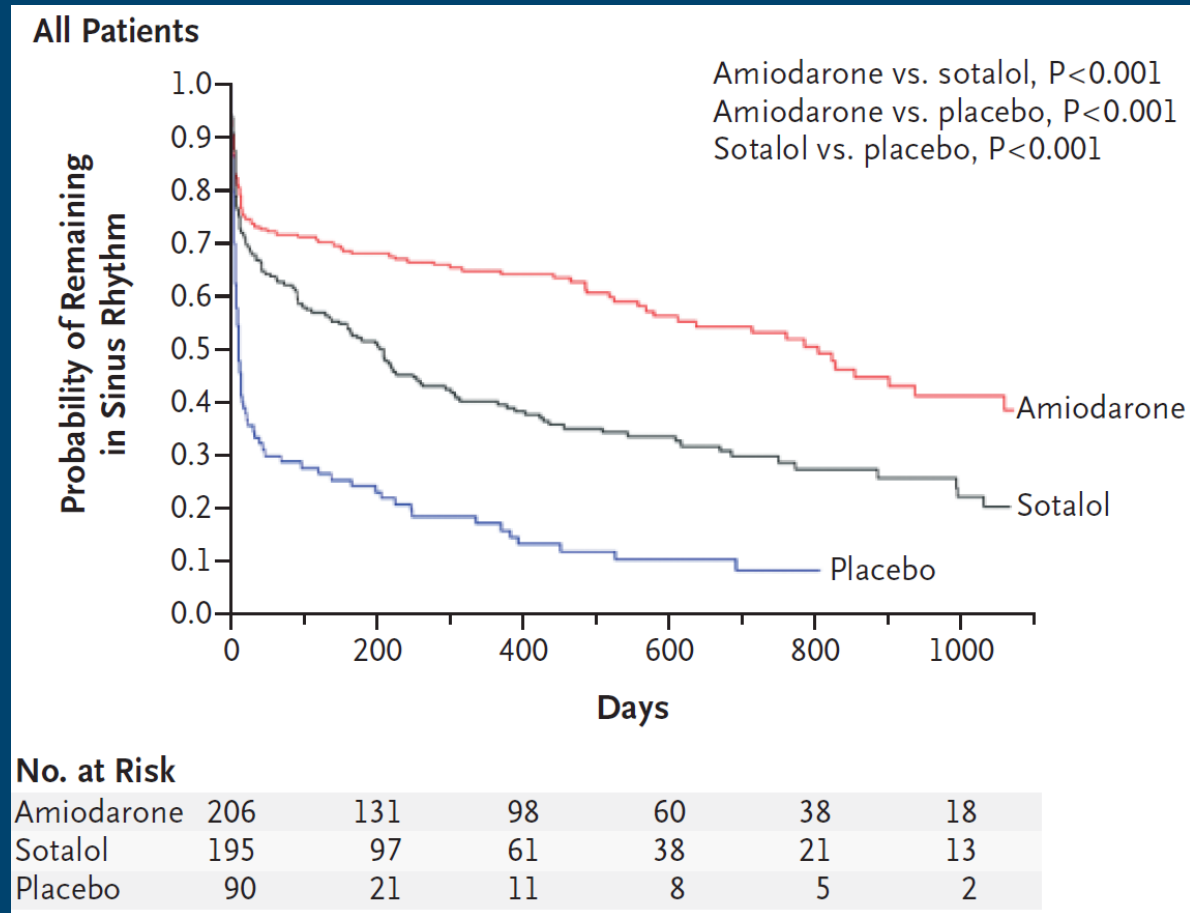
Observational Mortality Study of Rate vs. Rhythm Control in 26,130 Canadian Patients (66+ years old)



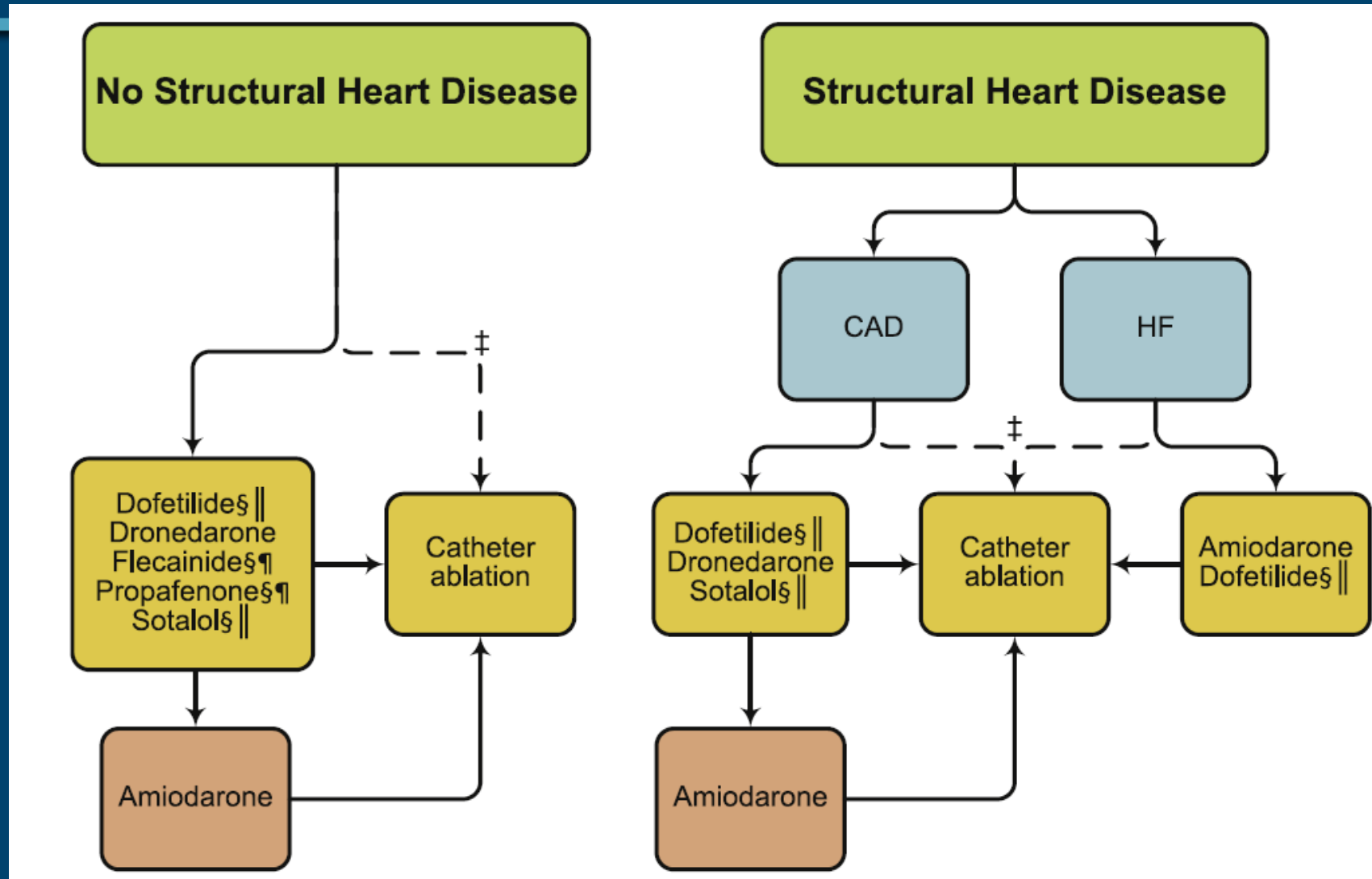
Drug Therapy: No Magic Pill...



Rhythm Control: Amiodarone vs. Sotalol vs. Placebo



Antiarrhythmic Drug Therapy for AF

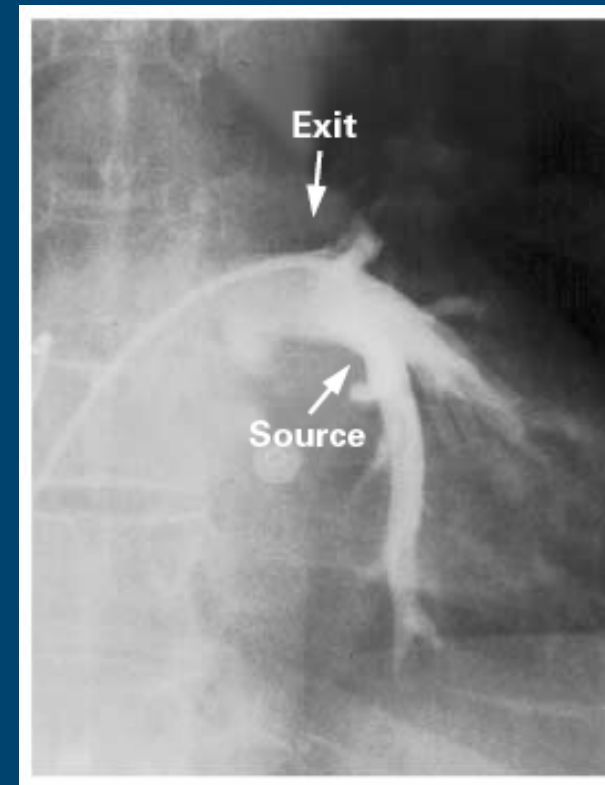
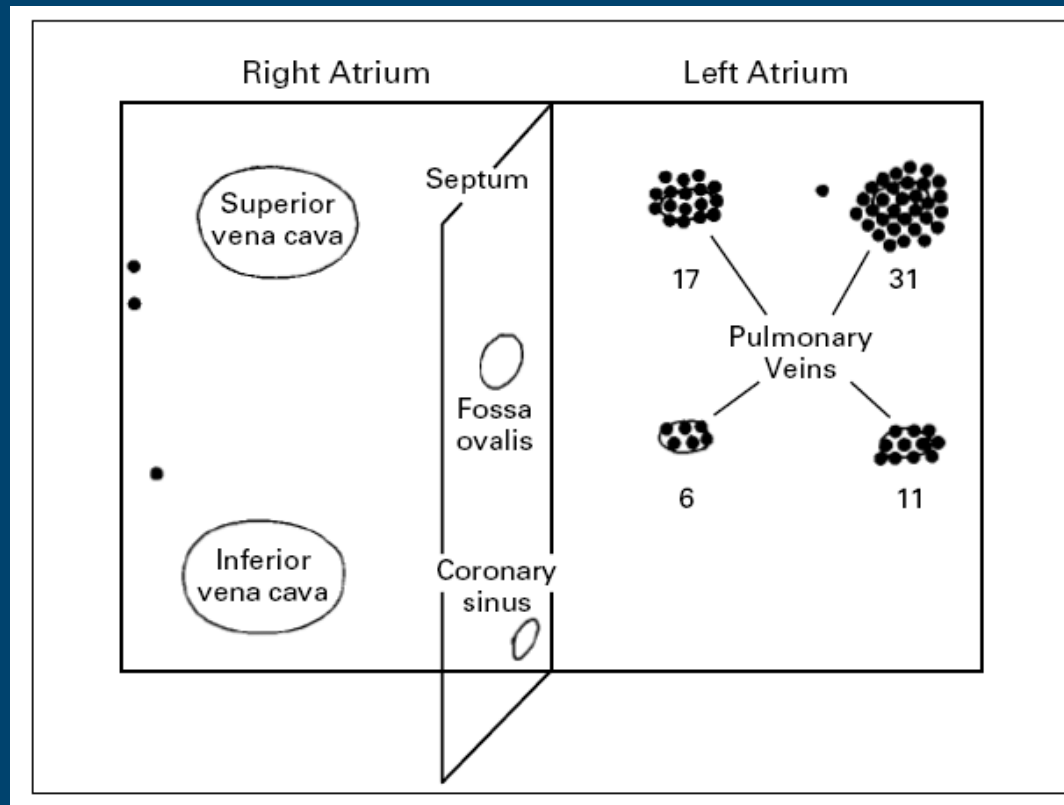


Drug Therapy for AF Summary

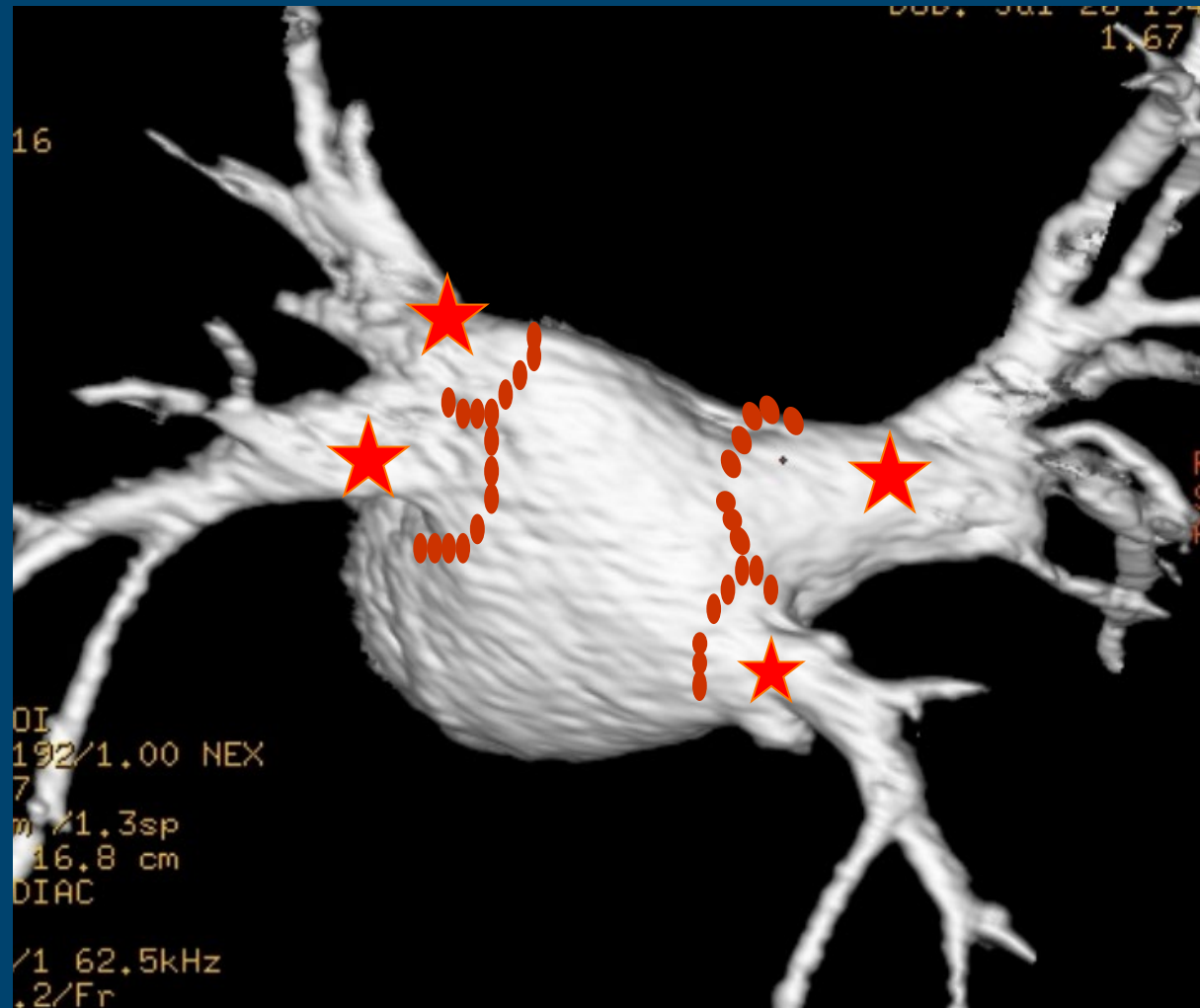
- Hard endpoints with AF rate control are as good as rhythm control (anti-arrhythmic drugs)
- Beta blockers and calcium channel blockers are good rate control choices, digoxin may increase mortality
- Antiarrhythmic drugs for AF have moderate efficacy and potential for drug toxicity

