

Novel Therapies for Atrial Fibrillation

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Disclosures

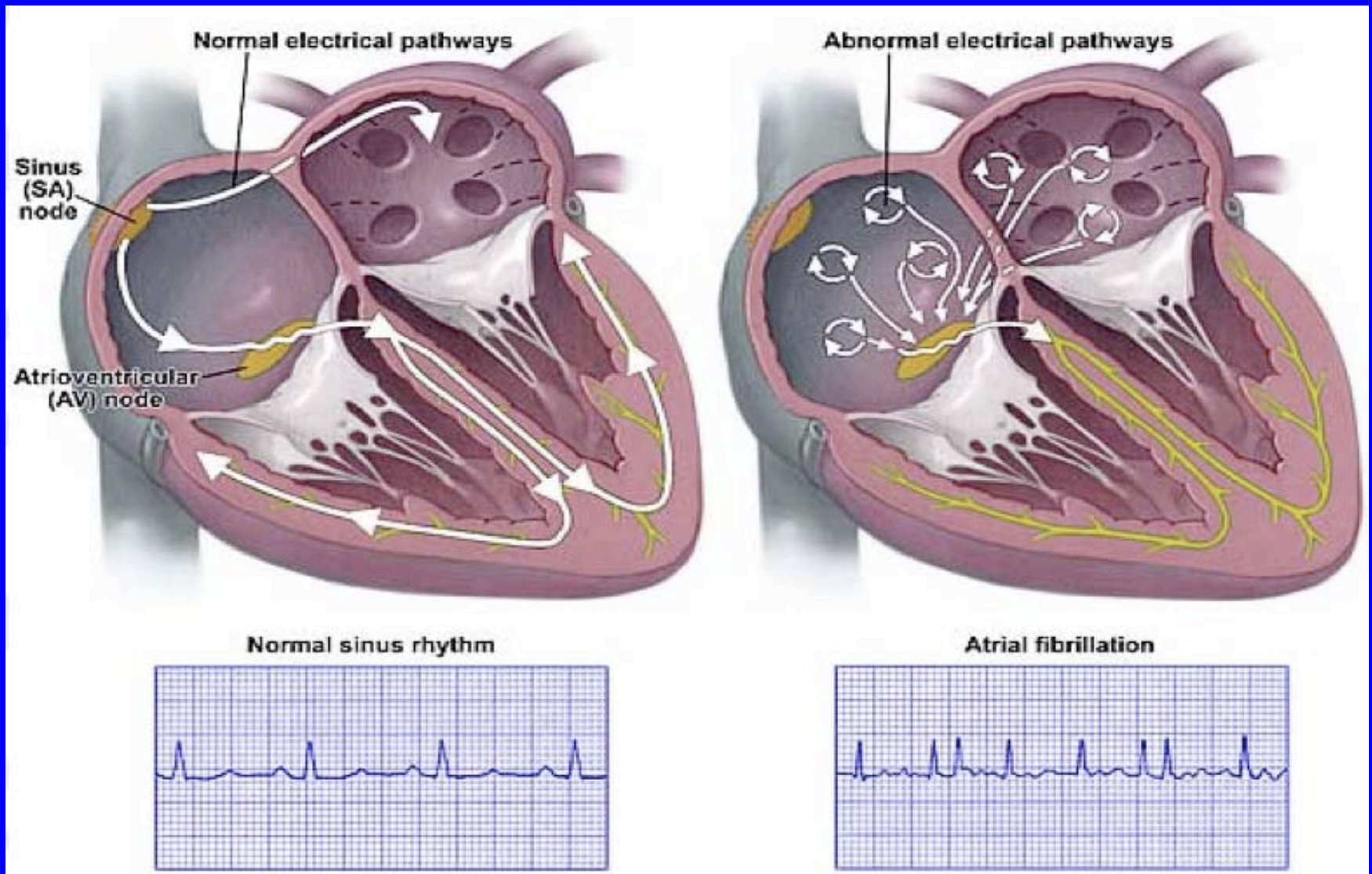
St Jude Medical

Boehringer Ingelheim

Medtronic

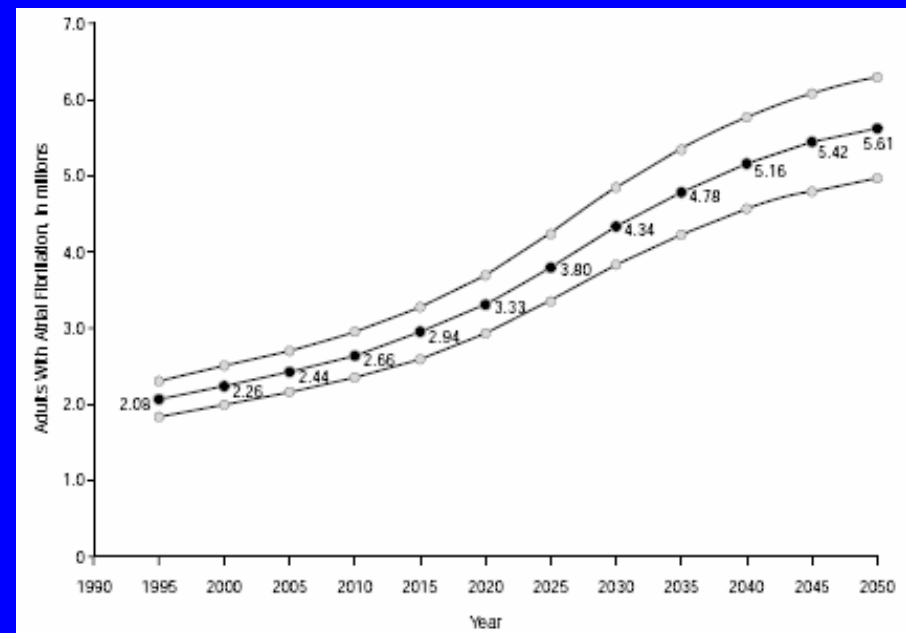
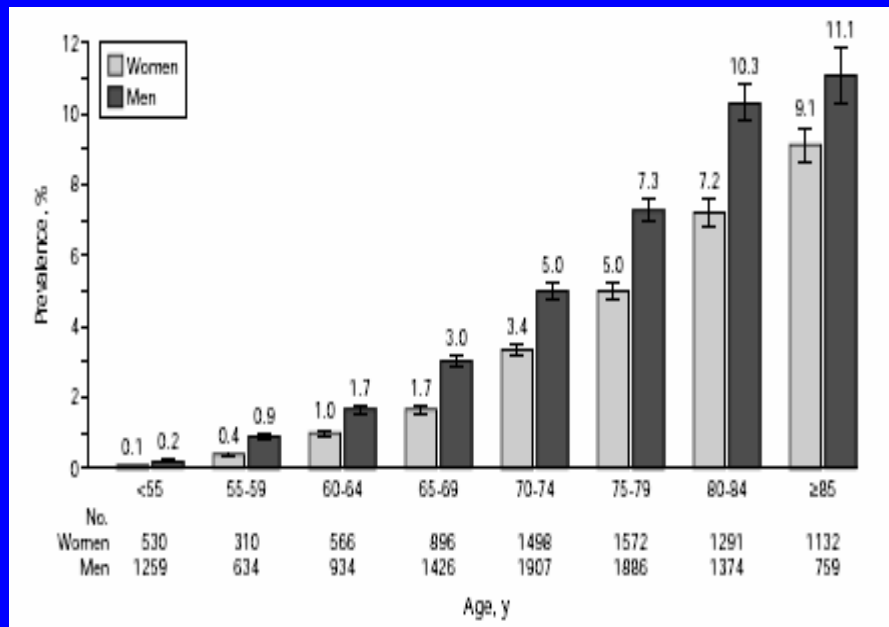
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Normal and Abnormal Cardiac Conduction



Atrial Fibrillation

- Anarchical and disorganized activation and contraction of the atrium
- Prevalence is progressively Increasing



