ATRIAL FIBRILLATION IN 2014

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DISCLOSURES

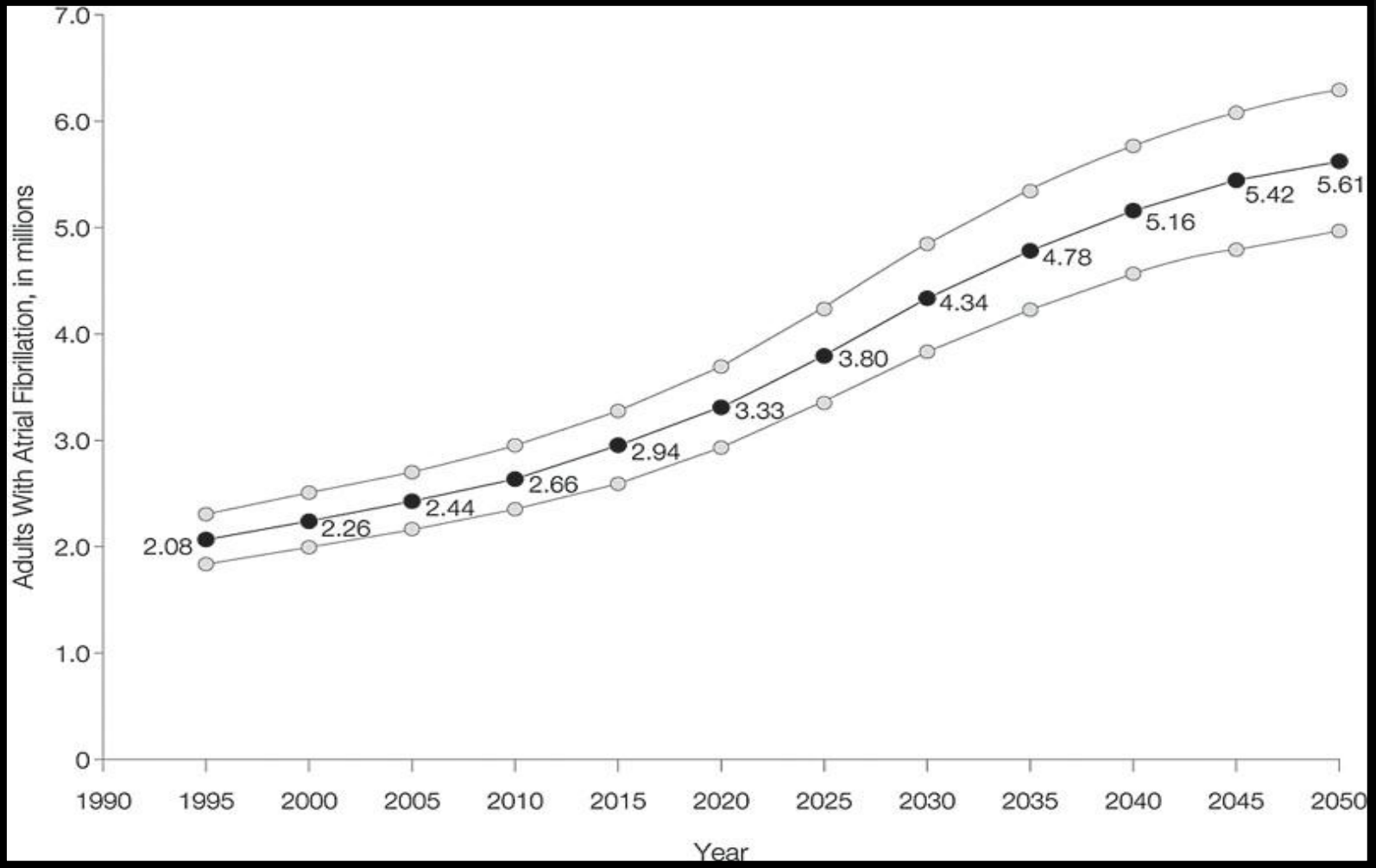
- I have received honoraria from Medtronic for speaking agreements.
- I am currently serving on the Scan Advisory Board for Medtronic for their upcoming Evera trial.

ATRIAL FIBRILLATION

- Atrial fibrillation (AF) is a major health problem in 2014.
- Single most common sustained arrhythmia.
- Major cause of hospitalization, stroke, disability and death.
- The CDC estimated in 2010 that 2.66 million Americans had AF.

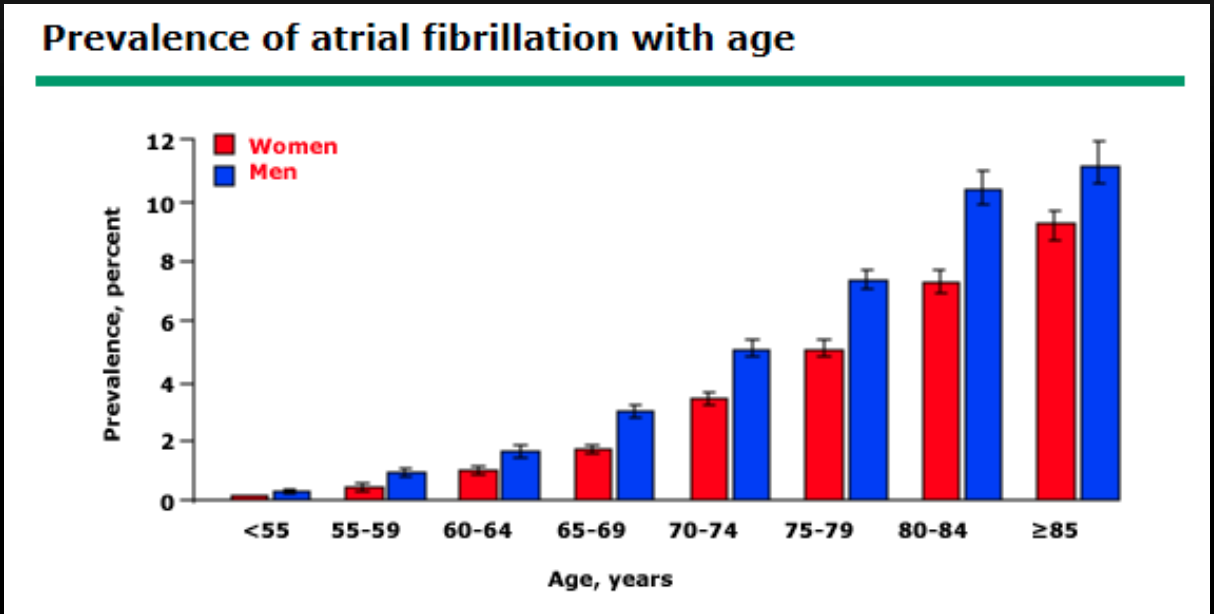
Deshpande, et al. Card Electrophys Clin. 6;2014:1-4.

AN INCREASING EPIDEMIC



Go et al. *JAMA*. 2001;285:2370-2375.

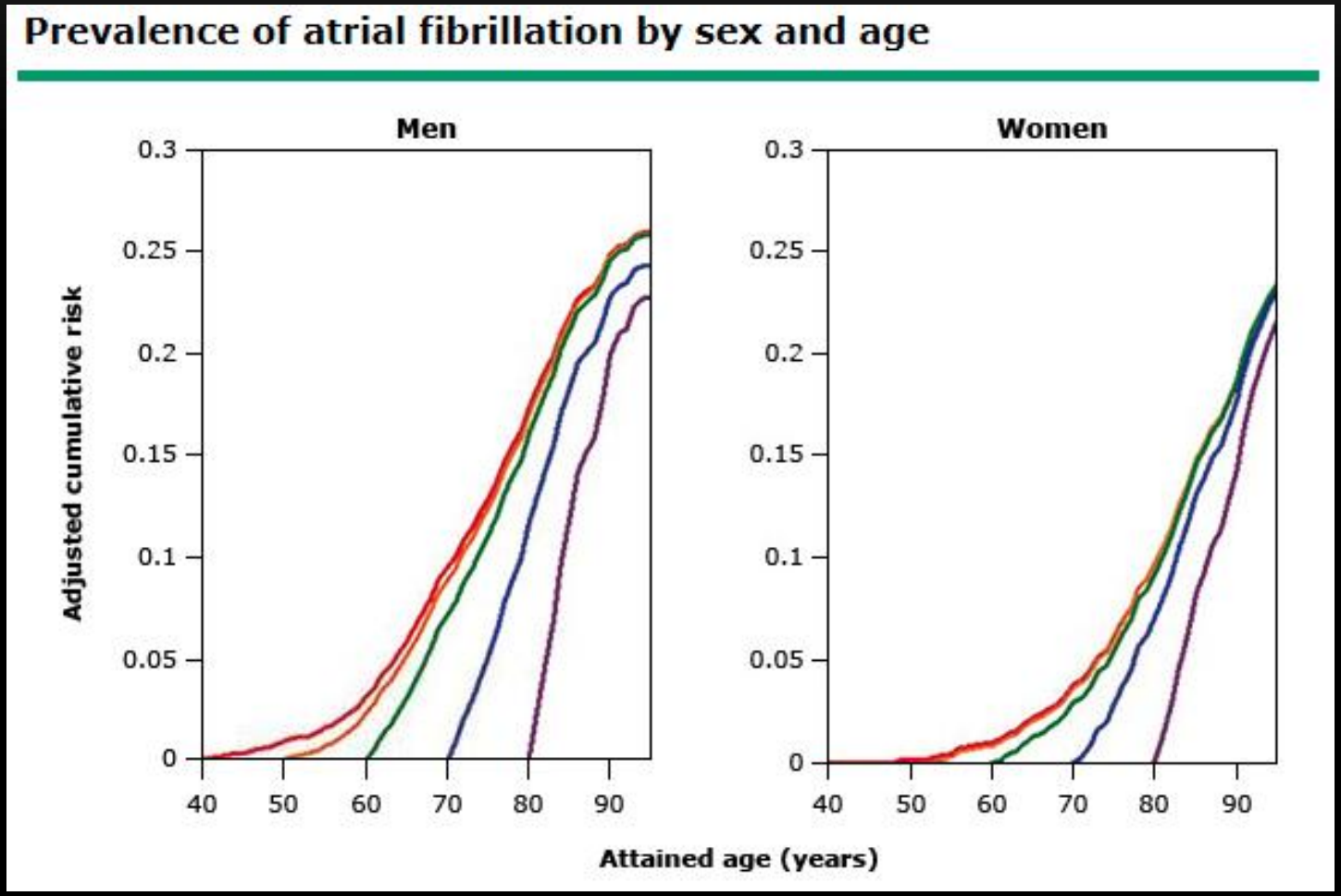
EPIDEMIOLOGY



- Over the past 20 years, there has been a 66% increase in hospital admissions for AF.
  - Aging population
  - Rising prevalence of chronic heart disease

Go, et al. JAMA 2001;285:2370.

INCIDENCE



Magnani, et al. Circulation 2011; 124:1982.

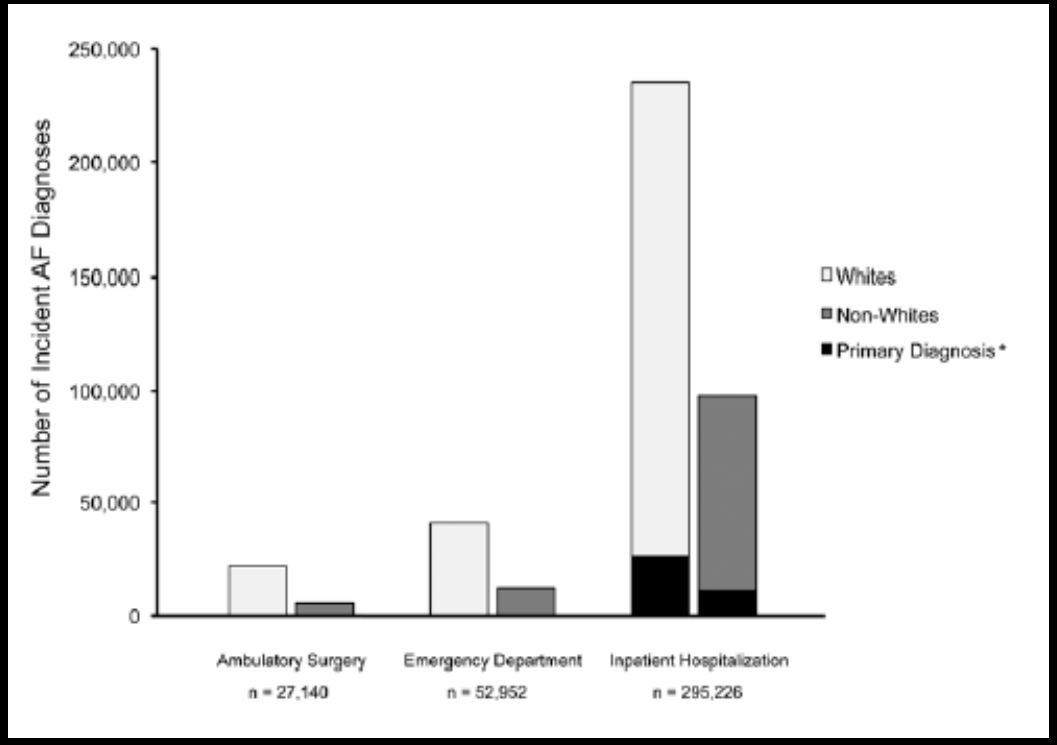
IMPACT OF RACE

- The Healthcare Cost and Utilization Project.
- Patients receiving hospital-based care in California between January 2005 and December 2009.
- 14 million patients
- 2.7% incidence of AF

Dewland, et al. Circulation 2013;128:2470-2477.

IMPACT OF RACE

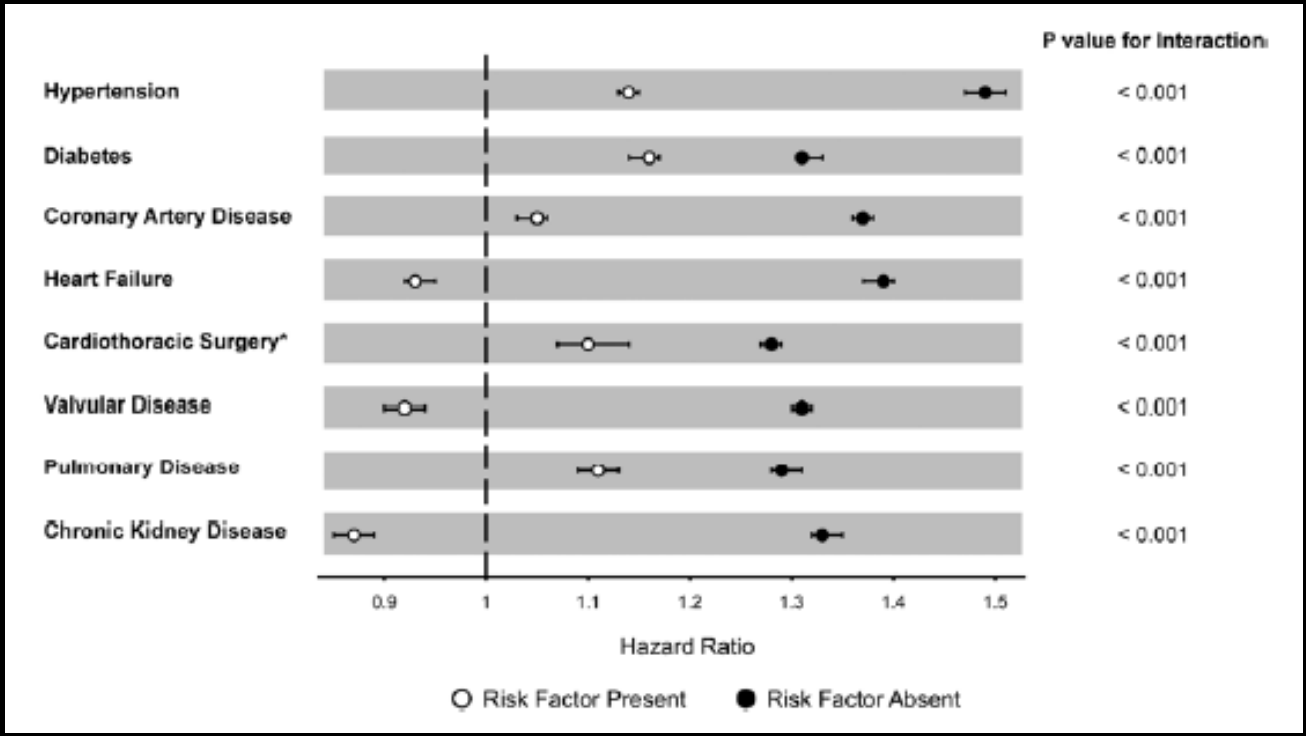
- Whites had a lower risk of AF compared with Blacks, Hispanics and Asians



Dewland, et al. Circulation 2013;128:2470-2477.

IMPACT OF RACE

- In the presence of cardiovascular risk factors, these differences disappeared.

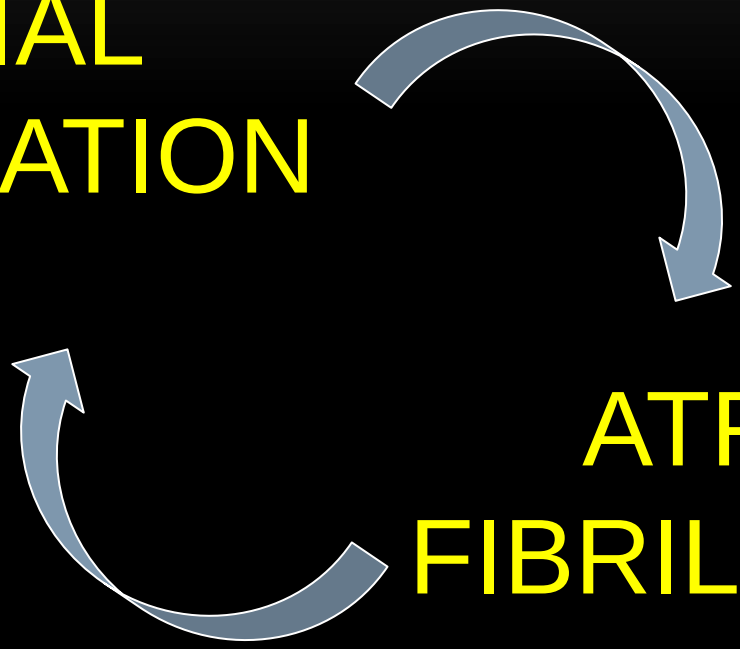


Dewland, et al. Circulation 2013;128:2470-2477.

PATHOGENESIS OF AF

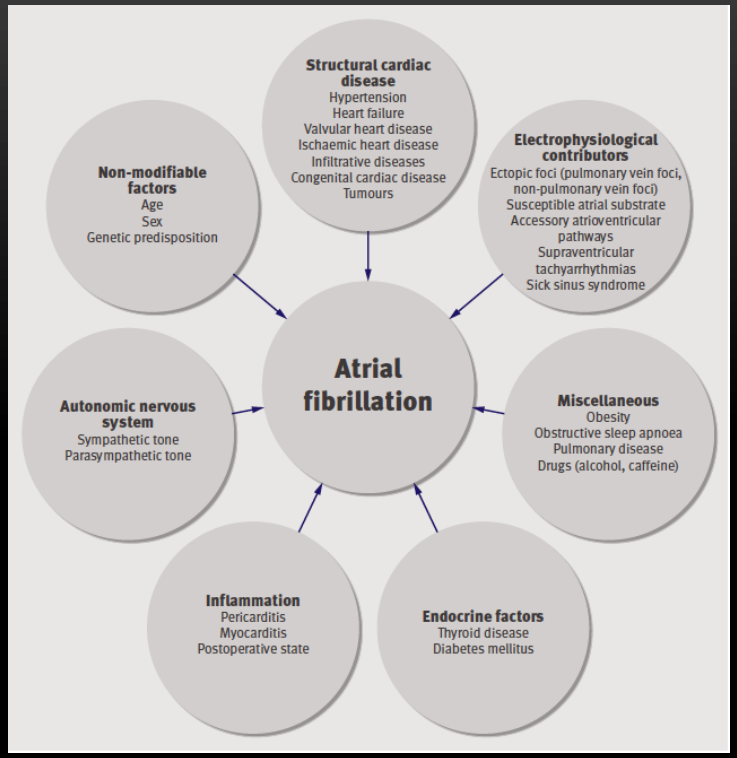
- Interaction of several mechanisms
  - Triggers (pulmonary veins)
  - Localized re-entry (rotors)
  - Multiple re-entry circuits
- The atrial substrate determines if AF sustained
  - Influenced by co-morbidities

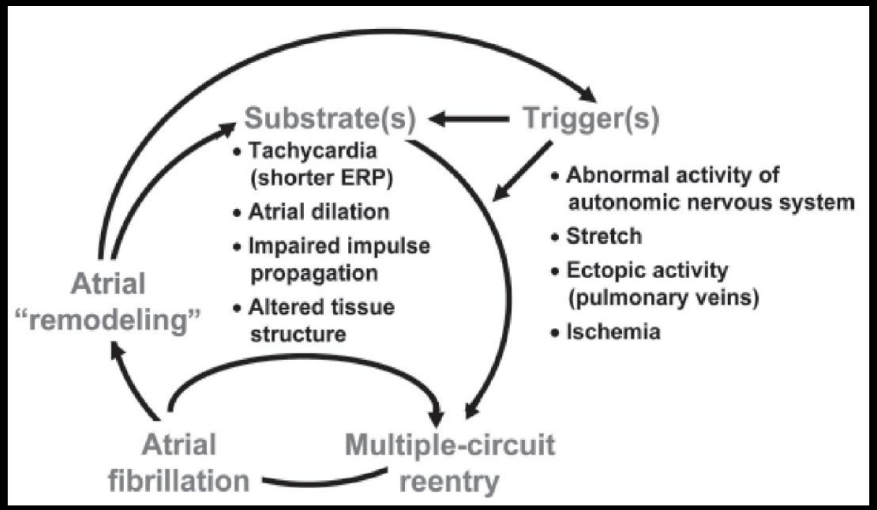
ATRIAL FIBRILLATION



ATRIAL FIBRILLATION

- As AF persists, the refractory period of the atrial tissue becomes shorter, making the initiation and maintenance of AF more likely.
- Maintenance of sinus rhythms appears to reverse this.





- Image of atrial fibrosis

ASSOCIATION WITH UNDERLYING HEART DISEASE

- Framingham Heart data.
- Non-rheumatic patients
- Left atrial enlargement was associated with and preceded the onset of AF.
- Also associated were left ventricular hypertrophy and reduced left ventricular fractional shortening.

Varizi, et al. Circulation 1994;89(2):724.

ASSOCIATION WITH DISEASE

- Most commonly associated with hypertension and CAD
  - High prevalence of hypertension in the population
- Rheumatic heart disease has a strong association but this is becoming less and less common in the U.S.

MANITOBA STUDY

- Almost 4,000 air force recruits in Canada

TABLE II

Adjusted Relative Risk for Atrial Fibrillation from Multivariate Cox Model

Variable	Relative Risk	95% Confidence Limits
Ischemic heart disease*		
Myocardial infarction	3.62	2.59–5.07
Angina	2.84	1.91–4.21
ST or T wave changes	2.21	1.62–3.00
Valvular disease	3.15	1.99–5.00
Congestive heart failure	3.37	2.29–4.96
Hypertension	1.42	1.10–1.84
Cardiomyopathy	4.07	1.45–11.45
Palpitations	2.22	1.24–2.97
Obesity	1.28	1.02–1.62
Supraventricular rhythm disturbance	2.28	1.74–2.98
Ventricular rhythm disturbance	1.37	1.06–1.78

*Reference category has no ischemic heart disease or ST or T wave changes.

Krahn, et al. Am J of Med. 1995. 98(5); 476-484.

ASSOCIATION WITH MI

- Occurs only in 6-10% of patients with an acute MI
- Atrial ischemia or atrial stretch due to HF
- Worse prognosis
- CASS study of chronic CAD, AF was associated with a 1.98 relative risk of death at 7 years

Cameron, et al. Am J of Card. 61(10); 714.

OTHER DISEASES

- Infrequently the presentation for ACS
- Rheumatic heart disease
  - TR, MR, and MS – 70%
  - MS and MR – 52%
  - Isolated MS – 29%
  - Isolated MR – 16%
- HCM – 10-28%
- ASD – 20%
- PE – 10-15%, rarely the only presenting symptom

Diker, et al. Am J of Card. 77(1); 96.

OTHER DISEASES

- Increased risk with BMI over 30 and metabolic syndrome
- Obstructive sleep apnea
- Thyroid disease
- Chronic kidney disease
- Diabetes mellitus
- Family history

Diker, et al. Am J of Card. 77(1); 96.