Ablation Procedures for Atrial Fibrillation

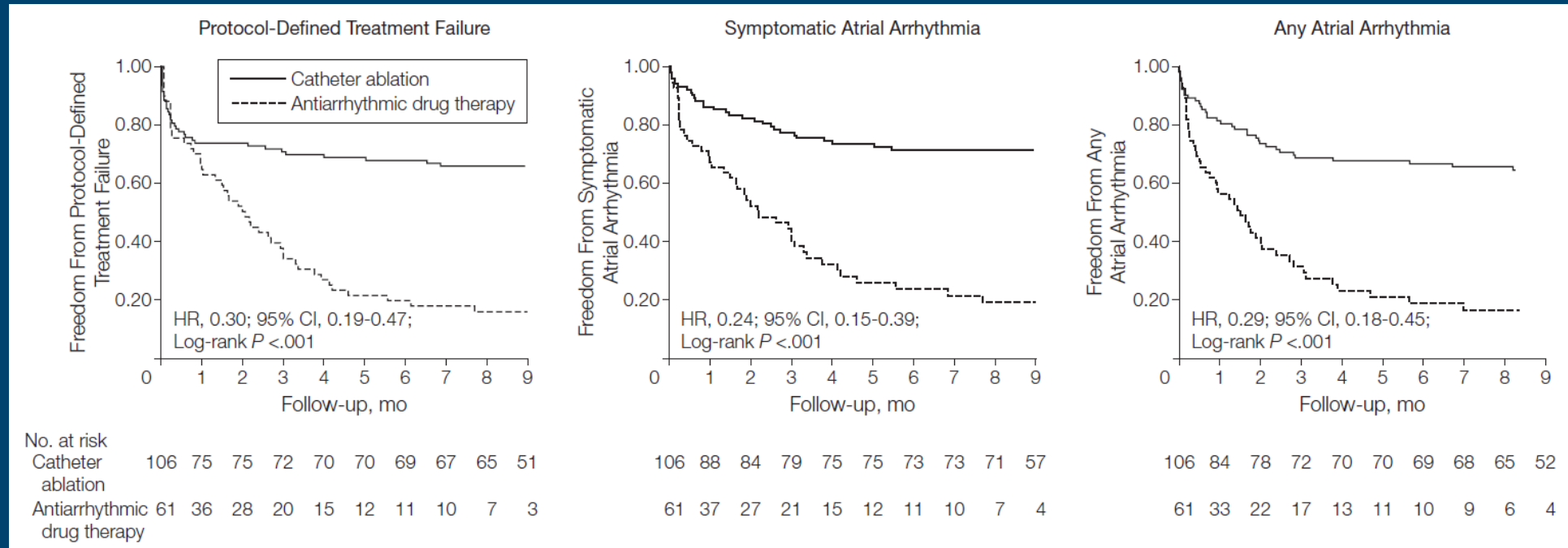
Pulmonary Veins as Triggers of Paroxysmal Atrial Fibrillation



Pulmonary Vein Isolation: Ablation for Paroxysmal AF

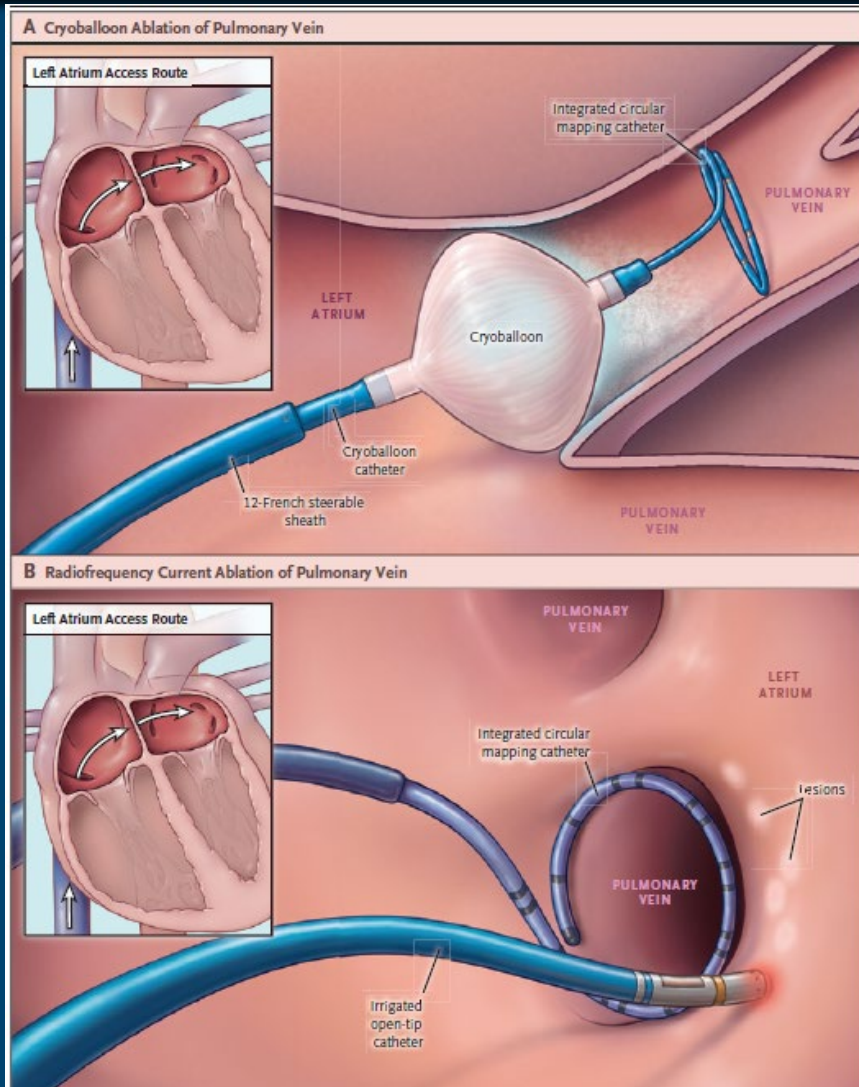


Catheter Ablation vs. Antiarrhythmic Drug Therapy for Paroxysmal AF

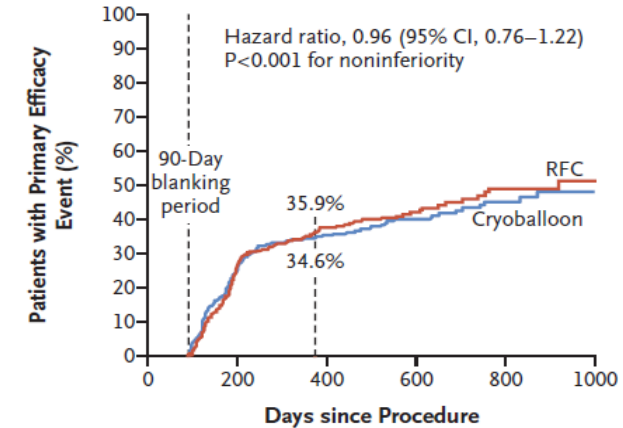


*Protocol-Defined Treatment Failure: documented symptomatic atrial fibrillation

AF Ablation Methods: Cryoballoon vs RA Ablation: “Fire and ICE”



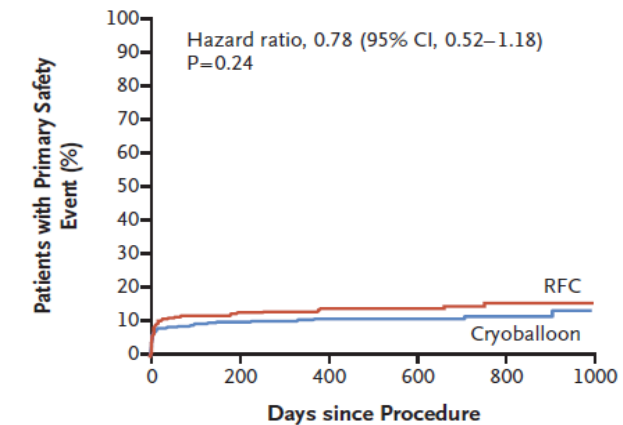
A Primary Efficacy End Point



No. at Risk
Cryoballoon
RFC

374	338	242	194	165	132	107	70	57	34	12
376	350	243	191	149	118	93	58	44	25	12

C Primary Safety End Point



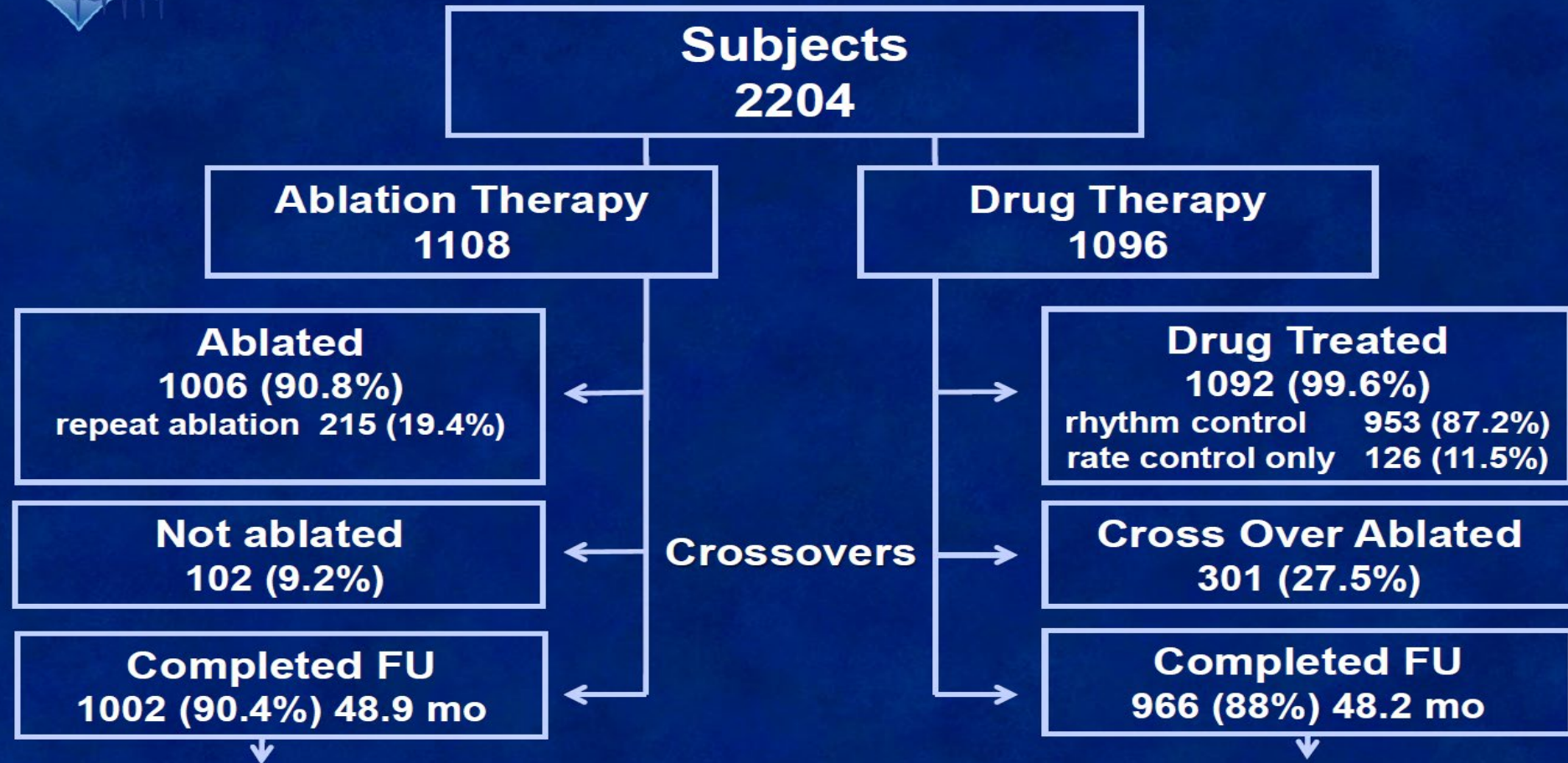
No. at Risk
Cryoballoon
RFC

374	323	298	261	229	189	159	117	94	55	21
376	315	292	247	215	176	146	110	87	52	27

CABANA Study: AF ablation vs drug therapy



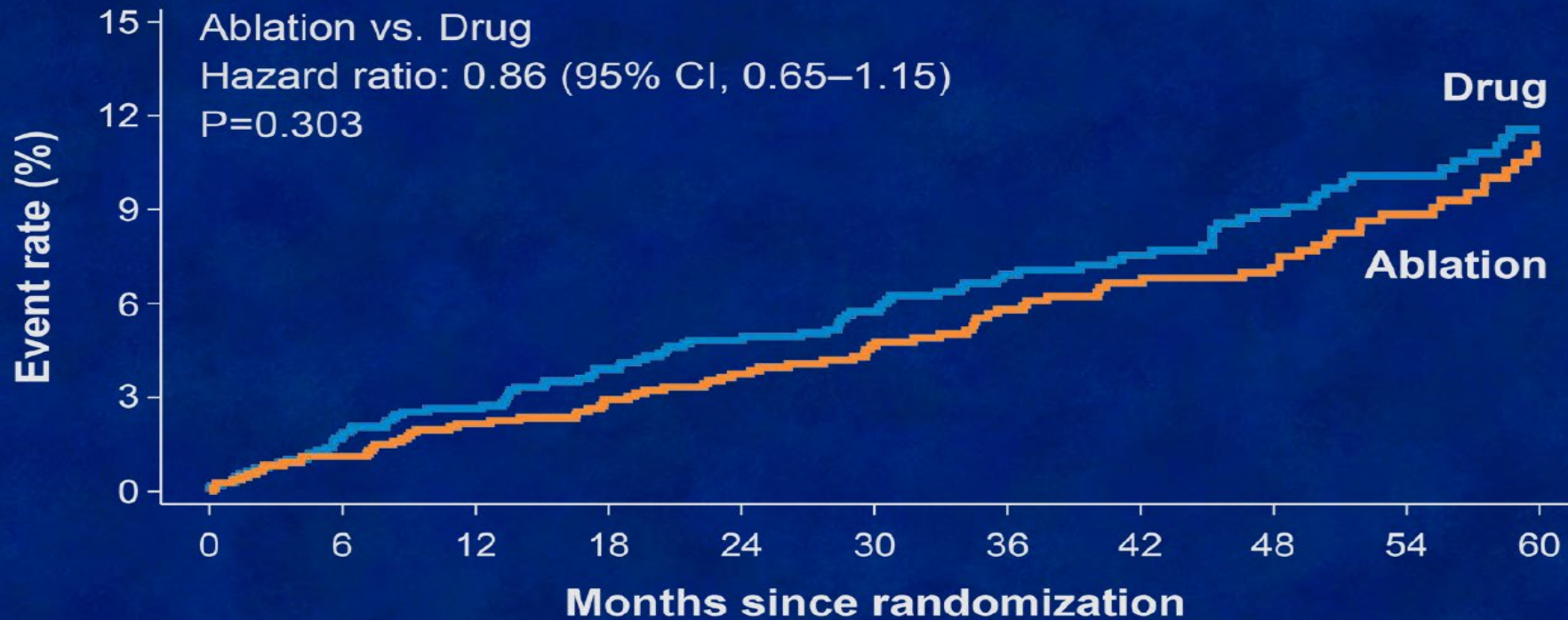
Patient Randomization



CABANA Study: AF ablation vs drug therapy



Primary Endpoint (Death, Disabling Stroke, Serious Bleeding, or Cardiac Arrest) (ITT)



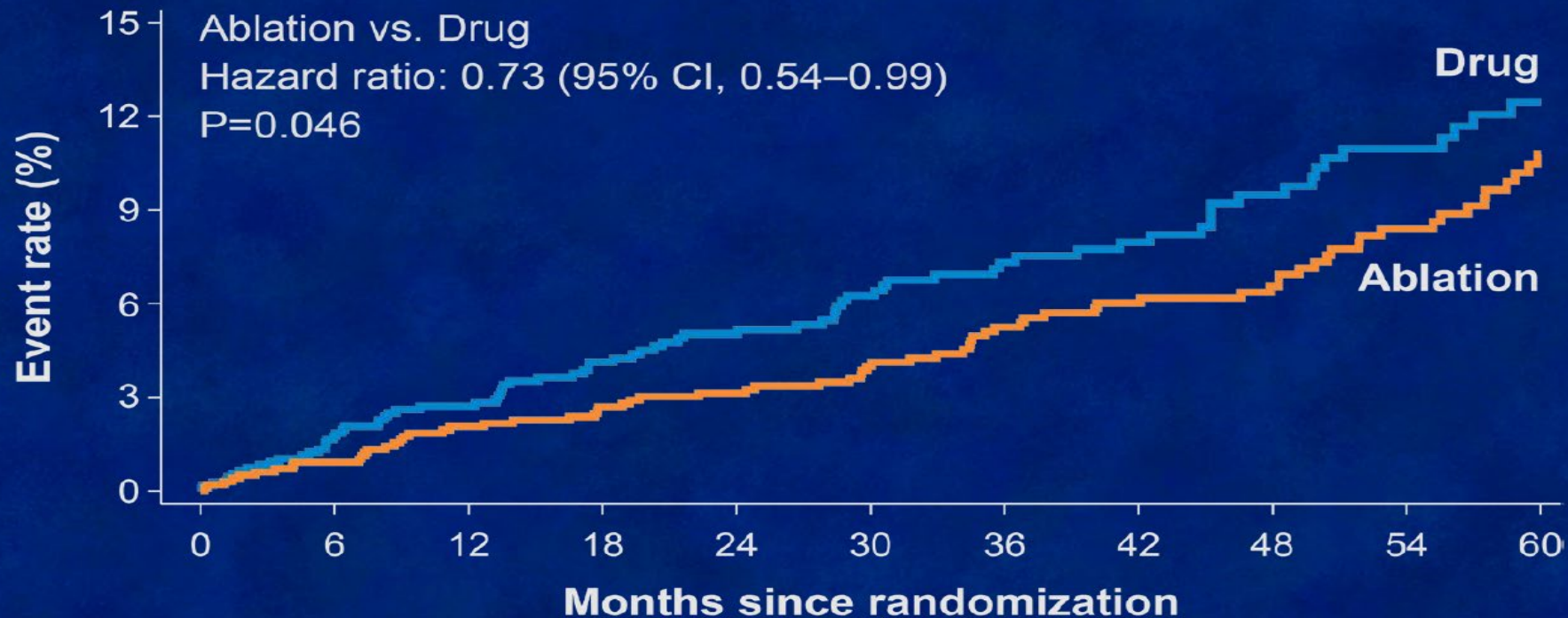
Number at risk

Drug	1096	1036	1006	970	880	763	652	578	499	418	312
Ablation	1108	1045	1021	996	915	793	700	614	535	432	309