Stroke in Atrial Fibrillation

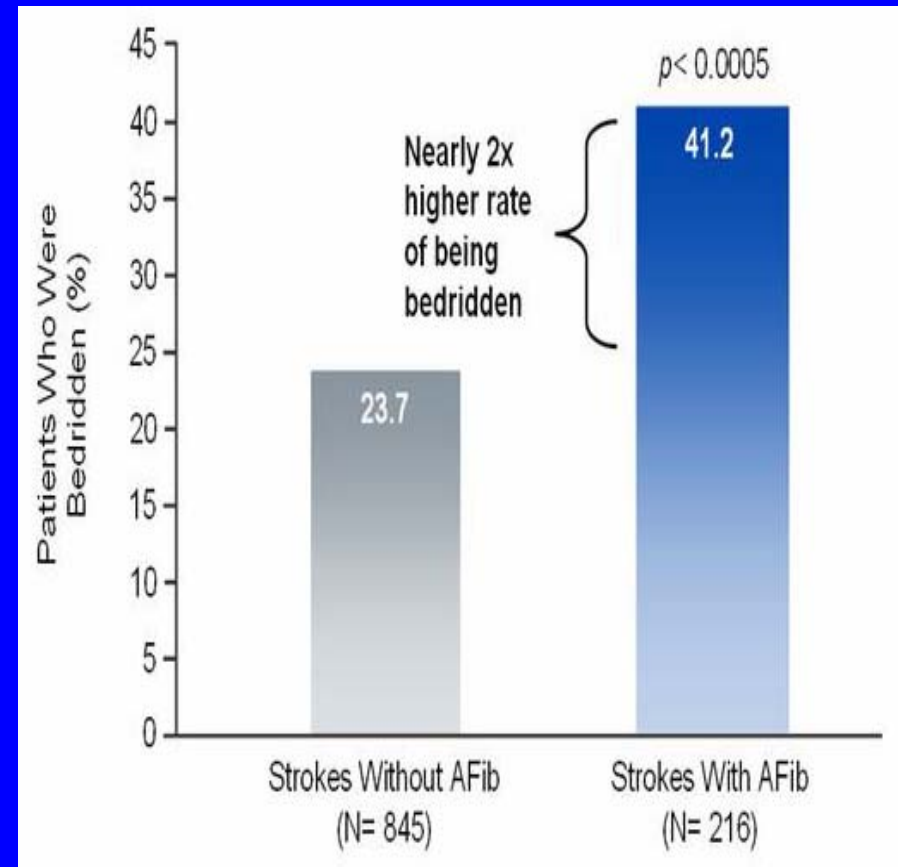
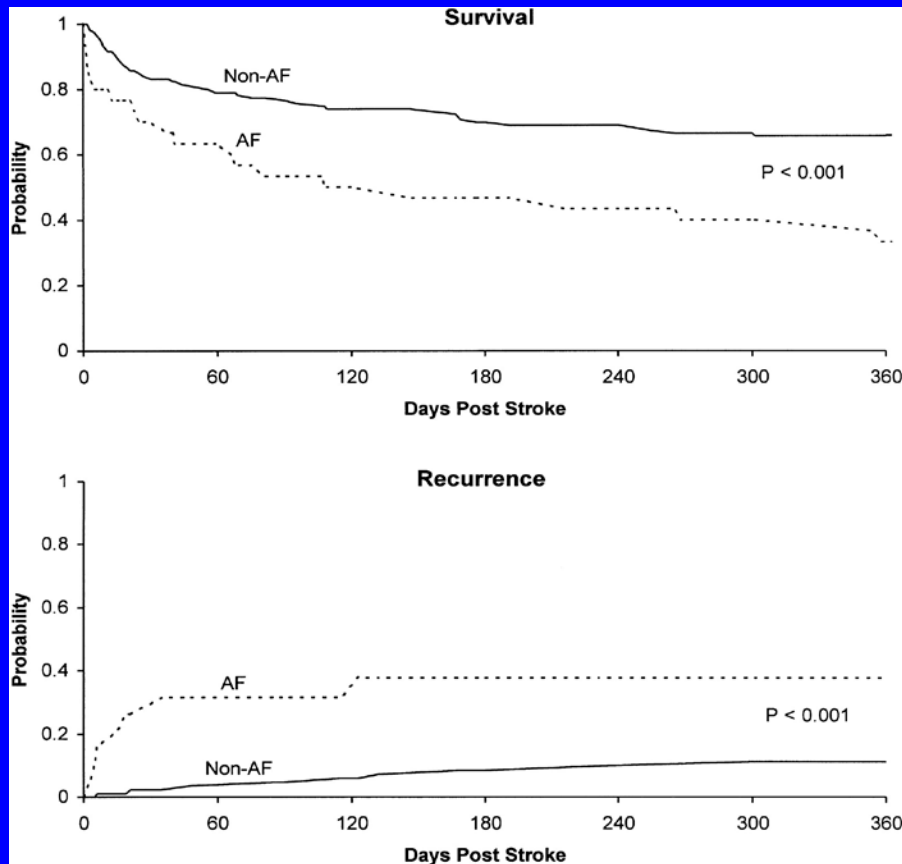
- 25-30% of ischemic strokes are due to a cardioembolic etiology
- 15-20% of all ischemic strokes are attributable to atrial fibrillation
- Patients with atrial fibrillation have a 4-5 fold increase in ischemic stroke
- Those with valvular heart disease have a much higher incidence (up to 15 fold)

Arboix et al. Curr Card Rev, 2010,6,150-161

Anersen et al. Stroke 2007, 38:259-263

Wolf PA et al, Stroke. 1991, 22:983-988

Strokes in Atrial Fibrillation are Associated with Increased Mortality and Morbidity



Anticoagulation with Coumadin Prevents Stroke in the Context of Atrial Fibrillation

Adjusted-Dose Warfarin Compared With Placebo or No Treatment

Study	Participants (N)	Target INR	Relative Risk Reduction (%)
AFASAK	671	2.8-4.2	54
SPAF I	421	2.0-4.5	60 [†]
BAATAF	420	1.5-2.7	78 [†]
CAFA	378	2.0-3.0	33
SPINAF	571	1.4-2.8	70 [†]
EAFT [‡]	439	2.5-4.0	68 [†]
6 Trials [§]	2900	—	64 (95% CI: 49 to 74)

Anticoagulation with Warfarin in AF Reduces Morbidity and Mortality

- Treatment with coumadin reduces stroke risk in atrial fibrillation to control levels
- All cause mortality is reduced by 26%
- Post stroke mortality was 18.9% vs 45.2% seen in patients with coumadin
- SSS score 42+/-15 vs 33.6+/-18.
P<0.0001

Warfarin Under Use

Warfarin Underuse in AF

Year	Survey	Population	% Warfarin
1999	ATRIA ¹	N = 11,082 USA HMO	60% (high-risk)
2005	NABOR ²	N = 945 US teaching/community/VA hospital	55% (high-risk)
2006	EuroHeart Survey ³	N = 2706; outpatients 35 European countries	64%
2006	Hylek ⁴	N = 402; age ≥ 65 USA, teaching hospital	51%
2006	Birman-Deych ⁵	N = 16,007 USA Medicare	49% (at discharge)

Go et al. Ann Intern Med 1999;131:927-934

Waldo et al. JACC 2005;46:1729-1736

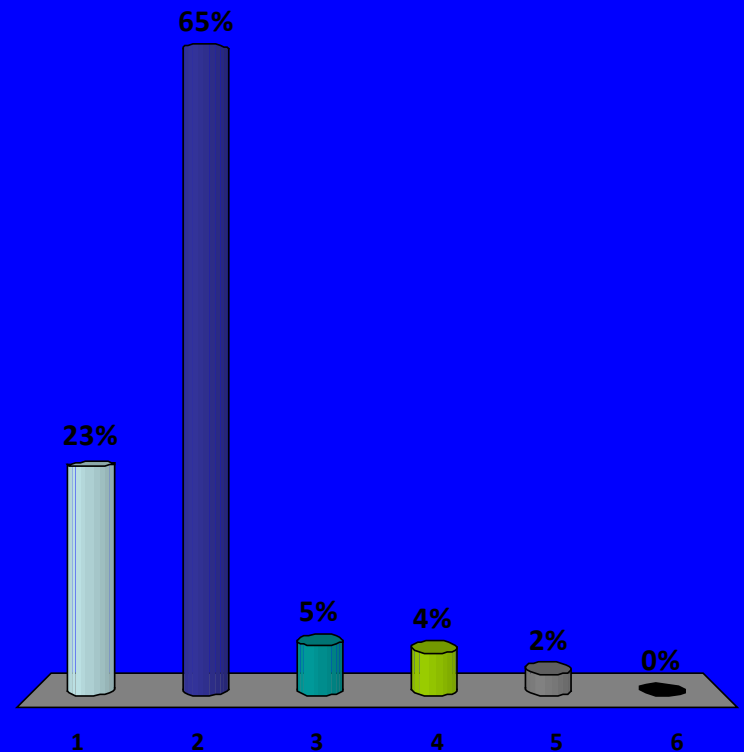
Nieuwlaat et al. Eur Heart 2006;27:3018-3026

Hylek et al. Stroke 2006;37:1075-1080

Birman-Deych et al. Stroke 2006;37:1070-1074

What is the Most Common Physician-Cited Reason for Not Prescribing Warfarin in Atrial Fibrillation in Patients?

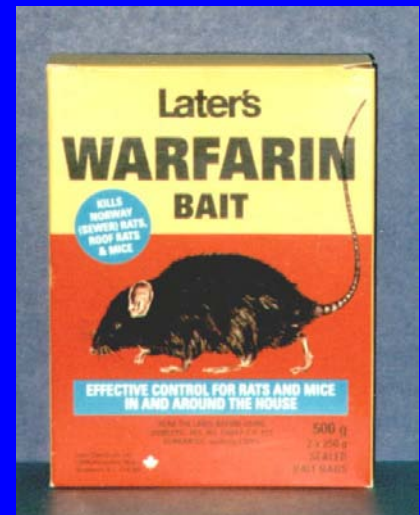
1. Hemorrhage
- ✓ 2. Falls
3. Patient Refusal
4. Cognitive Impairment
5. Advanced Illness
6. Alcohol Abuse



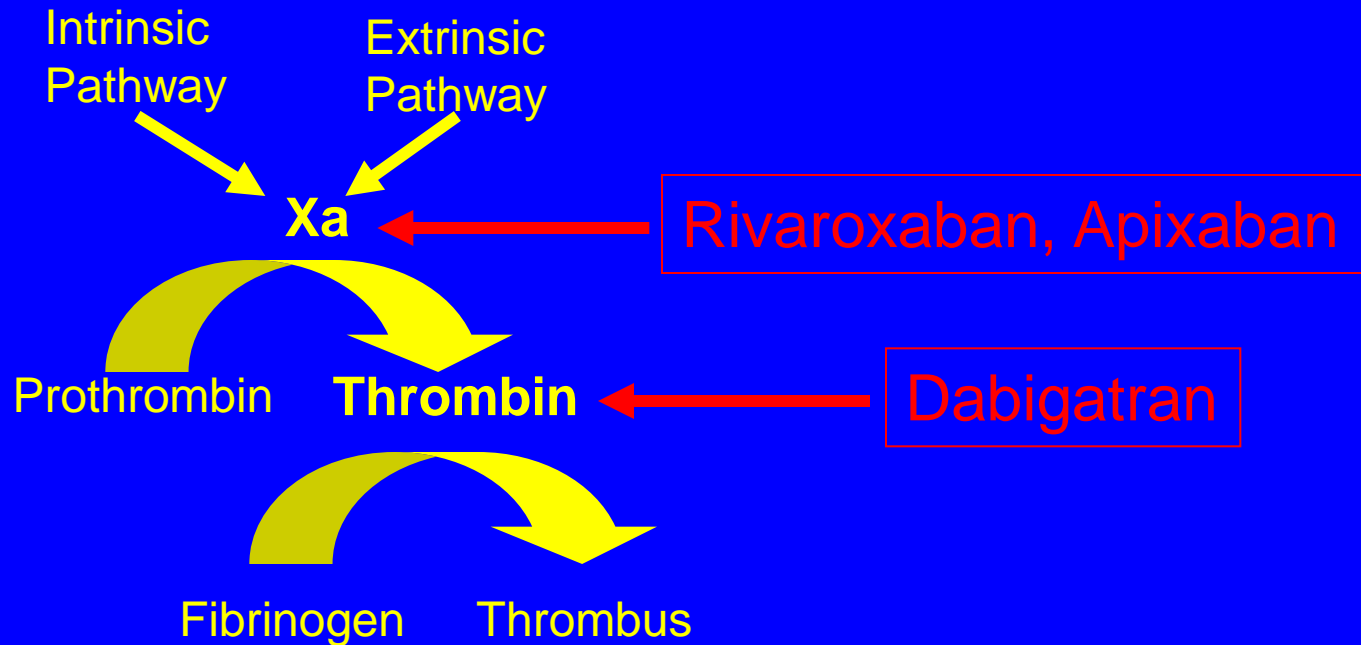
New Therapies

Prevent Clots from Forming
During Atrial Fibrillation

Novel Oral Anticoagulant
Therapies



Novel Oral Anticoagulants



Dabigatran (Pradaxa™)