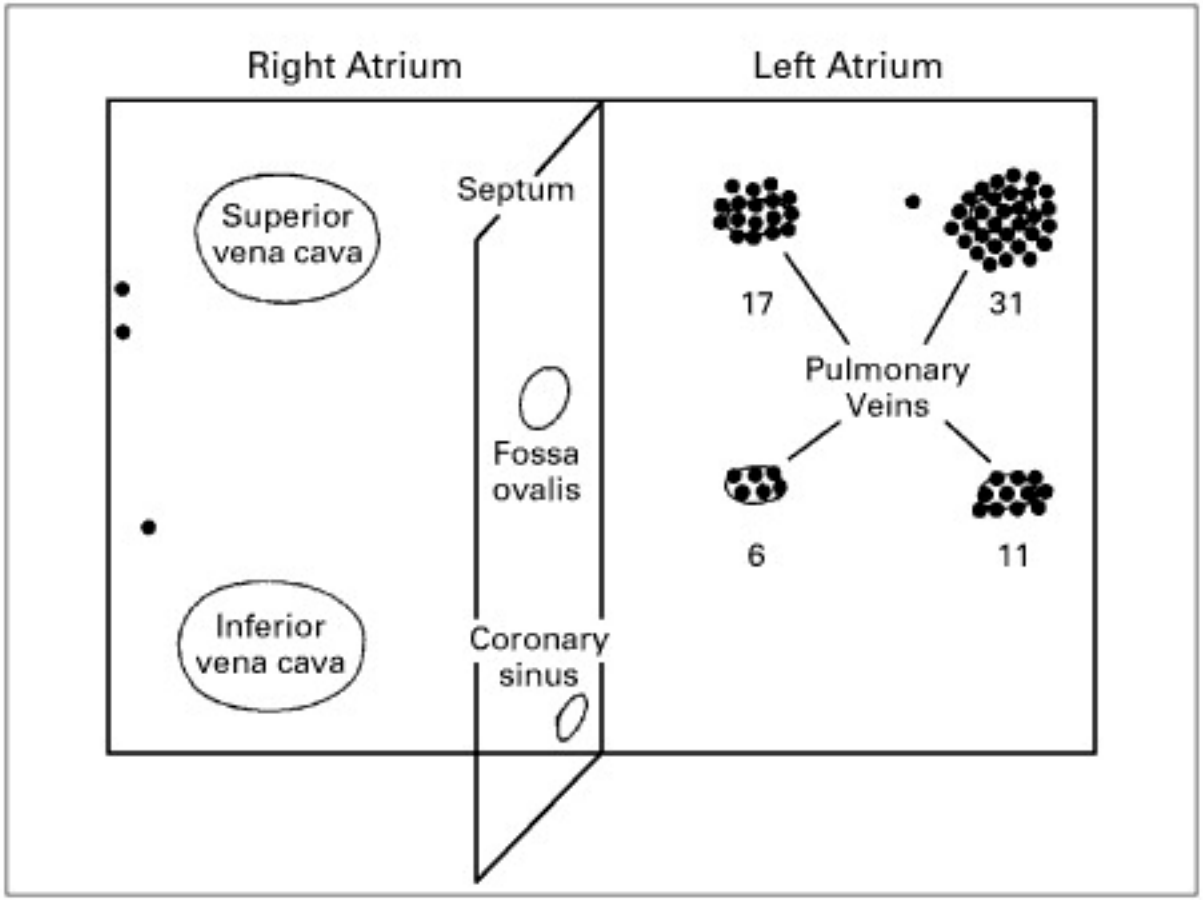
SURGERY

- Cardiac surgery
  - CABG – 30-40%
  - Valve surgery – 37-50%
  - CABG and valve replacement – 60%
- Cardiac transplant – 10-24%
  - Most episodes within 2 weeks
  - Episodes occurring after 2 weeks are associated with an increased mortality

Pavri, et al. JACC 1995.25(7);1673.

HOLTER STUDIES

- AF episodes were preceded by premature atrial beats
- Ectopic foci are most often located near the pulmonary veins
- Pulmonary vein triggers are most important in patients with paroxysmal AF



Haissaguerre, et al. N Engl J Med 1998; 339:659-666

TABLE IV

Adjusted Relative Risk of Atrial Fibrillation for Eight End Points

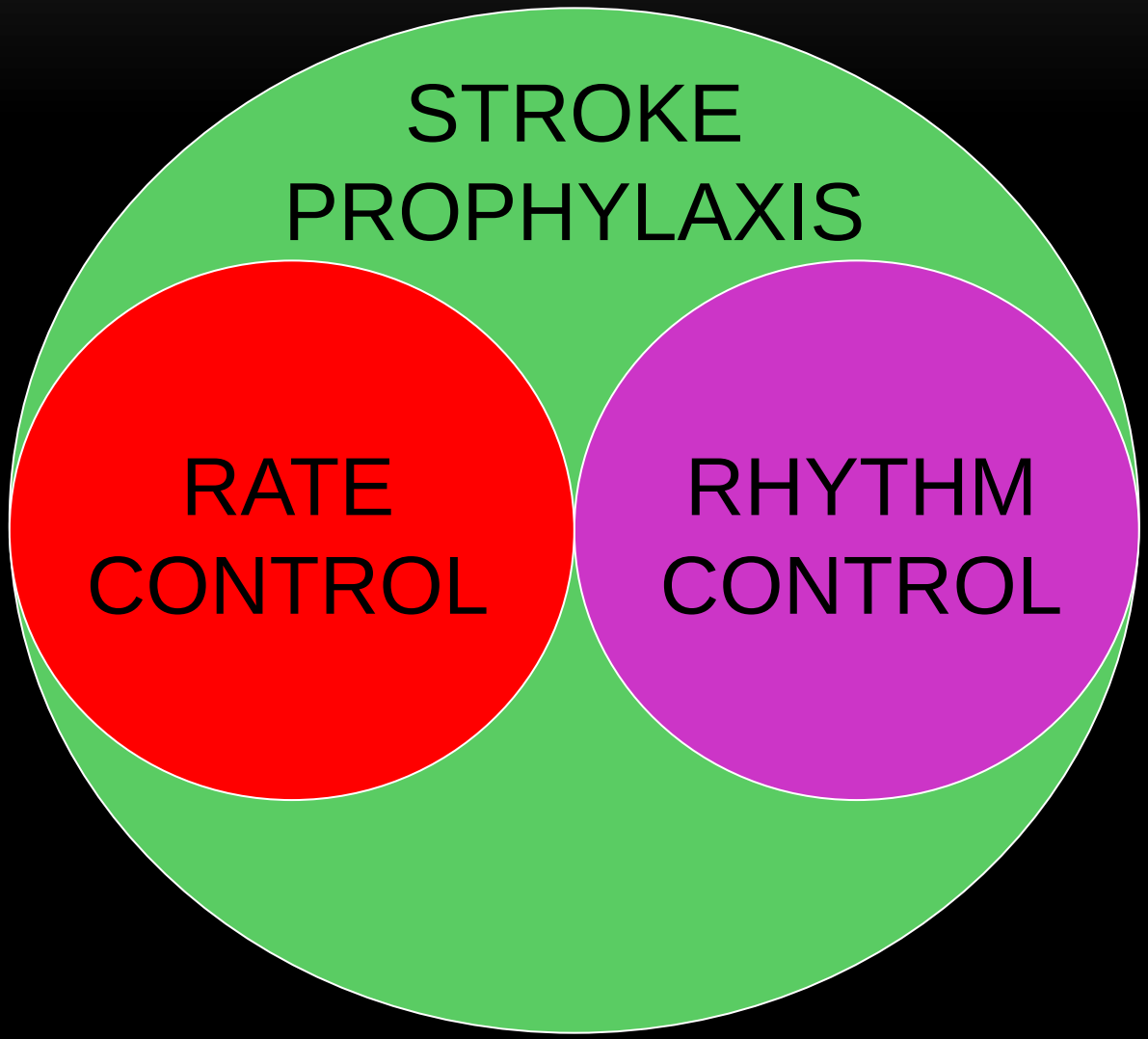
End Point	Cohort (n)	After Atrial Fibrillation (n)	Relative Risk	95% Confidence Limits
Total mortality	1,603	136	1.31	1.08–1.59
Cardiovascular mortality	662	92	1.41	1.11–1.80
Stroke mortality	83	15	2.48	1.35–4.57
Nonstroke cardiovascular mortality	579	77	1.37	1.05–1.78
Noncardiovascular mortality	941	44	1.10	0.80–1.53
Stroke	371	32	2.07	1.43–3.01
Congestive heart failure	258	35	2.98	2.09–4.26
Myocardial infarction	590	19	1.02	0.64–1.54

Krahn, et al. Am J of Med. 1995. 98(5); 476-484.

AFIB CLASSIFICATION

Type	Characteristics
Lone	<60 years, no clinical or echo cause
Recurrent	2 or more episodes
Paroxysmal	Episodes that terminate spontaneously (< 7 days)
Persistent	Sustained for more than 7 days or converts only with cardioversion
Permanent	Afib unresponsive to cardioversion
Secondary	CT surgery, valvular dz, hyperthyroidism, HF, etc

MANAGEMENT OF AF



RHYTHM VS. RATE CONTROL

- Several hypothetical reasons that rhythm control may be favored over rate control.
  - Decreased symptoms and improved QOL
  - Decreased stroke risk
  - Decreased risk of heart failure
  - Decreased mortality

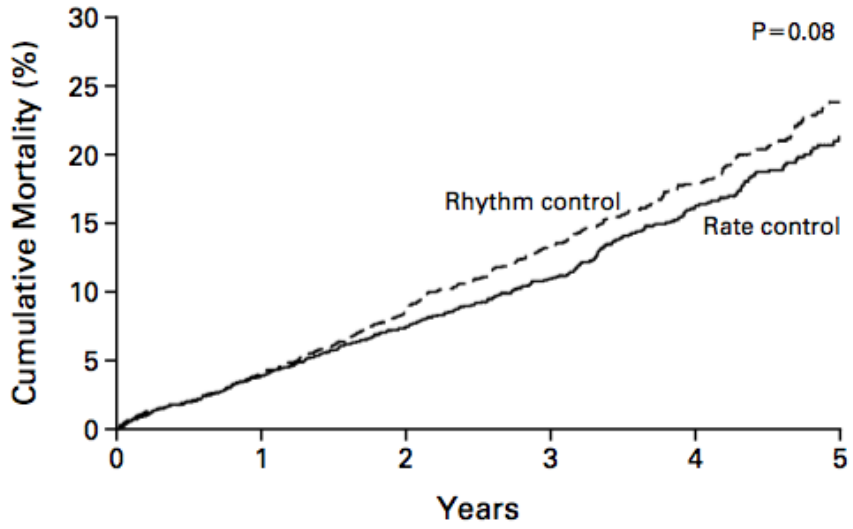
AFFIRM TRIAL

The New England
Journal of Medicine

VOLUME 347 DECEMBER 5, 2002 NUMBER 23

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

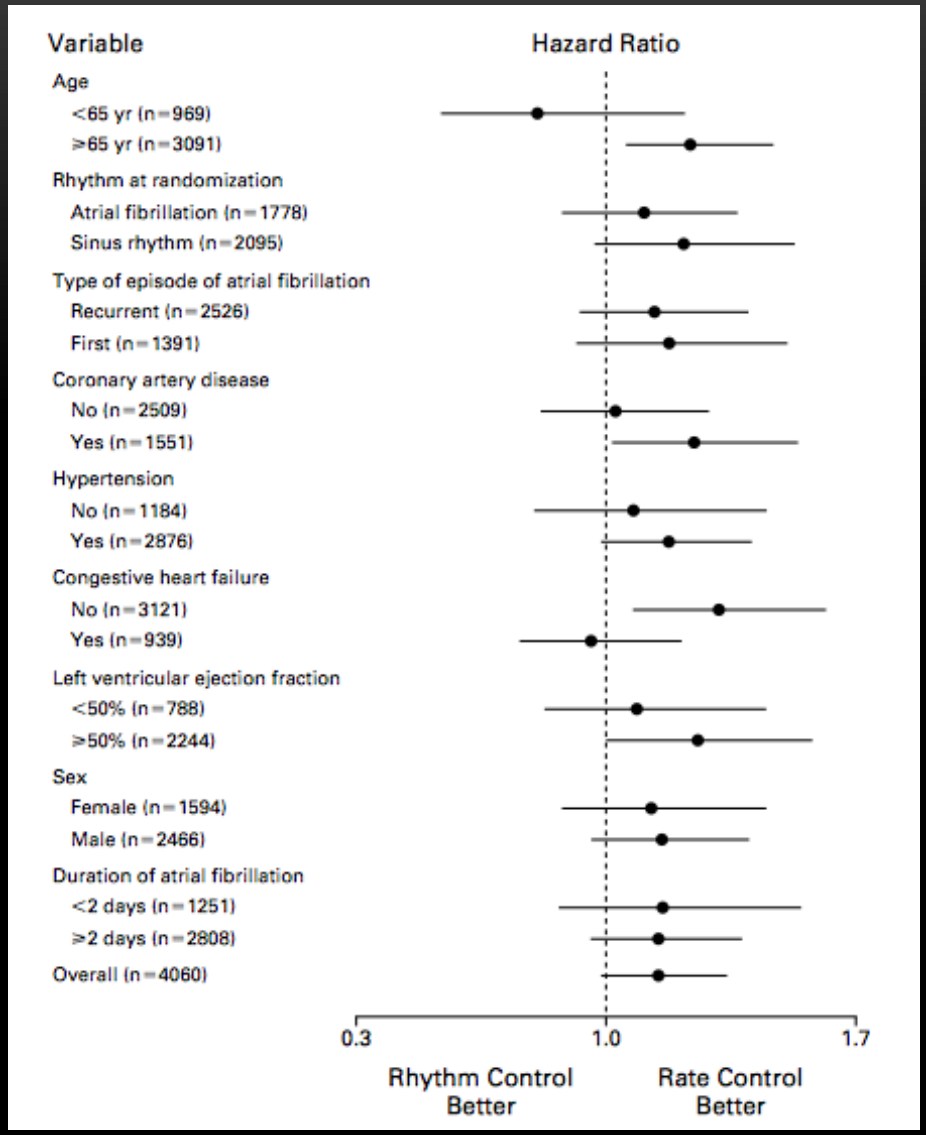
THE ATRIAL FIBRILLATION FOLLOW-UP INVESTIGATION OF RHYTHM MANAGEMENT (AFFIRM) INVESTIGATORS*



No. of Deaths		number (percent)				
Rhythm control	0	80 (4)	175 (9)	257 (13)	314 (18)	352 (24)
Rate control	0	78 (4)	148 (7)	210 (11)	275 (16)	306 (21)

Figure 1. Cumulative Mortality from Any Cause in the Rhythm-Control Group and the Rate-Control Group.
Time zero is the day of randomization. Data have been truncated at five years.

- No clear survival advantage for rhythm control over rate control.
- Trend towards increased mortality in the rhythm control group.



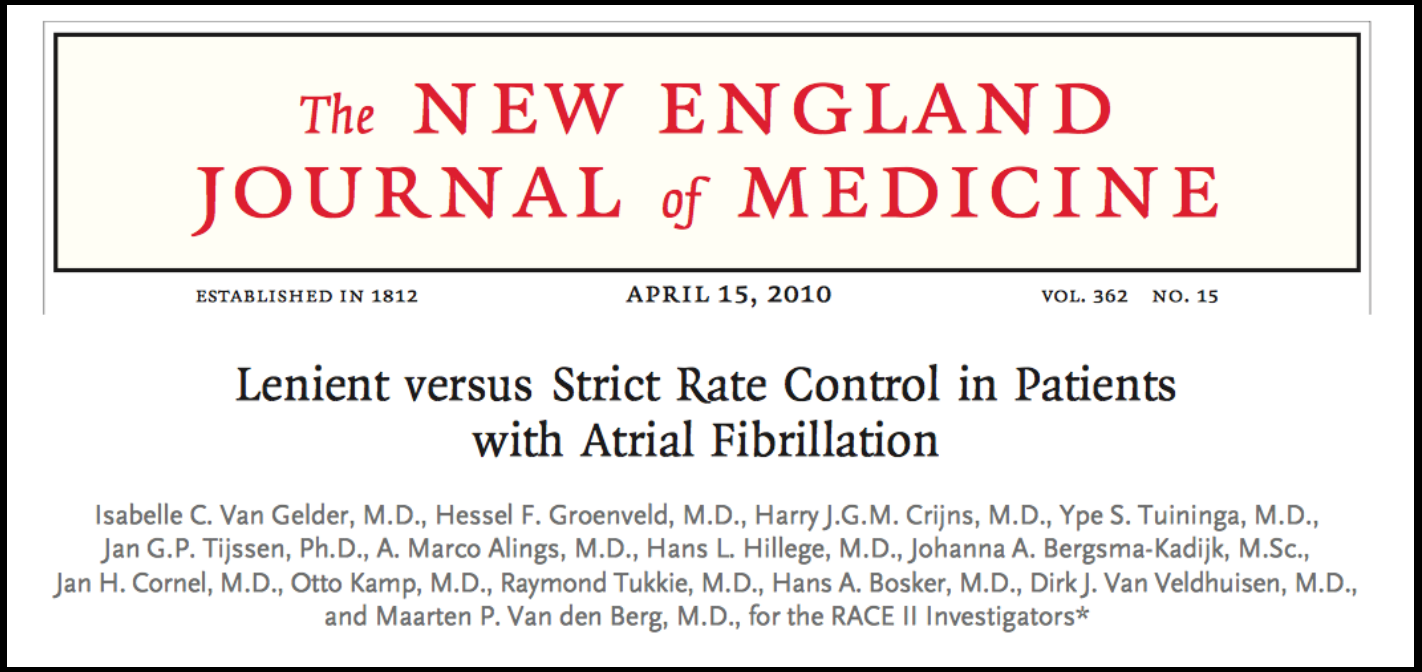
- Held true for all pre-specified sub-groups

TABLE 3. ADVERSE EVENTS.*

EVENT	OVERALL (N=4060)	RATE-CONTROL GROUP (N=2027)	RHYTHM-CONTROL GROUP (N=2033)	P VALUE
		no. of patients (%)		
Primary end point (death)	666 (26.3)	310 (25.9)	356 (26.7)	0.08†
Secondary end point (composite of death, disabling stroke, disabling anoxic encephalopathy, major bleeding, and cardiac arrest)	861 (32.3)	416 (32.7)	445 (32.0)	0.33
Torsade de pointes	14 (0.5)	2 (0.2)‡	12 (0.8)	0.007
Sustained ventricular tachycardia	15 (0.6)	9 (0.7)	6 (0.6)	0.44
Cardiac arrest followed by resuscitation				
Ventricular fibrillation or ventricular tachycardia	19 (0.6)	10 (0.7)	9 (0.5)	0.83
Pulseless electrical activity, bradycardia, or other rhythm	10 (0.3)	1 (<0.1)	9 (0.6)	0.01
Central nervous system event				
Total	211 (8.2)	105 (7.4)	106 (8.9)	0.93
Ischemic stroke§	157 (6.3)	77 (5.5)	80 (7.1)	0.79
After discontinuation of warfarin	69	25	44	
During warfarin but with INR <2.0	44	27	17	
Concurrent atrial fibrillation	67	42	25	
Primary intracerebral hemorrhage	34 (1.2)	18 (1.1)	16 (1.3)	0.73
Subdural or subarachnoid hemorrhage	24 (0.8)	11 (0.8)	13 (0.8)	0.68
Disabling anoxic encephalopathy	9 (0.3)	4 (0.2)	5 (0.4)	0.74
Myocardial infarction	140 (5.5)	67 (4.9)	73 (6.1)	0.60
Hemorrhage not involving the central nervous system	203 (7.3)	107 (7.7)	96 (6.9)	0.44
Systemic embolism	16 (0.5)	9 (0.5)	7 (0.4)	0.62
Pulmonary embolism	8 (0.3)	2 (0.1)	6 (0.5)	0.16
Hospitalization after base line	2594 (76.6)	1220 (73.0)	1374 (80.1)	<0.001

RATE CONTROL

- What is rate control?



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 15, 2010 VOL. 362 NO. 15

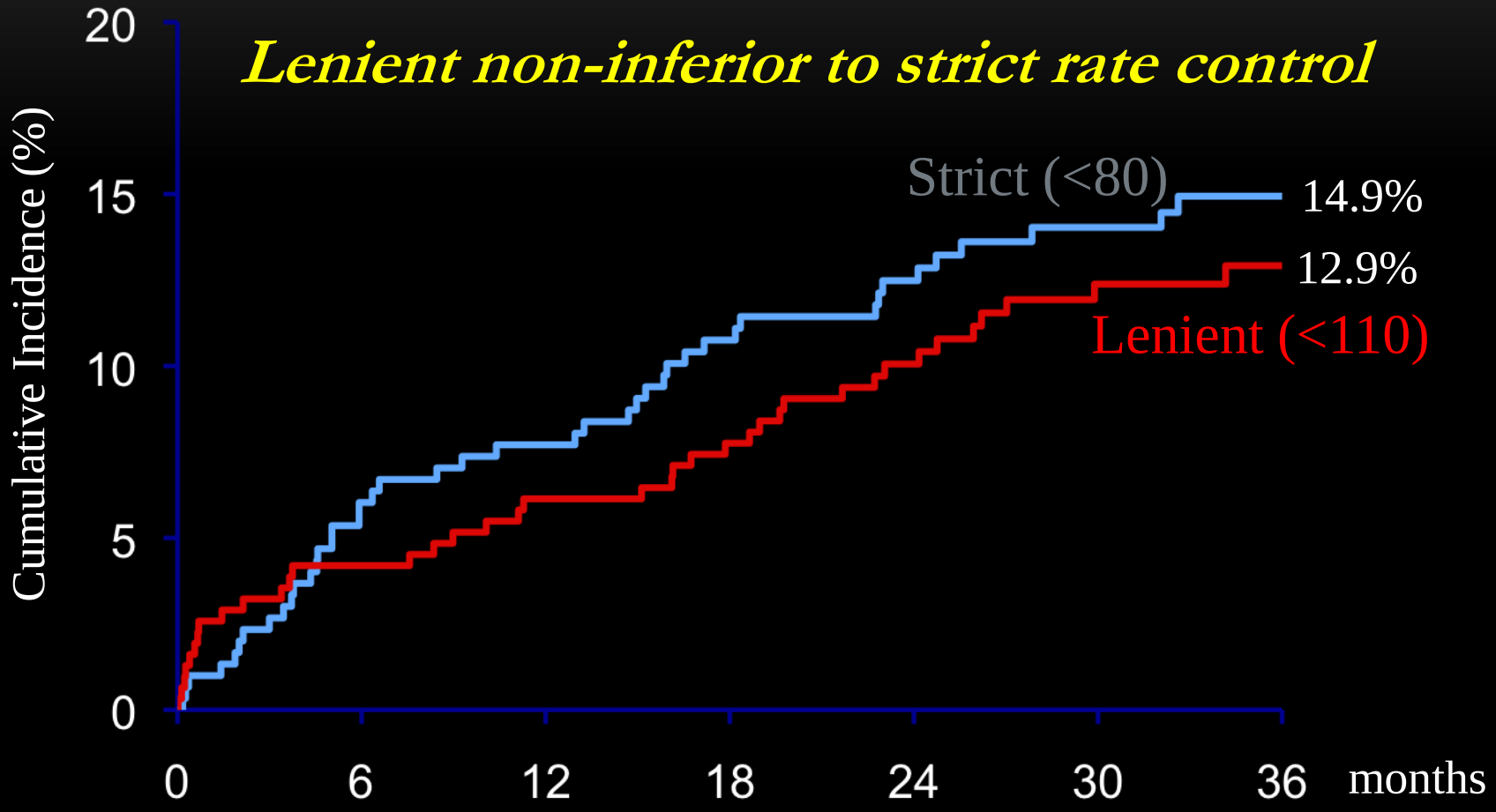
Lenient versus Strict Rate Control in Patients with Atrial Fibrillation

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*

RACE II

- 614 patients were randomized to strict rate control (80 bpm) vs. lenient rate control (110 bpm).
- Primary outcome: composite of cardiovascular death, heart failure hospitalization, stroke, systemic embolism, bleeding, and life-threatening arrhythmic event.