CABANA Study: AF ablation vs drug therapy



Primary Endpoint (Death, Disabling Stroke, Serious Bleeding, or Cardiac Arrest (Per Protocol))



Number at risk

Drug	1096	954	860	778	680	566	464	396	330	275	204
Ablation	987	958	937	918	849	735	648	566	494	404	291

MASSACHUSETTS
GENERAL HOSPITAL

HEART CENTER

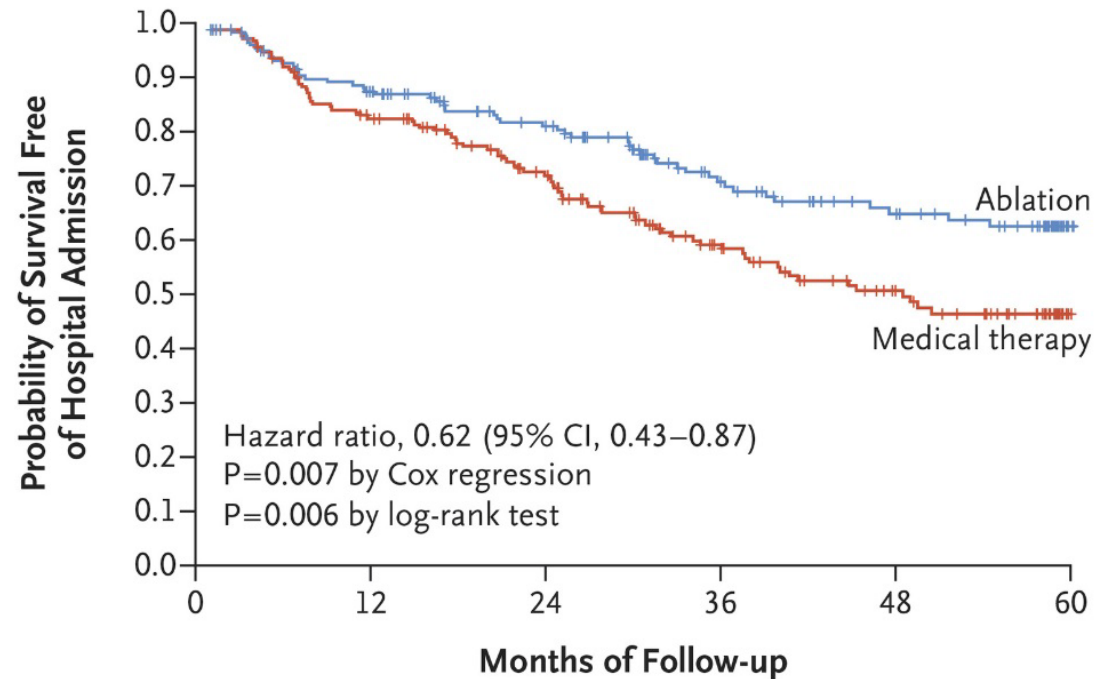
AF and CHF

Is There Benefit to AF Ablation?

CASTLE-AF

AF Ablation vs Medical Therapy in AF with CHF (EF $\leq$ 35%)

A Death or Hospitalization for Worsening Heart Failure



No. at Risk

Ablation	179	141	114	76	58	22
Medical therapy	184	145	111	70	48	12



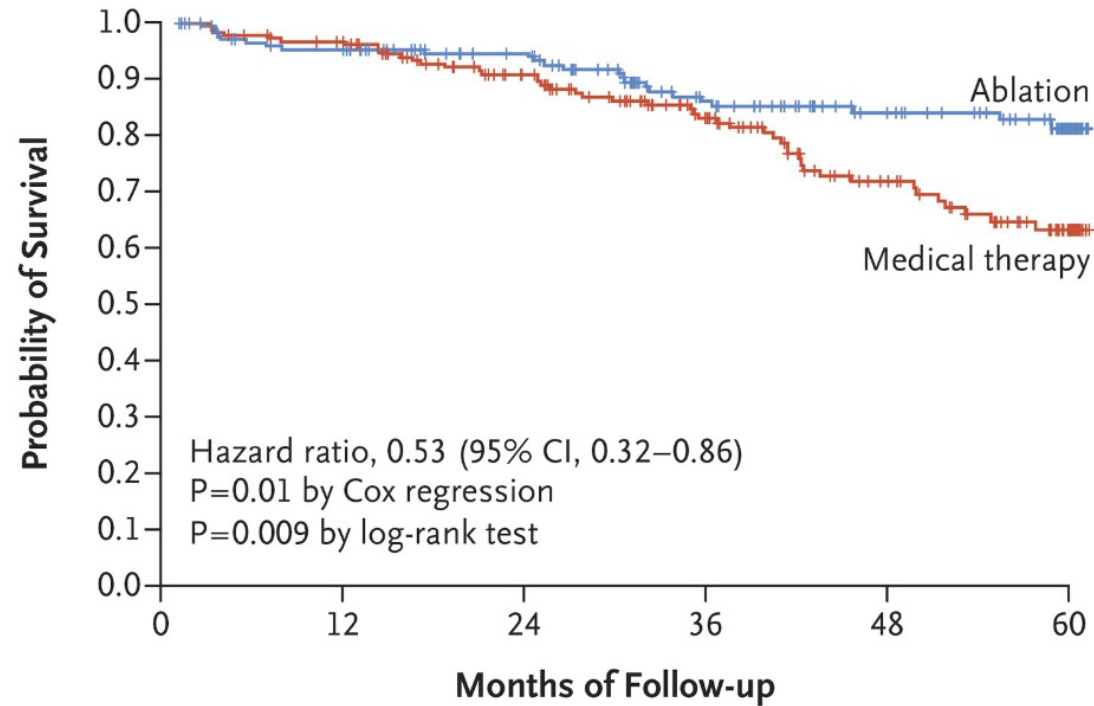
MASSACHUSETTS
GENERAL HOSPITAL

HEART CENTER

CASTLE-AF

AF Ablation vs Medical Therapy in AF with CHF (EF $\leq$ 35%)

B Death from Any Cause



No. at Risk

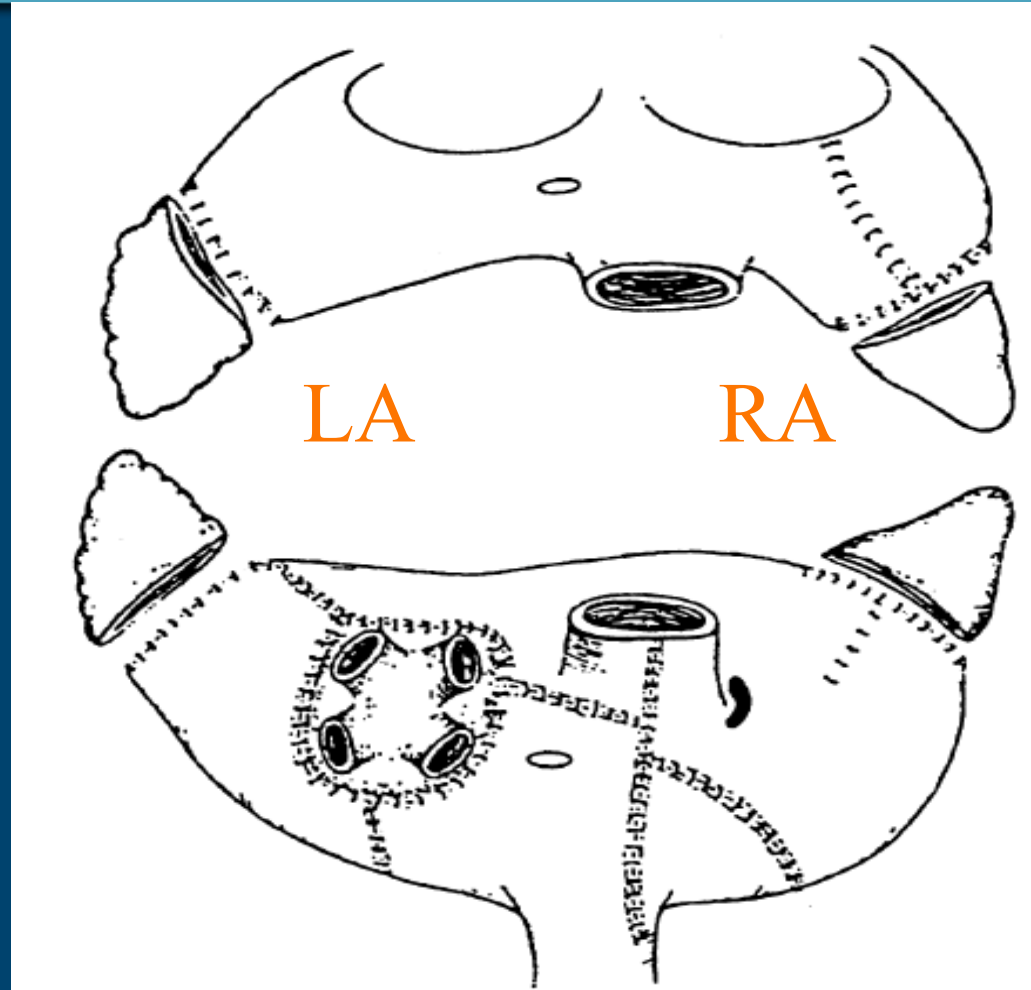
Ablation	179	154	130	94	71	27
Medical therapy	184	168	138	97	63	19



MASSACHUSETTS
GENERAL HOSPITAL

HEART CENTER

Surgical Approaches to AF



FAST Study: Catheter or Surgical Ablation for AF

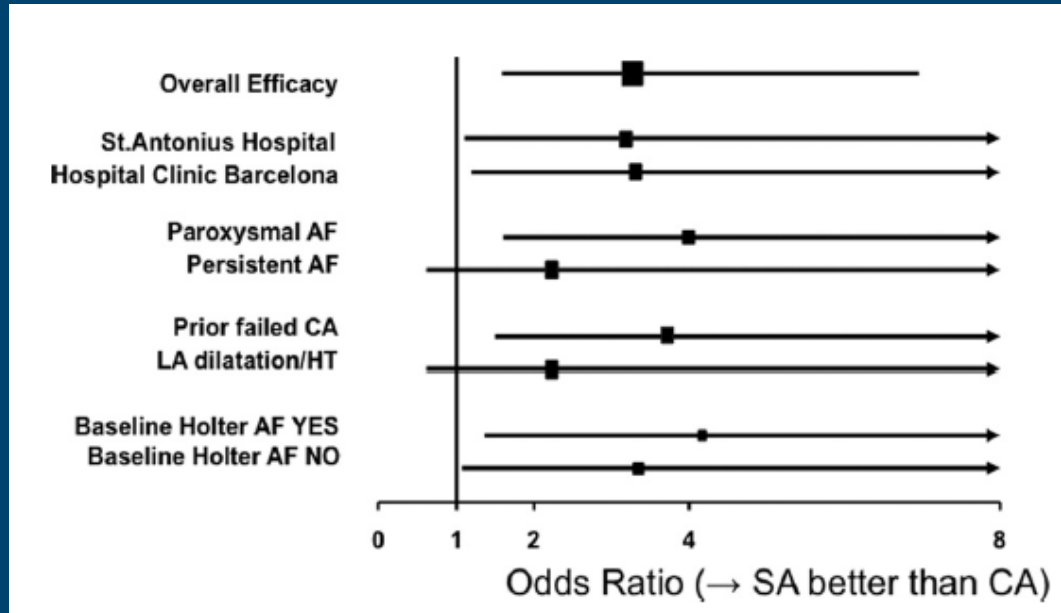


Table 4. Procedural Adverse Events of CA and SA

Adverse Events	CA N=63	SA N=61	P-Value
Pericardial effusion/tamponade	1	1	
TIA/Stroke	1	1	
Pneumothorax	...	6	
Hemothorax	...	1	
Rib fracture	...	1	
Sternotomy for bleeding	...	1	
Pneumonia	...	1	
Death	...	...	
PM implant	...	2	
Total	2 (3.2%)	14 (23.0%)	P=0.001
Minor			
Groin hematoma/bleed	4 (6.3%)	...	

Catheter Ablation: radiofrequency PVI (additional ablation lines at operator discretion)

Surgical Ablation: VATS approach, radiofrequency PVI + LA ganglionated plexus ablation + LAA excision (additional ablation lines at operator discretion)

FAST Study: Catheter or Surgical Ablation for AF

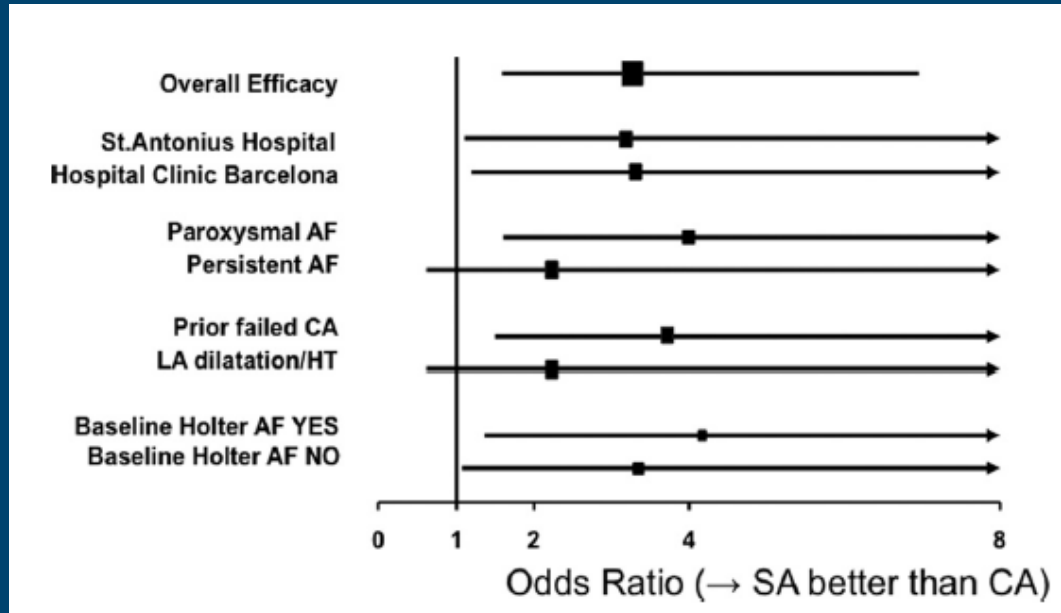


Table 4. Procedural Adverse Events of CA and SA

Adverse Events	CA N=63	SA N=61	P-Value
Pericardial effusion/tamponade	1	1	
TIA/Stroke	1	1	
Pneumothorax	...	6	
Hemothorax	...	1	
Rib fracture	...	1	
Sternotomy for bleeding	...	1	
Pneumonia	...	1	
Death	...	...	
PM implant	...	2	
Total	2 (3.2%)	14 (23.0%)	P=0.001
Minor			
Groin hematoma/bleed	4 (6.3%)	...	