- Direct thrombin inhibitor
- Specific and reversible binding to free and clot bound thrombin
- Converted to active form by liver esterases
- Peak effect 1.5 hours after ingestion
- Half life 12-17 hours
- Metabolized by the Kidney (80%)
- Dose 150 mg bid
- If CrCl <30 ml/min 75 mg bid

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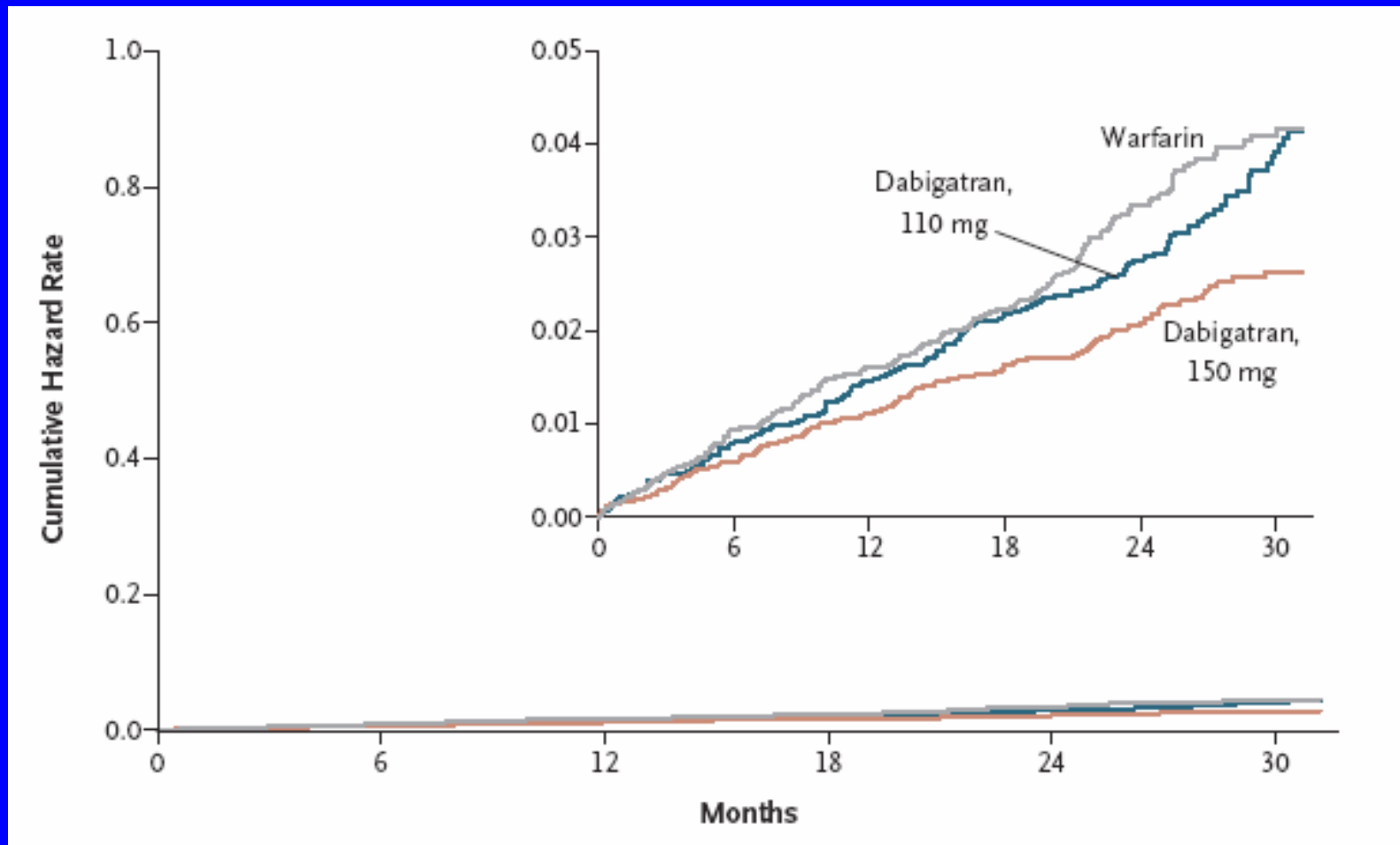
Dabigatran versus Warfarin in Patients with Atrial Fibrillation

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

Study Design

- 18,113 patients randomized to coumadin
- (InR 2-3), Dabigatran 110 mg BID or 150 mg BID
- Median follow up 2 years
- Primary outcome – stroke or systemic embolism
- Primary safety outcome – major bleeding

Dabigatran (Pradaxa™)



Dabigatran (Pradaxa™)

Event	Dabigatran, 110 mg (N=6015)		Dabigatran, 150 mg (N=6076)		Warfarin (N=6022)		Dabigatran, 110 mg, vs. Warfarin		Dabigatran, 150 mg, vs. Warfarin		Dabigatran, 150 mg vs. 110 mg	
	no. of patients	%/yr	no. of patients	%/yr	no. of patients	%/yr	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
Stroke or systemic embolism*	182	1.53	134	1.11	199	1.69	0.91 (0.74–1.11)	<0.001 for noninferiority, 0.34	0.66 (0.53–0.82)	<0.001 for noninferiority, <0.001	0.73 (0.58–0.91)	0.005
Stroke	171	1.44	122	1.01	185	1.57	0.92 (0.74–1.13)	0.41	0.64 (0.51–0.81)	<0.001	0.70 (0.56–0.89)	0.003
Hemorrhagic	14	0.12	12	0.10	45	0.38	0.31 (0.17–0.56)	<0.001	0.26 (0.14–0.49)	<0.001	0.85 (0.39–1.83)	0.67
Ischemic or unspecified	159	1.34	111	0.92	142	1.20	1.11 (0.89–1.40)	0.35	0.76 (0.60–0.98)	0.03	0.69 (0.54–0.88)	0.002
Nondisabling stroke	60	0.50	44	0.37	69	0.58	0.86 (0.61–1.22)	0.40	0.62 (0.43–0.91)	0.01	0.72 (0.49–1.07)	0.10
Disabling or fatal stroke	112	0.94	80	0.66	118	1.00	0.94 (0.73–1.22)	0.65	0.66 (0.50–0.88)	0.005	0.70 (0.53–0.94)	0.02
Myocardial infarction	86	0.72	89	0.74	63	0.53	1.35 (0.98–1.87)	0.07	1.38 (1.00–1.91)	0.048	1.02 (0.76–1.38)	0.88
Pulmonary embolism	14	0.12	18	0.15	11	0.09	1.26 (0.57–2.78)	0.56	1.61 (0.76–3.42)	0.21	1.27 (0.63–2.56)	0.50
Hospitalization	2311	19.4	2430	20.2	2458	20.8	0.92 (0.87–0.97)	0.003	0.97 (0.92–1.03)	0.34	1.06 (1.00–1.12)	0.04
Death from vascular causes	289	2.43	274	2.28	317	2.69	0.90 (0.77–1.06)	0.21	0.85 (0.72–0.99)	0.04	0.94 (0.79–1.11)	0.44
Death from any cause	446	3.75	438	3.64	487	4.13	0.91 (0.80–1.03)	0.13	0.88 (0.77–1.00)	0.051	0.97 (0.85–1.11)	0.66

Rivaroxaban (Xarelto™)

- Direct Factor Xa Inhibitor
- Binds to both free Factor Xa and Factor Xa bound in prothrombinase complex
- Peak action 3 hours after ingestion
- Serum half life 8-12 hours
- 66% metabolized by the liver
- Dose 20 mg QD
- If CrCl 30-49 ml/min 15 mg QD

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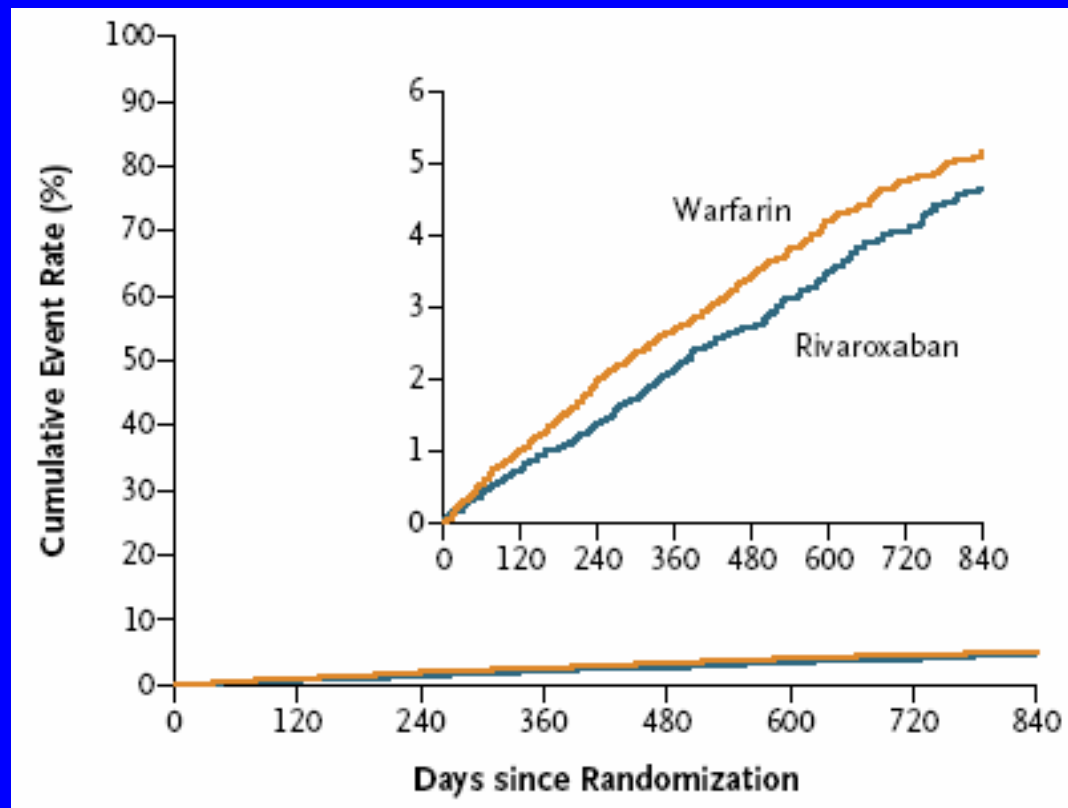
Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