RACE II (RATE CONTROL EFFICACY IN PERMANENT ATRIAL FIBRILLATION)

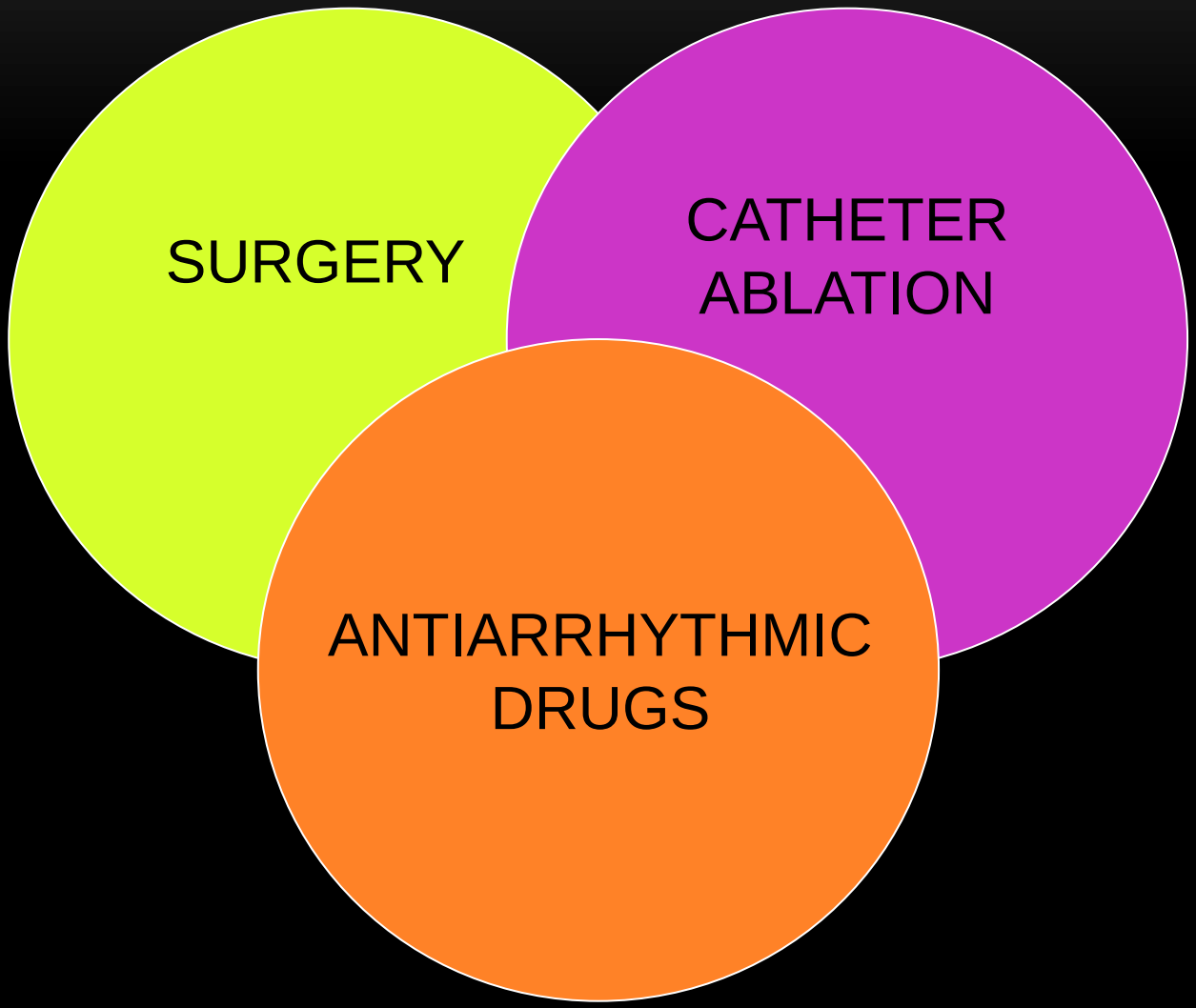


Strict	303	282	273	262	246	212	131
Lenient	311	298	290	285	255	218	138

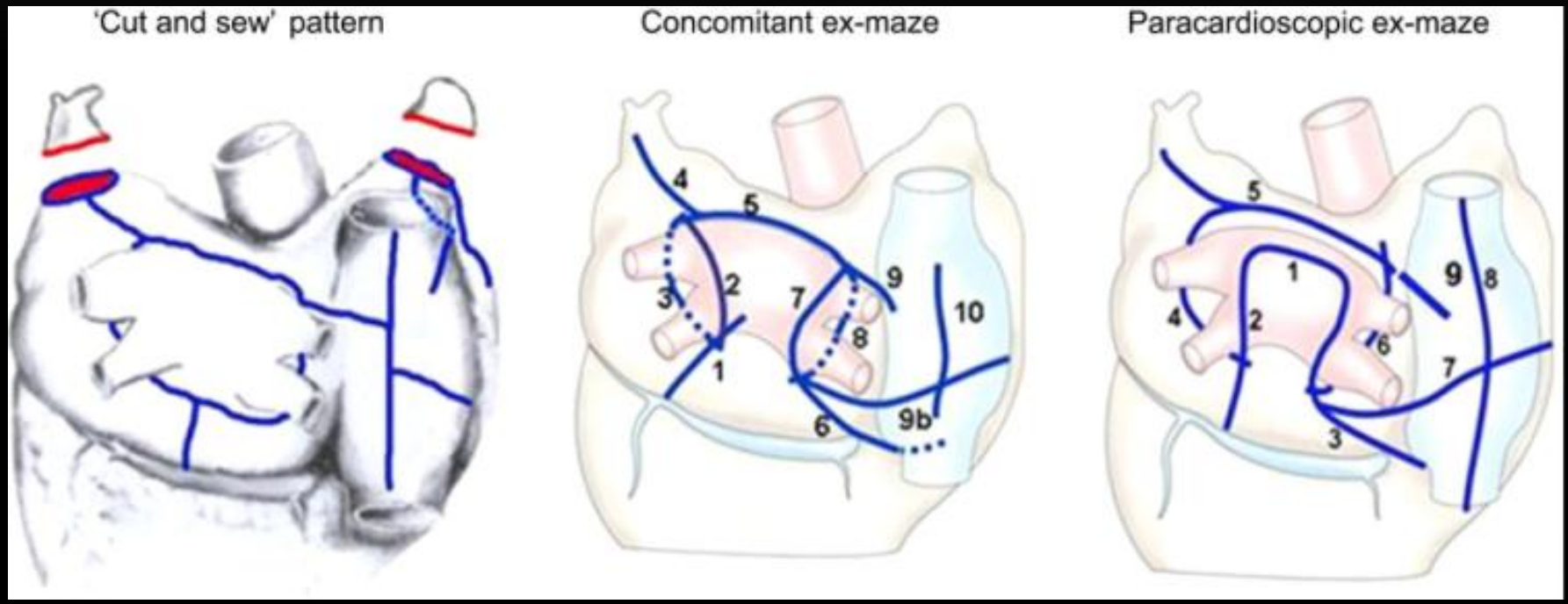
RACE II

- 97.7% of the patients in the lenient control group met the HR goal (compared with 67% in the strict group).
  - 75 visits for the lenient group
  - 684 visits for the strict group
- Conclusion: lenient rate control is non-inferior to strict rate control

RHYTHM CONTROL



SURGERY


'Cut and sew' pattern
Concomitant ex-maze
Paracardioscopic ex-maze
4
5
3
2
7
9
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9b
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2
6
7
3

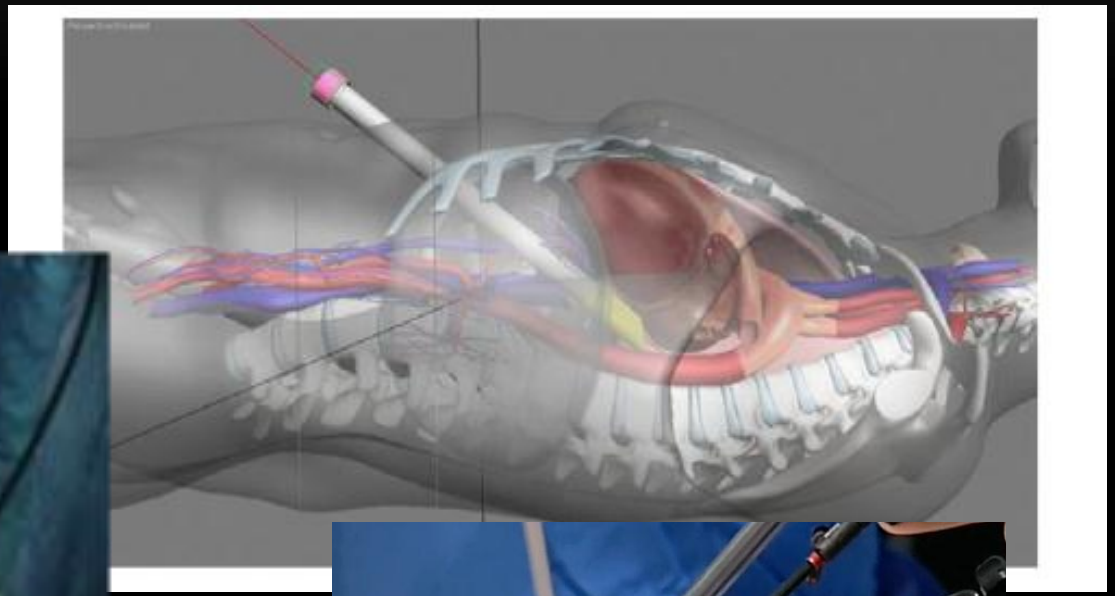
HYBRID EPICARDIAL-ENDOCARDIAL PROCEDURE

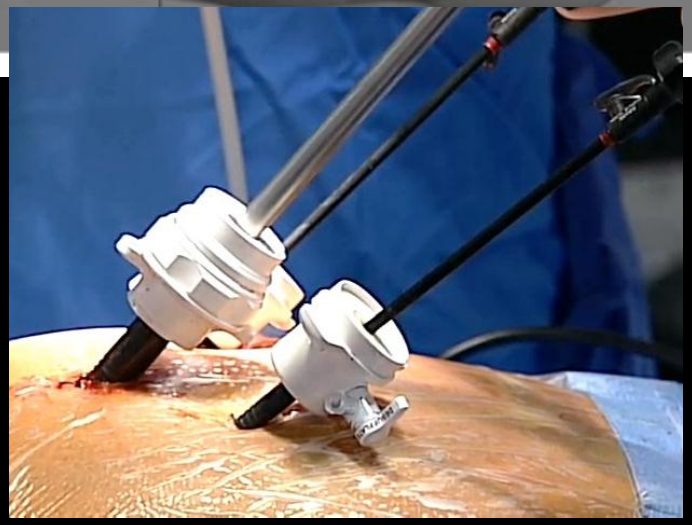
Hybrid epicardial-endocardial ablation using a pericardioscopic technique for the treatment of atrial fibrillation

Anil K. Gehi, MD, FHRS,[*] J. Paul Mounsey, MD, PhD,[*] Irion Pursell, RN,[*] Mark Landers, MD,[†] Ker Boyce, MD,[†] Eugene H. Chung, MD, FHRS,[*] Jennifer Schwartz, MD,[*] T. Jennifer Walker, NP,[*] Kimberly Guise, NP,[*] Andy C. Kiser, MD[‡]

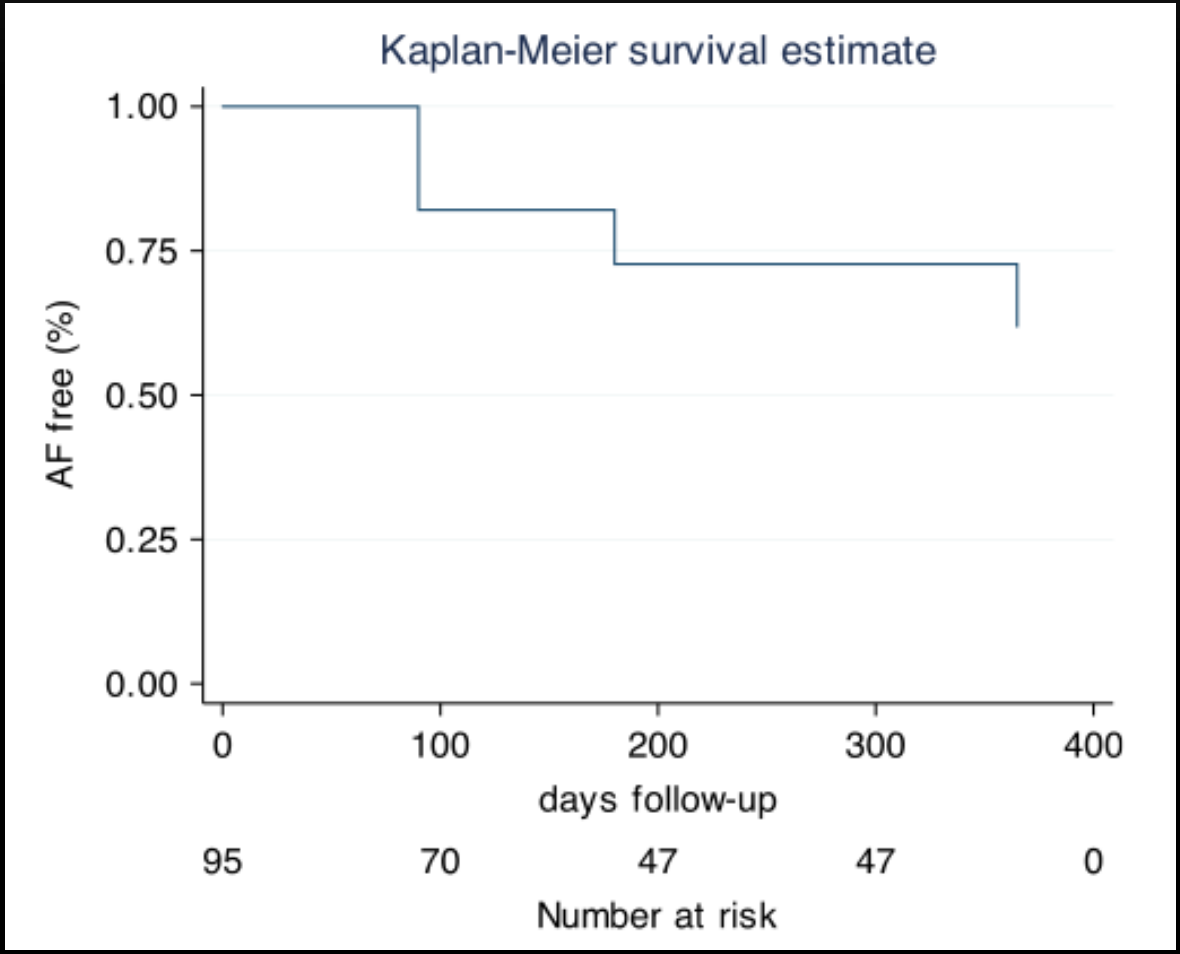
From the [*]Division of Cardiology, Department of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, [†]Firsthealth Arrhythmia Center, Pinehurst, North Carolina and [‡]Division of Cardiothoracic Surgery, Department of Surgery, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina.

HYBRID EPICARDIAL-ENDOCARDIAL PROCEDURE



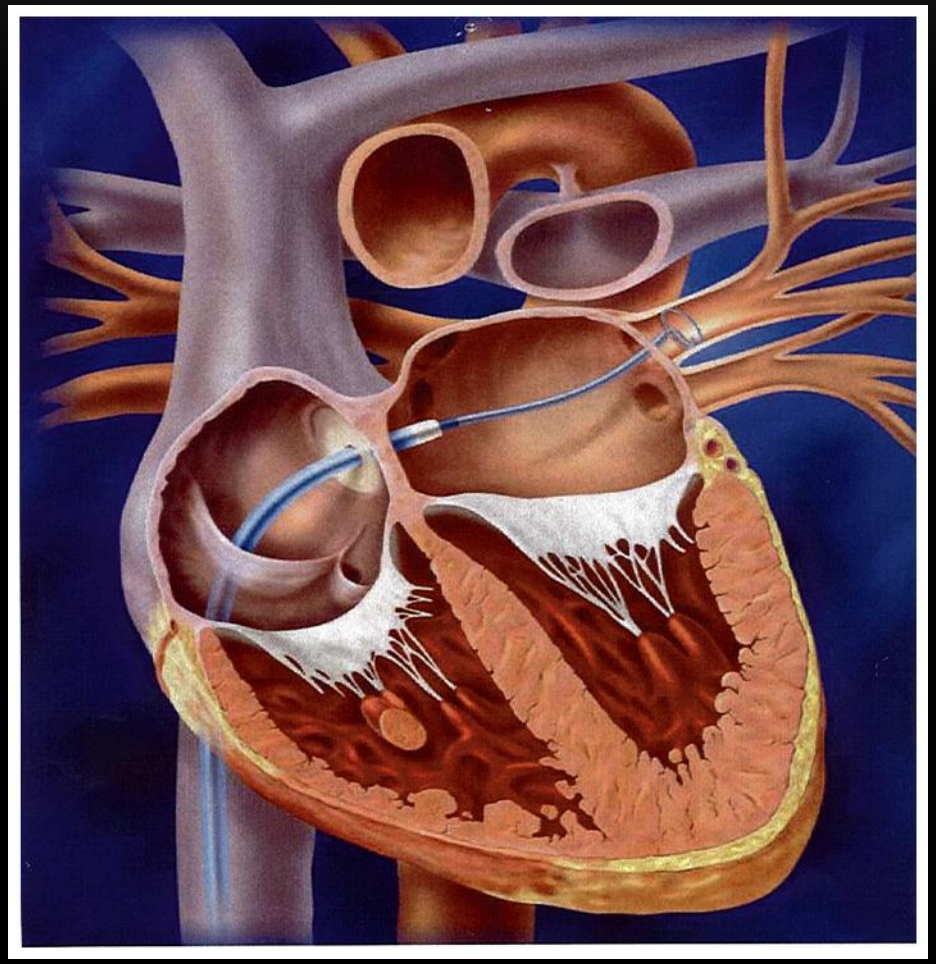


HYBRID EPICARDIAL-ENDOCARDIAL PROCEDURE

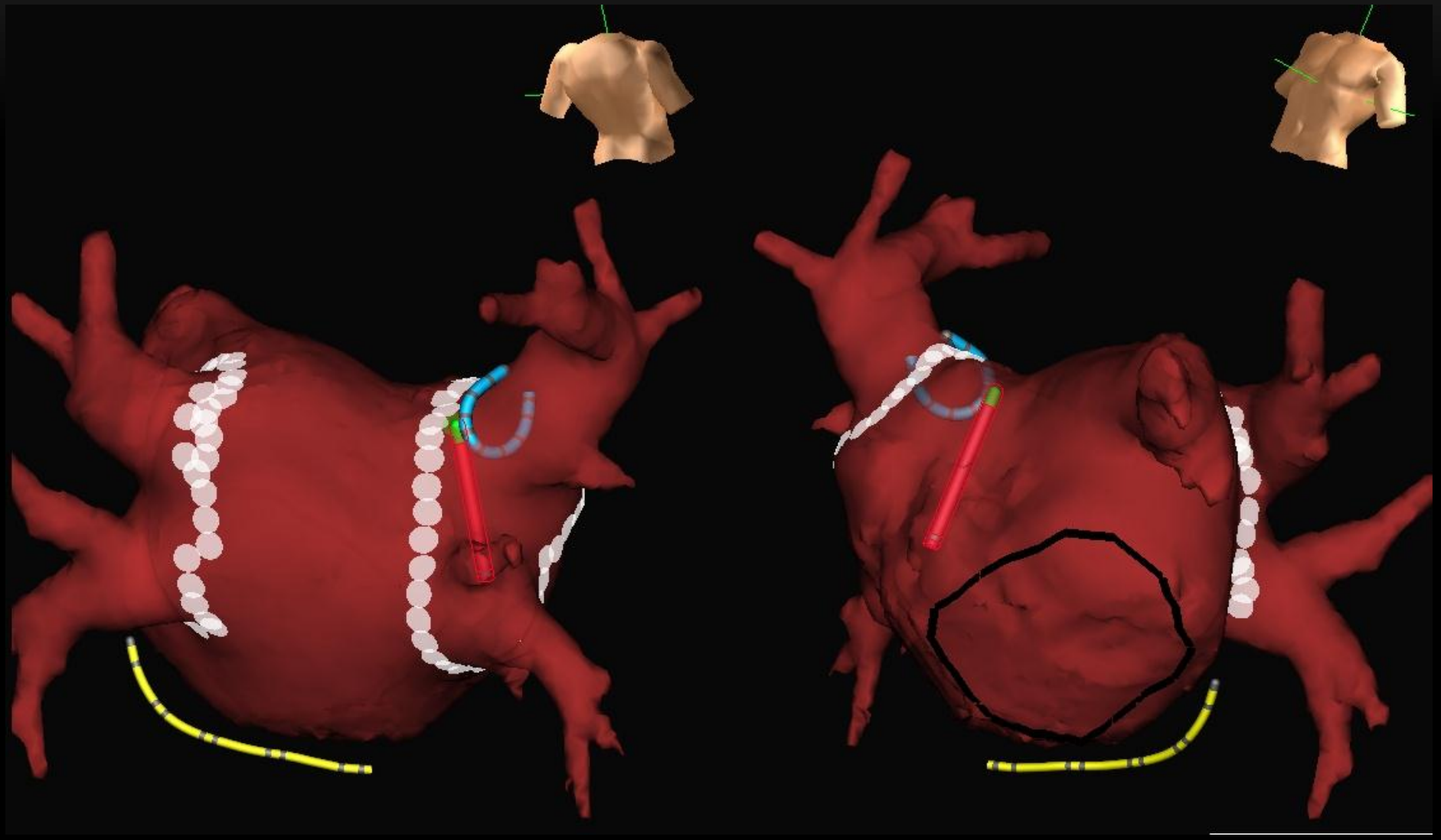


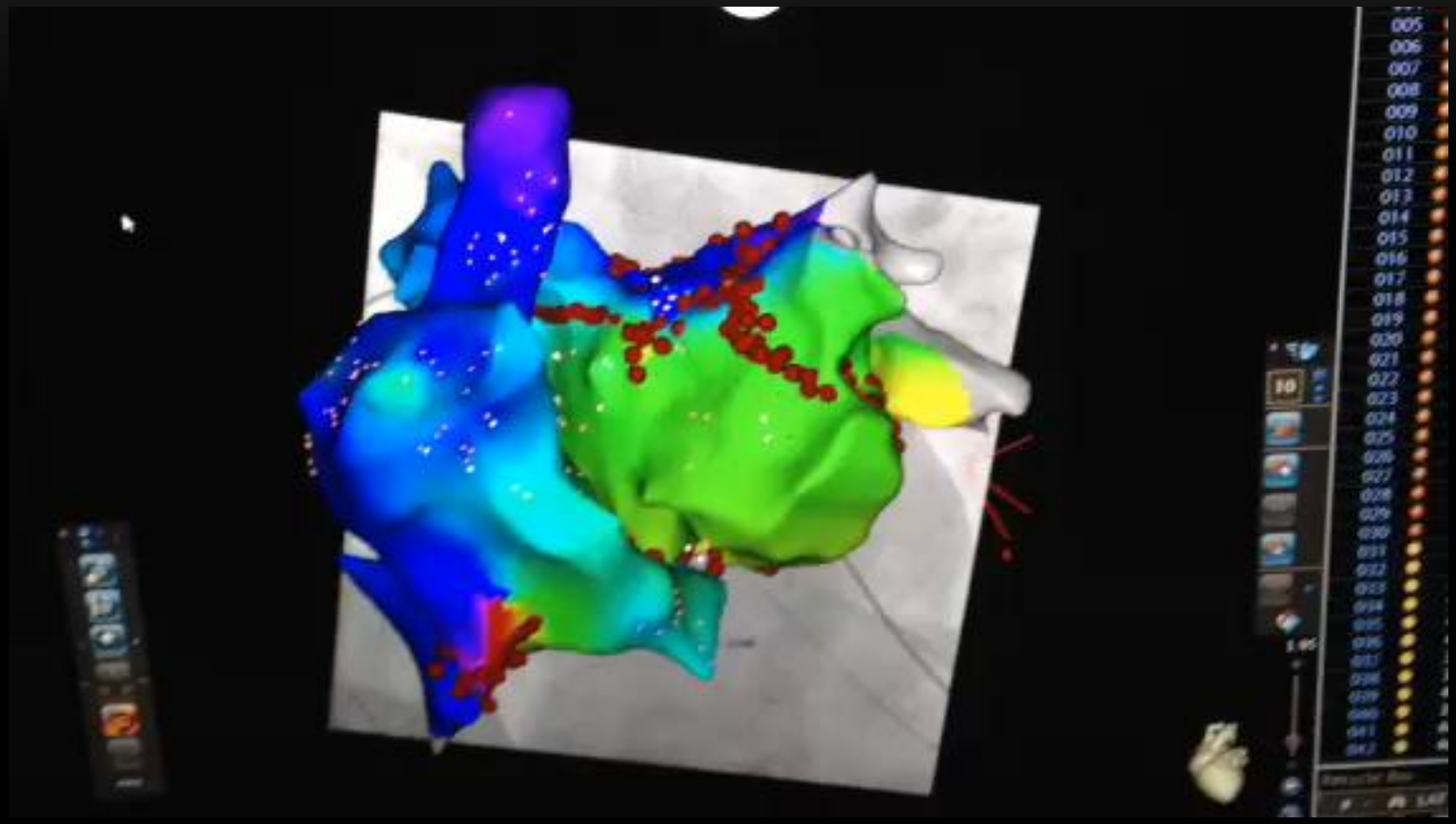
CATHETER ABLATION

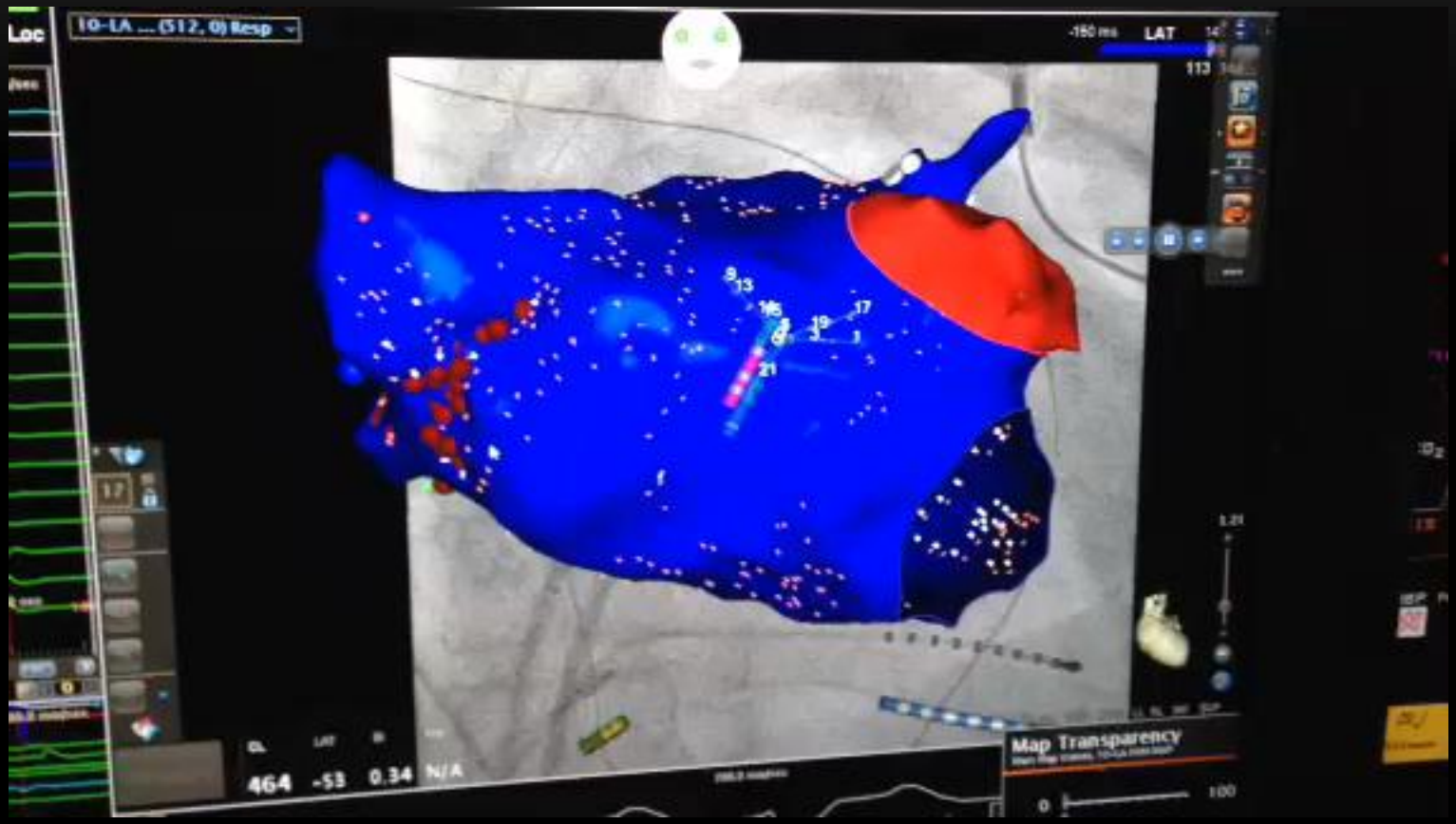
- Ablation lesions placed to isolate pulmonary veins and destroy AF triggers
- Up front risk of procedure-related complications