Catheter Ablation: radiofrequency PVI (additional ablation lines at operator discretion)

Surgical Ablation: VATS approach, radiofrequency PVI + LA ganglionated plexus ablation + LAA excision (additional ablation lines at operator discretion)

Conclusion Regarding AF Ablation

- AF catheter ablation is more effective than antiarrhythmic drugs, but is not a guarantee of no AF
- Tools and strategies for AF ablation are evolving
- AF ablation may particularly benefit CHF patients
- Surgical AF ablation (Maze) appears more effective and more risky than catheter AF ablation



MASSACHUSETTS
GENERAL HOSPITAL

HEART CENTER

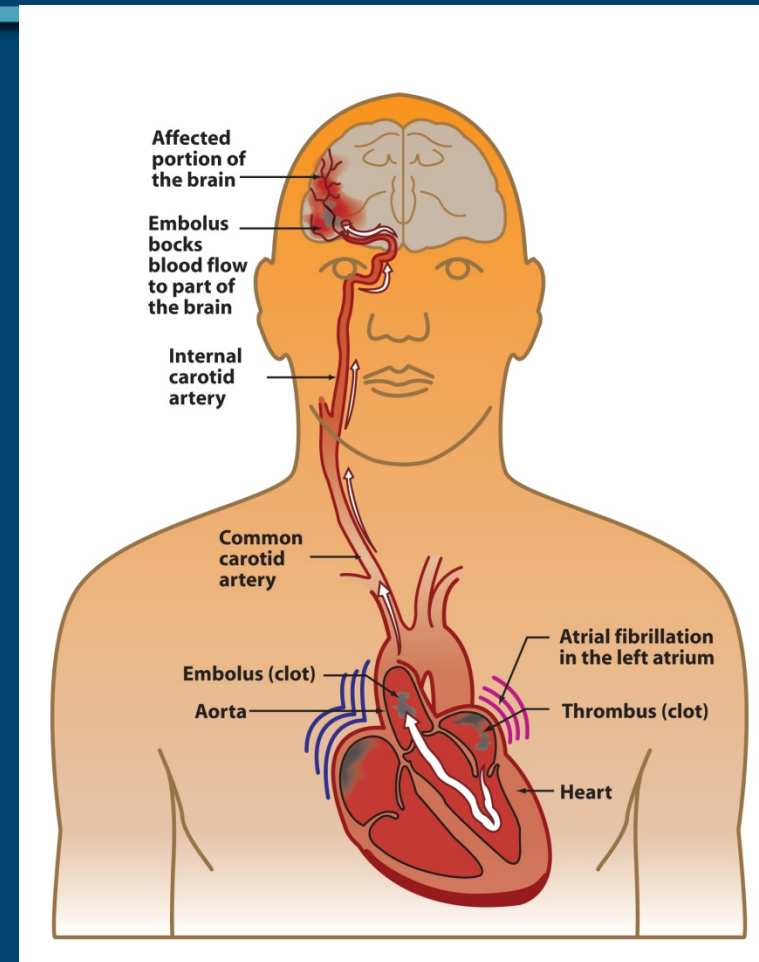
Stroke Prevention in Atrial Fibrillation



A Teaching Affiliate
of Harvard Medical School

Stroke Is One of the Most Common and Devastating Complications of AF

- All-cause stroke rate with AF is 5% per year
- AF - independent risk factor for stroke
 - ~5-fold increase in stroke risk
 - ~15% of all strokes caused by AF
 - Stroke risk increases with age
- Stroke risk persists in asymptomatic AF



Fuster V, et al. *Circulation*. 2006;114:e257-e354.
Wolf PA, et al. *Stroke*. 1991;22:983-988.
Page RL, et al. *Circulation*. 2003;107:1141-1145.
Hart RG, et al. *J Am Coll Cardiol*. 2000;35:183-187.



MASSACHUSETTS
GENERAL HOSPITAL
HEART CENTER

Stroke Risk Without Anticoagulation: CHADS₂ and CHADS₂-VASc

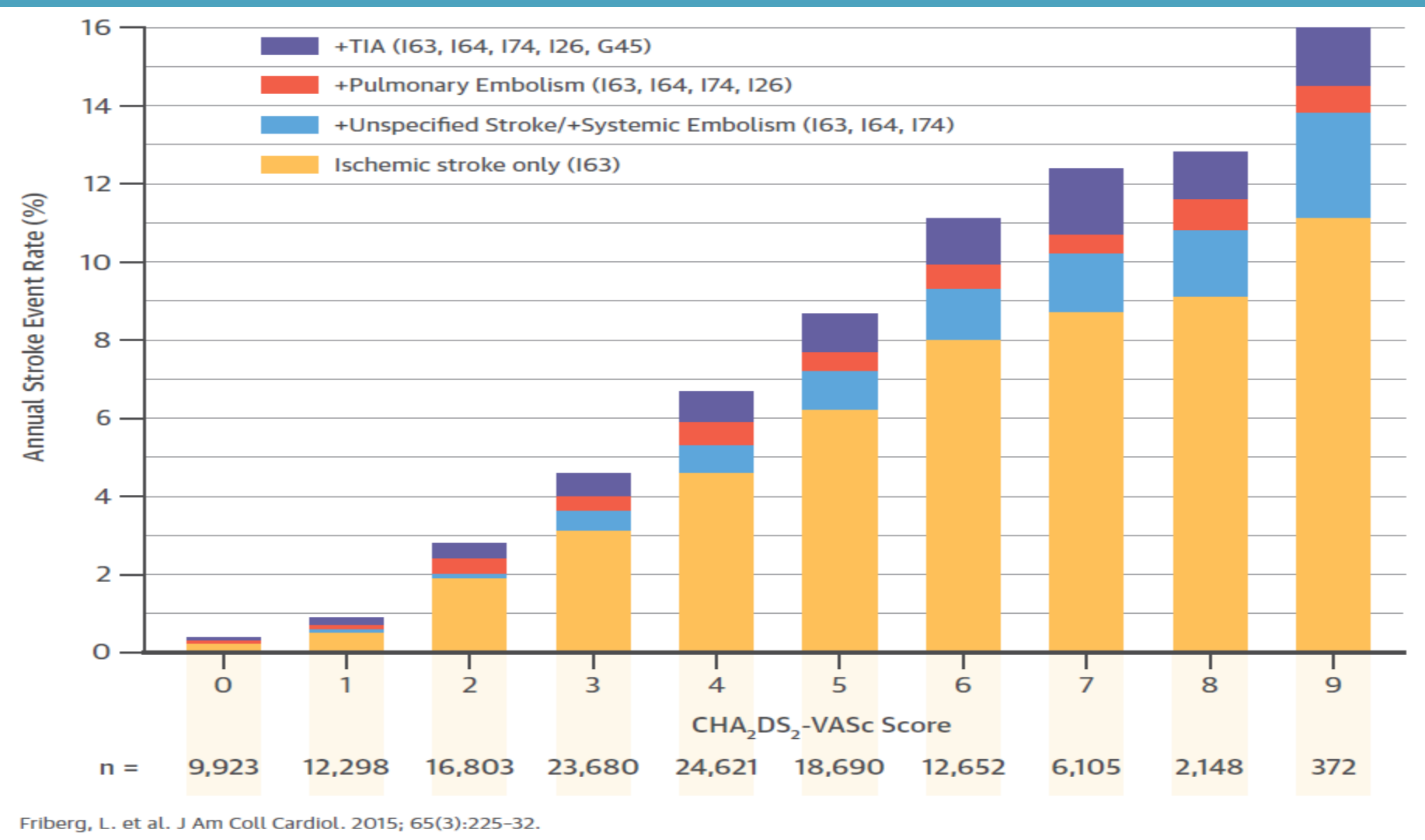
Definition and Scores for CHADS₂ and CHA₂DS₂-VASc

	Score
CHADS₂	
Congestive HF	1
Hypertension	1
Age ≥75 y	1
Diabetes mellitus	1
Stroke/TIA/TE	2
Maximum score	6
CHA₂DS₂-VASc	
Congestive HF	1
Hypertension	1
Age ≥75 y	2
Diabetes mellitus	1
Stroke/TIA/TE	2
Vascular disease (prior MI, PAD, or aortic plaque)	1
Age 65-74 y	1
Sex category (i.e., female sex)	1
Maximum score	9

Stroke Risk Stratification With the CHADS₂ and CHA₂DS₂-VASc Scores

	Adjusted Stroke Rate (% per y)
CHADS₂*	
0	1.9
1	2.8
2	4.0
3	5.9
4	8.5
5	12.5
6	18.2
CHA₂DS₂-VASc†	
0	0
1	1.3
2	2.2
3	3.2
4	4.0
5	6.7
6	9.8
7	9.6
8	6.7
9	15.20

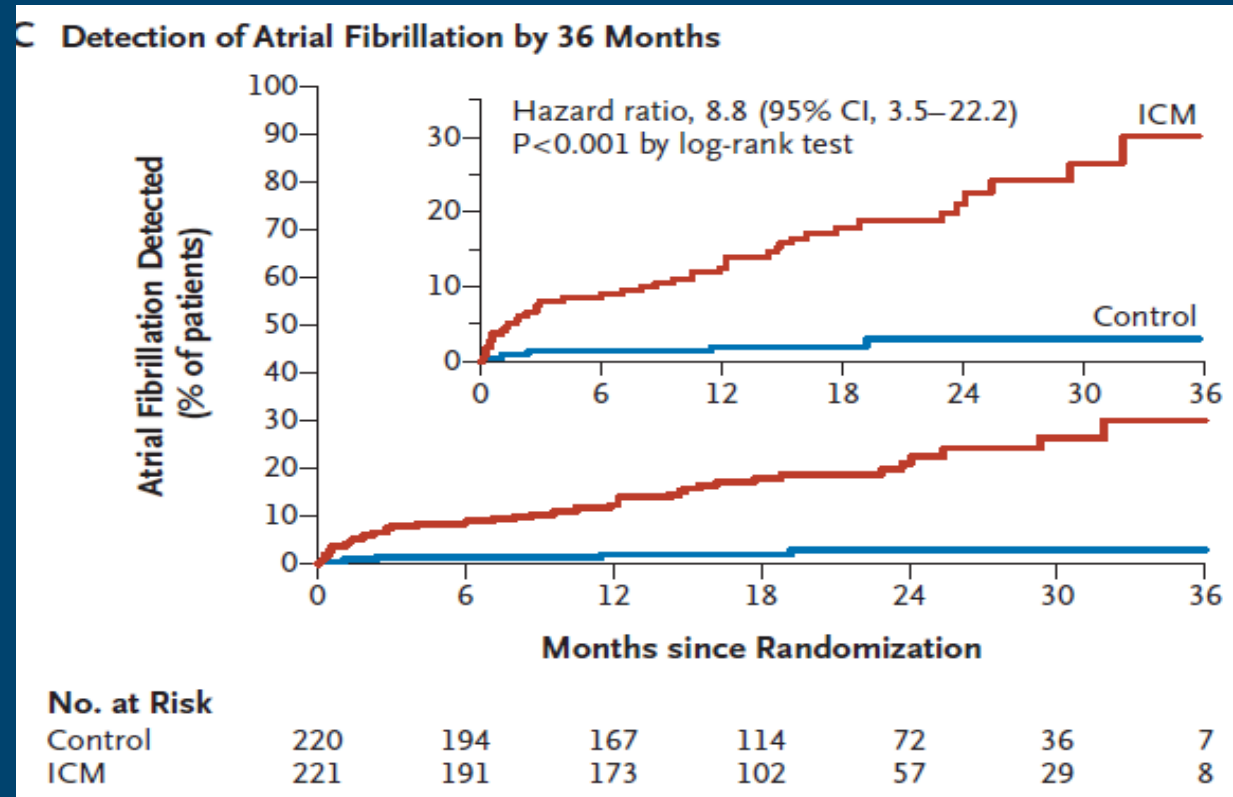
Stroke Risk Without Anticoagulation: CHADS₂-VASc



CRYSTAL AF Study

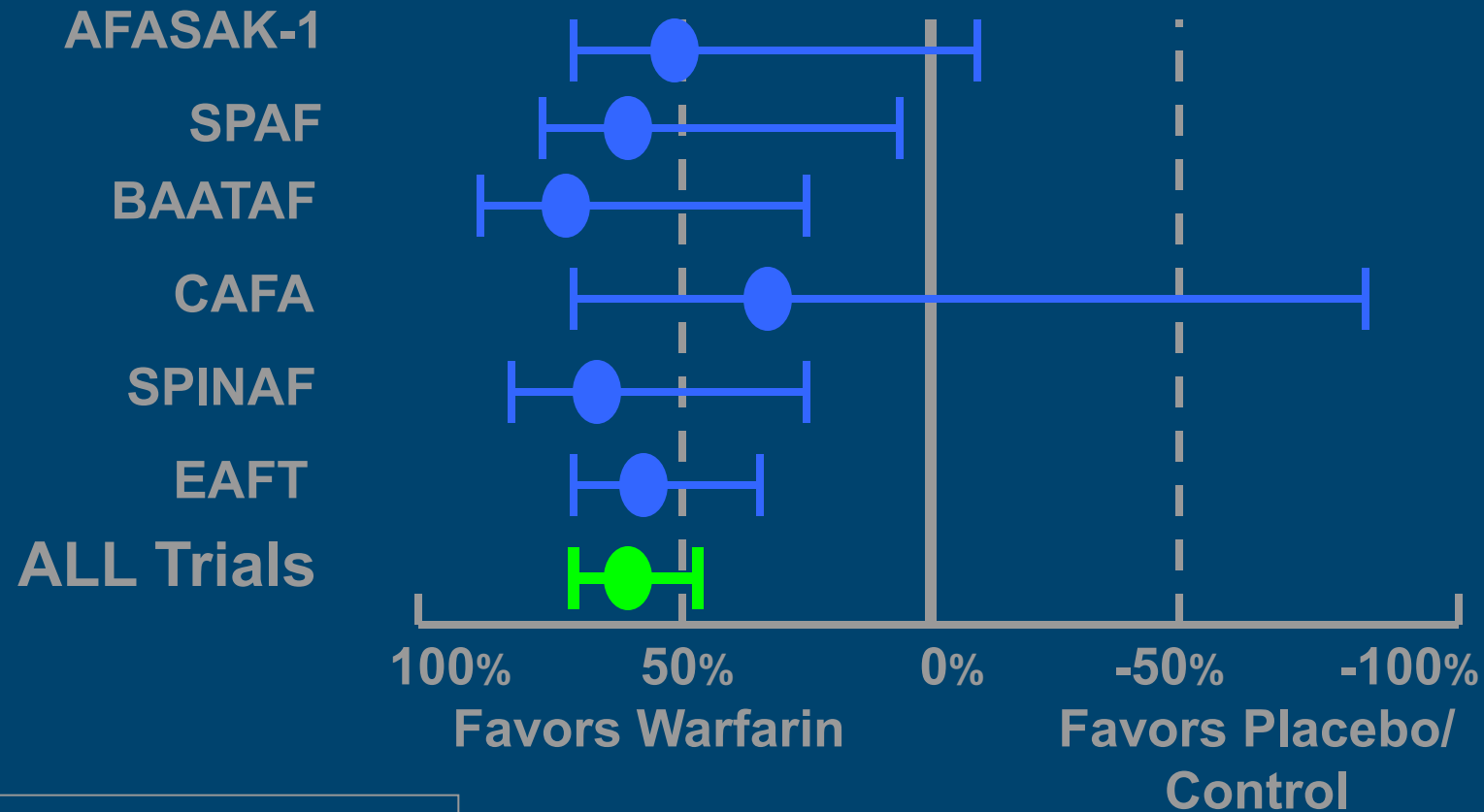
Detection of AF in cryptogenic stroke

- 441 patients age ≥ 40 with cryptogenic stroke
 - No h/o AF and no AF on 24+ hour EKG monitor
 - Randomized to implantable cardiac monitor or usual care



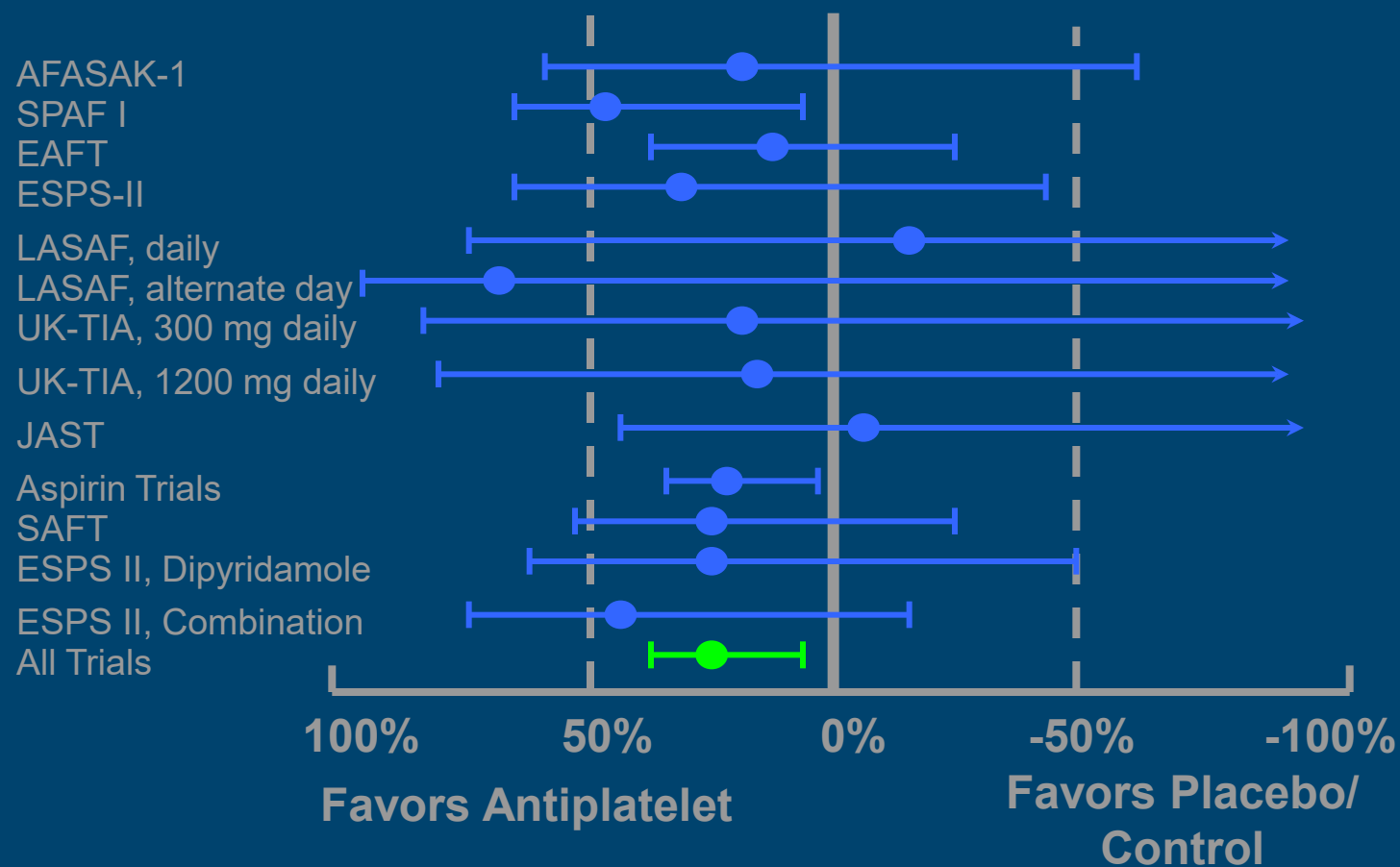
Anticoagulation and Antiplatelet Therapy