Manesh R. Patel, M.D., Kenneth W. Mahaffey, M.D., Jyotsna Garg, M.S., Guohua Pan, Ph.D., Daniel E. Singer, M.D., Werner Hacke, M.D., Ph.D., Günter Breithardt, M.D., Jonathan L. Halperin, M.D., Graeme J. Hankey, M.D., Jonathan P. Piccini, M.D., Richard C. Becker, M.D., Christopher C. Nessel, M.D., John F. Paolini, M.D., Ph.D., Scott D. Berkowitz, M.D., Keith A.A. Fox, M.B., Ch.B., Robert M. Califf, M.D., and the ROCKET AF Steering Committee, for the ROCKET AF Investigators*

Study Design

- 14,264 patients with NVAf randomized to coumadin (InR 2-3) or Rivaroxaban 20 mg QD
- Median follow up 1.9 years
- Primary outcome – stroke or systemic embolism
- Primary safety outcome – major bleeding

Rivaroxaban (Xarelto™)



Rivaroxaban (Xarelto™)

Variable	Rivaroxaban (N=7111)		Warfarin (N=7125)		Hazard Ratio (95% CI) [†]	P Value [‡]
	Events	Event Rate	Events	Event Rate		
	no. (%)	no./100 patient-yr	no. (%)	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

Apixaban (Eliquis™)

- Direct factor Xa inhibitor
- Binds to both free Factor Xa and Factor Xa bound in prothrombinase complex
- Peak action 3-4 hours
- Half life 10-14 hours
- Metabolized by the liver (75%) and kidneys (25%)
- Dose 5 mg BID
- IF age > 80, < 60 kg, or Cr > 1.5 – 2.5 mg BID

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Apixaban versus Warfarin in Patients with Atrial Fibrillation

Christopher B. Granger, M.D., John H. Alexander, M.D., M.H.S., John J.V. McMurray, M.D., Renato D. Lopes, M.D., Ph.D., Elaine M. Hylek, M.D., M.P.H., Michael Hanna, M.D., Hussein R. Al-Khalidi, Ph.D., Jack Ansell, M.D., Dan Atar, M.D., Alvaro Avezum, M.D., Ph.D., M. Cecilia Bahit, M.D., Rafael Diaz, M.D., J. Donald Easton, M.D., Justin A. Ezekowitz, M.B., B.Ch., Greg Flaker, M.D., David Garcia, M.D., Margarida Gernaldes, Ph.D., Bernard J. Gersh, M.D., Sergey Golitsyn, M.D., Ph.D., Shinya Goto, M.D., Antonio G. Hermosillo, M.D., Stefan H. Hohnloser, M.D., John Horowitz, M.D., Puneet Mohan, M.D., Ph.D., Petr Jansky, M.D., Basil S. Lewis, M.D., Jose Luis Lopez-Sendon, M.D., Prem Pais, M.D., Alexander Parkhomenko, M.D., Freek W.A. Verheugt, M.D., Ph.D., Jun Zhu, M.D., and Lars Wallentin, M.D., Ph.D., for the ARISTOTLE Committees and Investigators*

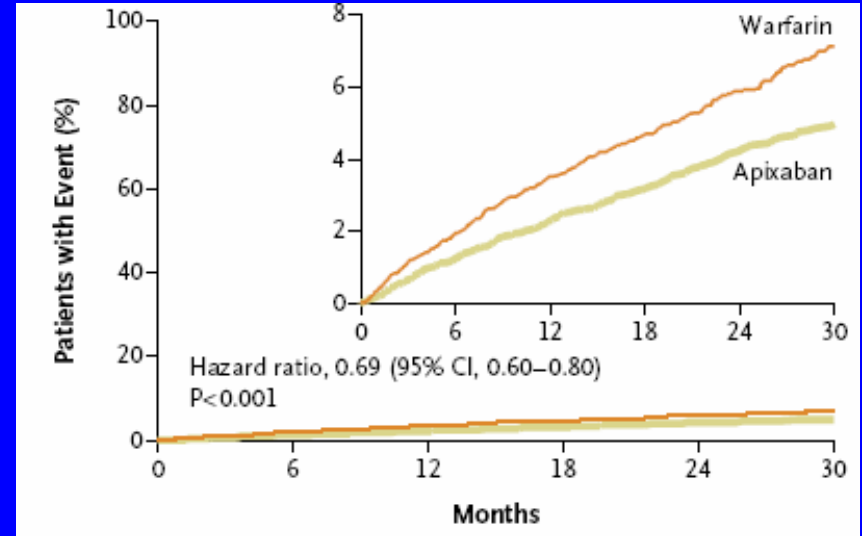
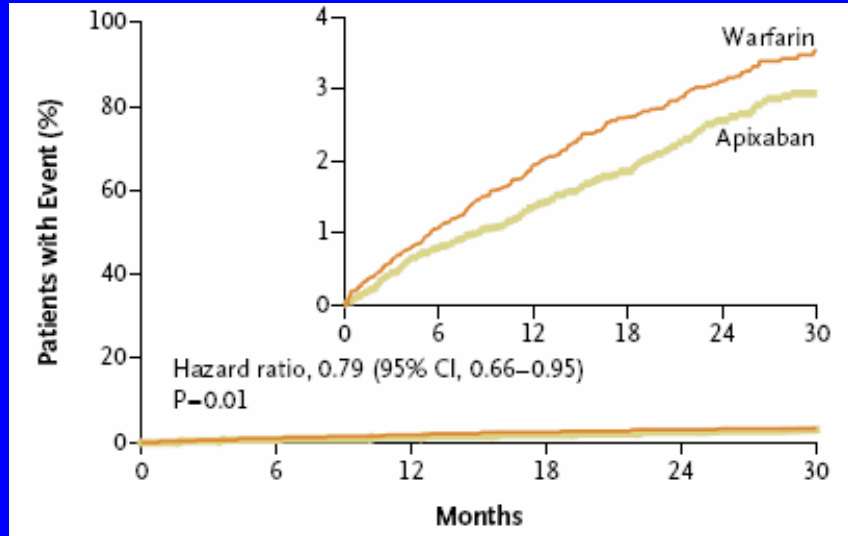
Study Design

- 18, 201 patients randomized to coumadin (InR 2-3) or Apixaban 5 mg BID
- Median follow up 1.8 years
- Primary outcome – stroke or systemic embolism
- Primary safety outcome – major bleeding

Apixaban (Eliquis™)

Primary Outcome: Stroke or Systemic Embolism

Major Bleeding



Apixaban (Eliquis™)

Outcome	Apixaban Group (N= 9120)		Warfarin Group (N= 9081)		Hazard Ratio (95% CI)	P Value
	Patients with Event	Event Rate	Patients with Event	Event Rate		
	<i>no.</i>	<i>%/yr</i>	<i>no.</i>	<i>%/yr</i>		
Primary outcome: stroke or systemic embolism	212	1.27	265	1.60	0.79 (0.66–0.95)	0.01
Stroke	199	1.19	250	1.51	0.79 (0.65–0.95)	0.01
Ischemic or uncertain type of stroke	162	0.97	175	1.05	0.92 (0.74–1.13)	0.42
Hemorrhagic stroke	40	0.24	78	0.47	0.51 (0.35–0.75)	<0.001
Systemic embolism	15	0.09	17	0.10	0.87 (0.44–1.75)	0.70
Key secondary efficacy outcome: death from any cause	603	3.52	669	3.94	0.89 (0.80–0.998)	0.047
Other secondary outcomes						
Stroke, systemic embolism, or death from any cause	752	4.49	837	5.04	0.89 (0.81–0.98)	0.02
Myocardial infarction	90	0.53	102	0.61	0.88 (0.66–1.17)	0.37
Stroke, systemic embolism, myocardial infarction, or death from any cause	810	4.85	906	5.49	0.88 (0.80–0.97)	0.01
Pulmonary embolism or deep-vein thrombosis	7	0.04	9	0.05	0.78 (0.29–2.10)	0.63

Salient Points

DABIGATRAN

Superior to Coumadin – primary outcome
Superior to Coumadin in preventing ischemic stroke
Increased GI bleeding