CATHETER ABLATION FOR AF



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Map Transparency
464
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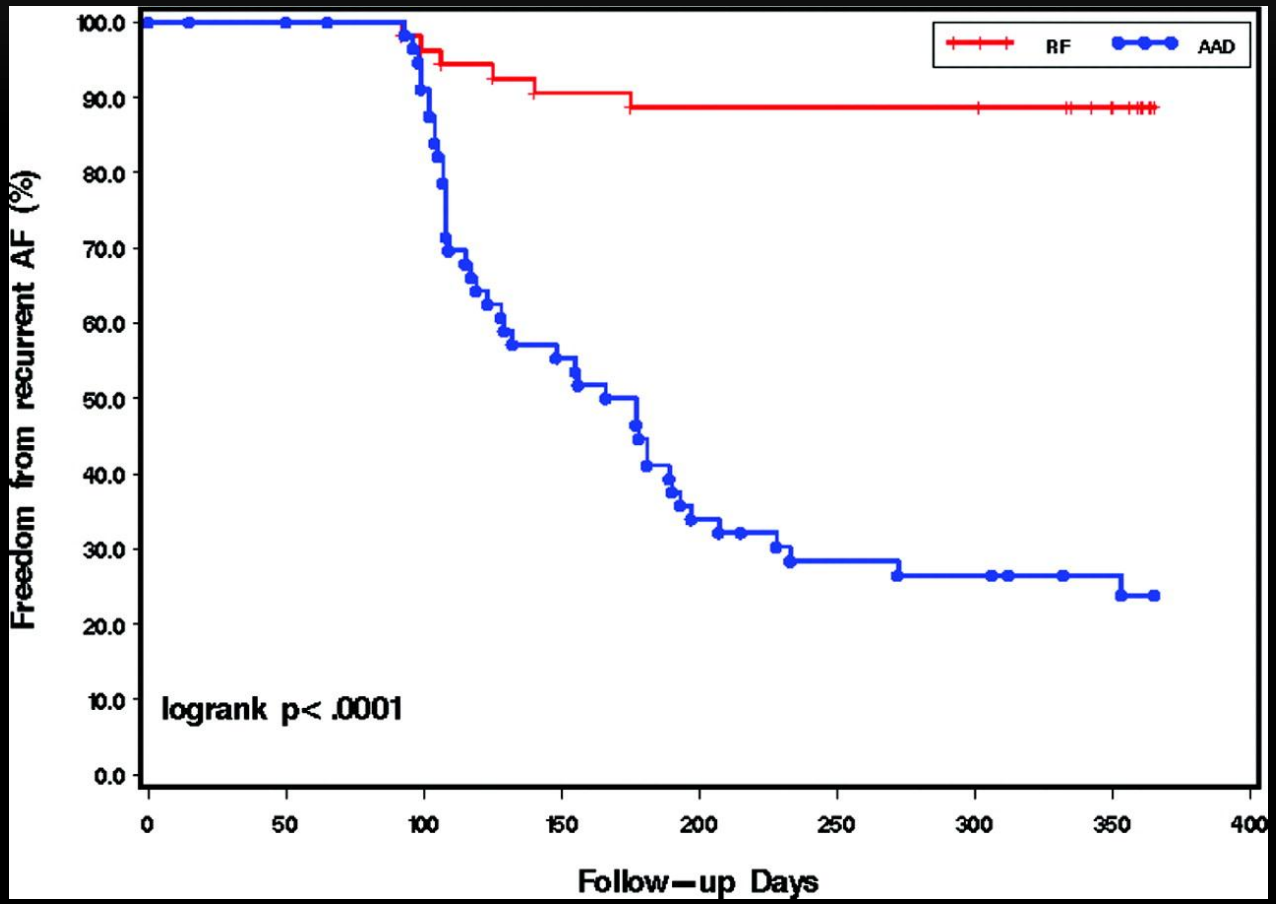
N/A

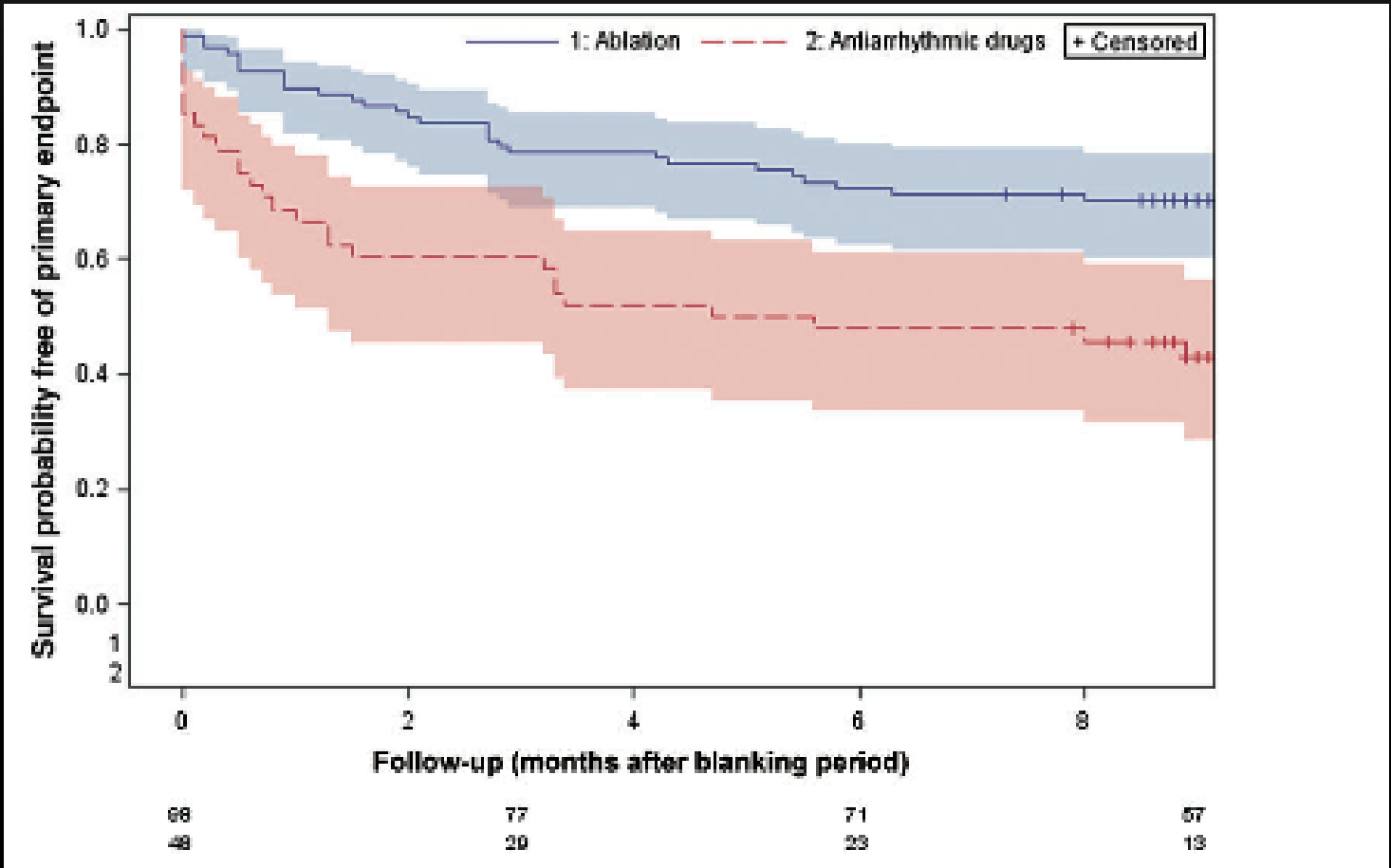
PAROXYSMAL AF



Jaïs P et al. *Circulation*. 2008;118:2498-2505

American Heart Association

PERSISTANT AF



Mont, et al. Eur Heart J. 2013.

PERSISTANT AF

Table 2 **Secondary outcomes**

Outcome	Ablation ($n = 98$)	Drug therapy ($n = 48$)
Free of any recurrence of AF or flutter (confirmed during >30 s)	59 (60.2)	14 (29.2)[a,***]
Crossovers	35 (35.7)	0 (0)[a,***]
Cardioversions		
None	64 (65.3)	24 (50.0)[b,*]
1	22 (22.4)	10 (20.8)
2 or more	12 (12.2)	14 (29.2)
Hospitalizations related to arrhythmia	2 (2.0)	3 (6.25)[c]

Mont, et al. Eur Heart J. 2013.

ANTIARRHYTHMIC DRUGS

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association.

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

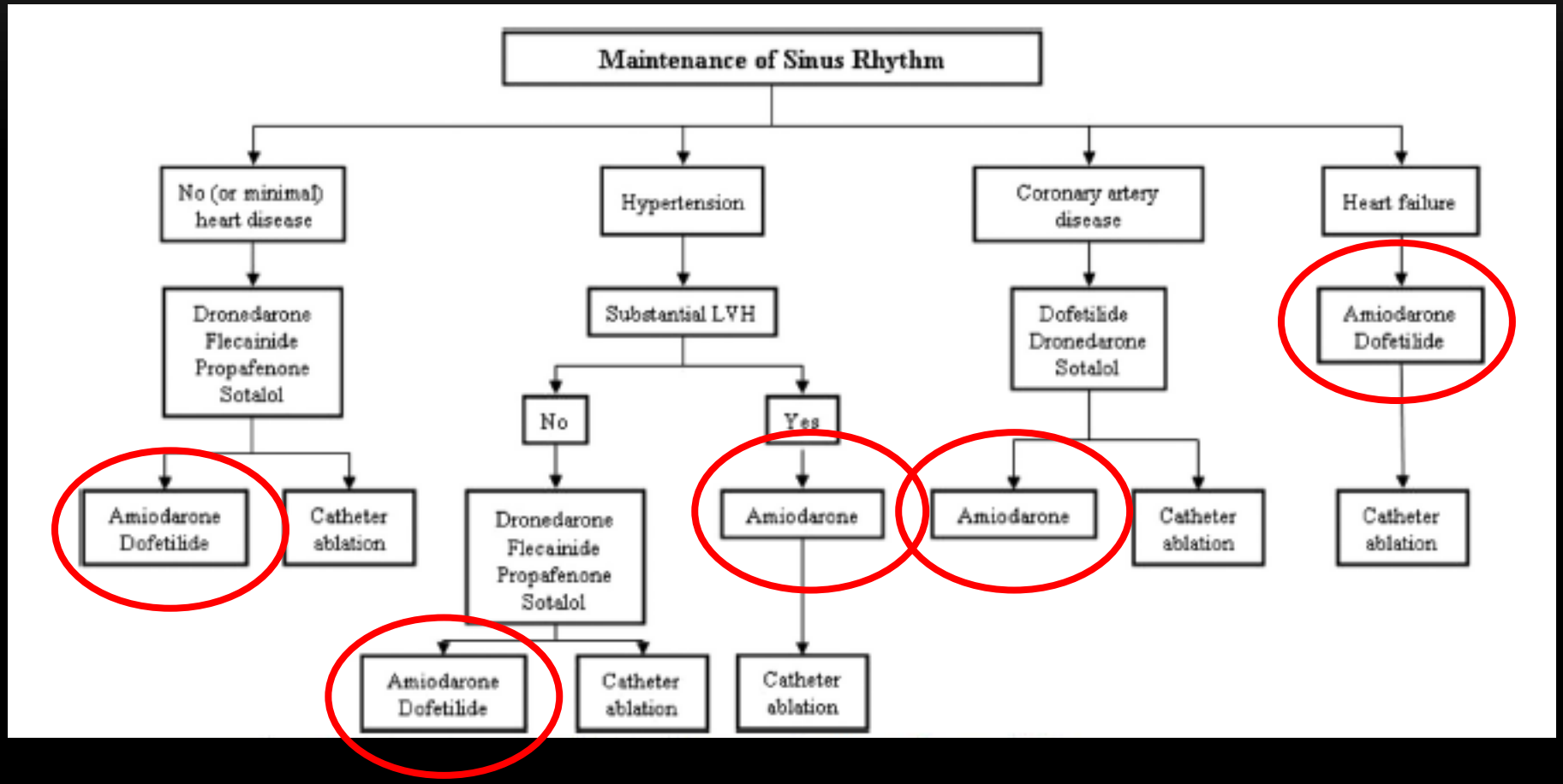
2011 Writing Group Members, L. Samuel Wann, Anne B. Curtis, Craig T. January, Kenneth A. Ellenbogen, James E. Lowe, N.A. Mark Estes III, Richard L. Page, Michael D. Ezekowitz, David J. Slotwiner, Warren M. Jackman, William G. Stevenson and Cynthia M. Tracy

Circulation. 2011;123:104-123; originally published online December 20, 2010;
doi: 10.1161/CIR.0b013e3181fa3cf4
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

Agent	Success	Toxicities	Notes
Amiodarone	80%	Pulmonary, Hepatic, Thyroid, Optic, Dermatologic	Common adverse effects are listed, mostly seen with long-term use
Dofetilide	70%	Proarrhythmia	QT prolongation; Initiation requires inpatient admission C/I if CrCl < 20 mL/min
Flecainide	70%	Proarrhythmia	C/I in structural heart disease
Propafenone	60%	Proarrhythmia	C/I in structural heart disease
Sotalol	50%	Proarrhythmia Exacerbation of airway disease	QT prolongation, C/I in severe heart failure, severe COPD
Dronedarone		Permanent Afib ?Hepatic Gastrointestinal	C/I in severe heart failure, permanent AF

Circulation 2006; 114; e257-e354; Arch Intern Med. 2006;166:719-728.


Maintenance of Sinus Rhythm
No (or minimal) heart disease
Hypertension
Coronary artery disease
Heart failure
Dronedarone
Flecainide
Propafenone
Sotalol
Substantial LVH
Dofetilide
Dronedarone
Sotalol
Amiodarone
Dofetilide
No
Yes
Amiodarone
Dofetilide
Catheter ablation
Amiodarone
Catheter ablation
Dronedarone
Flecainide
Propafenone
Sotalol
Amiodarone
Catheter ablation
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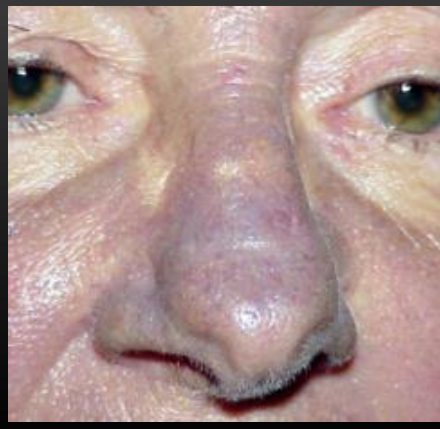
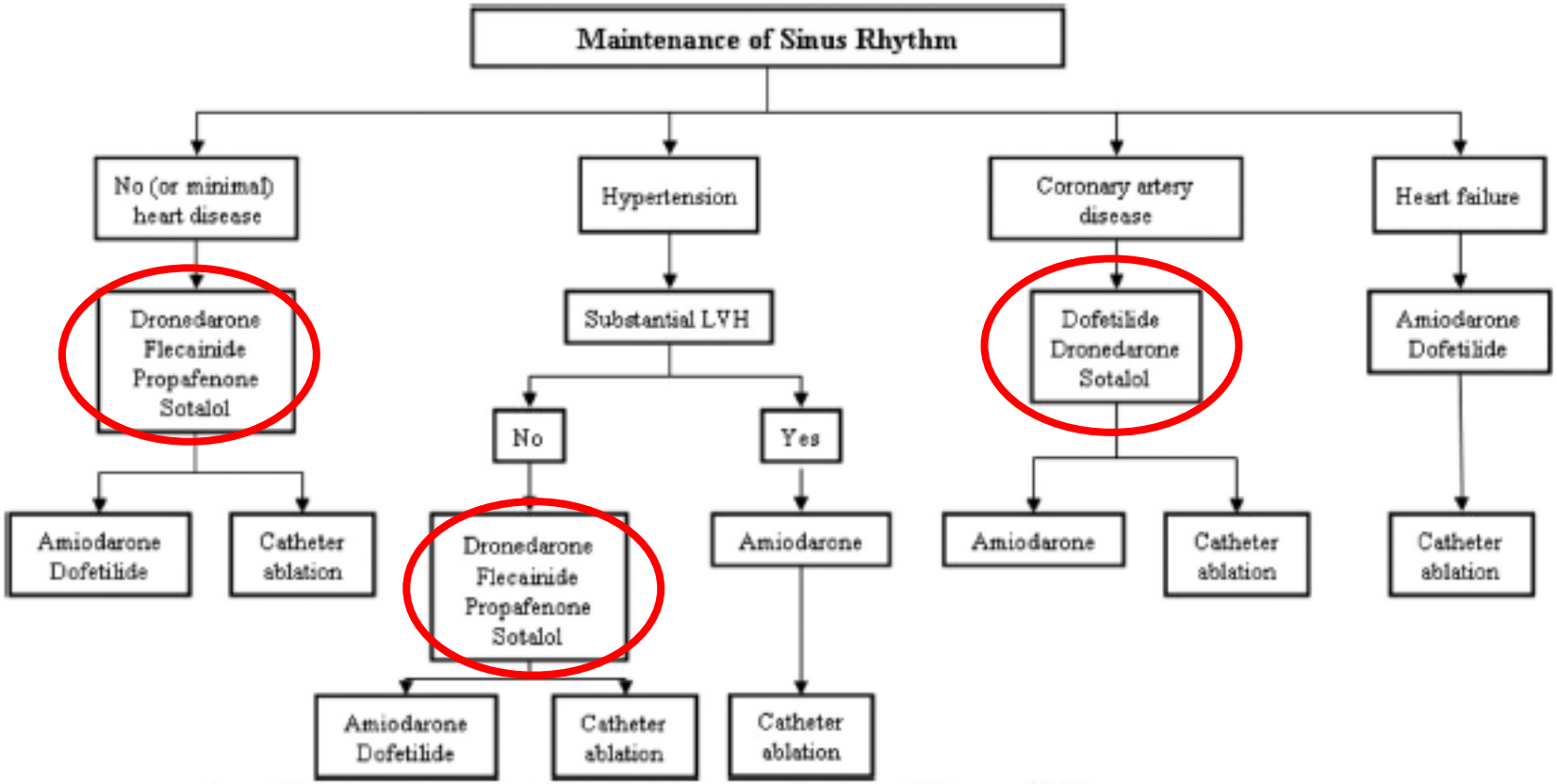
Catheter ablation

AMIODARONE



- Long half-life (56 days)
- Side Effects: liver/thyroid/pulmonary toxicity; eye problems, photosensitivity, blue-gray skin, neuropathy
- Warfarin metabolism: reduce dose, monitor INRs closely
- CYP3A4 inhibitor = increased statin concentration = increased risk of myopathy
- P-glycoprotein inhibitor = increased digoxin concentration