Warfarin vs Placebo in Stroke Prevention in AF



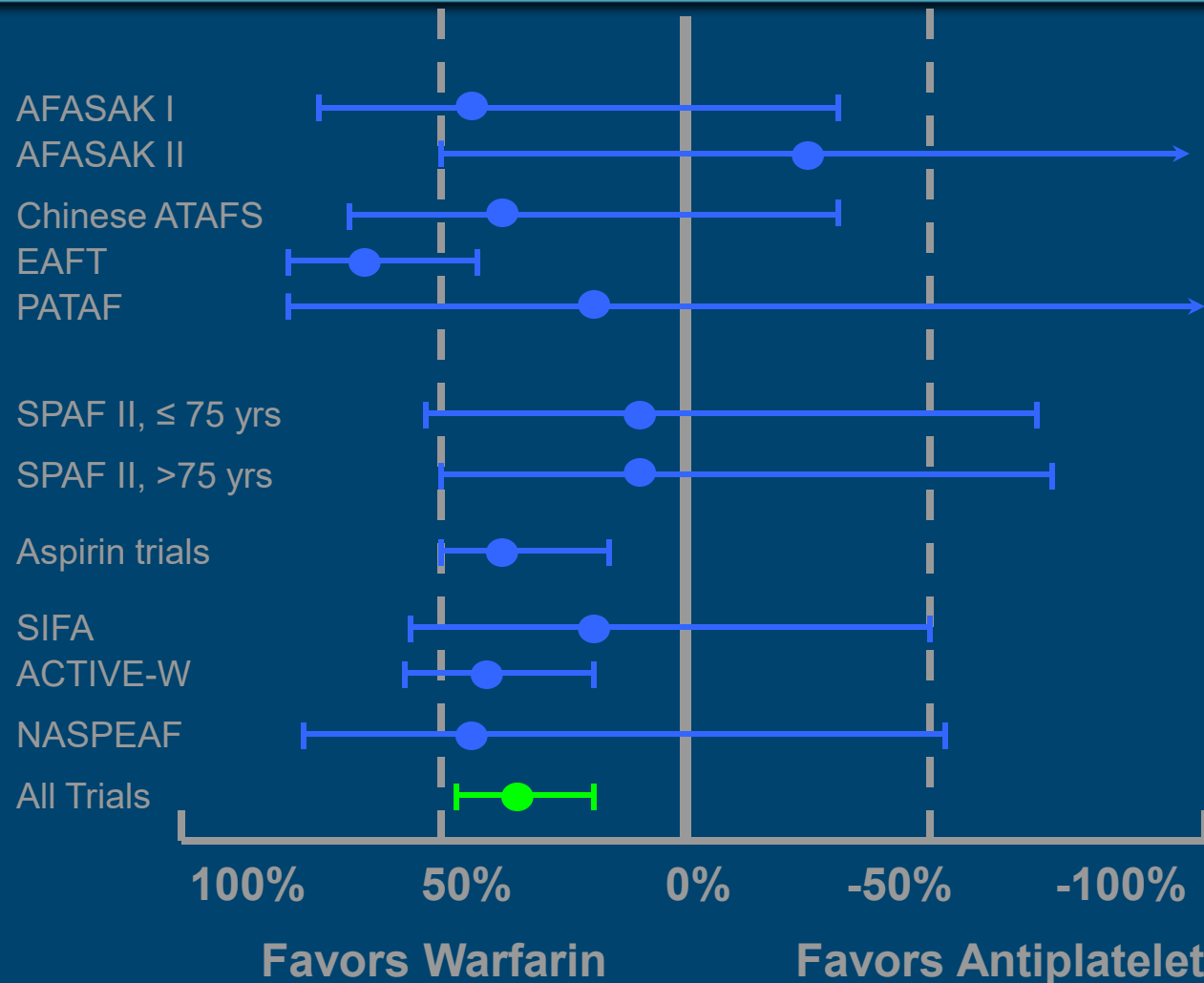
Warfarin reduces incidence of stroke by about 64%

Aspirin vs Placebo in Stroke Prevention in AF

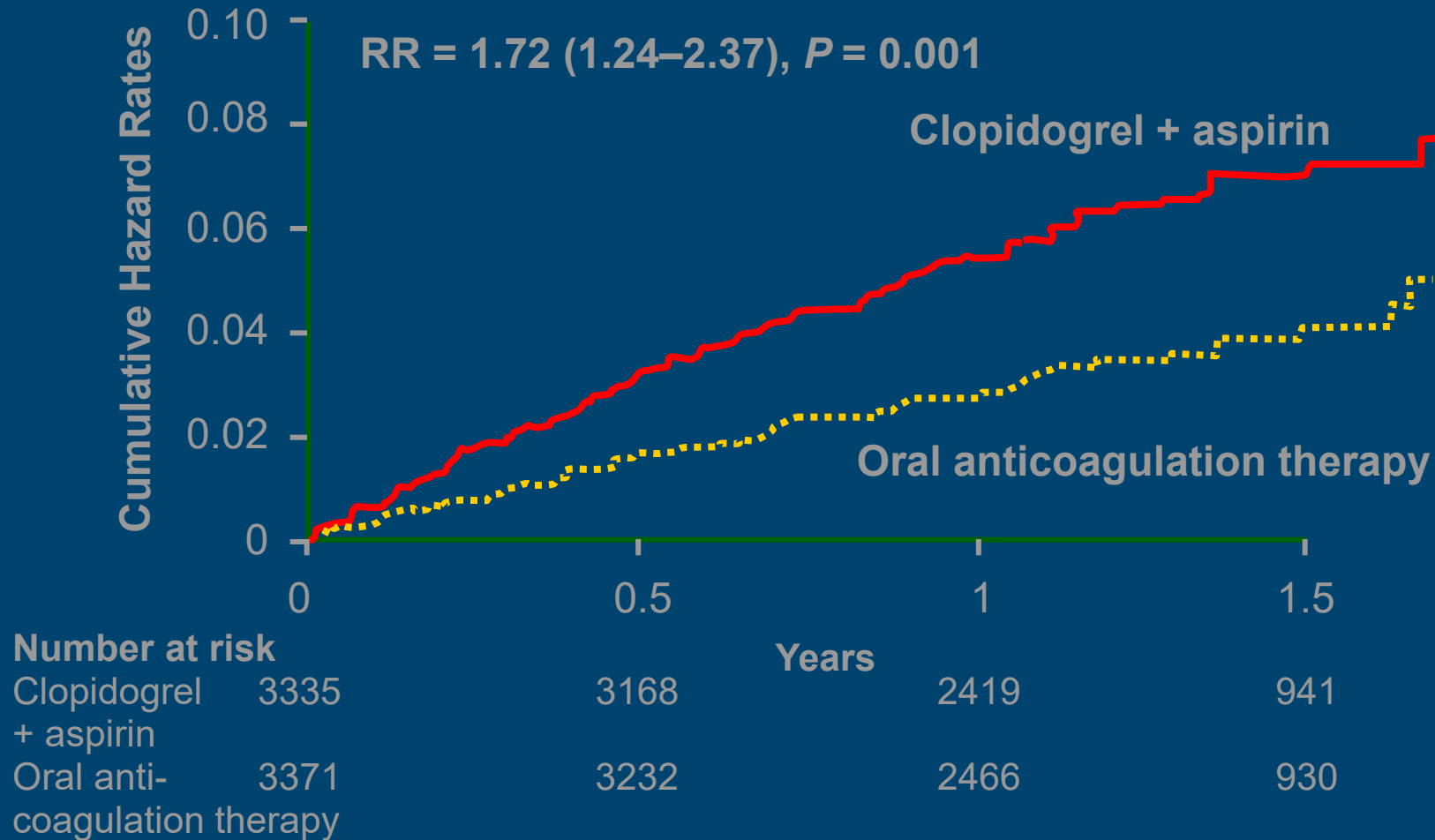


Antiplatelet therapy reduces incidence of stroke by about 22%

Warfarin vs Antiplatelet Therapy in Stroke Prevention in AF



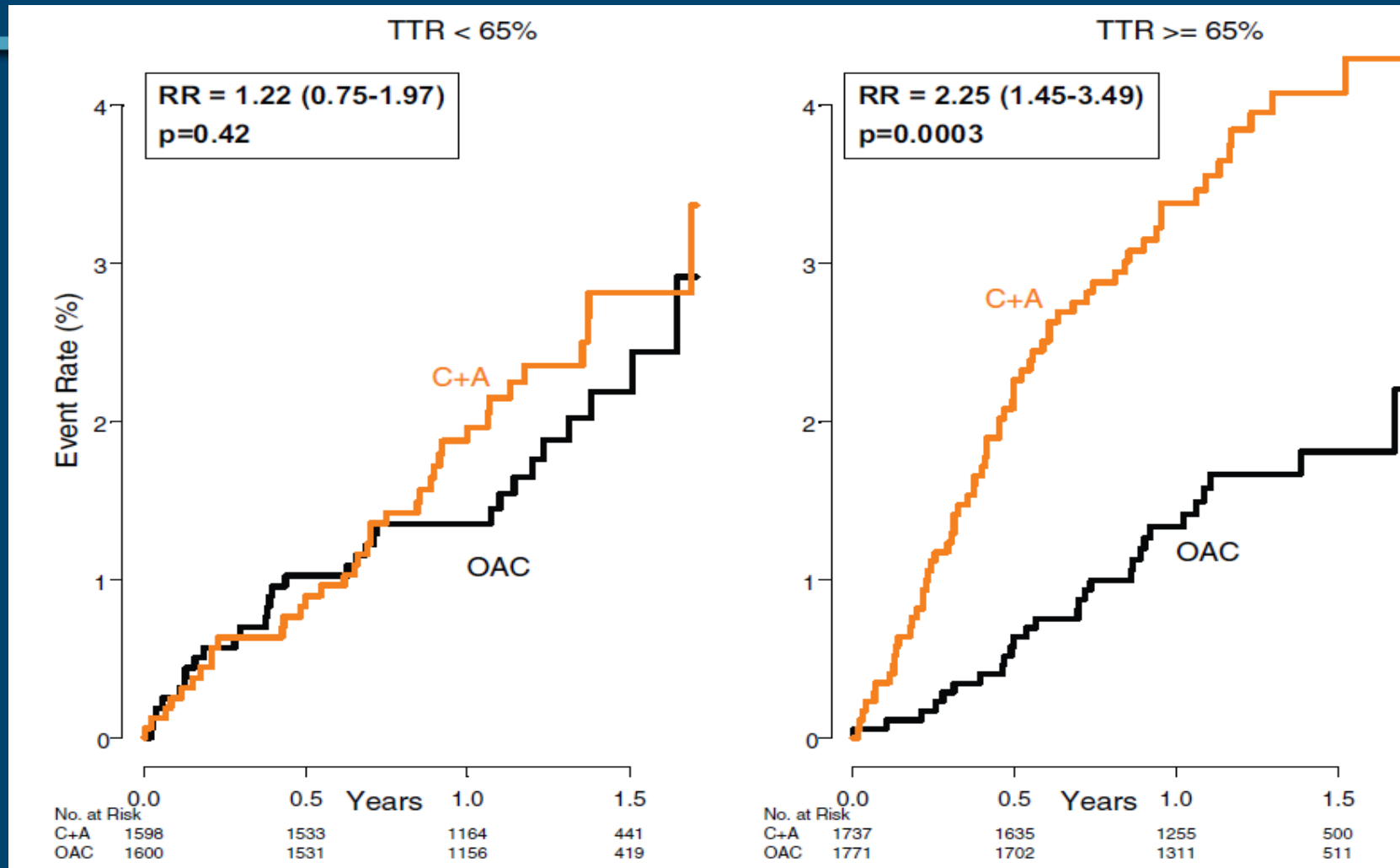
ACTIVE* W: Cumulative Risk of Stroke



Primary outcome: stroke, systemic embolus, MI, vascular death.
Connolly et al. *Lancet*. 2006;367:1903-1912.

Importance of Time within Therapeutic Range

Patients Treated at Centers with TTR Below or Above 65%



C+A: clopidogrel plus aspirin; OAC: oral anticoagulation therapy
RR: relative risk of stroke C+A vs OAC

Connolly S, et al. *Circulation*. 2008;118:2029-2037.

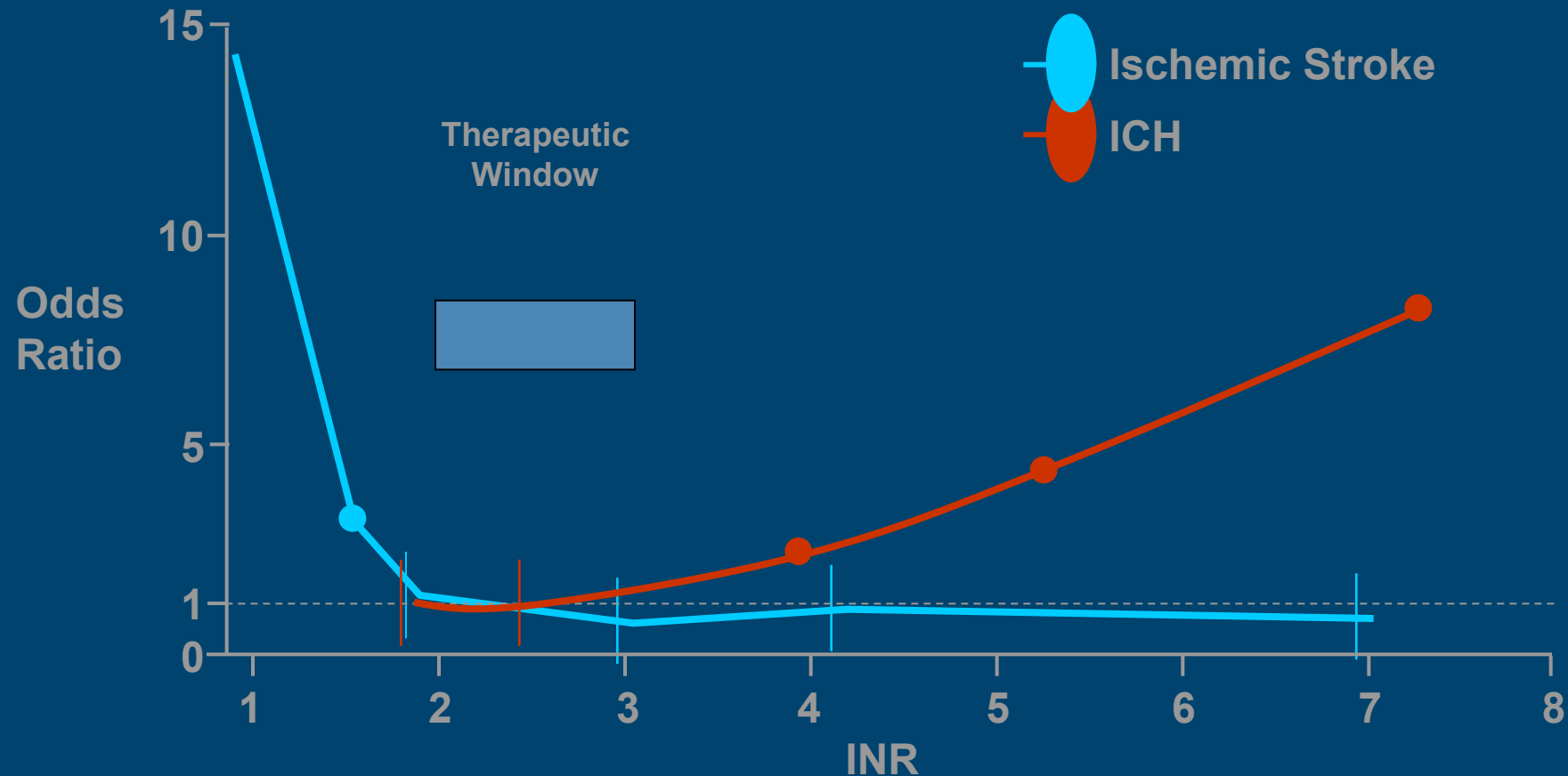


MASSACHUSETTS
GENERAL HOSPITAL

HEART CENTER

Warfarin Has a Narrow Therapeutic Window

Relationship Between Clinical Events and INR
Intensity in Patients with Atrial Fibrillation