RIVAROXABAN

Once a day dosing
Control arm/Coumadin TTR – 55% but still not superior

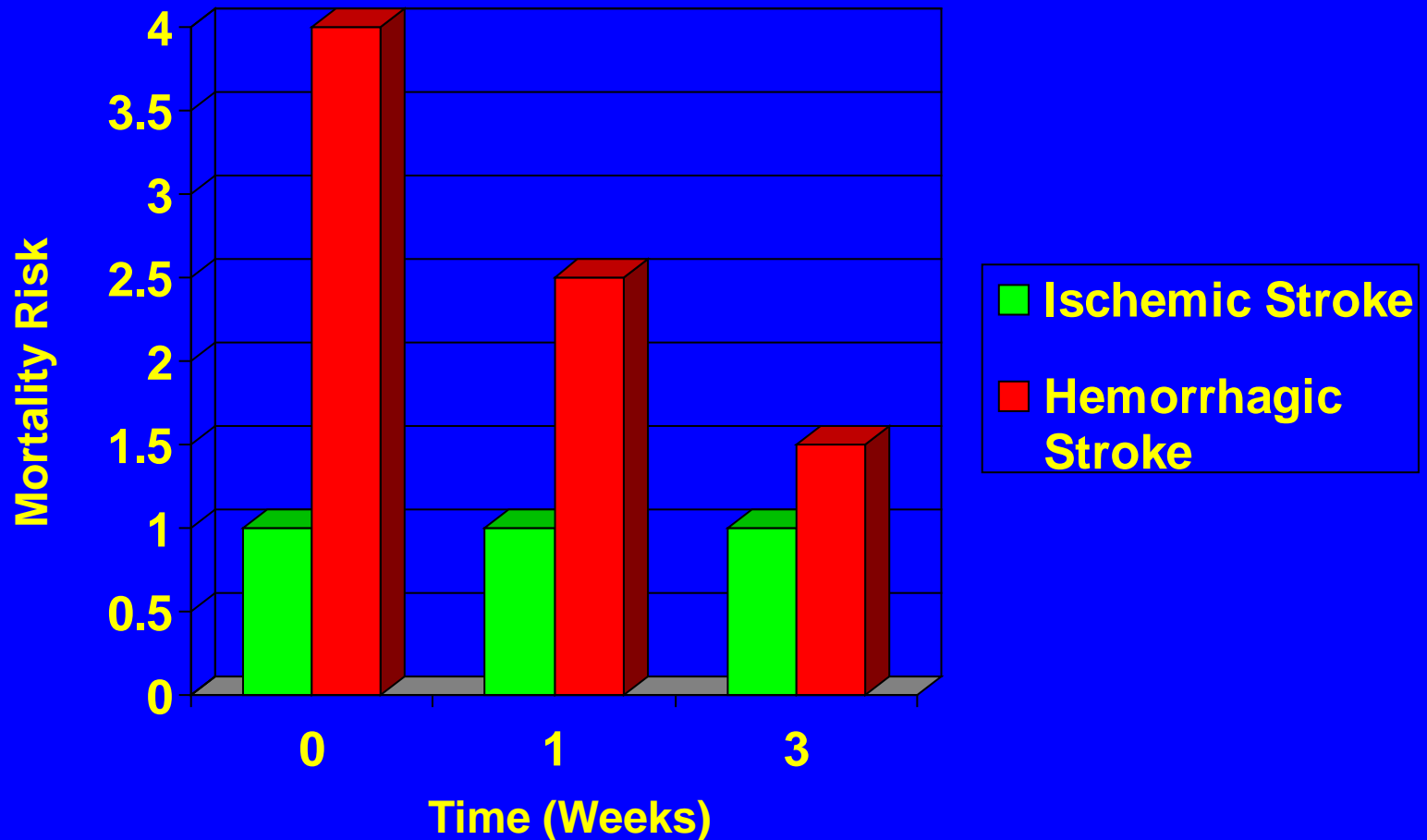
APIXABAN

Superior to Coumadin – primary outcome
Improved mortality
Decreased bleeding compared to coumadin
Not superior to coumadin for ischemic stroke

Improved mortality with: Apixaban (Hazard Ratio 0.89 p 0.047)
However:
Dabigatran (Relative Risk 0.88 p 0.051)

In all 3 trials – novel agents had less intracranial hemorrhage than with coumadin

Hemorrhagic Stroke is Worse than Ischemic Stroke



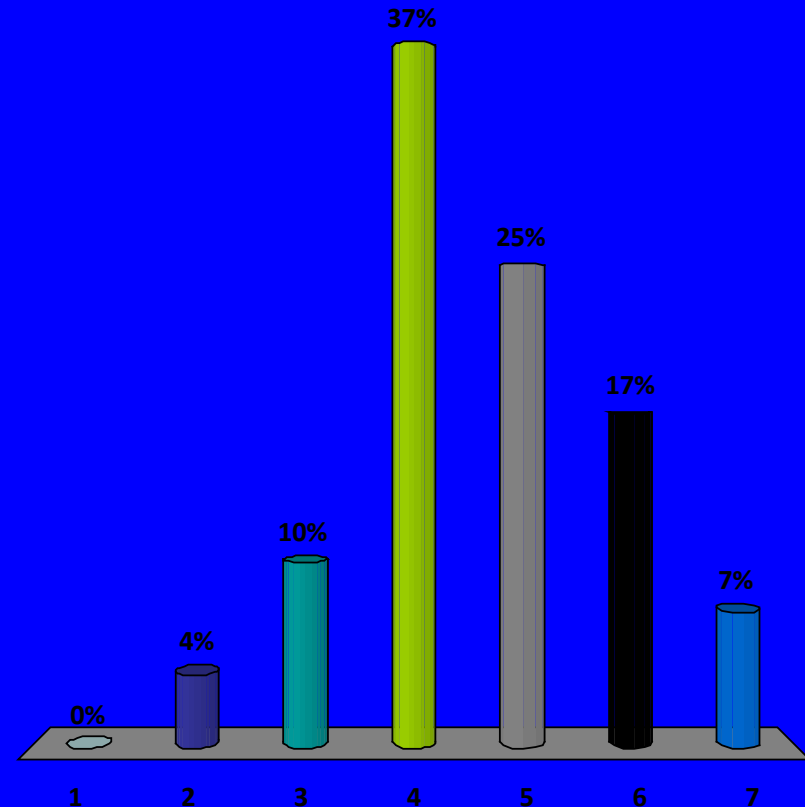
New Agents are Superior to Warfarin in Preventing ICH

Risk of Hemorrhagic Stroke

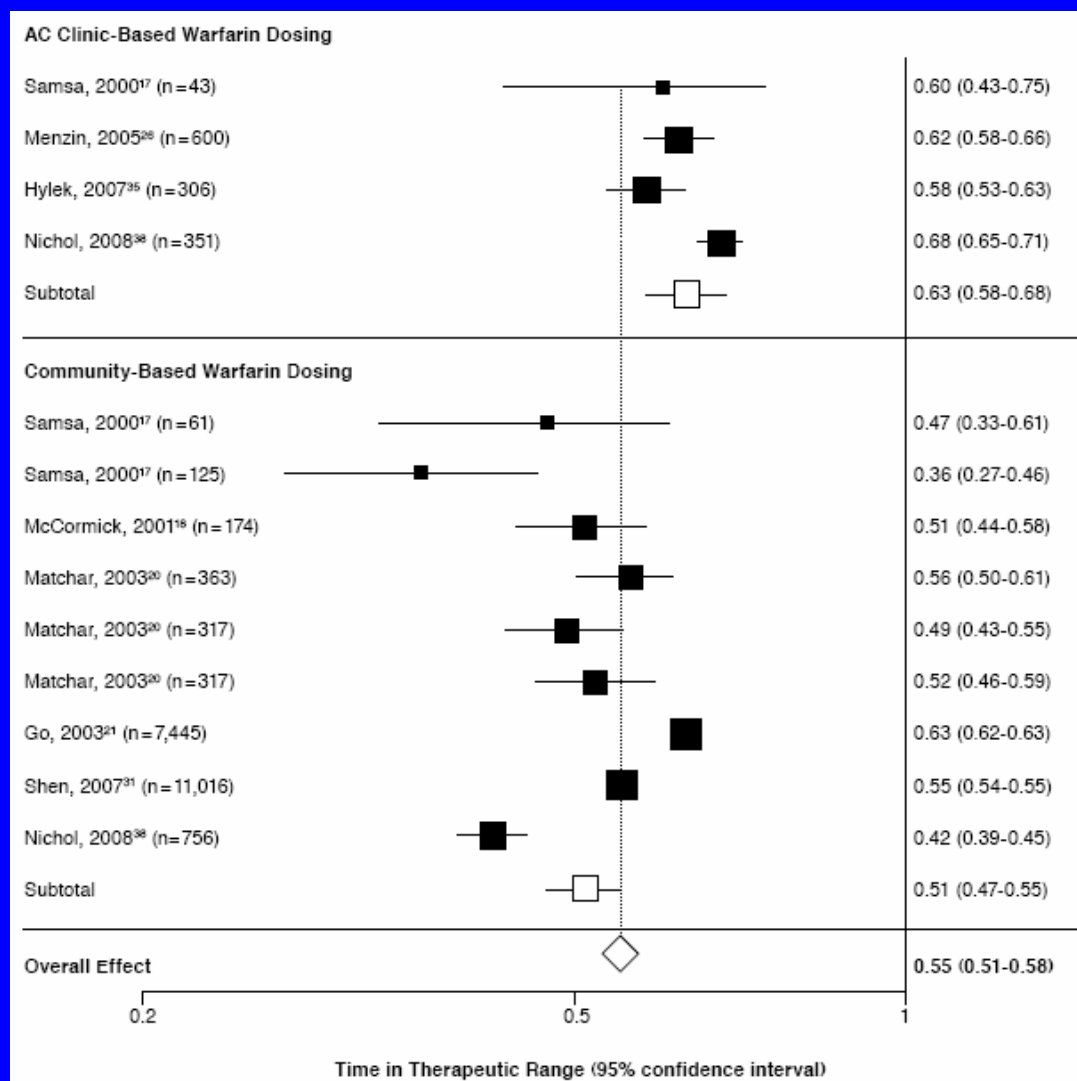
- Dabigatran – Relative Risk 0.26 $p < 0.0001$
- Rivaroxaban – Hazard Ratio 0.67 $p < 0.02$
- Abixaban - Hazard Ratio 0.51 $p < 0.001$

What Percentage of Time Do Patients With Atrial Fibrillation in a Community Setting Spend in a Therapeutic InR Range?