Maintenance of Sinus Rhythm
No (or minimal) heart disease
Hypertension
Coronary artery disease
Heart failure
Dronedarone
Flecainide
Propafenone
Sotalol
Substantial LVH
Dofetilide
Dronedarone
Sotalol
Amiodarone
Dofetilide
No
Yes
Amiodarone
Dofetilide
Catheter ablation
Dronedarone
Flecainide
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Amiodarone
Catheter ablation
Amiodarone
Dofetilide
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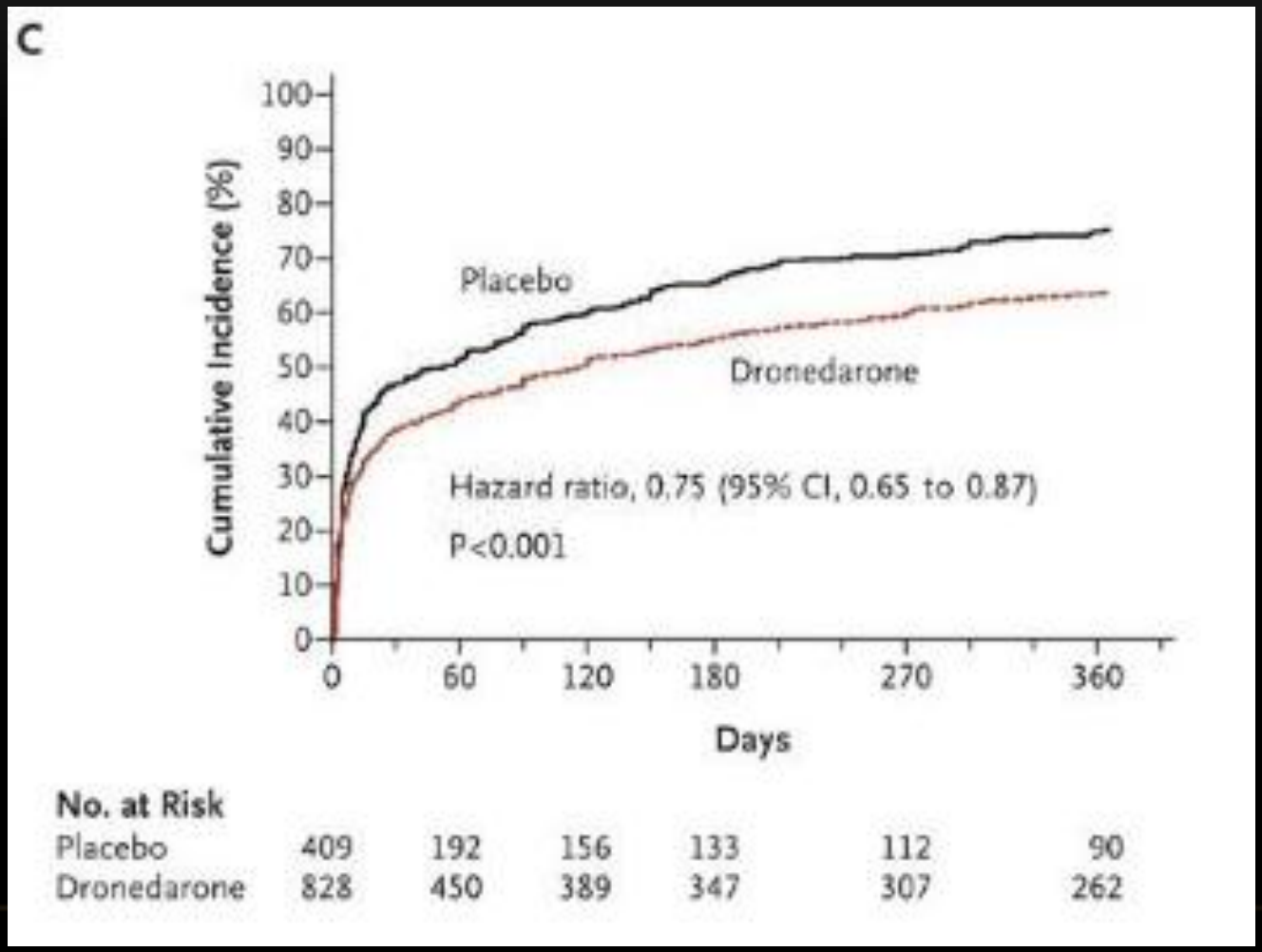
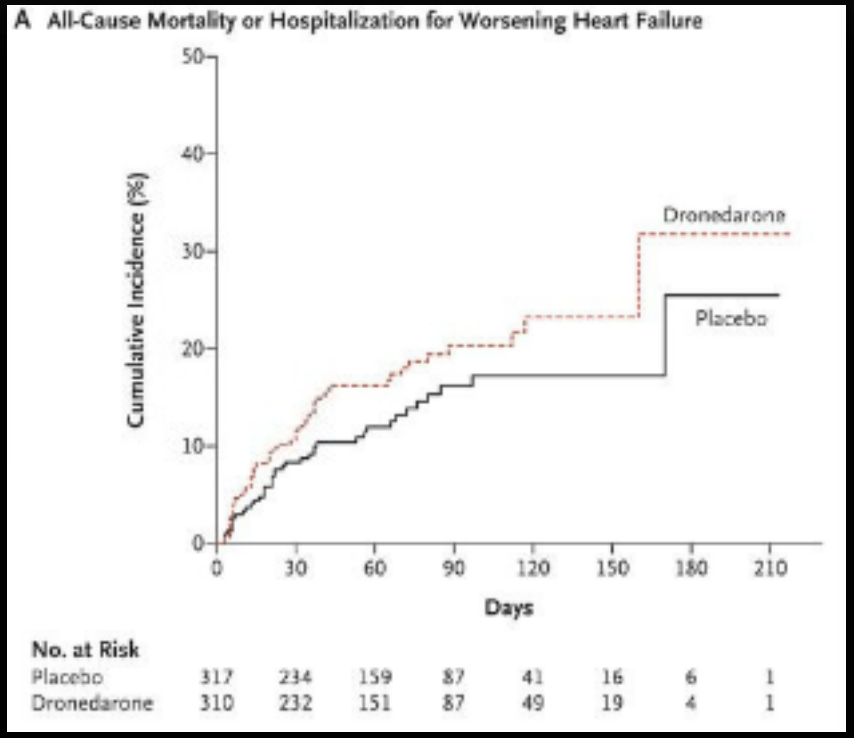
Amiodarone
Catheter ablation
Catheter ablation

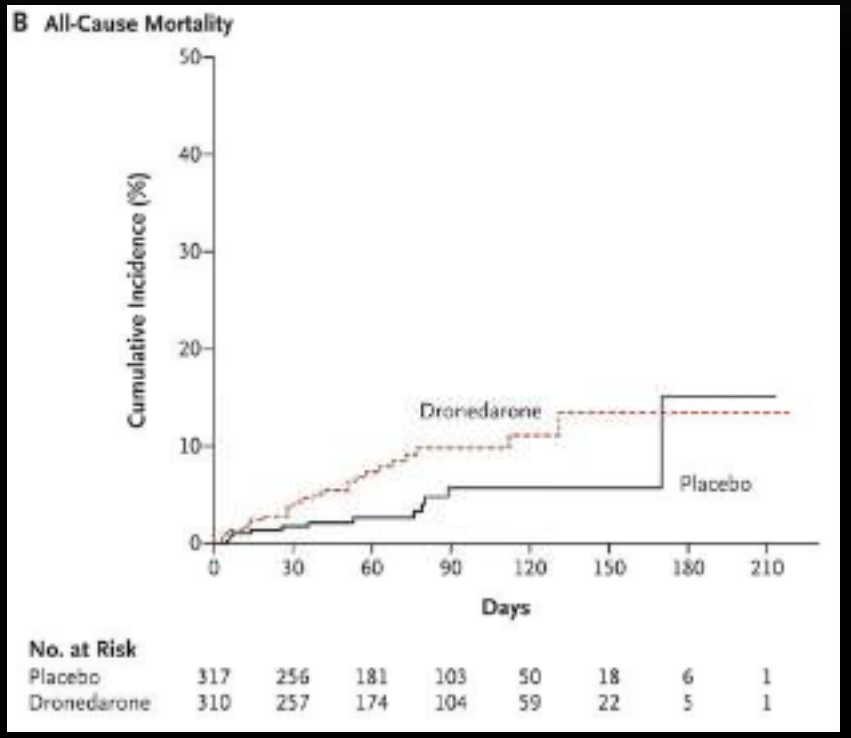
DRONEDERONE: TIME TO AFIB RECURRENCE



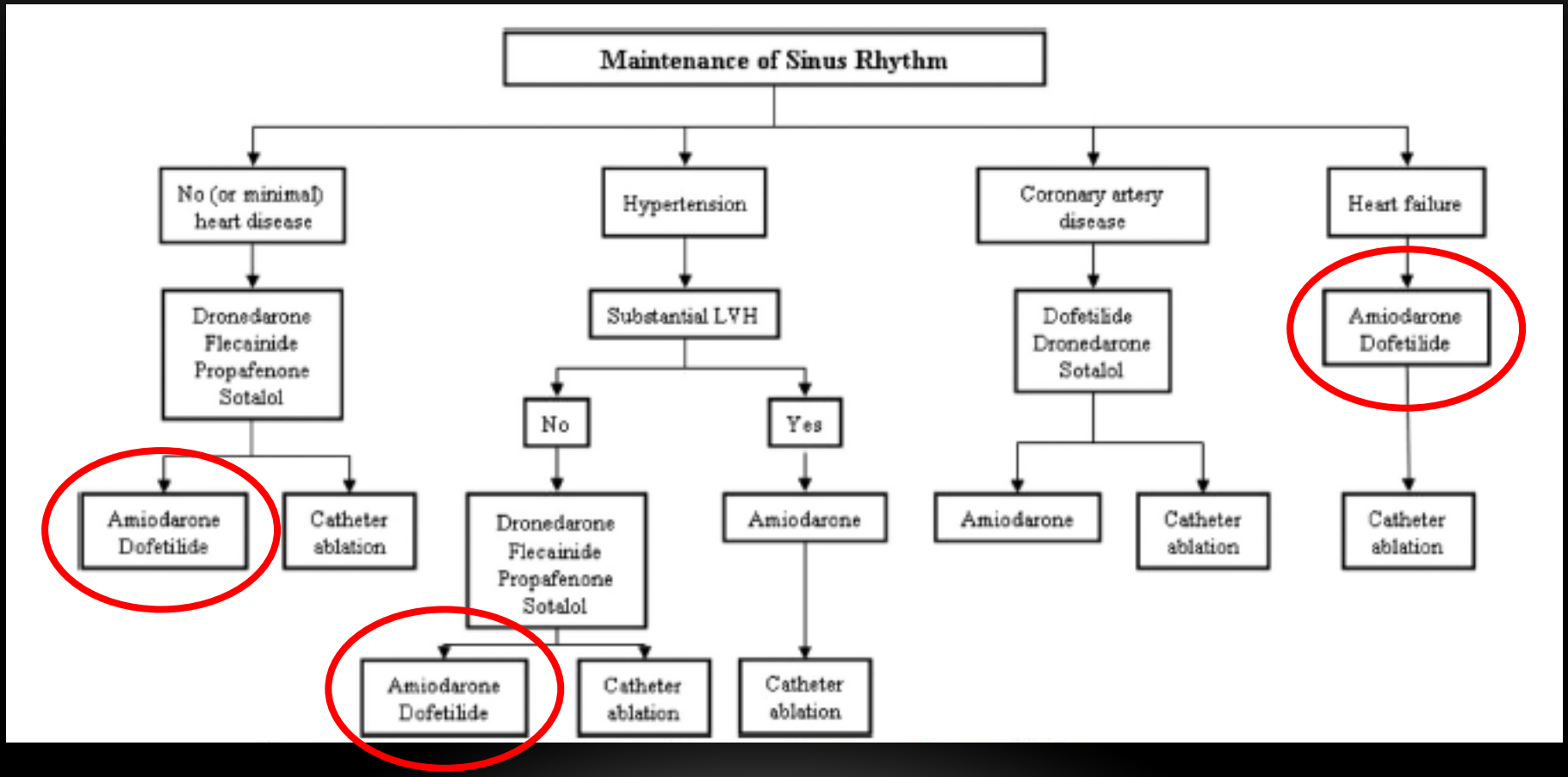
Singh, et al. NEJM 2007;357:987-999.

DRONEDERONE AND HEART FAILURE





Kober, et al. NEJM 2008;358:2678-2687.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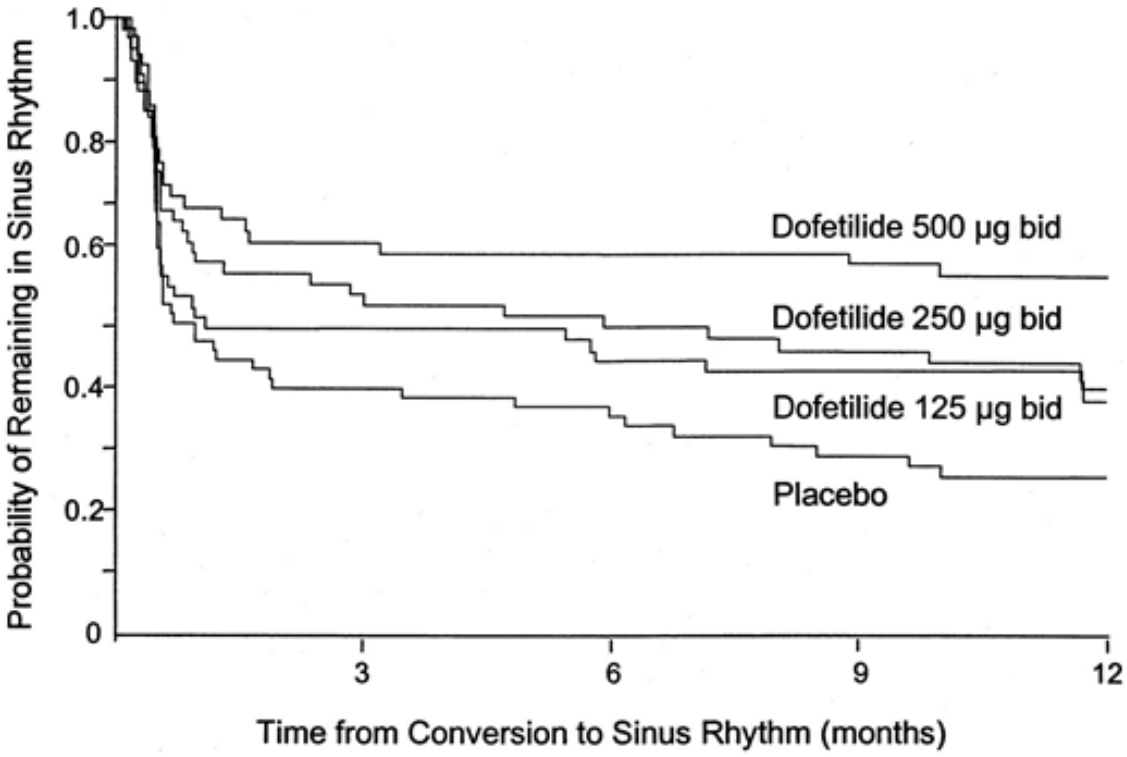
Amiodarone
Catheter ablation
Catheter ablation

TIKOSYN

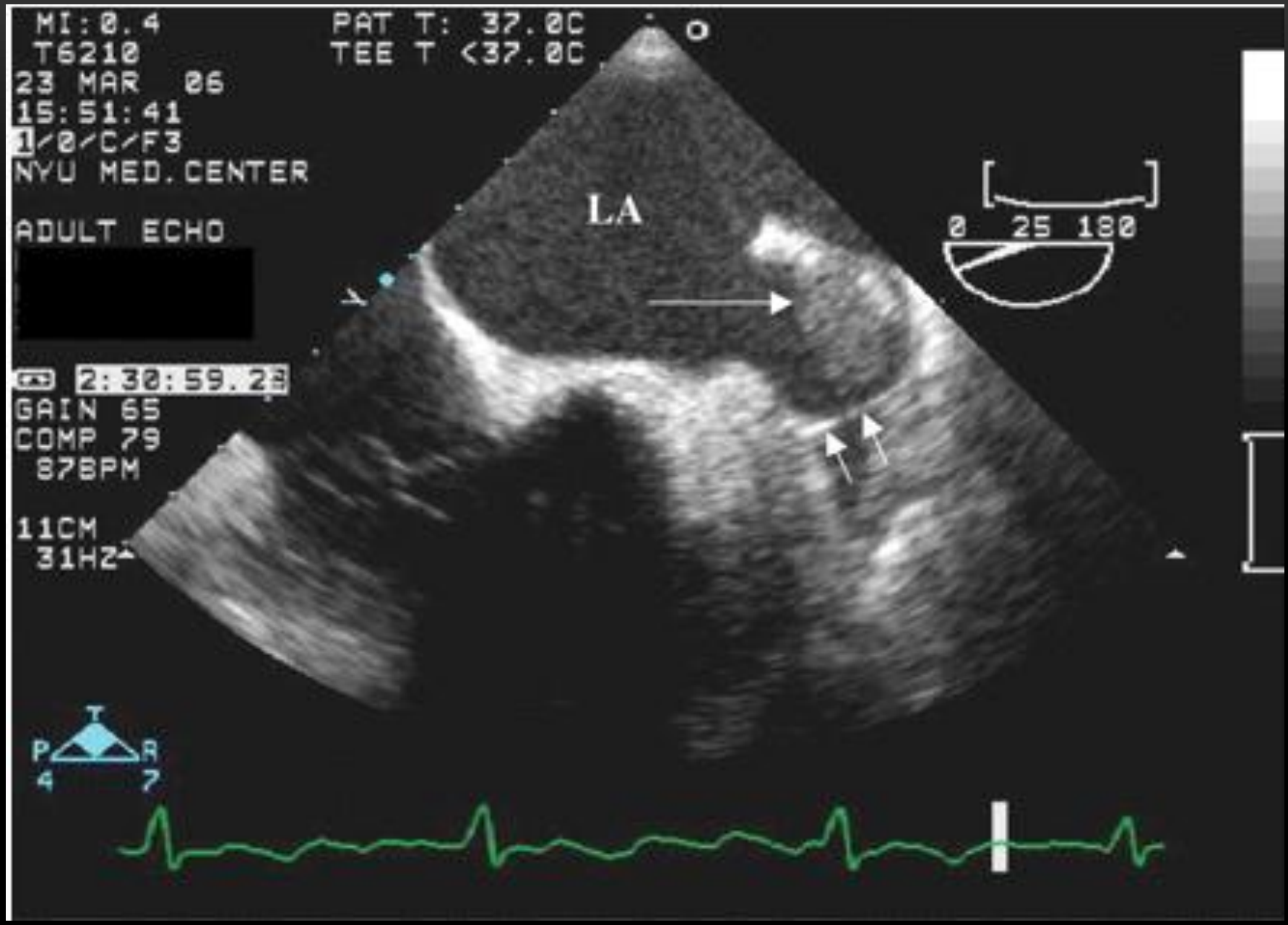


Singh S et al. *Circulation*. 2000;102:2385-2390

American Heart Association.

TIKOSYN AND HEART FAILURE

ANTICOAGULATION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NYU MED. CENTER
ADULT ECHO
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TEE T <37.0C
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COMP 79
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31HZ
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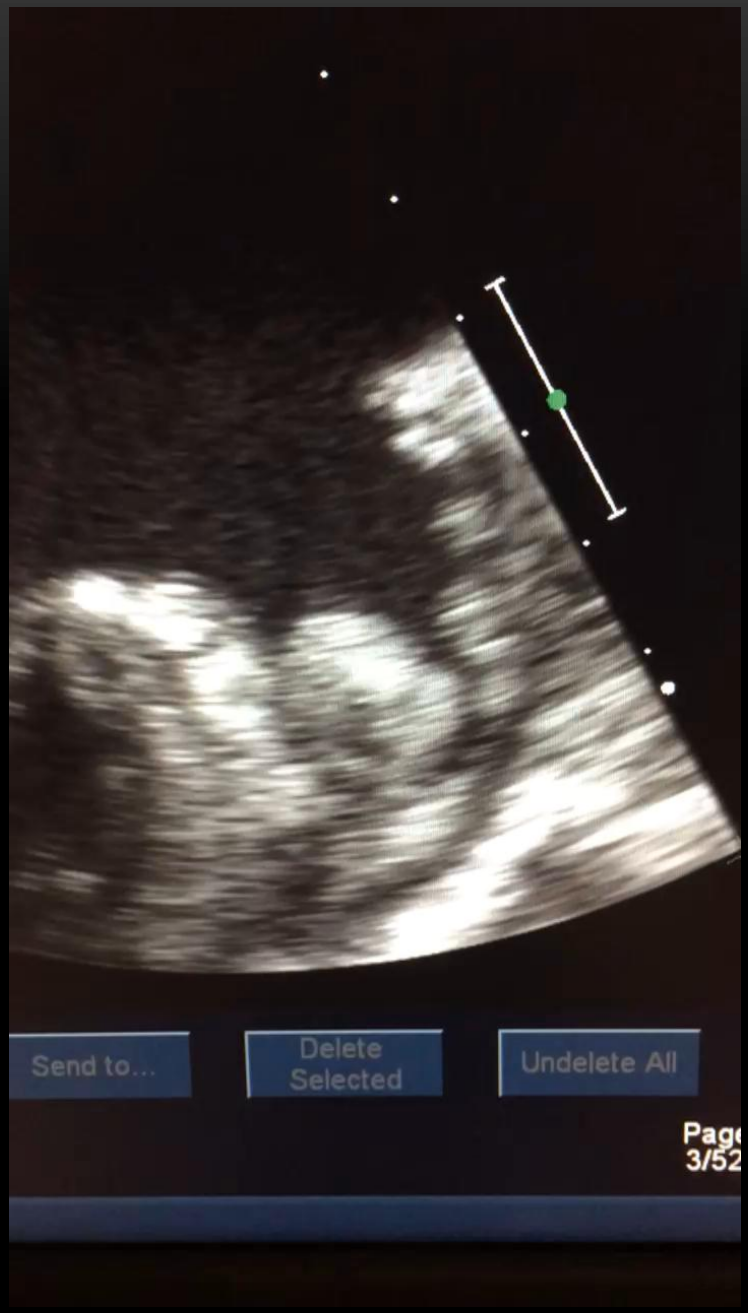
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3/52

EVALUATING RISK OF THROMBOEMBOLISM IN ATRIAL FIBRILLATION

- $CHADS_2$ risk criteria
  - Hypertension 1 point
  - CHF1 point
  - Diabetes 1 point
  - Age >75 1 point
  - TIA/CVA 2 points

$CHADS_2$ score	Stroke rate/year
0	1.0%
1	1.5%
2	2.5%
3	5.0%
≥4	7.0%

Stroke 2008;39:1901-10

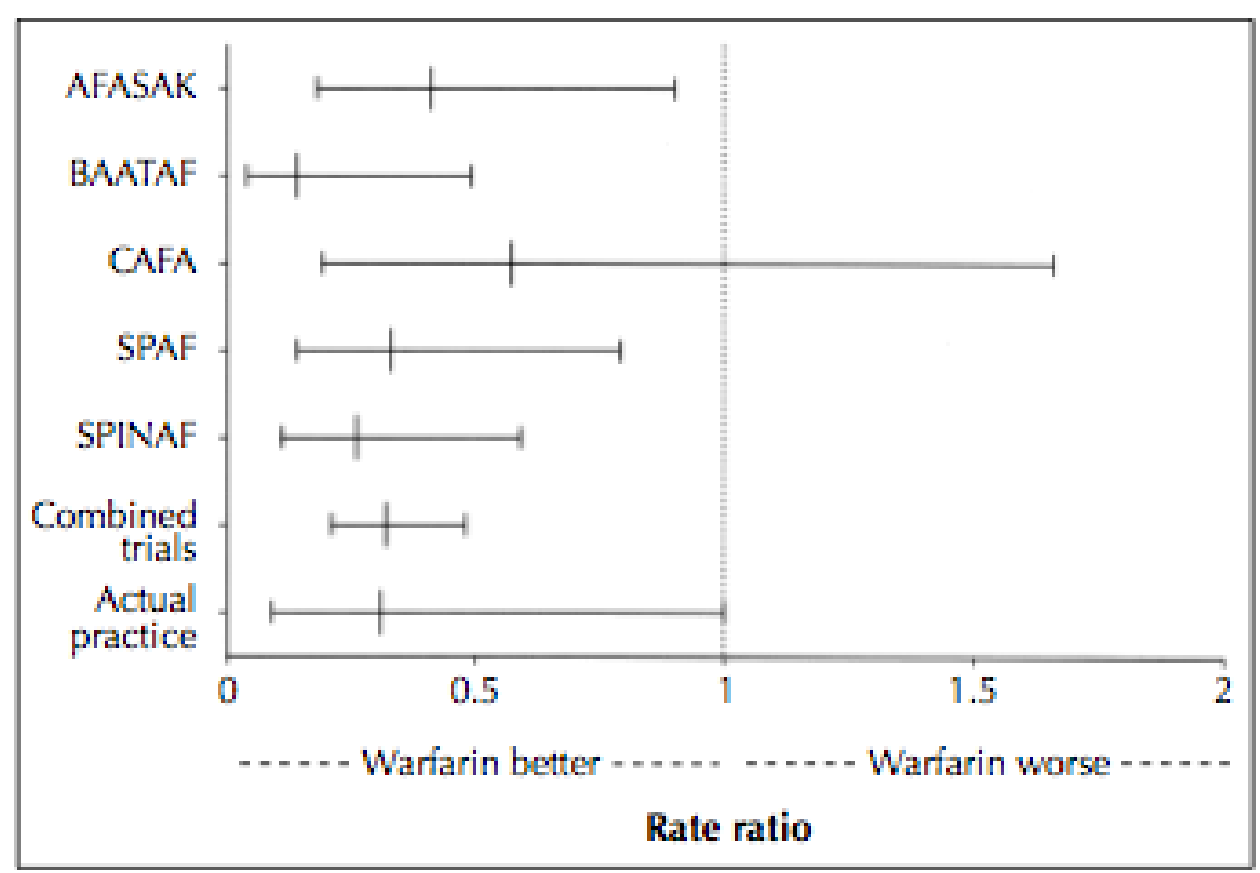
CHA_2DS_2VASc

- CHF or LV dysfunction 1 point
- Hypertension 1 point
- Age ≥75 2 points
- Diabetes 1 point
- Stroke or TIA 2 points
- Vascular disease 1 point
- Age 65-74 1 point
- Female gender 1 point

Score	Stroke (%/yr)
0	0
1	0.7
2	1.9
3	2.3
4	3.9
5	4.5
6	4.7
7	10.1
8	14.2

Lip GY, et al. Am J Med 2010; 123:484-8

WARFARIN PROTECTS
65% RR REDUCTION



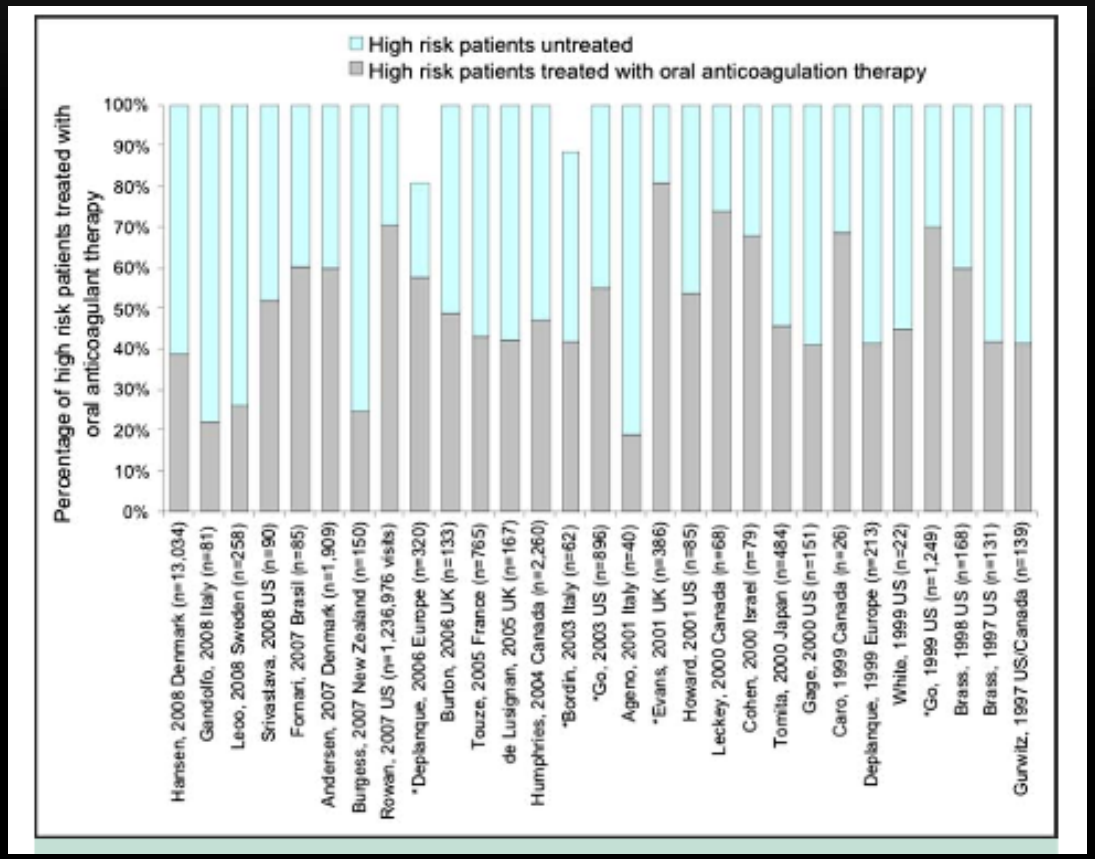
Caro JJ, et al. CMAJ 1999; 161(5);493-7.