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

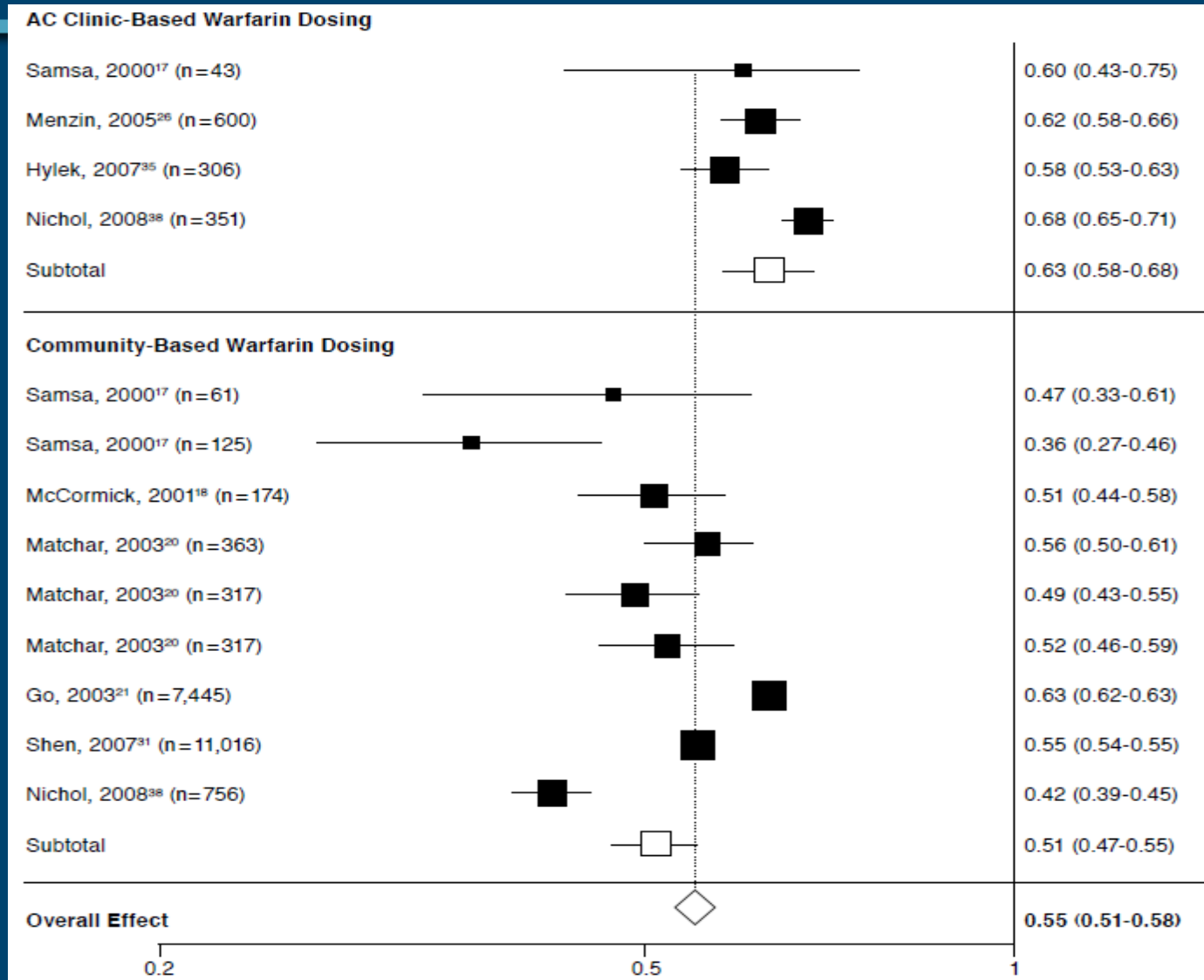
Hylek EM, et al. *N Engl J Med.* 1996;335:540-546.



MASSACHUSETTS
GENERAL HOSPITAL

HEART CENTER

Atrial Fibrillation Patients – 55%-63% of Their Time in Therapeutic INR Range



Baker W, et al. *J Manag Care Pharm.* 2009;15:244-252.



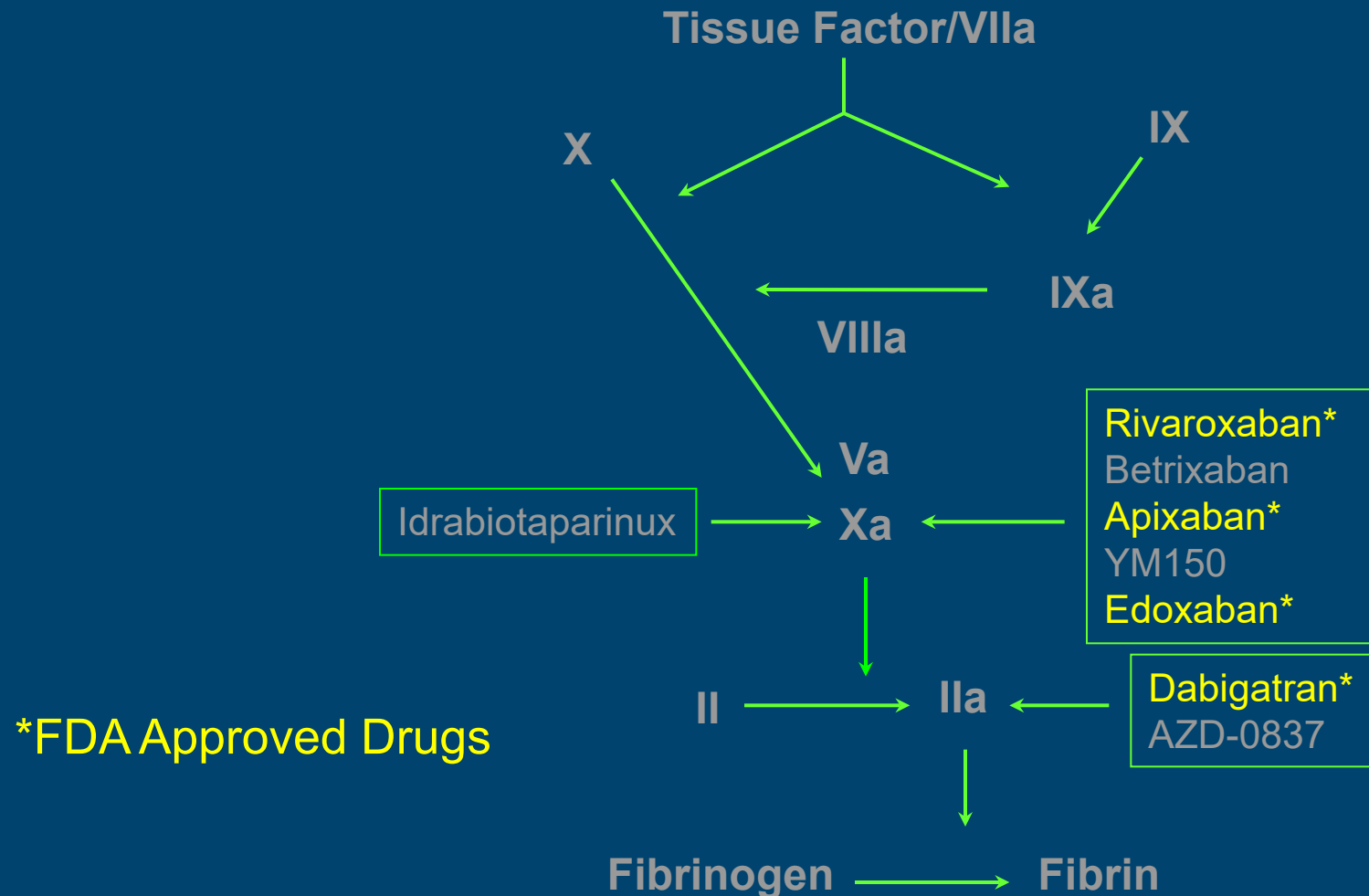
MASSACHUSETTS
GENERAL HOSPITAL
HEART CENTER

An Ideal Anticoagulant

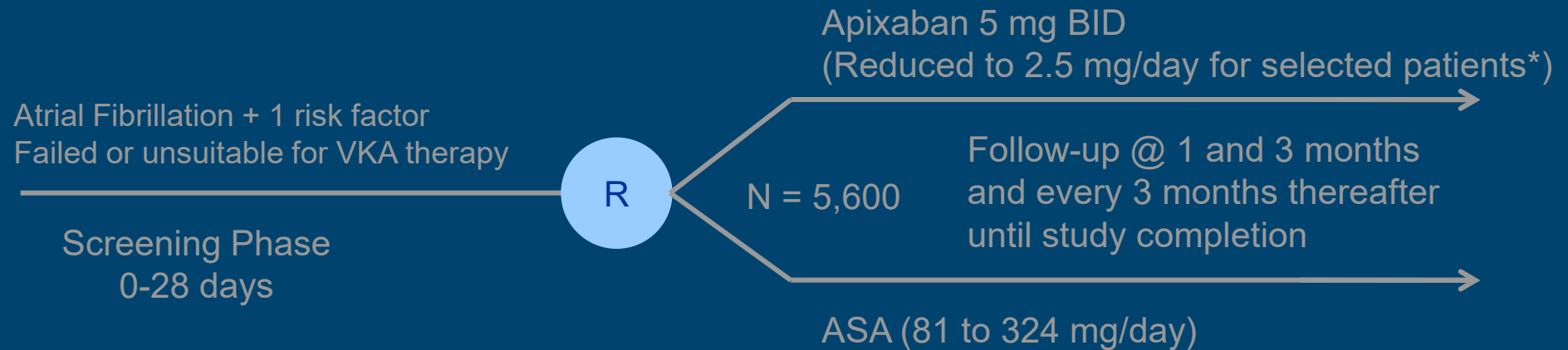
Desired Characteristic	Practical Advantage
Rapid onset of action	No need for overlap with heparin
Wide therapeutic index	Increased safety
Minimal side effects	Improved compliance; less monitoring
Oral formulation	Convenient administration
Predictable anticoagulant response	Fixed-dose unmonitored treatment
No food or drug interaction	No need for monitoring
Availability of antidote	Able to reverse in case of bleeding or urgent surgery
Cost effective	Accessibility

Emerging Therapies

Factor Xa Inhibitors and Direct Thrombin Inhibitors



Apixaban vs Aspirin– AVERROES



*Patients with ≥ 2 of the following:

- Age ≥ 80 yrs
- Body weight ≤ 60 kg
- Serum creatinine ≥ 1.5 mg/dL or $133 \mu\text{mol/L}$

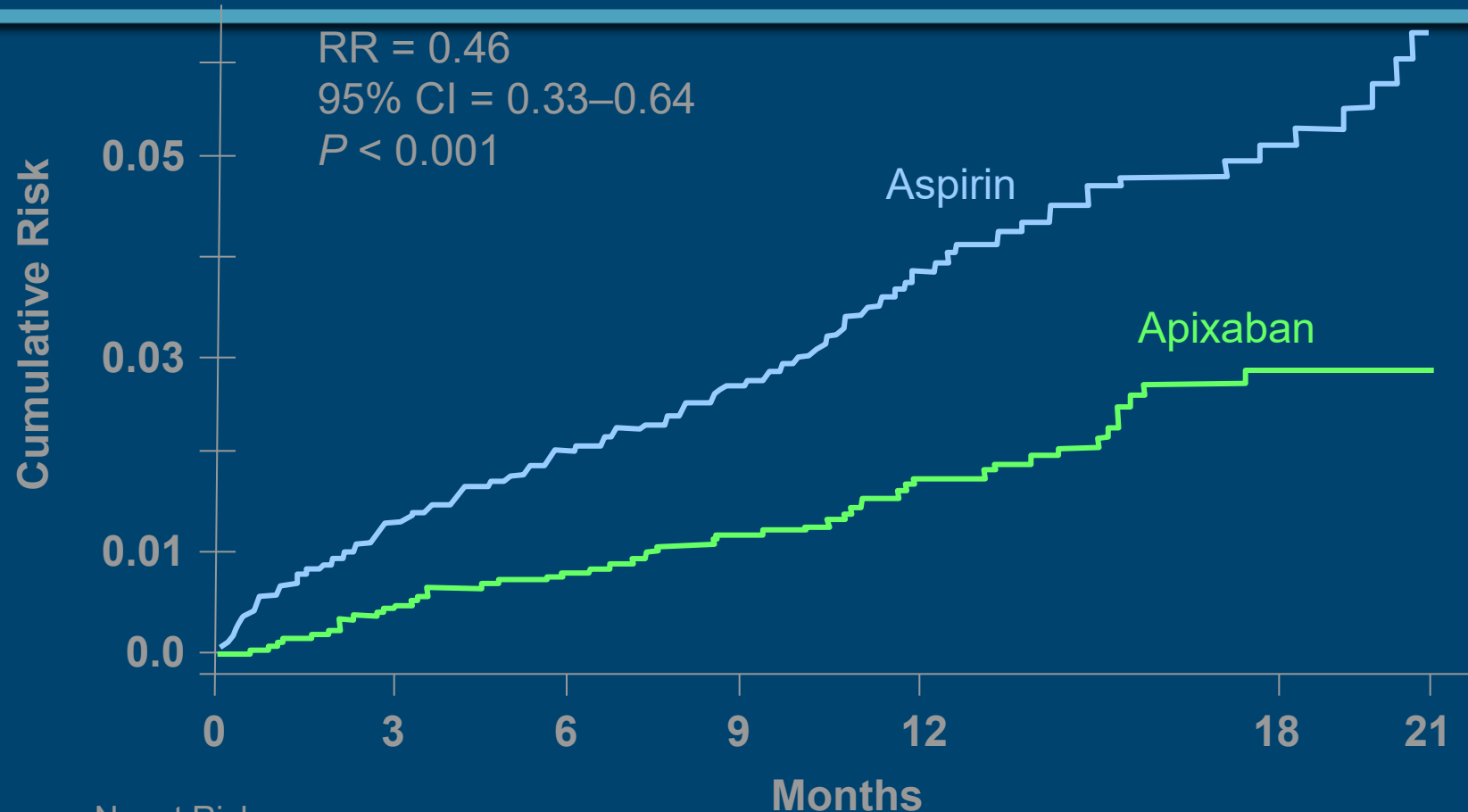
Primary efficacy outcome: stroke or systemic embolism

Primary safety outcome: major bleeds

Other outcomes: myocardial infarction, vascular death, all-cause death

Apixaban – AVERROES

Stroke or Systemic Embolic Event



No. at Risk

ASA 2791

2720

2541

2124

1541

626

329

Apix 2809

2761

2567

2127

1523

617

353



MASSACHUSETTS
GENERAL HOSPITAL

HEART CENTER

Connolly S, et al. <http://www.escardio.org/congresses/esc-2010/congress-reports/Pages/708-3-AVERROES.aspx>. Accessed Sept 2010.