1. 90%
2. 80%
3. 70%
4. 60%
- ✓ 5. 50%
6. 40%
7. 30%

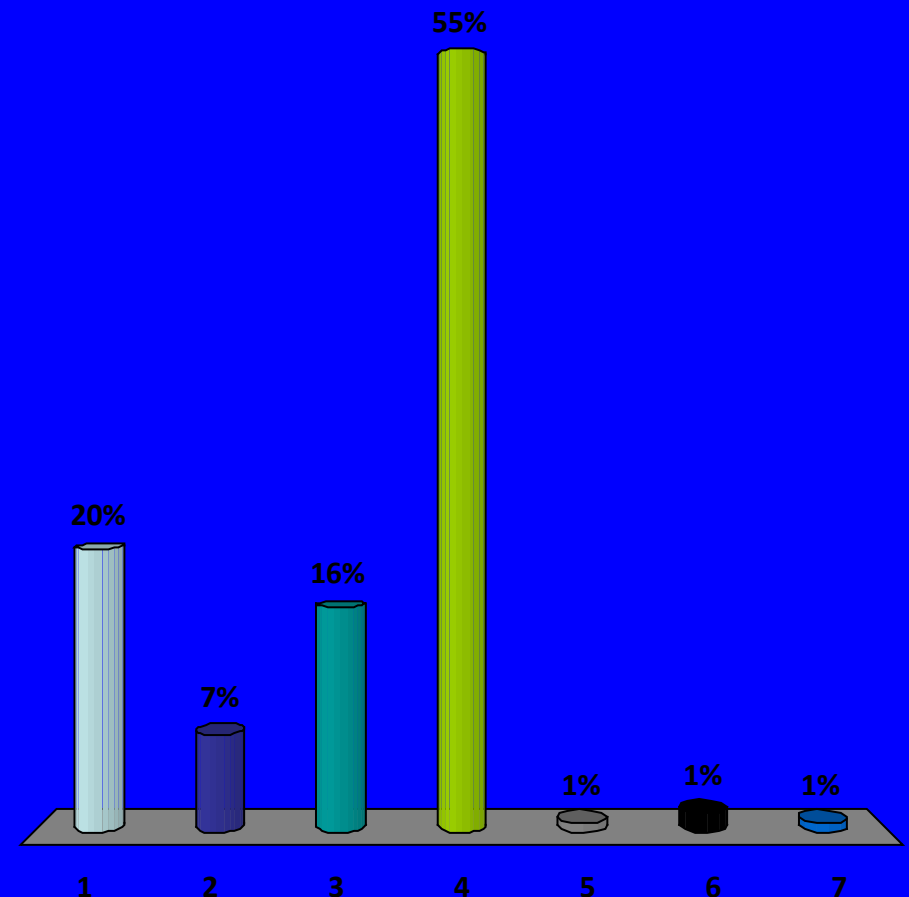


Quality of Warfarin Control



Where Do Most Clots Form in Atrial Fibrillation?

1. Right Atrium
2. Right Ventricle
3. Left Ventricle
- ✓ 4. Left Atrial Appendage
5. Aorta
6. Pulmonary Veins
7. Superior Vena Cava



New Therapies

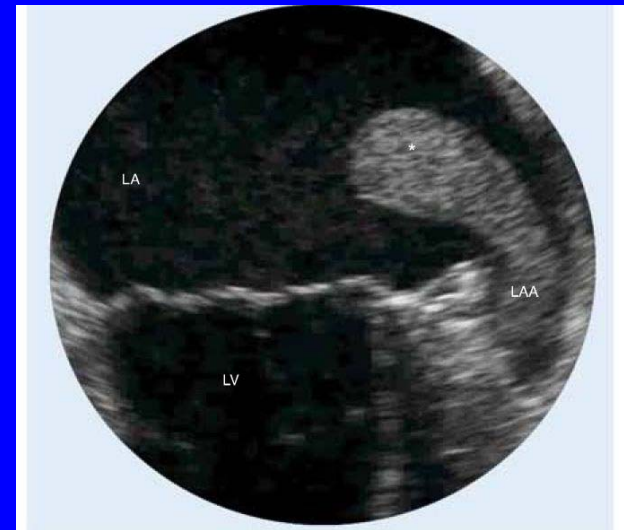
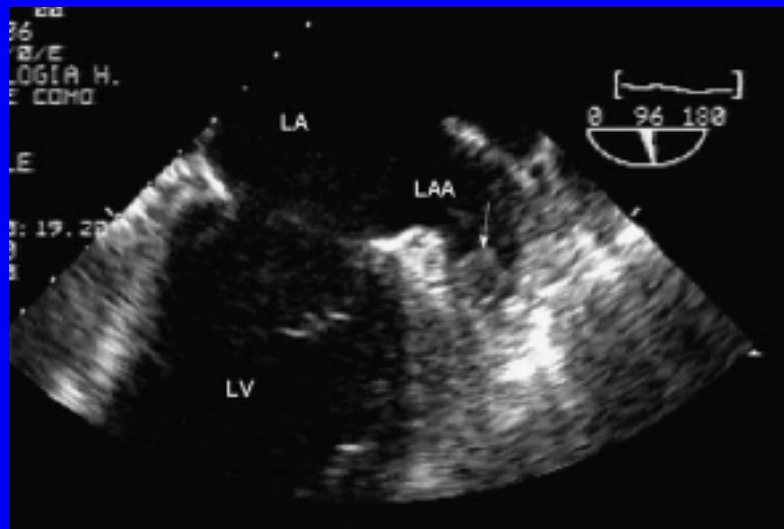
**Prevent Clots from Forming in
the Left Atrial Appendage
During Atrial Fibrillation**

**Left Atrial Appendage
Occlusion Devices**

In Atrial Fibrillation, Thrombus Forms in the Left Atrial Appendage

TEE on 233 patients with atrial fibrillation >48 hours not on A/C: 15% had left atrial thrombus – all but one in the left atrial appendage

Nearly all thrombus formation in non-valvular atrial fibrillation occurs in the left atrial appendage



Manning et al. JACC 1994;23:1535-40

Corrado et al. Eur J Echocardi 2004;5:257-261

Eur J Cardiothorac Surg 2000;17:718-722

© 2000 [Elsevier Science NL](#)

The left atrial appendage: our most lethal human attachment! Surgical implications

W. Dudley Johnson, A.K. Ganjoo, Christopher D. Stone, Ramahalli C. Srivyas, Mary Howard

Some Patients Cannot be Anticoagulated

- Over 50% of patients with atrial fibrillation are > 75 years
- Up to 20% have a contraindication to Warfarin treatment
- Patients with a history of a previous stroke have an annual stroke rate of 12% per year

So...Get Rid of the Appendage!

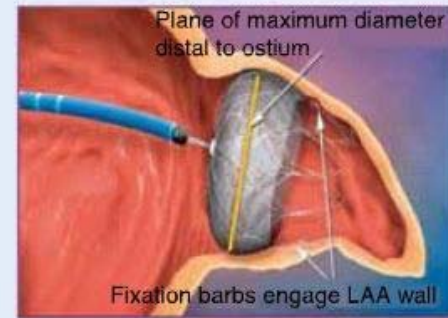
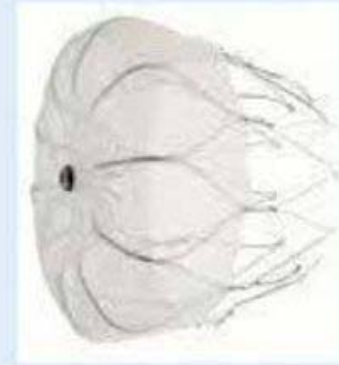
PLAATO™



Amplatzer™



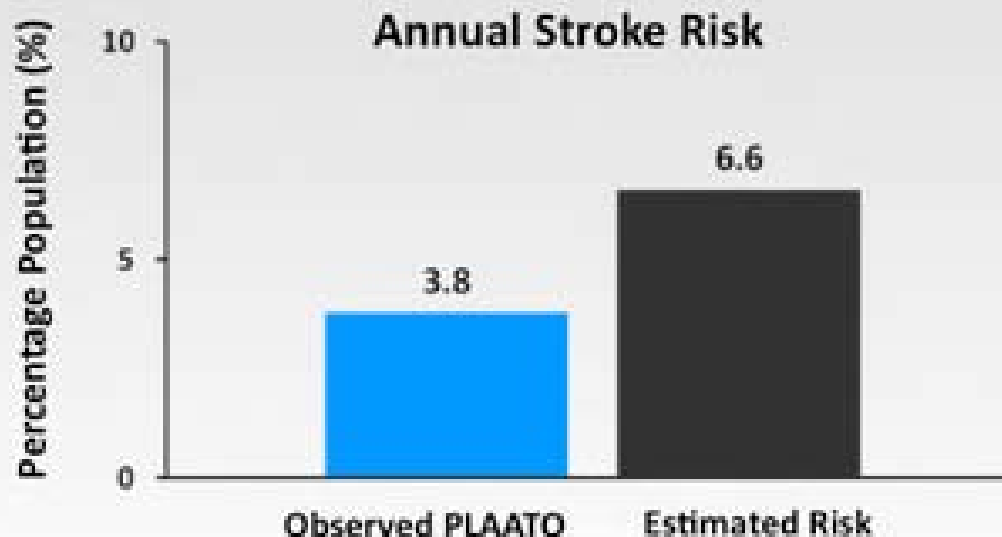
Watchman™



PLAATO

PLAATO: Stroke Risk at 5 Years

N = 64 patients with permanent/paroxysmal AF and contraindication for warfarin, mean CHADS₂ = 2.5



PROTECT-AF

PROTECT-AF: Enrollment

Inclusion: Nonvalvular AF, CHADS₂ ≥ 1, eligible for warfarin

Enrolled = 800
Feb 2005-June 2008
59 Centers US & Europe

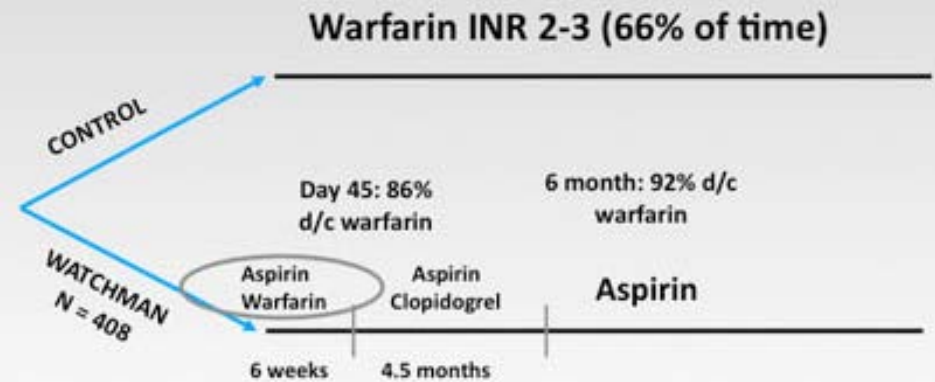
Roll in = 93

2:1 randomization

LAA closure device
n = 463

Warfarin n = 244

PROTECT-AF: Anticoagulation

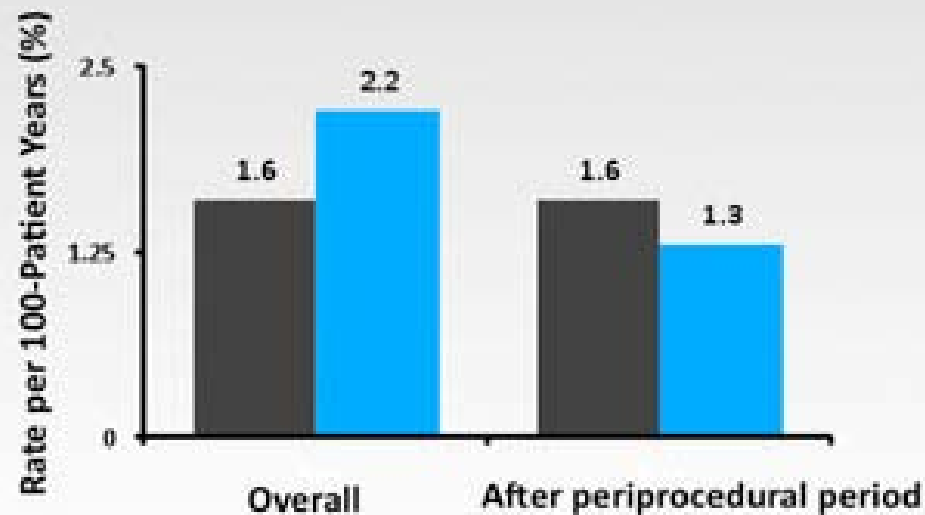


TEE criteria for warfarin discontinuation: complete closure LAA or residual peri-device flow (jet < 5 mm)