INCIDENCE OF STROKE BY INR

Only INR> 2.0 confers protection

Hylek et al NEJM 2003;349:1019-26

UNDERUSE OF ORAL ANTICOAGULANTS



- 54 studies
- 25/29 studies with prior stroke/TIA showed underuse
- Underuse defined as <70%

Ogilvie, et al. Am J Med 2010; 123:638-645.

REASONS FOR UNDERUSE

- Failure to initiate therapy
- Narrow therapeutic window with warfarin
- Inconvenience of INR monitoring
- Patient compliance
- 1/3 of patients in the US discontinue warfarin after 30 months
- Physician fear of bleeding risk
  - However, INR <2.0 is associated with a greater risk of stroke than an INR >3.0 is associated with a risk of bleeding

Ogilvie, et al. Am J Med 2010; 123:638-64

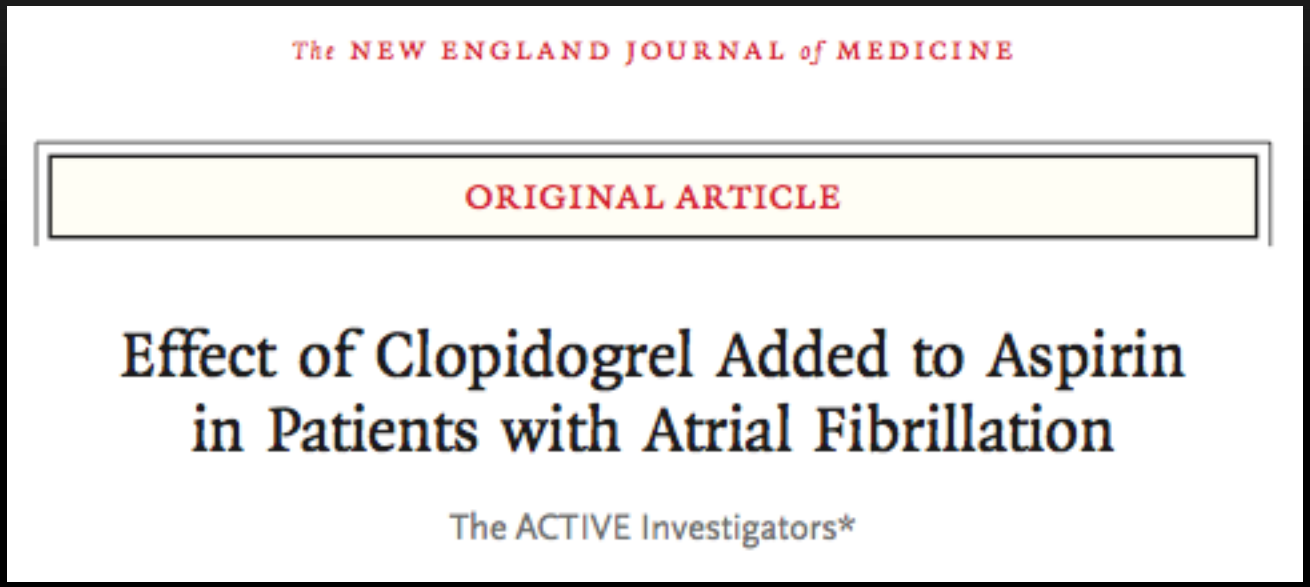
ACTIVE W
WARFARIN VS. ASA + CLOPIDOGREL

End point	Clopidogrel+ASA (%/y)	Warfarin (%/y)	Relative risk	95% CI	p
Vascular events	5.60	3.93	1.44	1.18–1.76	0.0003
Stroke	2.39	1.40	1.72	1.24–2.37	0.001
Major hemorrhage	2.42	2.21	1.10	0.83–1.45	0.53
Net benefit*	7.56	5.45	1.41	1.19–1.67	<0.0001

- 6600 patients with at least 1 risk factor for stroke
- Trial stopped early due to a significant increase in the combined endpoint of stroke, embolism, MI and vascular death in the clopidogrel plus ASA group

Connolly SJ, et al. Lancet 2006; 367(9526):1903-12.

ACTIVE A



The NEW ENGLAND JOURNAL of MEDICINE

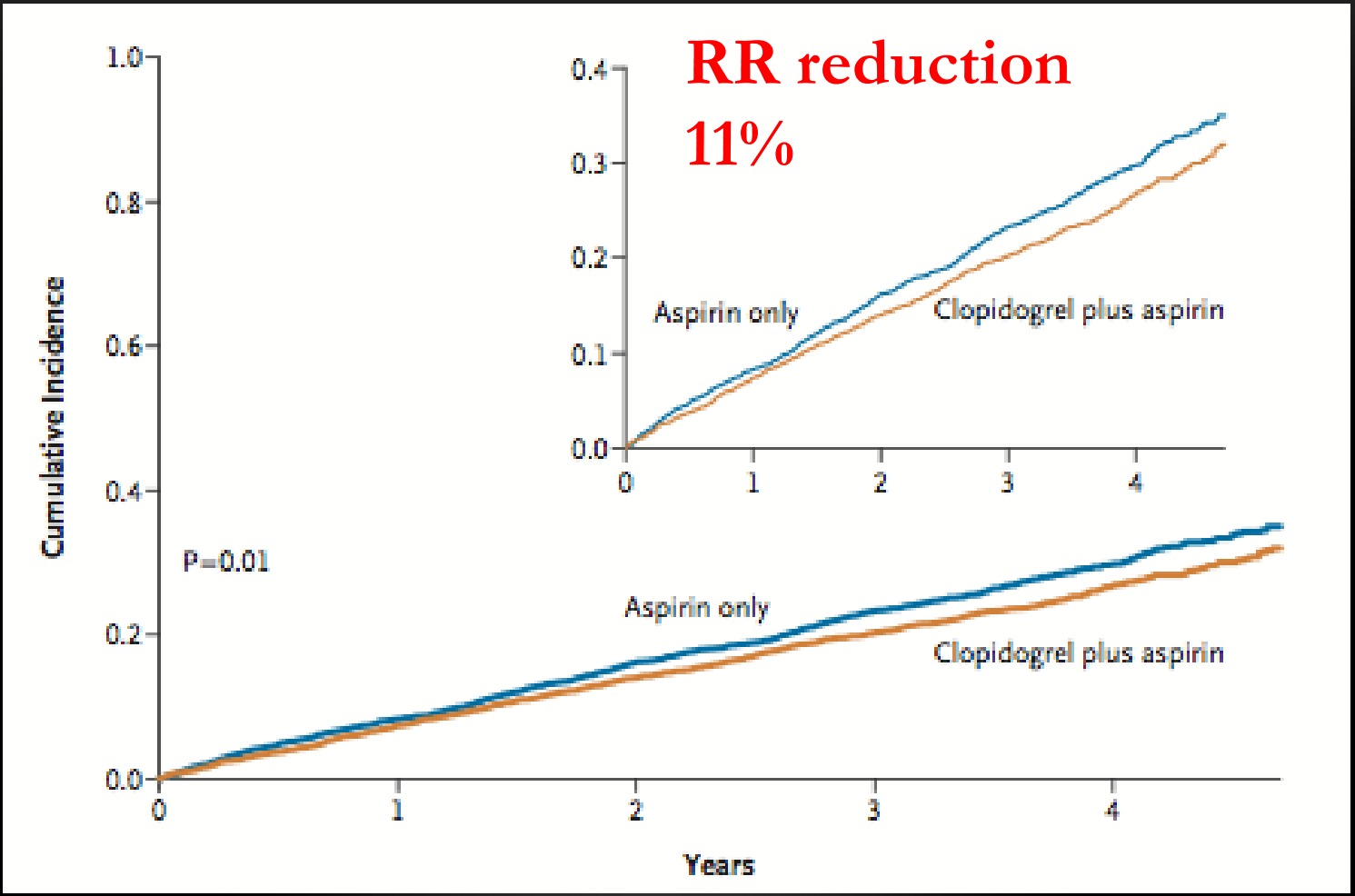
ORIGINAL ARTICLE

Effect of Clopidogrel Added to Aspirin in Patients with Atrial Fibrillation

The ACTIVE Investigators*

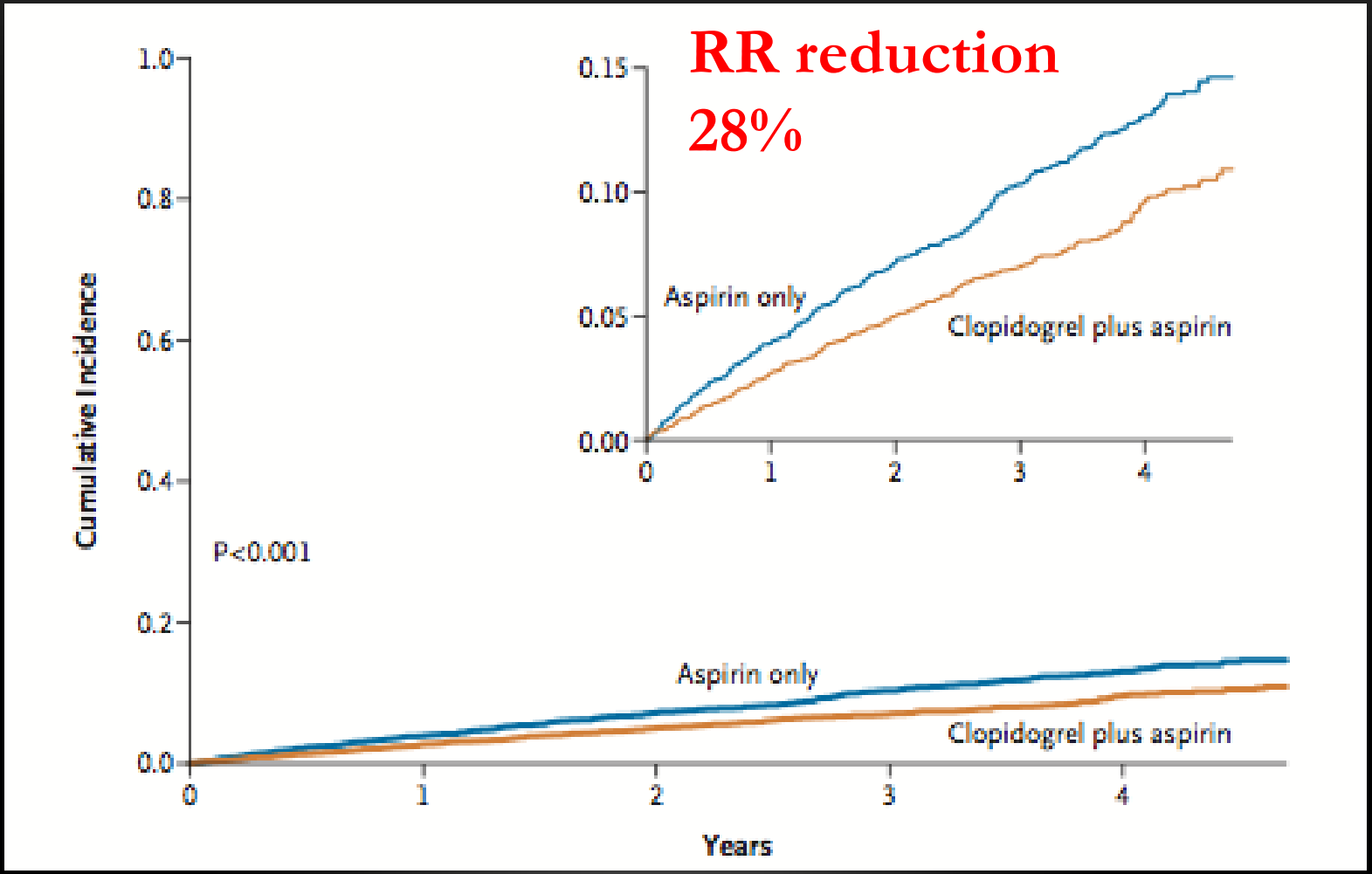
- 7554 patients in whom warfarin was deemed unsuitable
- ASA vs. Clopidogrel + ASA

PRIMARY OUTCOME (STROKE, MI, NON-CNS EMBOLIZATION, OR DEATH FROM VASCULAR CAUSES)



Connolly SJ, et al. NEJM 2009; 360:2066-78.

RISK OF STROKE



Connolly SJ, et al. NEJM 2009; 360:2066-78.

ANTITHROMBOTICS

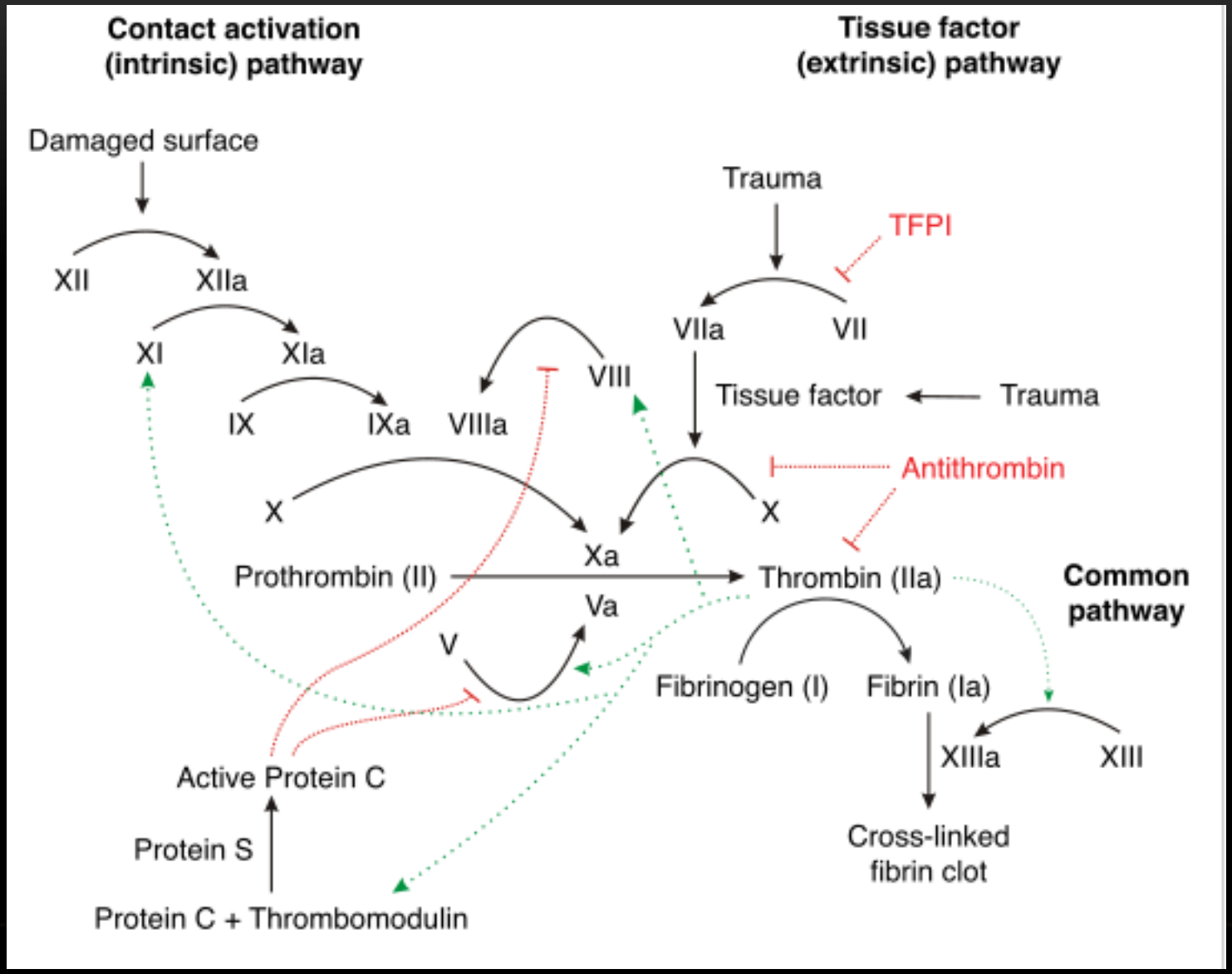
- Warfarin

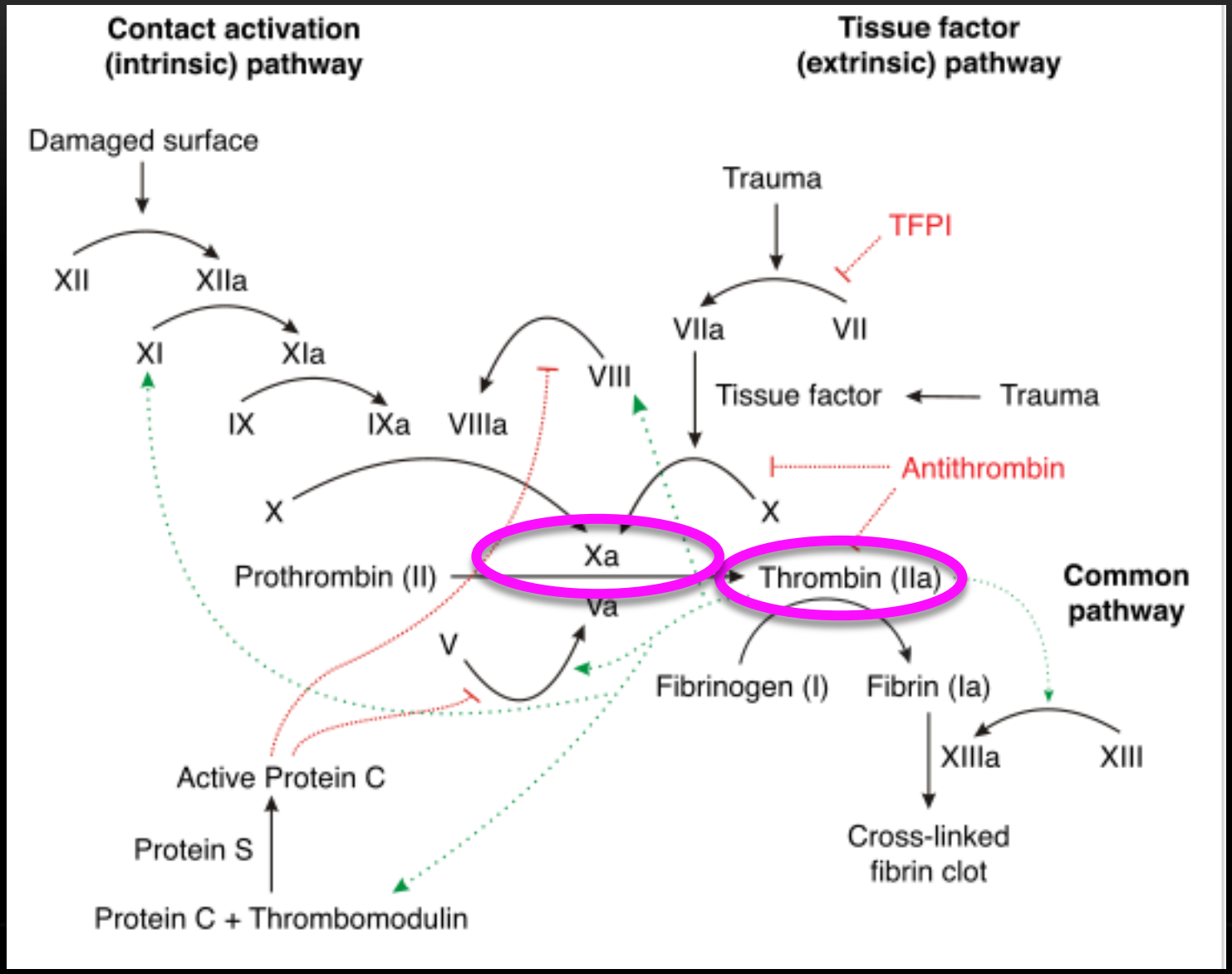
ANTITHROMBOTICS

- Warfarin
- Clopidogrel plus ASA (only when warfarin not suitable)

ANTITHROMBOTICS

- Warfarin
- Clopidogrel plus ASA(only when warfarin not suitable)
- Dabigatran
- Rivaroxaban
- Apixaban


Contact activation
(intrinsic) pathway
Tissue factor
(extrinsic) pathway
Damaged surface
XII
XIIa
XI
XIa
IX
IXa
VIIIa
VIII
Trauma
TFPI
VIIa
VII
Tissue factor
Trauma
Antithrombin
X
X
Xa
Prothrombin (II)
Thrombin (IIa)
Common
pathway
Va
V
Fibrinogen (I)
Fibrin (Ia)
XIIIa
XIII
Cross-linked
fibrin clot
Active Protein C
Protein S
Protein C + Thrombomodulin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VIIa
VII
Tissue factor
Trauma
Antithrombin
X
X
Xa
Va
Prothrombin (II)
Thrombin (IIa)
Common
pathway
V
Fibrinogen (I)
Fibrin (Ia)
XIIIa
XIII
Cross-linked
fibrin clot
Active Protein C
Protein S
Protein C + Thrombomodulin

RE-LY STUDY

CONNOLLY, ET AL. NEJM 2009;361:1139-51.

- Randomized, unblinded, noninferiority trial of 18,000+ patients
- 951 centers, 44 countries
- Documented afib
- Risk of stroke:
  - TIA/CVA
  - CHF
  - Age ≥75
  - LVEF <40%
  - Age 65-74 plus DM, hypertension, or CAD

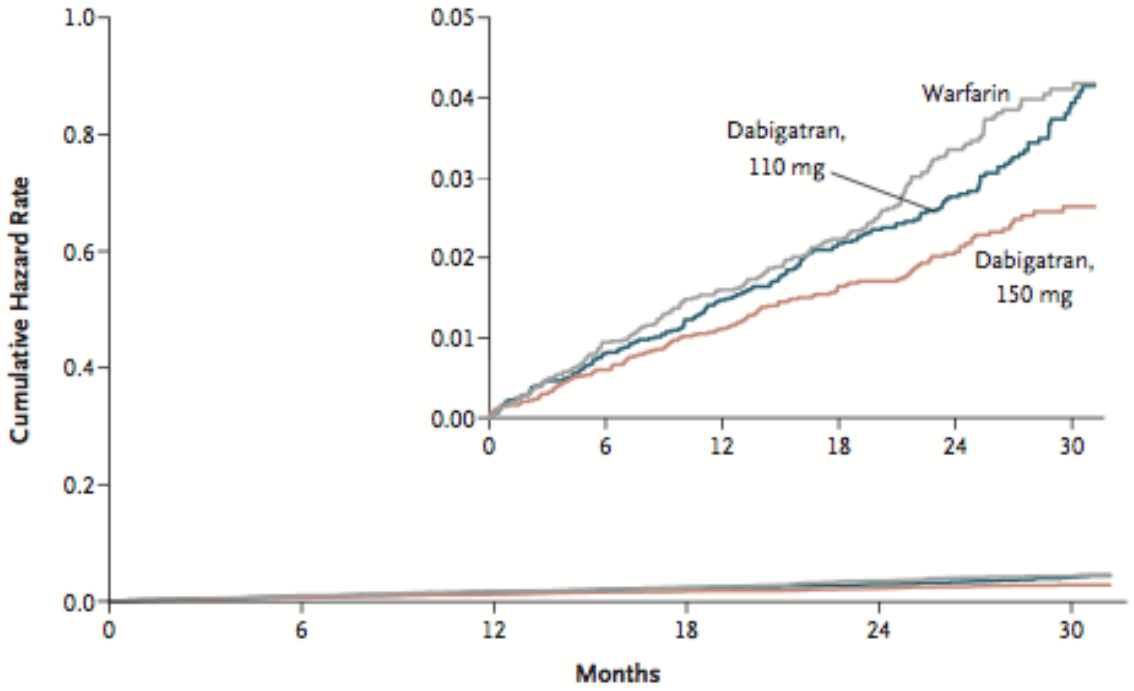
RE-LY STUDY

CONNOLLY, ET AL. NEJM 2009;361:1139-51.