Apixaban – AVERROES

Outcome	Apixaban (n = 2809)	Aspirin (n = 2791)	Relative Risk (95% CI)	P value
Stroke or systemic embolic event	1.6	3.6	0.46 (0.33-0.64)	< 0.001
Stroke, embolic event, MI, or vascular death	4.1	6.2	0.66 (0.53-0.83)	< 0.001
Major bleeding	1.4	1.2	1.14 (0.74-1.75)	0.56
Fatal bleeding	0.1	0.1	0.84 (0.26-2.75)	0.77
Intracranial bleeding	0.4	0.3	1.09 (0.50-2.39)	0.83

Apixaban – AVERROES

Outcome	Apixaban (n = 2809)	Aspirin (n = 2791)	Relative Risk (95% CI)	P value
Stroke or systemic embolic event	1.6	3.6	0.46 (0.33-0.64)	< 0.001
Stroke, embolic event, MI, or vascular death	4.1	6.2	0.66 (0.53-0.83)	< 0.001
Major bleeding	1.4	1.2	1.14 (0.74-1.75)	0.56
Fatal bleeding	0.1	0.1	0.84 (0.26-2.75)	0.77
Intracranial bleeding	0.4	0.3	1.09 (0.50-2.39)	0.83

Efficacy (stroke prevention): Eliquis superior to Aspirin

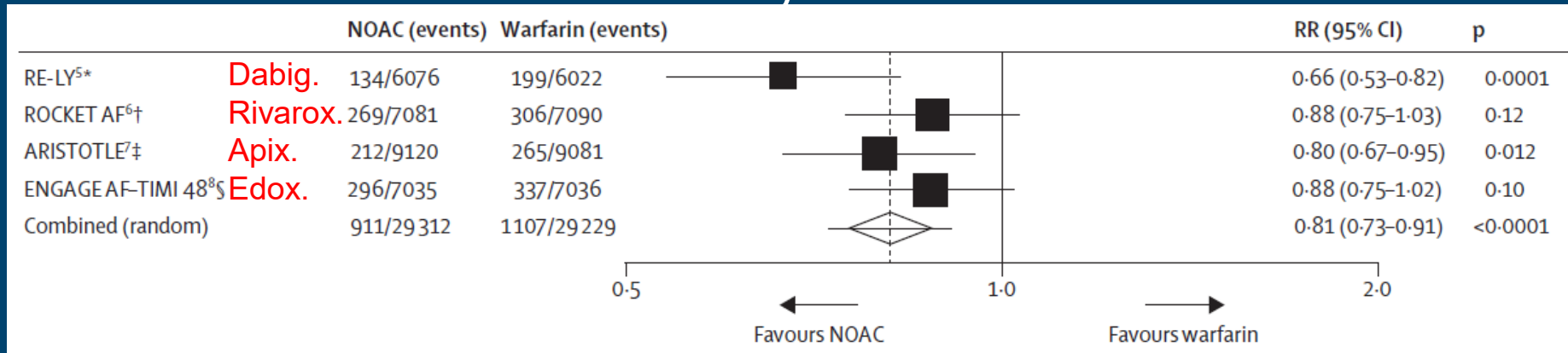
Apixaban – AVERROES

Outcome	Apixaban (n = 2809)	Aspirin (n = 2791)	Relative Risk (95% CI)	P value
Stroke or systemic embolic event	1.6	3.6	0.46 (0.33-0.64)	< 0.001
Stroke, embolic event, MI, or vascular death	4.1	6.2	0.66 (0.53-0.83)	< 0.001
Major bleeding	1.4	1.2	1.14 (0.74-1.75)	0.56
Fatal bleeding	0.1	0.1	0.84 (0.26-2.75)	0.77
Intracranial bleeding	0.4	0.3	1.09 (0.50-2.39)	0.83

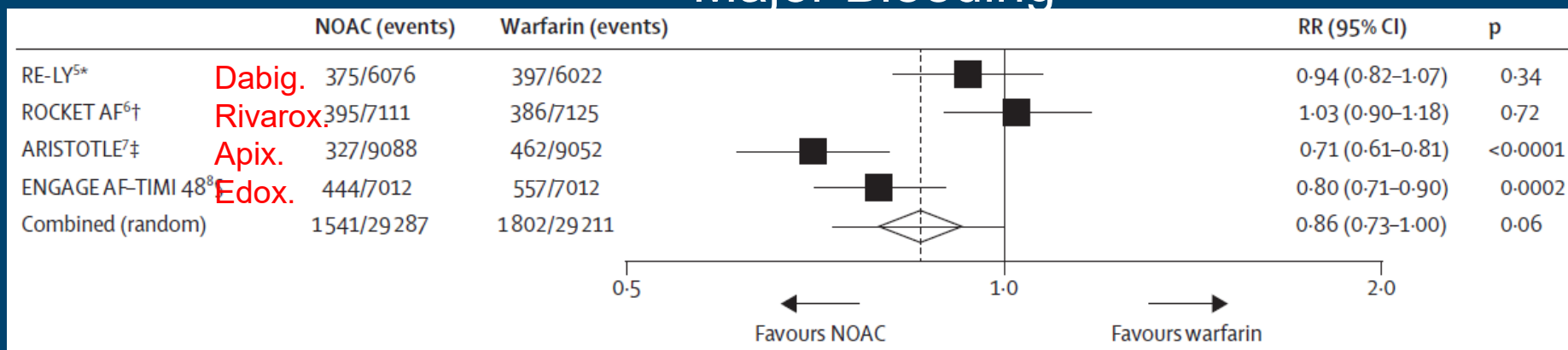
Safety (bleeding): Eliquis similar to Aspirin

Meta-Analysis: DOACs vs. Warfarin

Stroke or Systemic Embolism



Major Bleeding



MASSACHUSETTS
GENERAL HOSPITAL

HEART CENTER

DOACs vs Warfarin and All Cause Mortality

Drug	Dose	Hazard Ratio (all cause death)	P value (vs. warfarin)
Dabigatran*	High Dose (150 mg bid)	0.88	0.051
	Low Dose* (110 mg bid)	0.91	0.13
Rivaroxaban	20 or 15 mg daily	0.92	0.15
Apixaban	5 or 2.5 mg bid	0.89	0.047
Edoxaban	High Dose (60 or 30 mg daily)	0.92	0.08
	Low Dose (30 or 15 mg daily)	0.87	0.006

*Dabigatran 110 mg is not an FDA approved dose for stroke prevention in AF



MASSACHUSETTS
GENERAL HOSPITAL
HEART CENTER

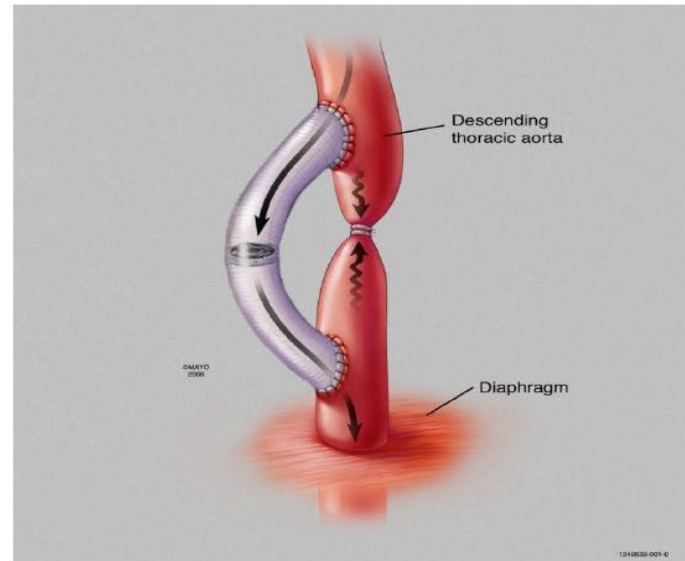
Approval for DOACs for Atrial Fibrillation

- To reduce risk of stroke for patients with non-valvular* atrial fibrillation
 - *Valvular atrial fibrillation: mechanical heart valve or moderate/severe mitral stenosis (biologic valve or any other valve problem = non-valvular AF)

Dabigatran for Mechanical Heart Valves

Preclinical studies with Dabigatran etexilate

Dabigatran is as effective as low-molecular weight heparin for mechanical valve thromboprophylaxis using a heterotopic aortic valve model in swine



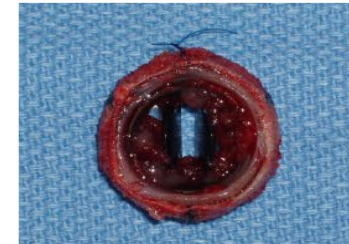
**Heterotopic valve implantation
in swine**

McKellar et al. J Thorac Cardiovasc Surg 2011;141:1410-1416

Representative valves



No therapy

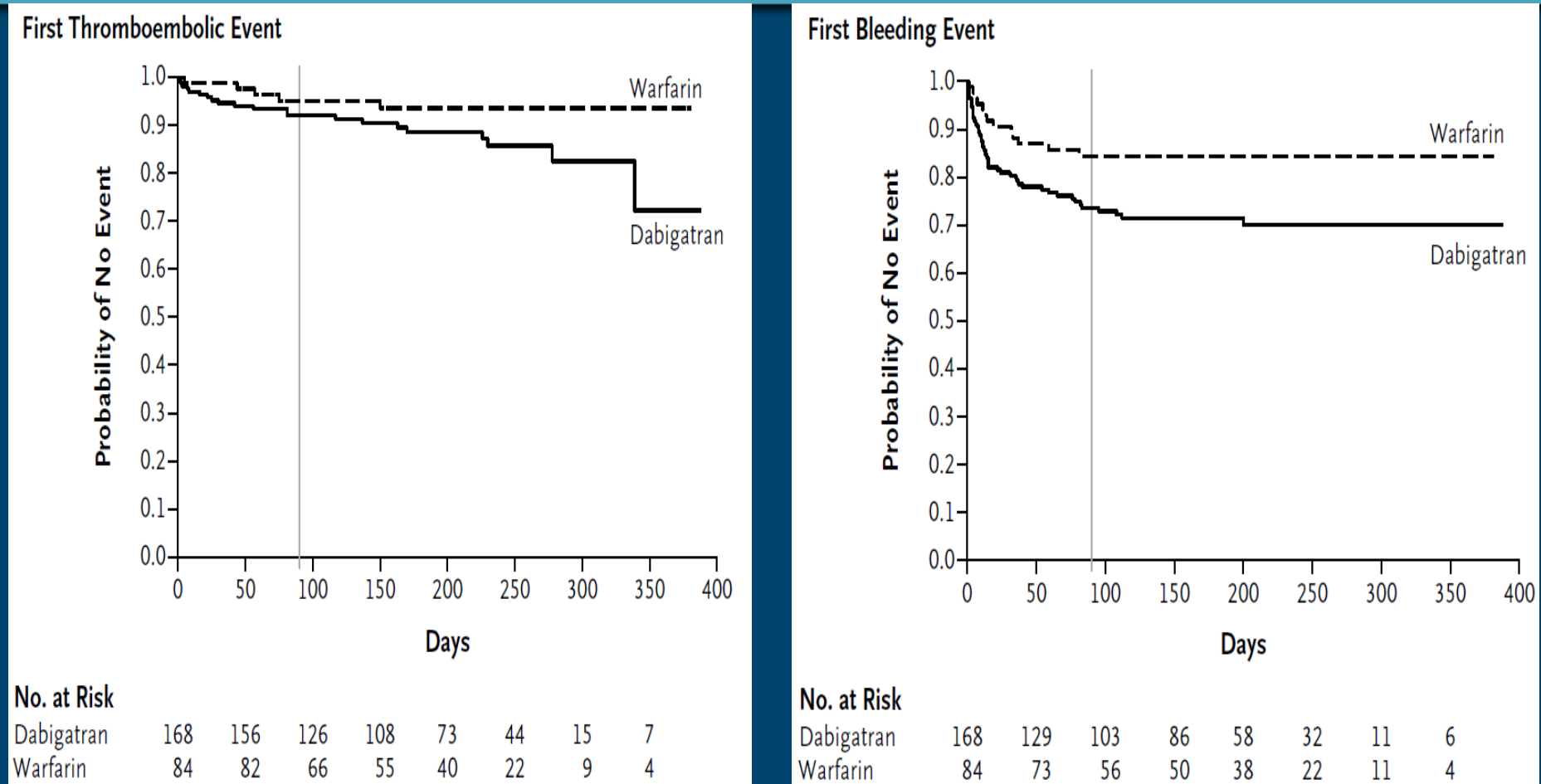


LMWH



Dabigatran

Dabigatran for Mechanical Heart Valves: RE-ALIGN



Dabigatran for mechanical valve: more clots and more bleeding than warfarin

Eikelboom et al, NEJM 2013;369:1206-14

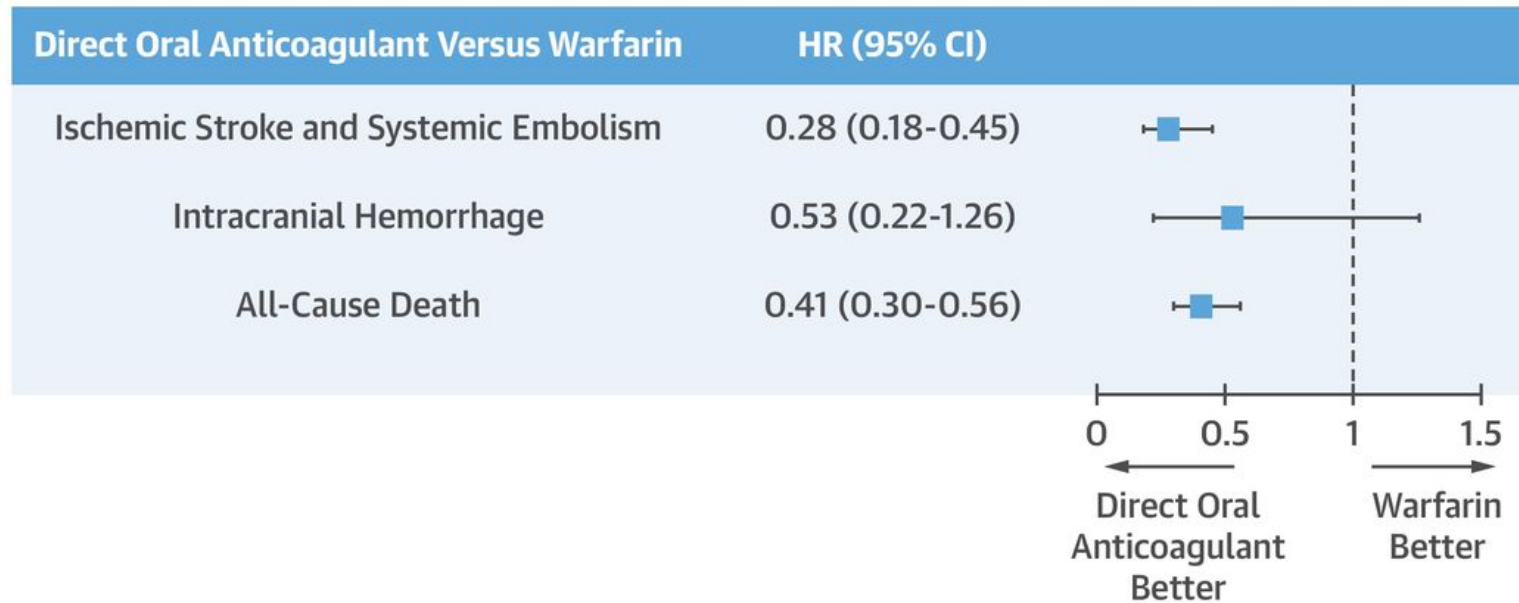


MASSACHUSETTS
GENERAL HOSPITAL

HEART CENTER

Outcomes of DOACs vs Warfarin for AF Patients with Mitral Stenosis (off-label use)

CENTRAL ILLUSTRATION: Mitral Stenosis and Atrial Fibrillation for Direct Oral Anticoagulant Versus Warfarin: Hazard Ratios



Kim, J.Y. et al. J Am Coll Cardiol. 2019;73(10):1123-31.

- 2230 propensity matched patients in Korea with AF and any degree of mitral stenosis (without MV surgery)
- Comparison of patients treated with warfarin vs DOAC



Holding/Reversal of anticoagulation

- Holding anticoagulation for planned procedures
- Reversal of anticoagulation for emergent bleeding or procedures

Holding anticoagulation for planned procedures

- Does anticoagulation need to be held for the procedure?
 - Catheter ablation of AF and pacemaker/ICD implants can be safely performed with uninterrupted warfarin or DOAC
- How long should anticoagulation be held?
 - Warfarin: 5-7 days
 - DOACs: 2-3 days (possibly 4 days if renal impairment)
- Is “bridging” anticoagulation required?