PROTECT-AF

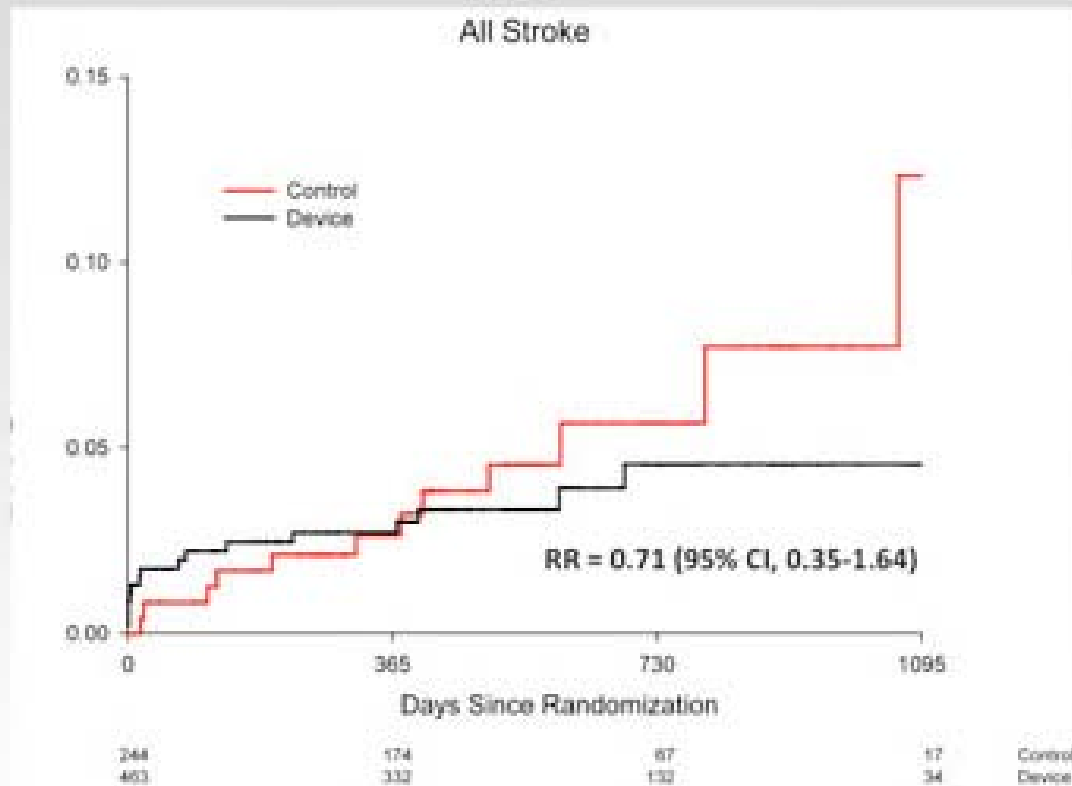
PROTECT-AF: Ischemic Stroke Risk

■ Control
■ LAA Closure Device



PROTECT-AF

PROTECT-AF: Stroke Risk



New Therapies

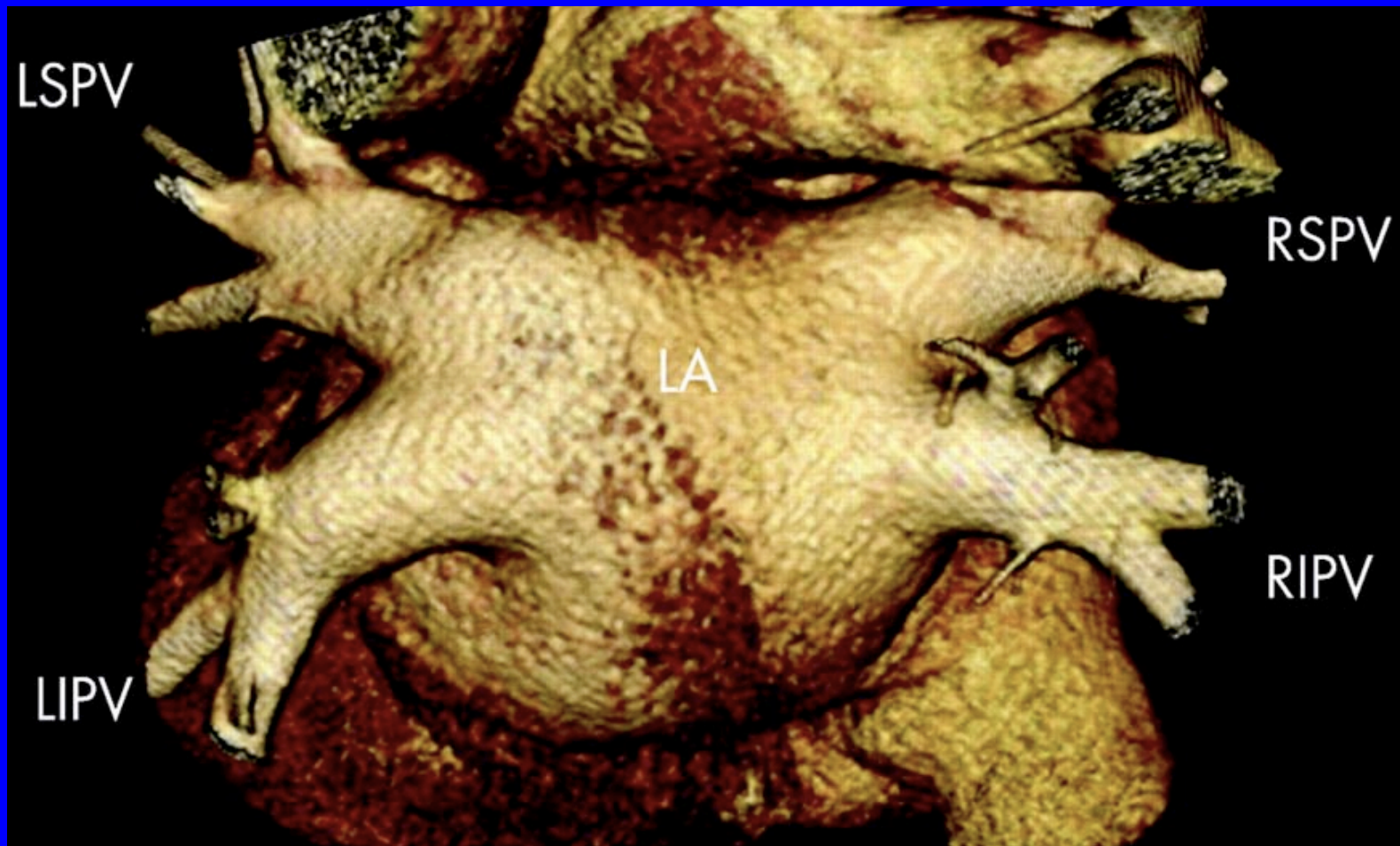
Abolishing Atrial Fibrillation

Ablation Techniques

Definitions

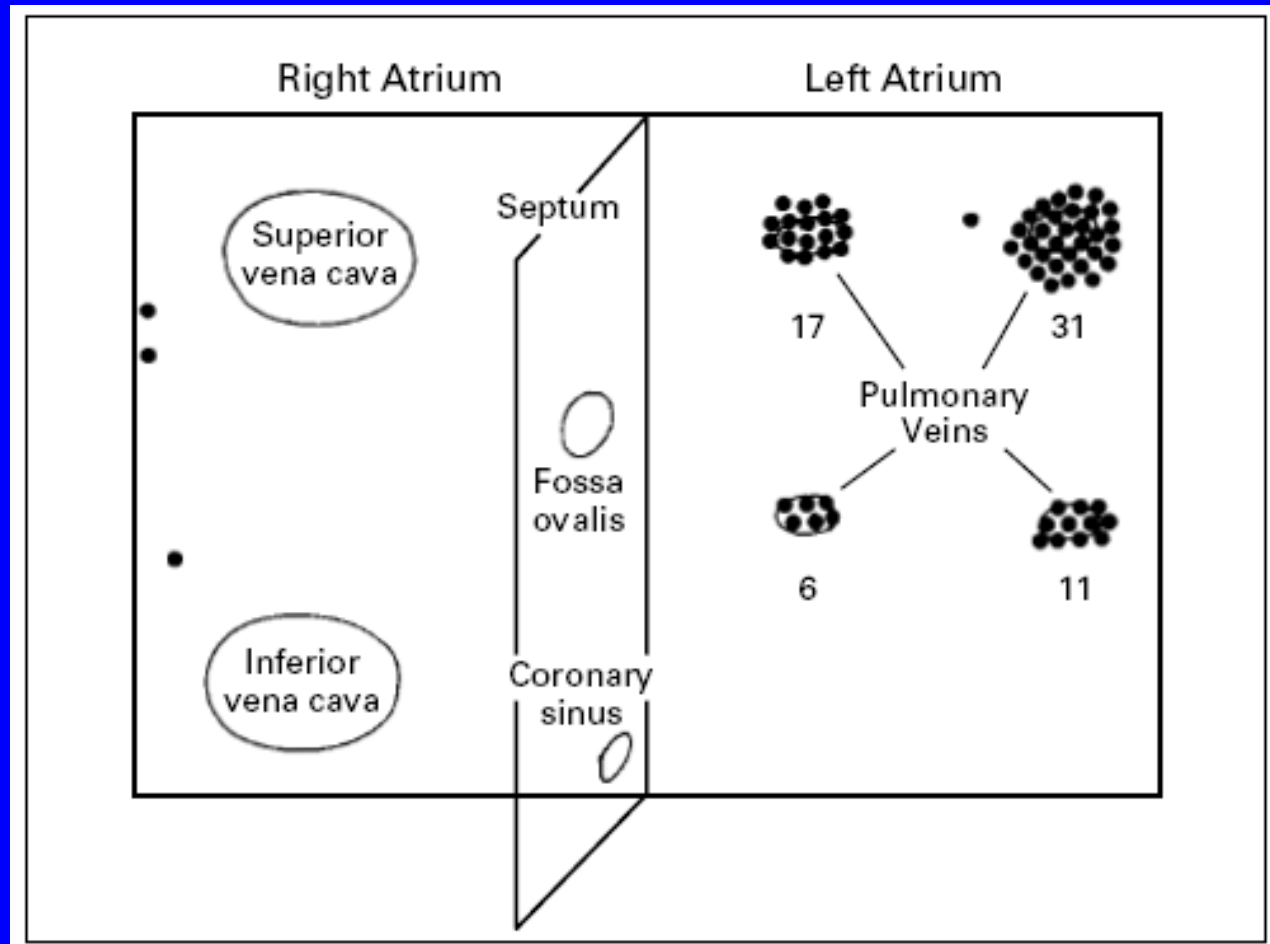
- Paroxysmal Afib – Spontaneously terminates in less than 7 days (Most terminate < 24 hrs)
- Persistent Afib – Lasts for greater than 7 days or requires cardioversion
- Permanent Afib – Cannot be cardioverted out of atrial fibrillation

Anatomy of the Left Atrium and Pulmonary Veins



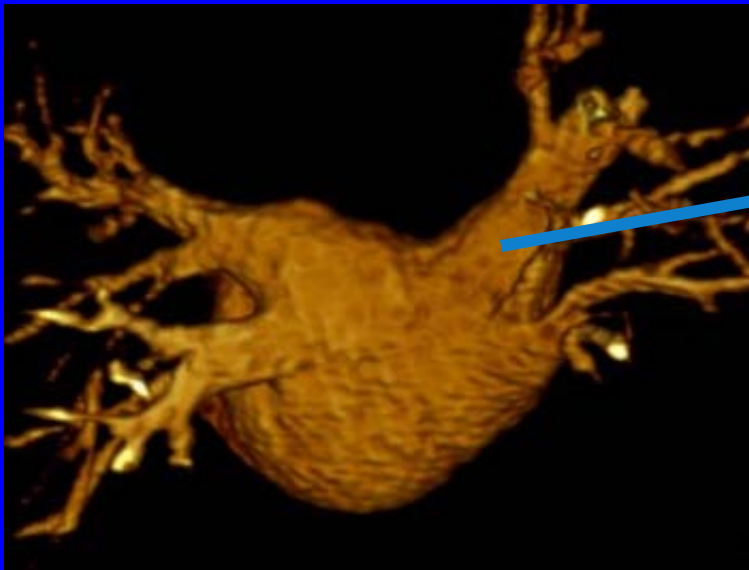
Paroxysmal Atrial Fibrillation Originates in the Pulmonary Veins

- 45 patients with PAF
Resistant to AAD therapy