- Dabigatran 110mg or 150mg
- Primary outcome was stroke or systemic embolism
- Mean $CHADS_2$ score was 2.1

RE-LY STUDY

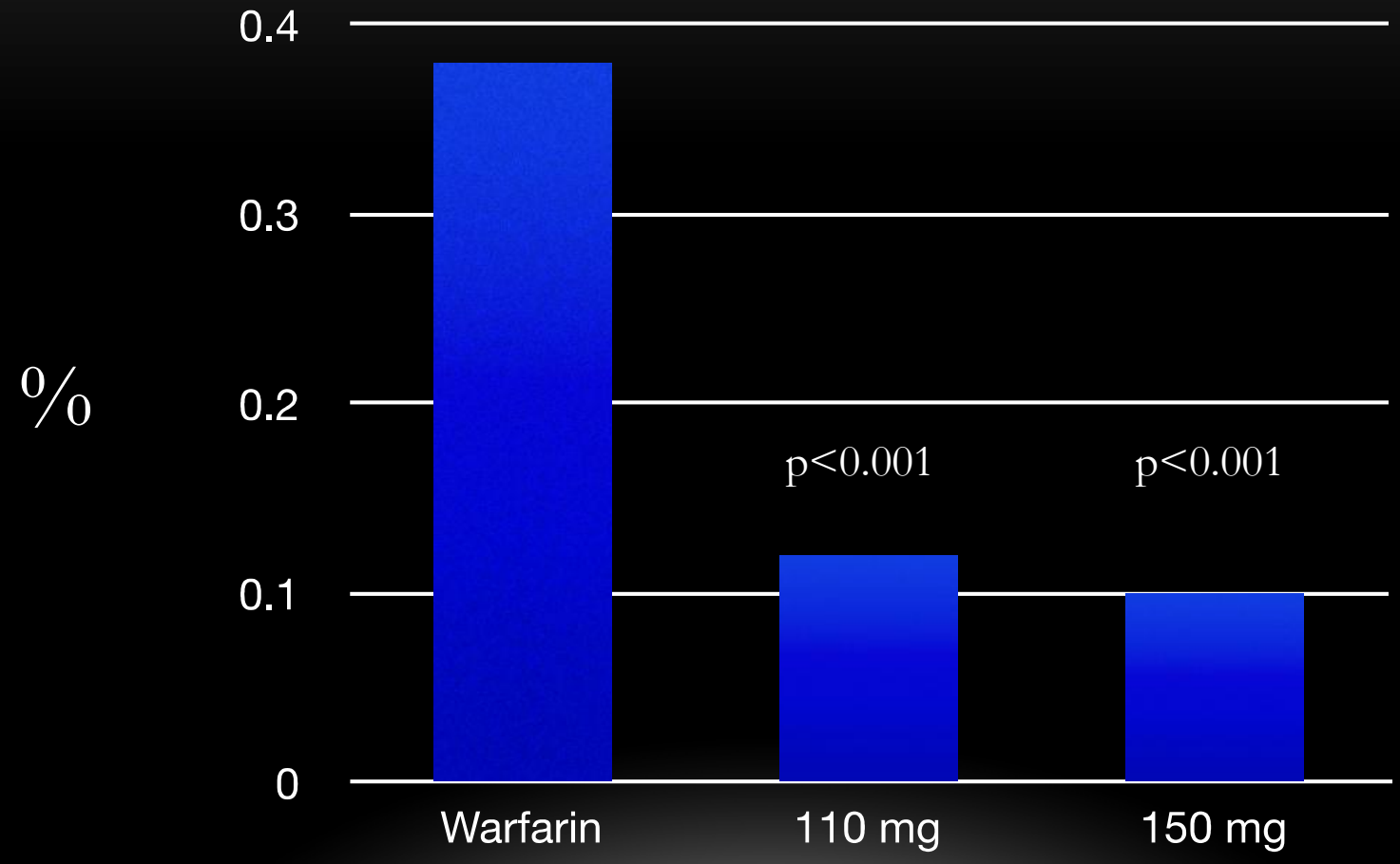
CONNOLLY, ET AL. NEJM 2009;361:1139-51.



No. at Risk						
Warfarin	6022	5862	5718	4593	2890	1322
Dabigatran, 110 mg	6015	5862	5710	4593	2945	1385
Dabigatran, 150 mg	6076	5939	5779	4682	3044	1429

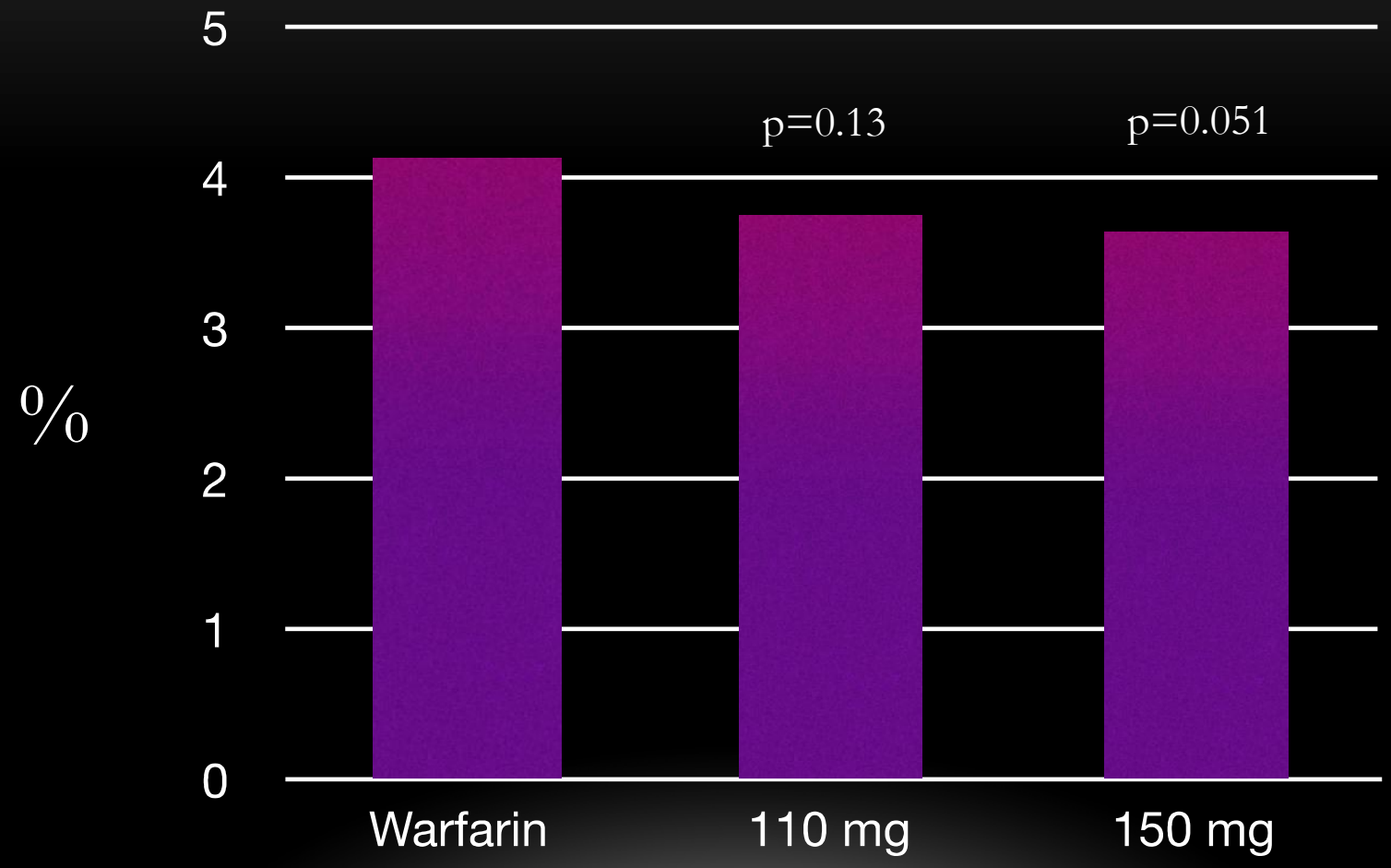
Figure 1. Cumulative Hazard Rates for the Primary Outcome of Stroke or Systemic Embolism, According to Treatment Group.

HEMORRHAGIC STROKE



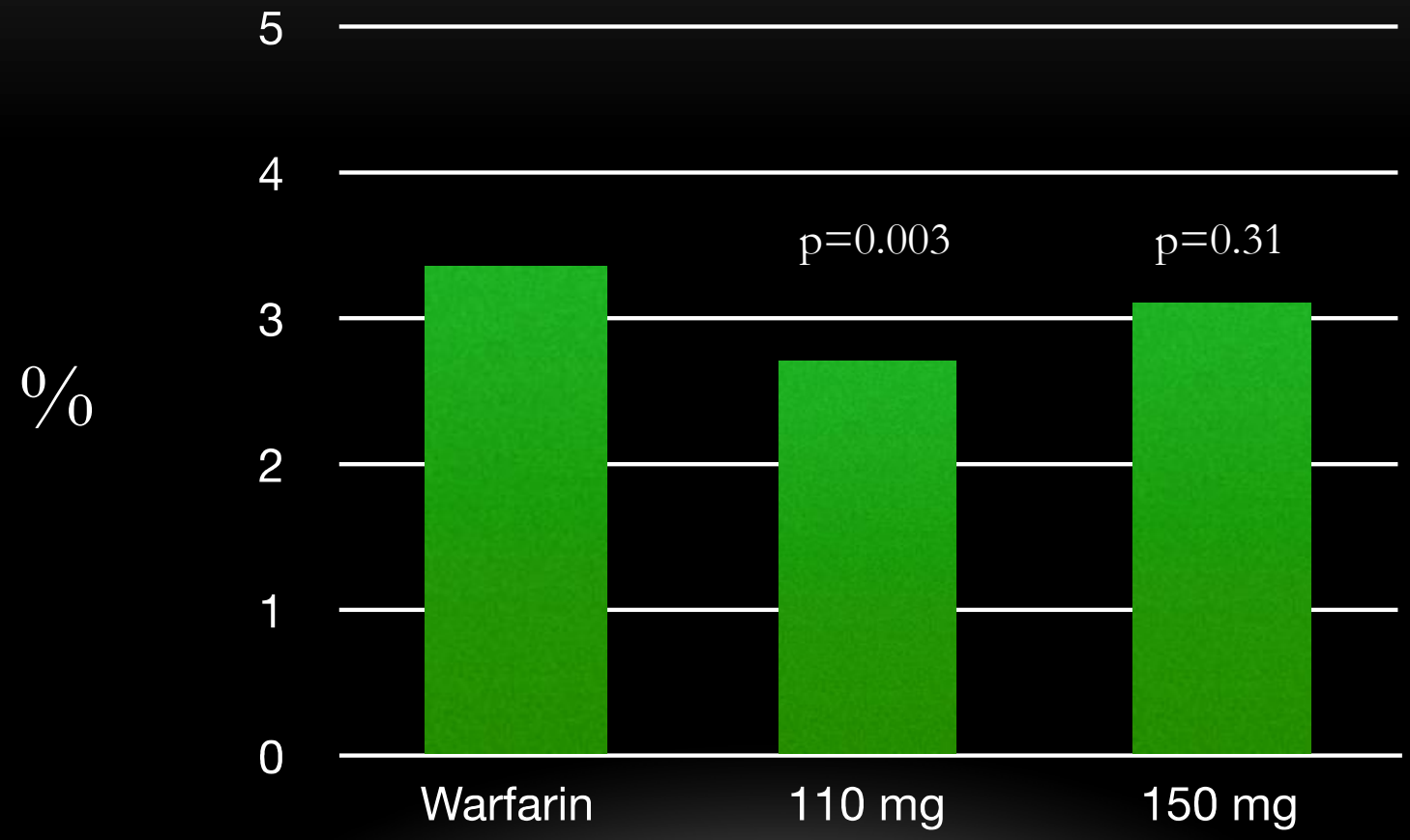
Connolly, et al. NEJM 2009;361:1139-51.

DEATH



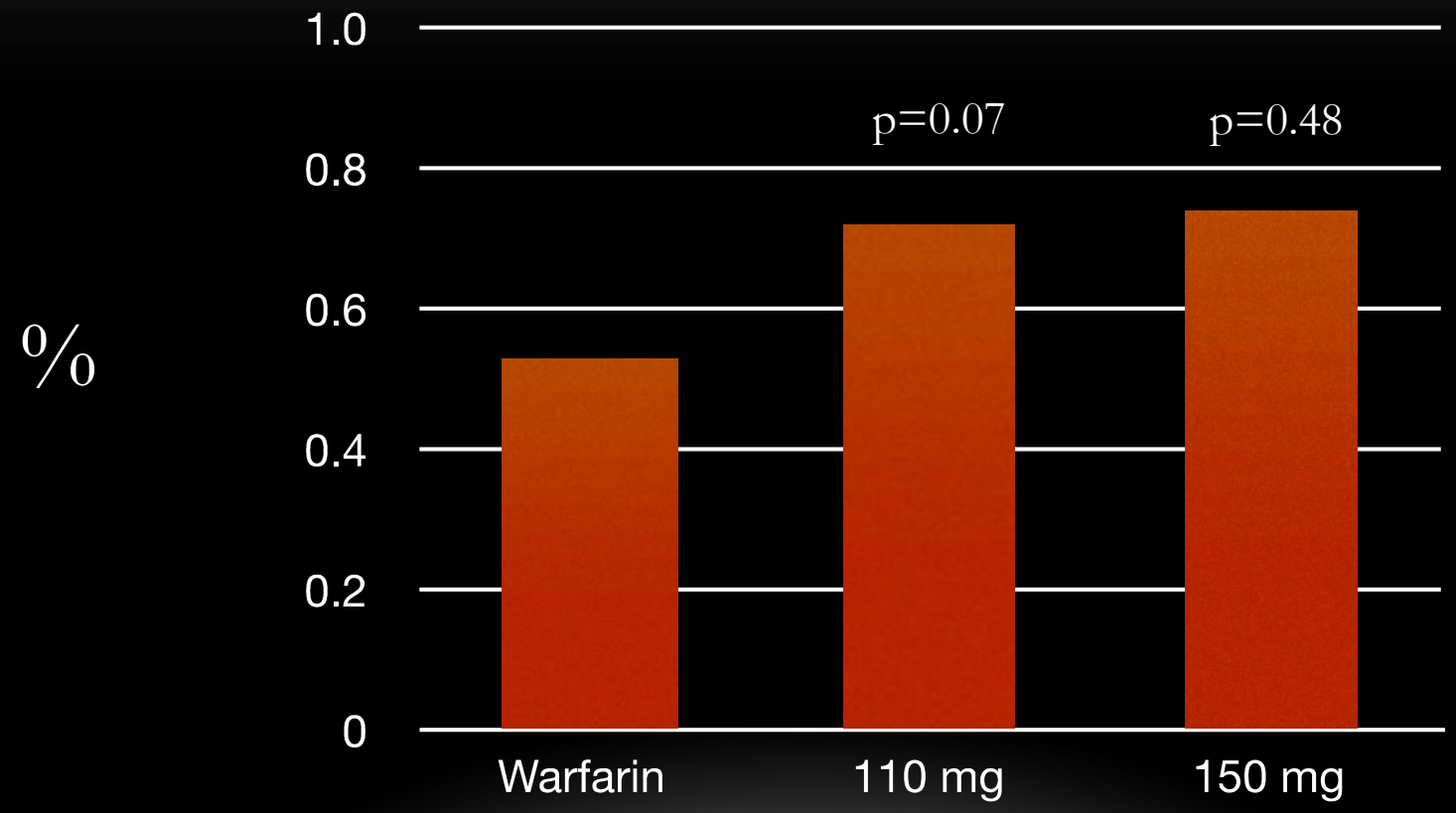
Connolly, et al. NEJM 2009;361:1139-51.

MAJOR BLEEDING



Connolly, et al. NEJM 2009;361:1139-51.

MYOCARDIAL INFARCTION



Connolly, et al. NEJM 2009;361:1139-51.

Bleeding Risk with Dabigatran in the Frail Elderly

TO THE EDITOR: Since July 1, 2011, the thrombin inhibitor dabigatran has been available in New Zealand for stroke prevention in patients with atrial fibrillation. There are no restrictions on prescribing, and access is free to patients through government funding. Approximately 7000 patients started treatment in the first 2 months.

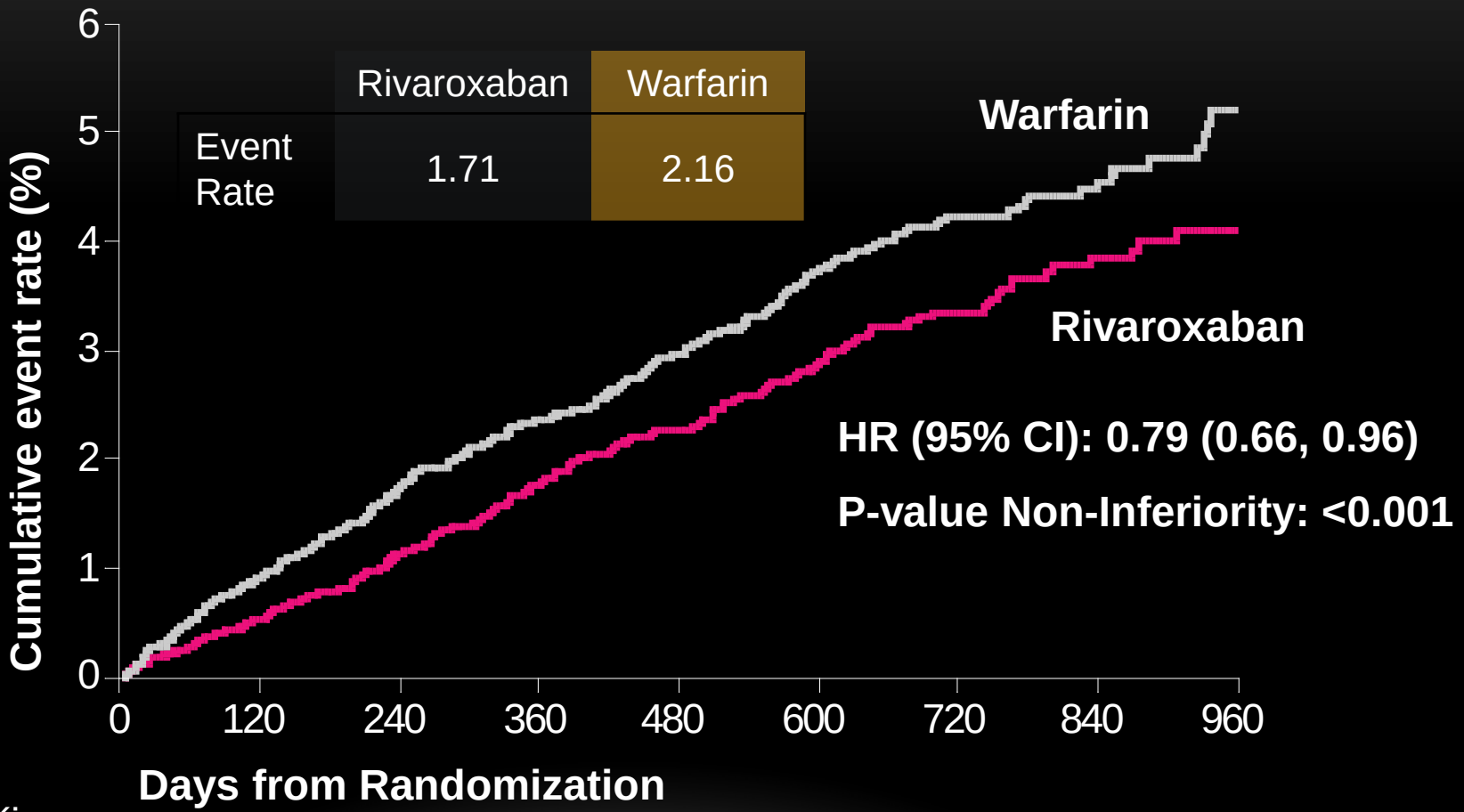
Concerns from hematologists led to an audit of bleeding events that was initiated in collaboration with the Haematology Society of Australia

- Report from New Zealand of 7000 patients
- First 2 months of use
- 78 episodes of bleeding
- 12 episodes of major bleeding
- Conclusion: Bleeding is confounded by low body weight and poor renal function which occurs more commonly in the elderly
- 2/3 of their patients were >80 yo, 58% had moderate or severe renal impairment, 50% weighed <60kg
- RE-LY: mean age 71, mean weight 83kg, mean CrCl 68

RIVAROXABAN

- Factor Xa inhibitor
- Rocket AF
  - Moderate to high risk of stroke ($CHADS_2$ score of 2 or more)
  - Primary endpoint of stroke or systemic embolism
  - 14, 264 patients

PRIMARY EFFICACY OUTCOME
STROKE AND NON-CNS EMBOLISM



No. at risk:

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

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

Table 3. Rates of Bleeding Events.*

Variable	Rivaroxaban (N=7111)		Warfarin (N=7125)		Hazard Ratio (95% CI)†	P Value‡
	Events no. (%)	Event Rate no./100 patient-yr	Events no. (%)	Event Rate no./100 patient-yr		
Principal safety end point: major and nonmajor clinically relevant bleeding§	1475 (20.7)	14.9	1449 (20.3)	14.5	1.03 (0.96–1.11)	0.44
Major bleeding						
Any	395 (5.6)	3.6	386 (5.4)	3.4	1.04 (0.90–1.20)	0.58
Decrease in hemoglobin ≥2 g/dl	305 (4.3)	2.8	254 (3.6)	2.3	1.22 (1.03–1.44)	0.02
Transfusion	183 (2.6)	1.6	149 (2.1)	1.3	1.25 (1.01–1.55)	0.04
Critical bleeding¶	91 (1.3)	0.8	133 (1.9)	1.2	0.69 (0.53–0.91)	0.007
Fatal bleeding	27 (0.4)	0.2	55 (0.8)	0.5	0.50 (0.31–0.79)	0.003
Intracranial hemorrhage	55 (0.8)	0.5	84 (1.2)	0.7	0.67 (0.47–0.93)	0.02
Nonmajor clinically relevant bleeding	1185 (16.7)	11.8	1151 (16.2)	11.4	1.04 (0.96–1.13)	0.35

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	Rivaroxaban		Warfarin		Rivaroxaban vs. Warfarin	
	Total	Event Rate (100 Pt-Yr)‡	Total	Event Rate (100 Pt-Yr)‡	Hazard Ratio (95% CI)§	P Value‖
Secondary efficacy endpoints, no. (%)¶						
Stroke, non-CNS embolism, and vascular death	346 (4.90)	3.11	410 (5.79)	3.63	0.86 (0.74,0.99)	0.034
Stroke, non-CNS embolism, vascular death, and myocardial infarction	433 (6.13)	3.91	519 (7.33)	4.62	0.85 (0.74,0.96)	0.010
Stroke	184 (2.61)	1.65	221 (3.12)	1.96	0.85 (0.70, 1.03)	0.092
Hemorrhagic	29 (0.41)	0.26	50 (0.71)	0.44	0.59 (0.37, 0.93)	0.024
Ischemic	149 (2.11)	1.34	161 (2.27)	1.42	0.94 (0.75, 1.17)	0.581
Unknown	7 (0.10)	0.06	11 (0.16)	0.10	0.65 (0.25, 1.67)	0.366
Stroke outcome#						
Death	47 (0.67)	0.42	67 (0.95)	0.59	0.71 (0.49, 1.03)	0.075
Disabling	43 (0.61)	0.39	57 (0.80)	0.50	0.77 (0.52, 1.14)	0.188
Nondisabling	88 (1.25)	0.79	87 (1.23)	0.77	1.03 (0.76, 1.38)	0.863
Unknown	7 (0.10)	0.06	12 (0.17)	0.11	0.59 (0.23, 1.50)	0.271
Non-CNS systemic embolism, no. (%)	5 (0.07)	0.04	22 (0.31)	0.19	0.23 (0.09, 0.61)	0.003
Myocardial infarction, no. (%)	101 (1.43)	0.91	126 (1.78)	1.12	0.81 (0.63, 1.06)	0.121
All-cause mortality, no. (%)**	208 (2.95)	1.87	250 (3.53)	2.21	0.85 (0.70, 1.02)	0.073
Vascular death	170 (2.41)	1.53	193 (2.73)	1.71	0.89 (0.73, 1.10)	0.289
Non-vascular death	21 (0.30)	0.19	34 (0.48)	0.30	0.63 (0.36, 1.08)	0.094
Unknown	17 (0.24)	0.15	23 (0.32)	0.20	0.75 (0.40, 1.41)	0.370