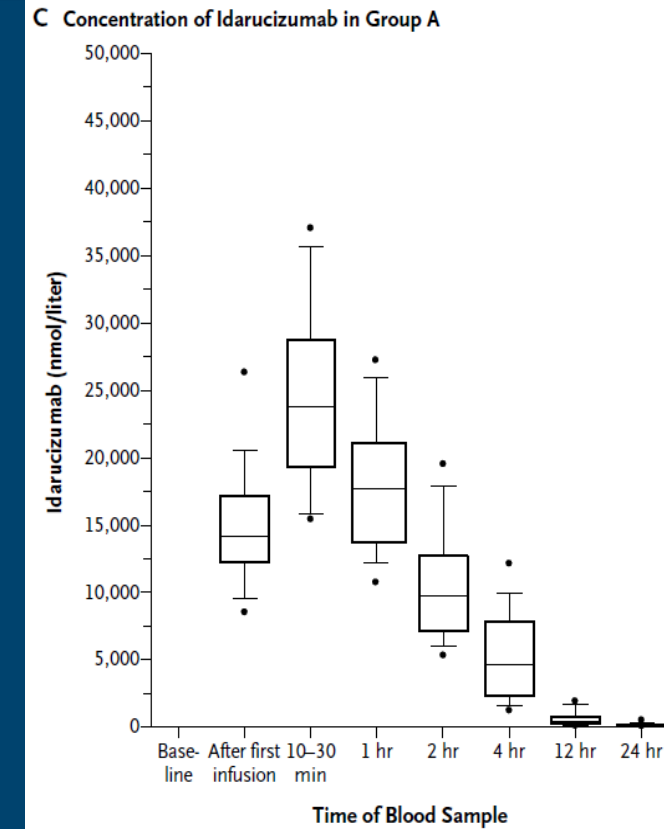
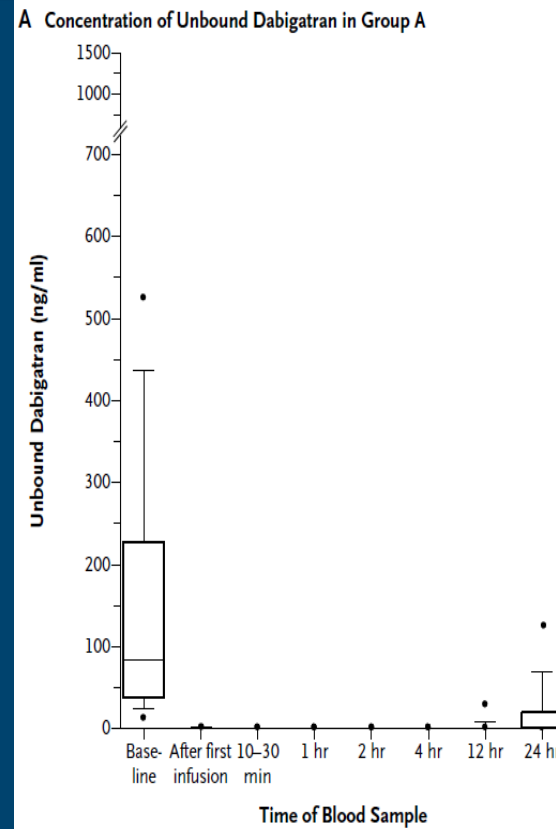
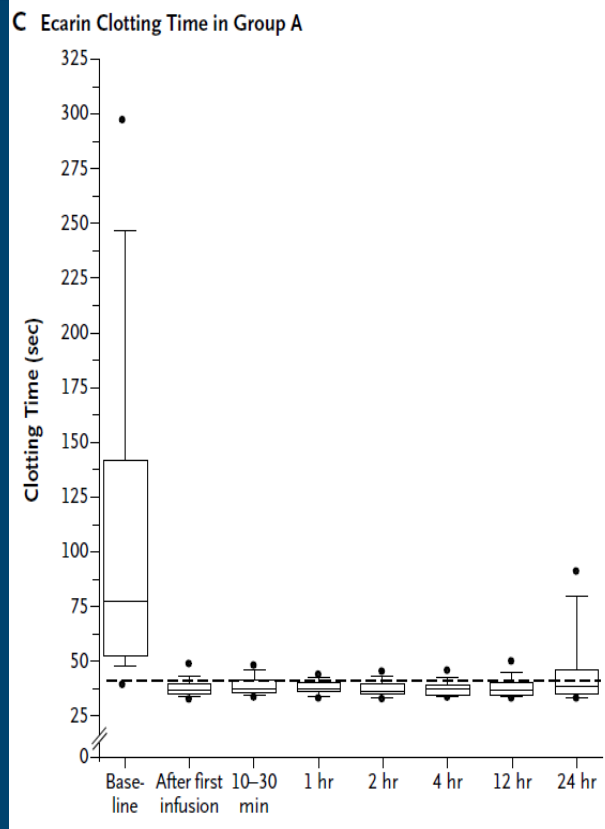
Should we “bridge” anti-coagulation before surgery?

- Randomized 1884 patients holding warfarin for 5 days before surgery to dalteparin bridge or control
- Stroke/Embolic/TIA:
 - Dalteparin: 0.3%
 - Control: 0.4% (p=NS)
- Major Bleeding
 - Dalteparin: 3.2%
 - Control: 1.3% (p=0.005)

Reversal of warfarin

- Vitamin K (IV, SQ or PO): slow anticoagulation reversal (0.5-2 days)
 - Allows the body to synthesize clotting factors
- FFP (Fresh Frozen Plasma) or PCC (Prothrombin Complex Concentrate: Kcentra): rapid but temporary anticoagulation reversal
 - Repletes clotting factors

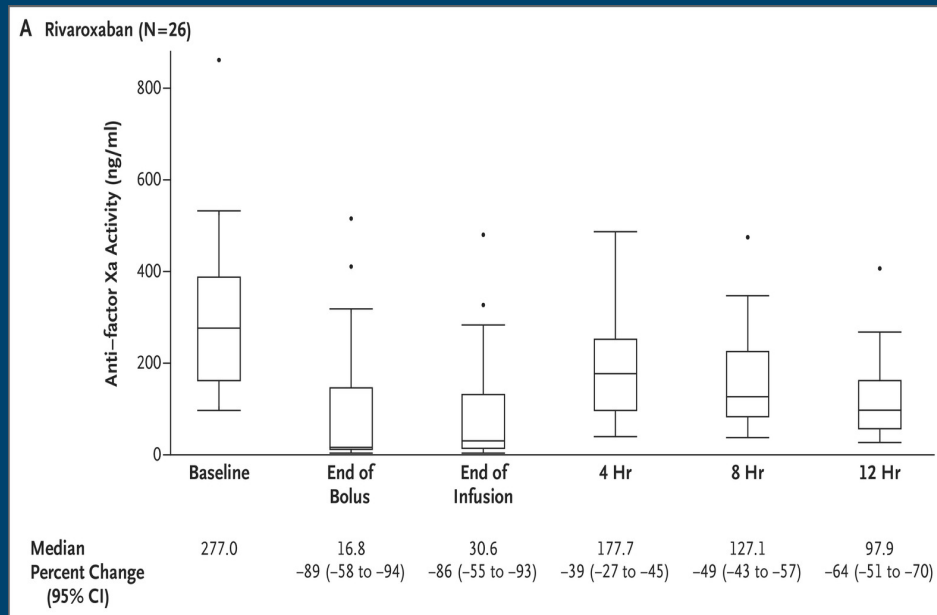
Idarucizumab (Praxbind) for reversal of dabigatran in patients with bleeding/urgent surgery on dabigatran



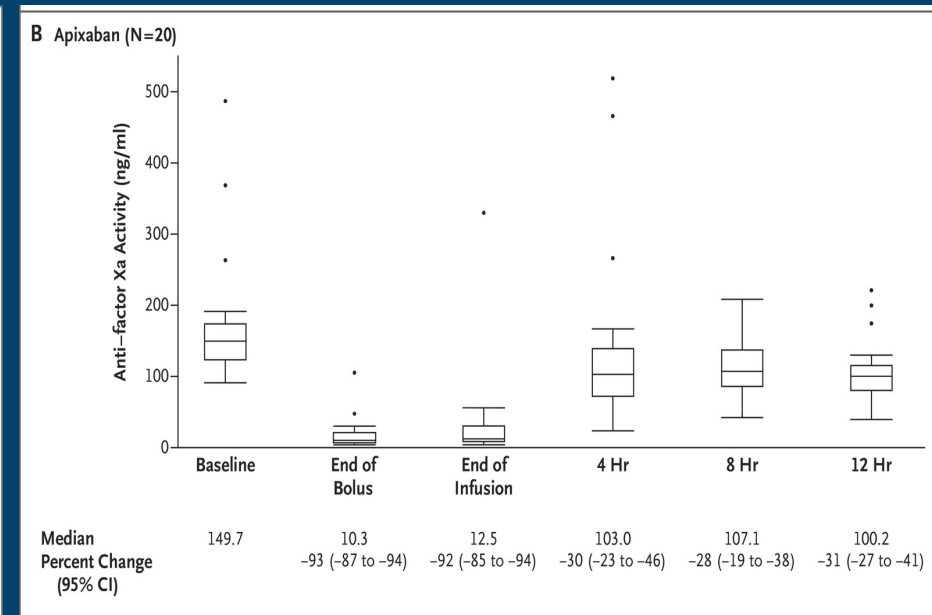
Dose: 5gm IV x1
FDA Approved: 10/16/2015

ANNEXA-4: Andexanet Alfa for reversal of Rivaroxaban and Apixaban in patients with bleeding within 18 hours of DOAC

Rivaroxaban Reversal



Apixaban Reversal



Dose: Bolus + 2 hour infusion for patients with bleeding within 18 hours of DOAC

FDA Approved: May 4, 2018

DOAC Reversal Agent in Development

- Ciraparantag* (PER977):
 - (small molecule, binds to anticoagulants)
 - Reversal agent for Direct Thrombin Inhibitors, Factor Xa inhibitors and LMWH

*Investigational agent, not FDA approved
for clinical use

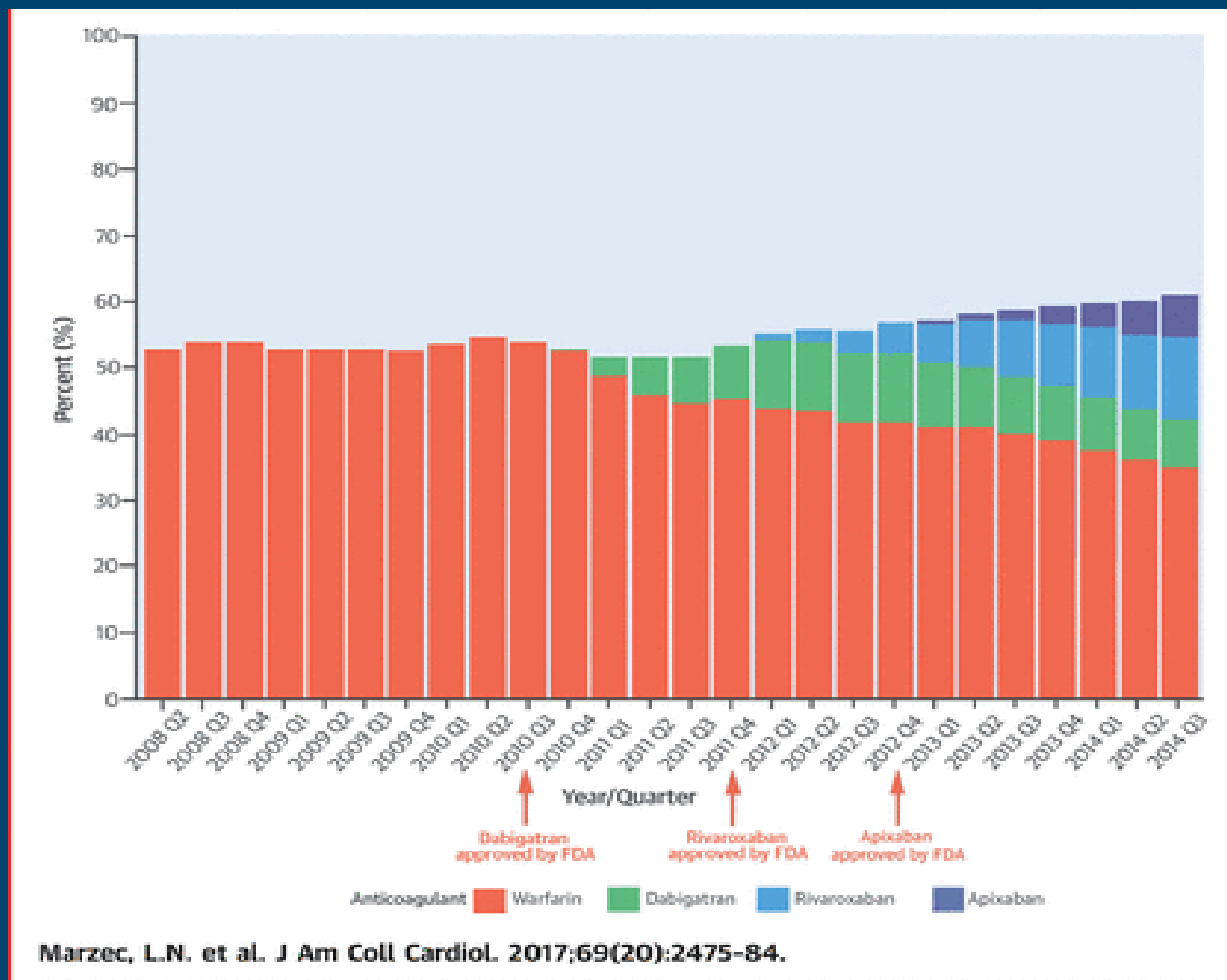
Clinical Challenges With New Anticoagulants

- No validated tests to measure anticoagulation effect
- No established therapeutic range
- Antidotes in various stages of development
- Assessment of compliance more difficult than with vitamin K antagonists
- Potential for unknown long-term adverse events
- Balancing cost against efficacy
- Lack of head-to-head studies comparing new agents
- Paucity of data on special populations (ESRD, prior major bleeds, extreme elderly, etc)

Cost Effectiveness of DOACs vs Warfarin for AF

- Large meta-analysis of 23 trials, over 94,000 patients
- On balance, DOACs were more effective at stroke prevention vs. warfarin
- DOACs had lower intracranial bleeding than warfarin
- DOACs were generally cost effective vs. warfarin (accounting for all health care costs)

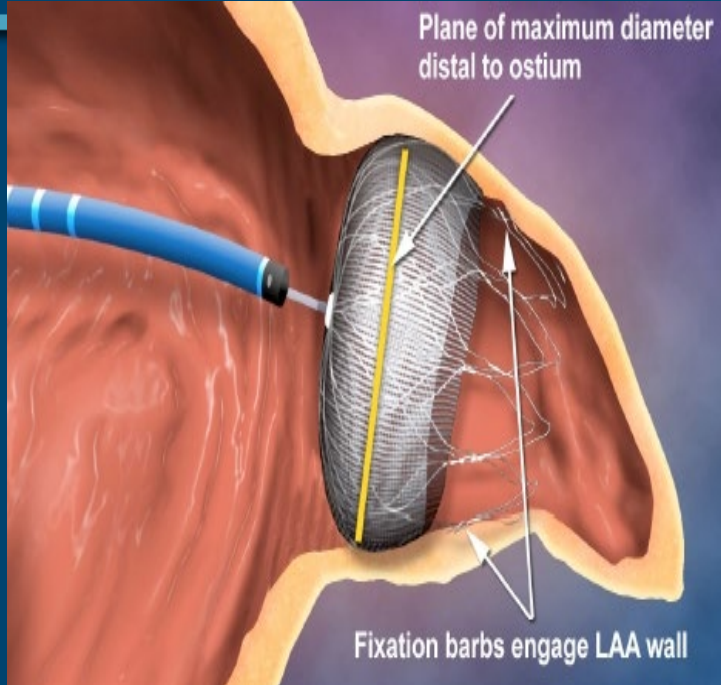
Trends in Anticoagulation Use for Atrial Fibrillation



Mechanical Approaches to Stroke Prevention:

LAA Occlusion and Ligation

Left Atrial Appendage (LAA) Closure vs Warfarin for Prevention of Stroke in Patients with AF



Control: warfarin INR 2.0-3.0

Intervention: percutaneous closure of LAA

4 Year Efficacy

Composite endpoint of stroke, cardiovascular death, and systemic embolism

- LAA Closure: 2.3%/year
- Warfarin: 3.8%/year

4 Year All Cause Mortality

- LAA Closure: 3.2%/year
- Warfarin: 4.8%/year
- Hazard Ratio 0.66, $p=0.04$

Key Points

- Rate control is non-inferior to rhythm control for asymptomatic patients
- Antiarrhythmic drugs have moderate efficacy with risks/side effects
- Ablation is more effective than drug therapy for maintenance of sinus rhythm
- Anticoagulation is useful for stroke prevention in AF
- New anticoagulants have an expanding role in stroke prevention
- Left atrial appendage occlusion is an emerging alternative to anticoagulation

Next Best Steps

- A patient shows up to my clinic with new AF...
 - Generally not a medical emergency, rarely requires transfer to the ER (*if clinically stable)
 - Basic laboratory testing (chemistry panel, thyroid) and structural heart assessment by echocardiography
 - Initial goals are anti-coagulation for stroke prevention and rate control
 - Cardioversion as an initial attempt at rhythm control is reasonable, especially for younger and/or symptomatic patients
 - Patients with recurrent symptomatic AF after cardioversion can consider anti-arrhythmic drug therapy or AF ablation



MASSACHUSETTS
GENERAL HOSPITAL

HEART CENTER

My patient has AF and needs surgery...

- Continue rate control and/or antiarrhythmic medicine
- The anticoagulated patient:
 - Low risk of bleeding: continue anticoagulant
 - High risk of bleeding: hold anticoagulant
 - Warfarin: 5 days
 - DOAC: 2-3 days
 - “Bridging” with heparin for AF patients: generally should not be done

Questions?