RE-LY VS. ROCKET AF

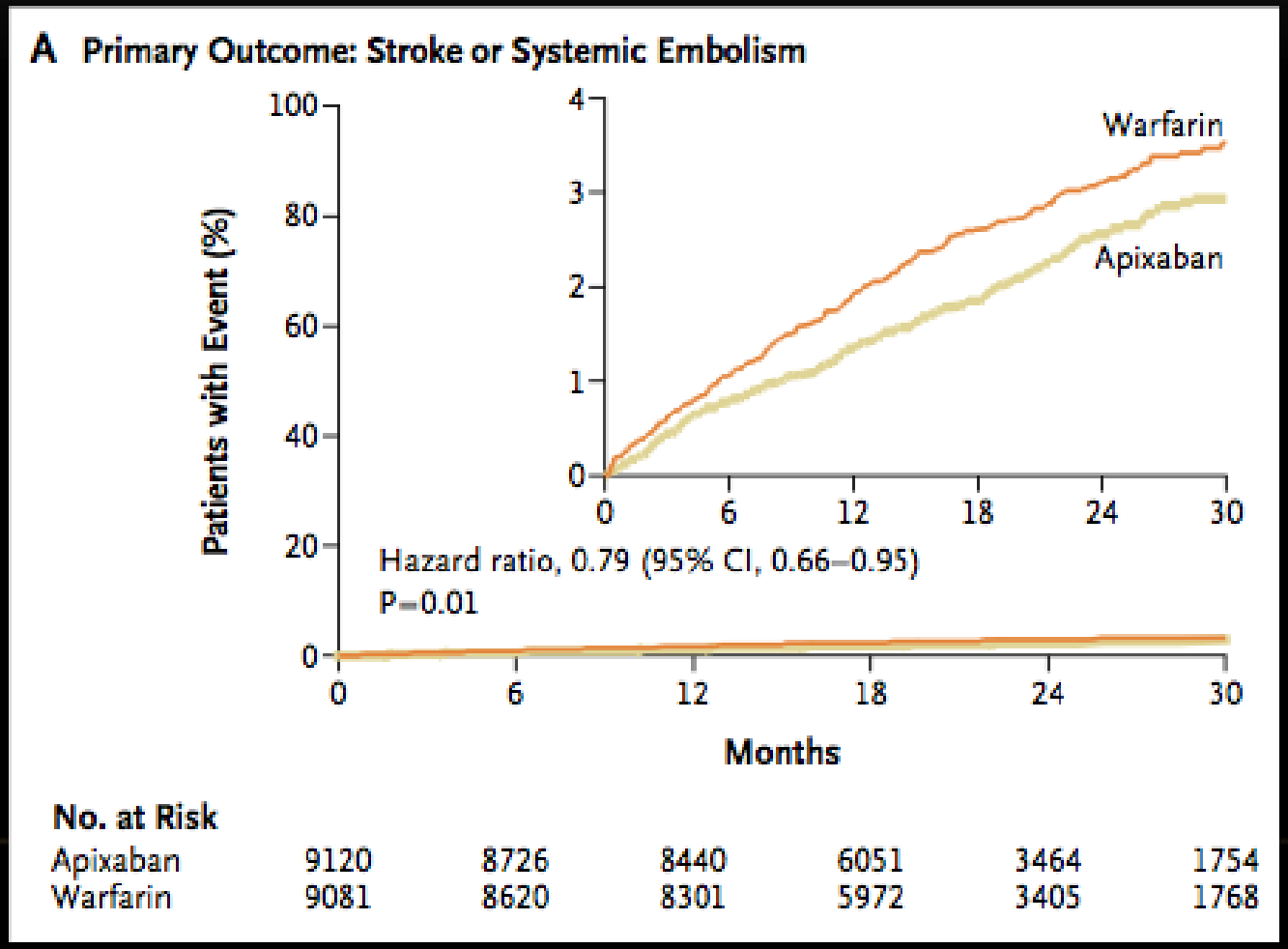
- Both noninferiority trials
- Rocket AF had 2 risk factors for stroke, RE-LY had 1 risk factor
- Higher rate of prior stroke in Rocket AF
- Rocket AF blinded, RE-LY was open-label for warfarin
- Dose adjustment for CrCl in Rocket AF, not in RE-LY

RE-LY VS. ROCKET AF

- 32.4% of patients in RE-:Y were CHADS 0-1, none in Rocket AF
- 32% of patients in RE-LY had CHADS ≥3, 85% in Rocket AF
- Prior CVA/TIA was 20% in RE-LY, 55% in Rocket AF

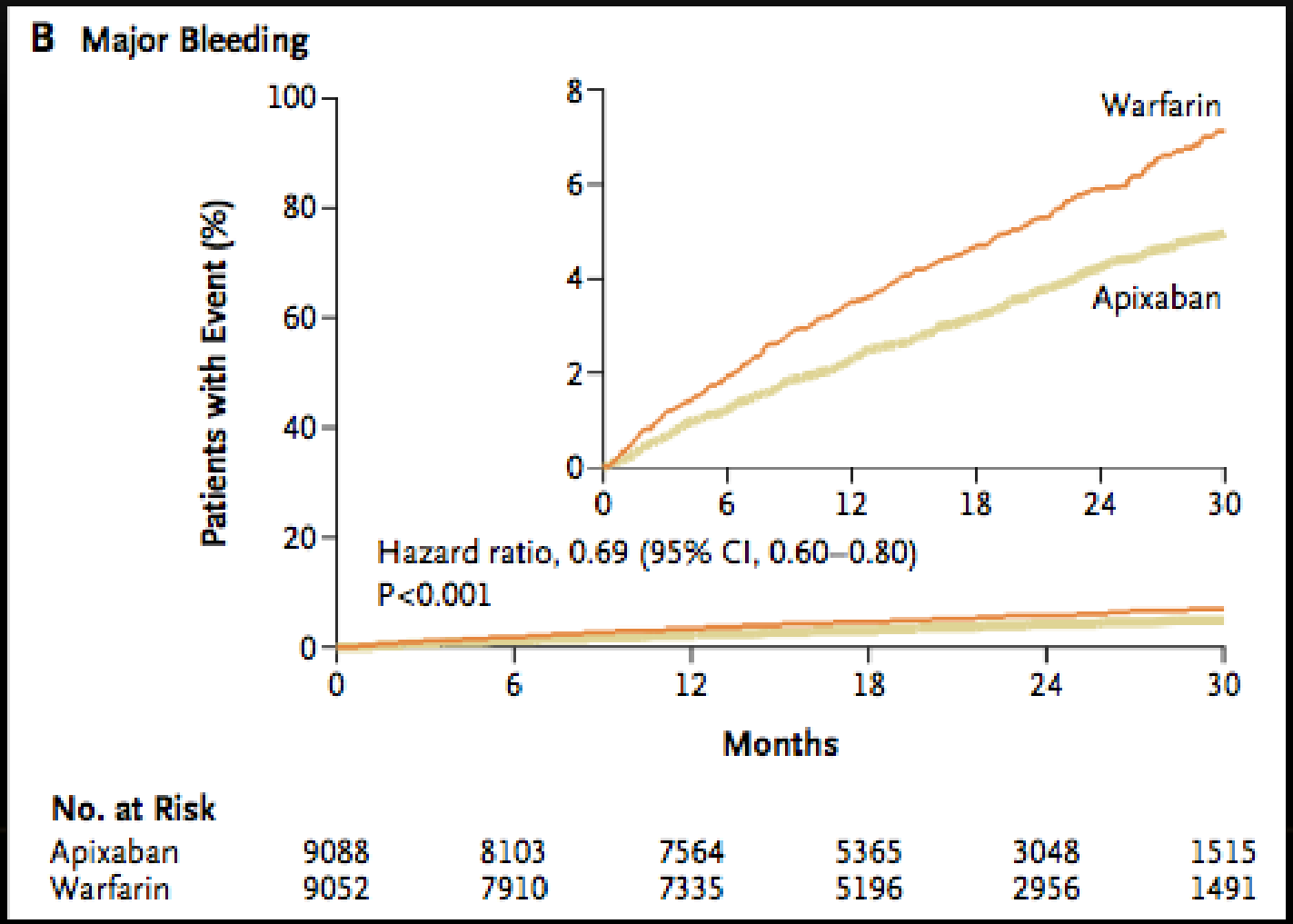
ARISTOTLE

GRANGER, ET AL. NEJM 2011;365:981-992.



ARISTOTLE

GRANGER, ET AL. NEJM 2011;365:981-992.



"REAL-WORLD" ANALYSIS OF NEW ANTITHROMBICS

- Dabigatran, apixaban and rivaroxaban
- CHA_2DS_2-VASc score ≥ 2
- Calculated the "net clinical benefit" by balancing the risk of ischemic stroke vs. intracranial hemorrhage
- Extrapolated data from the current trials and applied them to the Danish National Patient Registry

Banerjee A, et al. Thromb Haemost 2012; 107:584-589

- In patients with $CHADS_2$=0 but at high bleeding risk, apixaban and dabigatran 110 mg bid had a positive net clinical benefit.
- At CHA_2DS_2-VASc =1, apixaban and both doses of dabigatran (110 mg and 150 mg bid) had a positive net clinical benefit.
- In patients with $CHADS_2$ score≥1 or CHA_2DS_2-VASc ≥2, the three new OACs (dabigatran, rivaroxaban and apixaban) appear superior to warfarin for net clinical benefit, regardless of risk of bleeding. When risk of bleeding and stroke are both high, all three new drugs appear to have a greater net clinical benefit than warfarin.

Banerjee A, et al. Thromb Haemost 2012; 107:584-589

NEW HOPE FOR FACTOR XA REVERSAL

FUKUDA, ET AL. THROMB HAEMOST 2012;107:253-9.

- Prothrombin complex concentrate may be an antidote for rivaroxaban but not dabigatran
- PCC contains factors II, VII, IX and X and enhances thrombin generation
- 12 healthy male volunteers received either 20mg rivaroxaban or 150 mg of dabigatran twice a day, then received 50 IU/kg of PCC or placebo, crossed over and repeated the procedure with the other anticoagulant

NEW HOPE FOR FACTOR XA REVERSAL

FUKUDA, ET AL. THROMB HAEMOST 2012;107:253-9.

- Rivaroxaban prolonged the PT from 12.3 sec to 15.8 sec ($p<0.001$)
- Immediately and completely reversed by PCC to an average of 12.8 sec ($p<0.001$)
- Dabigatran increased PTT but PCC did not restore coagulability

NEW HOPE FOR FACTOR XA REVERSAL

FUKUDA, ET AL. THROMB HAEMOST 2012;107:253-9.

- Currently, PCC is all that we have available for reversal.
- PCC will work with rivaroxaban and presumably abixaban.
- PCC is not strong enough to reverse the effect of dabigatran
- Despite this, PCC has been effective in animal studies

CONCLUSIONS

- This is an exciting time in the management of atrial fibrillation.
- For the first time in our careers we are talking about alternatives to warfarin.
- Our patients require us to know the new data and offer them all alternatives.
- We need to reassess our patients regularly.

Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial

Jonathan Mant, FD Richard Hobbs, Kate Fletcher, Andrea Roalfe, David Fitzmaurice, Gregory YH Lip, Ellen Murray, on behalf of the BAFTA investigators and the Midland Research Practices Network (MidReC)**

Summary

Background Anticoagulants are more effective than antiplatelet agents at reducing stroke risk in patients with atrial fibrillation, but whether this benefit outweighs the increased risk of bleeding in elderly patients is unknown. We assessed whether warfarin reduced risk of major stroke, arterial embolism, or other intracranial haemorrhage compared with aspirin in elderly patients.

Methods 973 patients aged 75 years or over (mean age 81·5 years, SD 4·2) with atrial fibrillation were recruited from primary care and randomly assigned to warfarin (target international normalised ratio 2–3) or aspirin (75 mg per day). Follow-up was for a mean of 2·7 years (SD 1·2). The primary endpoint was fatal or disabling stroke (ischaemic or haemorrhagic), intracranial haemorrhage, or clinically significant arterial embolism. Analysis was by intention to treat. This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN89345269.

Findings There were 24 primary events (21 strokes, two other intracranial haemorrhages, and one systemic embolus) in people assigned to warfarin and 48 primary events (44 strokes, one other intracranial haemorrhage, and three systemic emboli) in people assigned to aspirin (yearly risk 1·8% *vs* 3·8%, relative risk 0·48, 95% CI 0·28–0·80, p=0·003; absolute yearly risk reduction 2%, 95% CI 0·7–3·2). Yearly risk of extracranial haemorrhage was 1·4% (warfarin) versus 1·6% (aspirin) (relative risk 0·87, 0·43–1·73; absolute risk reduction 0·2%, –0·7 to 1·2).

Interpretation These data support the use of anticoagulation therapy for people aged over 75 who have atrial fibrillation, unless there are contraindications or the patient decides that the benefits are not worth the inconvenience.

Lancet 2007; 370: 493–503

See Comment page 460

*Collaborators listed in full at end of report

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RISK OF WARFARIN IN ELDERLY OVERESTIMATED

	Warfarin (n=488)		Aspirin (n=485)		Warfarin vs aspirin	
	n	Risk per year	n	Risk per year	RR (95% CI)	p
Stroke	21	1·6%	44	3·4%	0·46 (0·26–0·79)	0·003
By severity						
Fatal	13	1·0%	21	1·6%	0·59 (0·27–1·24)	0·14
Disabling non-fatal	8	0·6%	23	1·8%	0·33 (0·13–0·77)	0·005
Type of stroke*						
Ischaemic	10	0·8%	32	2·5%	0·30 (0·13–0·63)	0·0004
Haemorrhagic	6	0·5%	5	0·4%	1·15 (0·29–4·77)	0·83
Unknown	5	0·4%	7	0·5%	0·69 (0·17–2·51)	0·53
Other intracranial haemorrhage†	2	0·2%	1	0·1%	1·92 (0·10–113·3)	0·65
Systemic embolism‡	1	0·1%	3	0·2%	0·32 (0·01–3·99)	0·36
Total number of events	24	1·8%	48	3·8%	0·48 (0·28–0·80)	0·0027

RR=relative risk. *Type of stroke was determined by the endpoint committee on the basis of brain imaging or post-mortem findings. If neither of these was available, the stroke was classified as unknown. †The three other intracranial haemorrhages were subdural; two of these were fatal (one in each treatment group). ‡Two of the systemic emboli were fatal (one in each treatment group).

Table 3: Nature of primary events

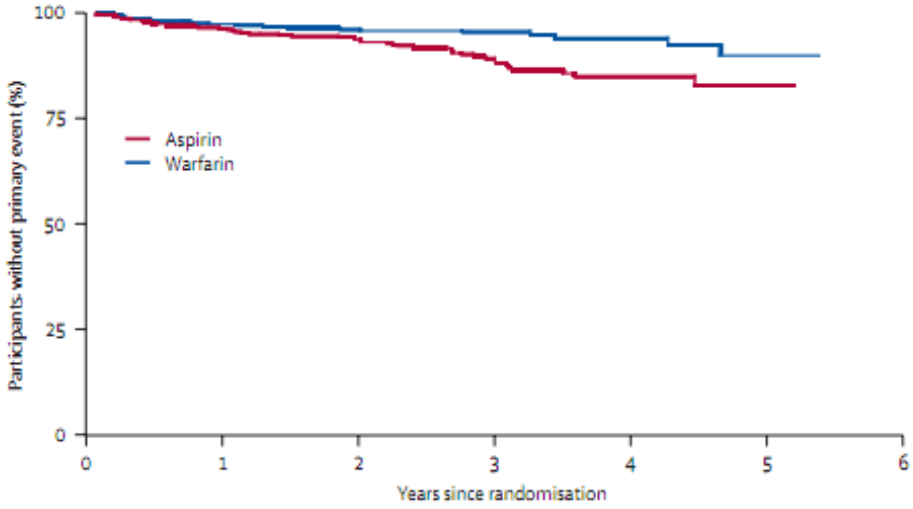


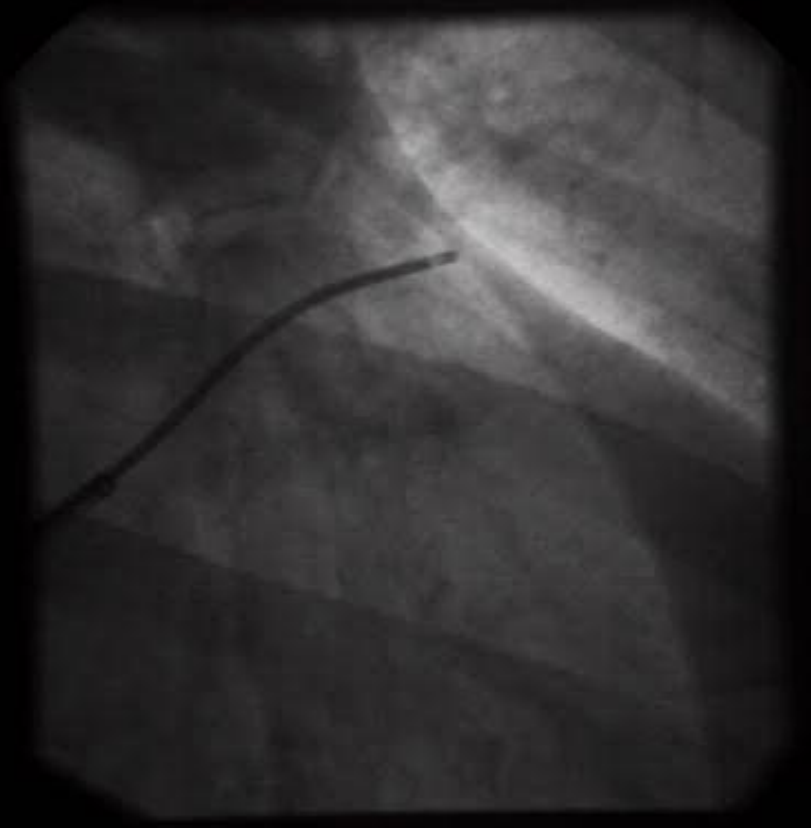
Figure 3: Kaplan-Meier plot of time to primary event

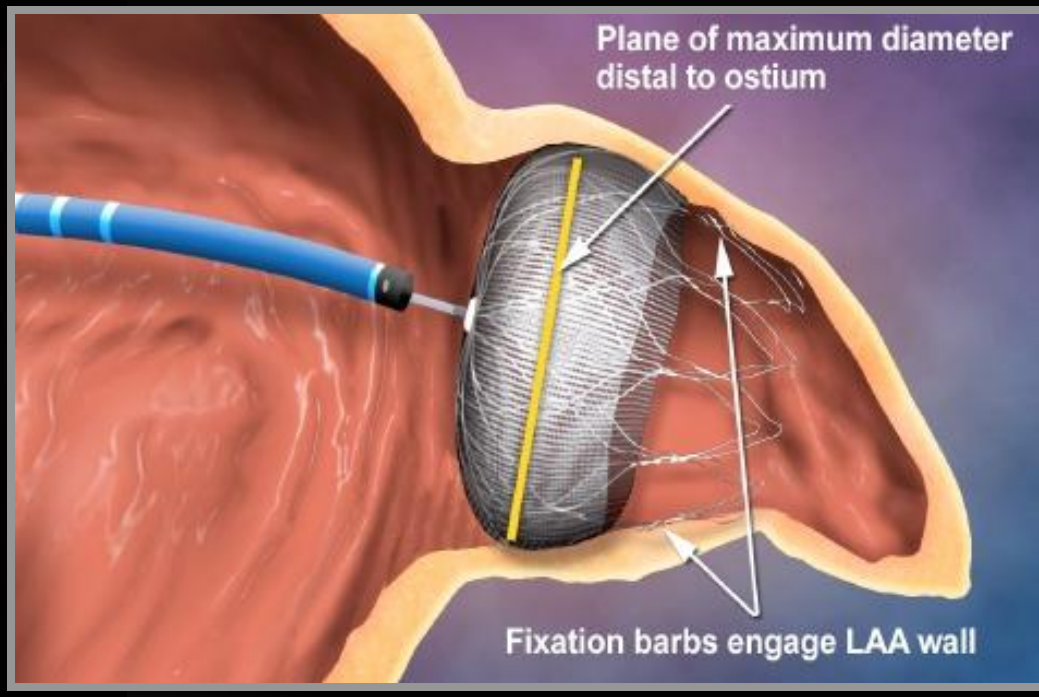
BETTER WAY TO ASSESS RISK OF BLEEDING: HAS-BLED SCORE

- Hypertension
- Abnormal renal or liver function (1 point each)
- Prior stroke
- Bleeding
- Labile INRs
- Elderly (>65 yrs)
- Drugs (anti-platelet) or excessive alcohol (1 point each)

Score	Bleeds/100 pt yrs
0	1.13
1	1.02
2	1.88
3	3.74
4	8.70

LA OCCLUSION DEVICE



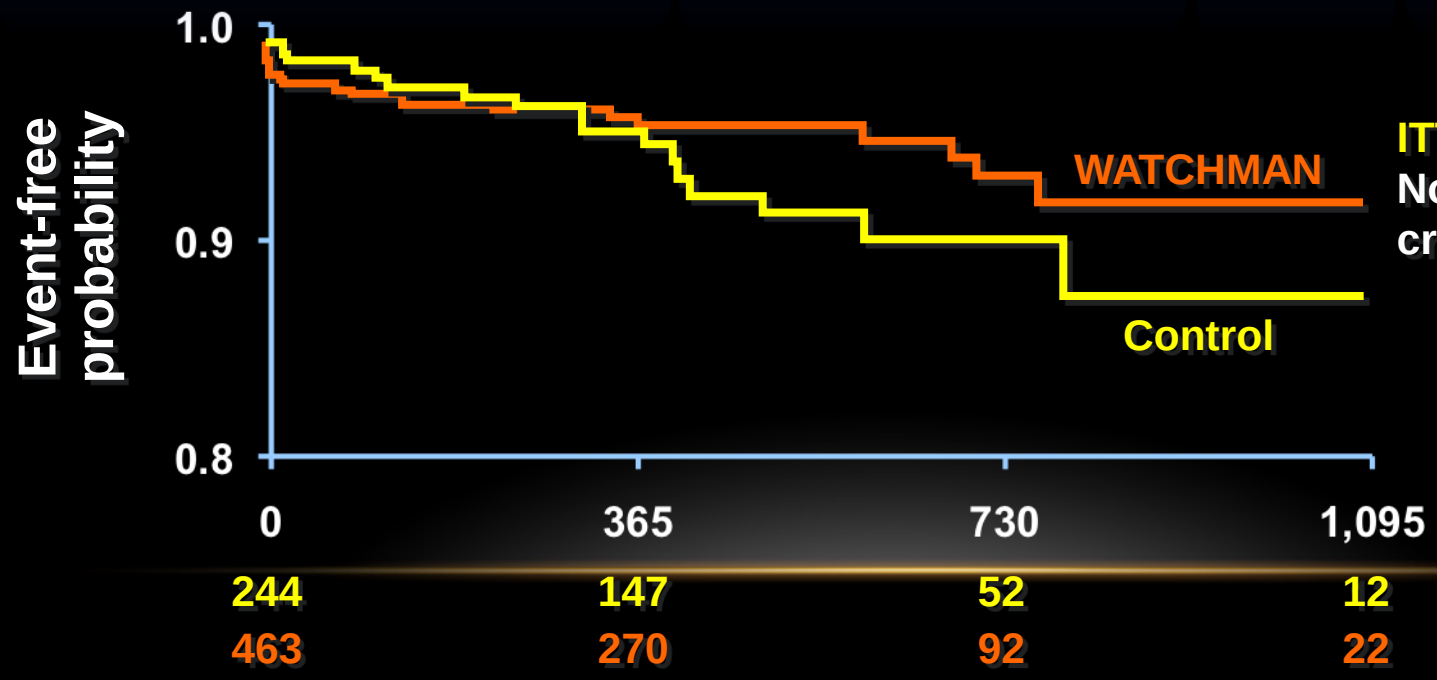


Sick et al J Am Coll Cardiol, 2007; 49:1490-1495

PROTECT AF - PRIMARY EFFICACY RESULTS

Randomization allocation (2 device : 1 control)

Cohort	Device Events (no.)	Device Total pt-yr	Device Rate (95% CI)	Control Events (no.)	Control Total pt-yr	Control Rate (95% CI)	Rel. Risk (95% CI)	Posterior Probabilities Non-inferiority	Posterior Probabilities Superiority
900 pt-yr	20	582.3	3.4 (2.1, 5.2)	16	318.0	5.0 (2.8, 7.6)	0.68 (0.37, 1.41)	0.998	0.837



ITT Cohort:
Non-inferiority criteria met

Protect AF Trial Holmes ACC 2009

LARIAT