- AF initiated with burst
Pacing, isoproterenol
- Earliest activation sites
noted

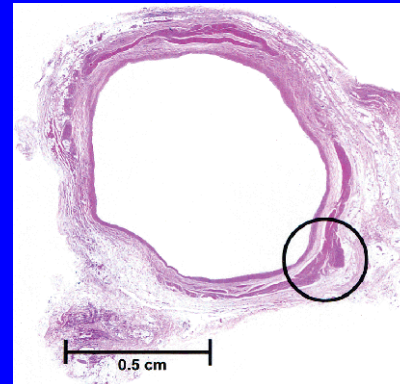


Pulmonary vein triggers are important for paroxysmal atrial fibrillation

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

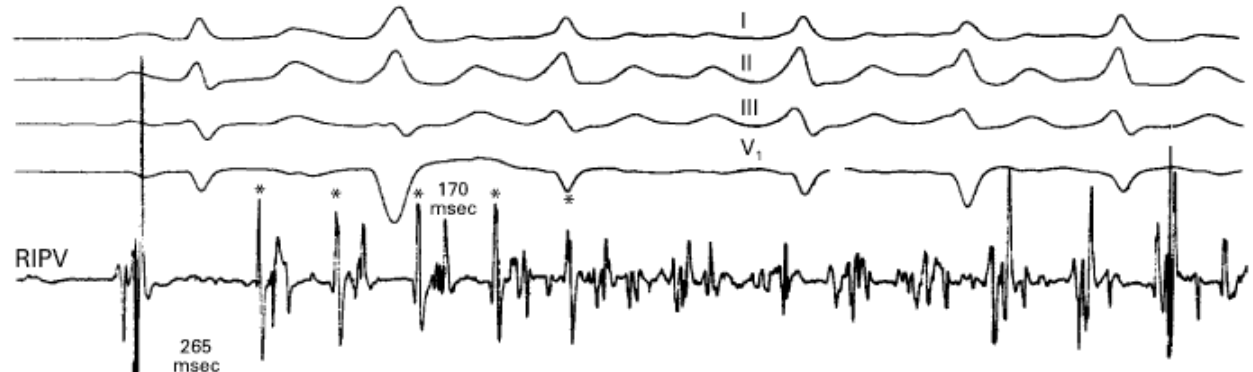


Myocardial sleeve around PV



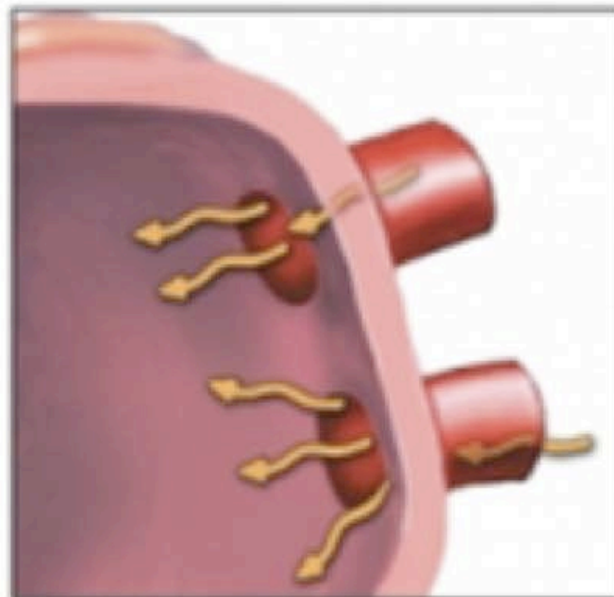
Perez-Lugones, et al. JCE 2003;14: 803

Initiation of AF by rapid firing in a PV



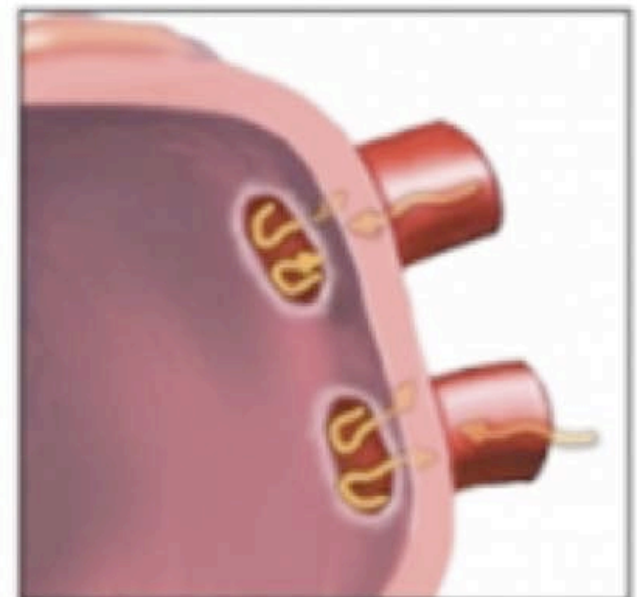
Electrical Isolation of the Pulmonary Veins

Atrial Fibrillation
Before Ablation

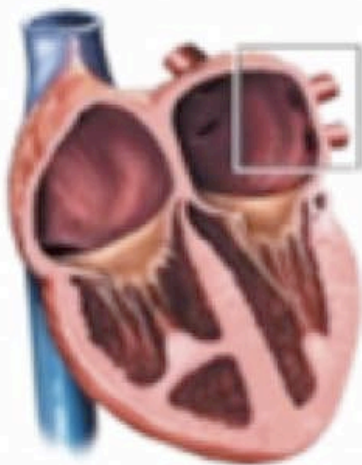


Impulses escape
into the atrium

After Ablation



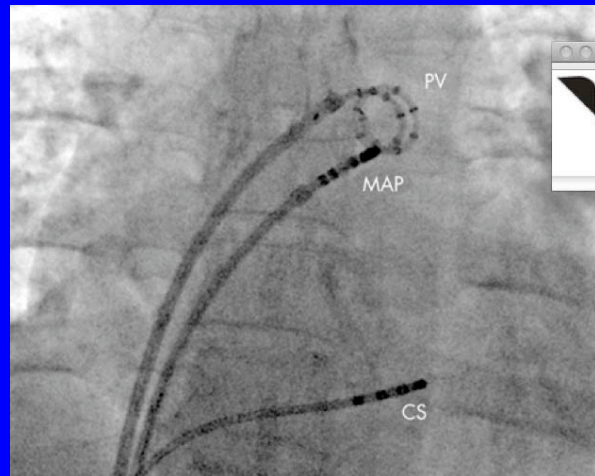
Impulses cannot pass
the ablated tissue



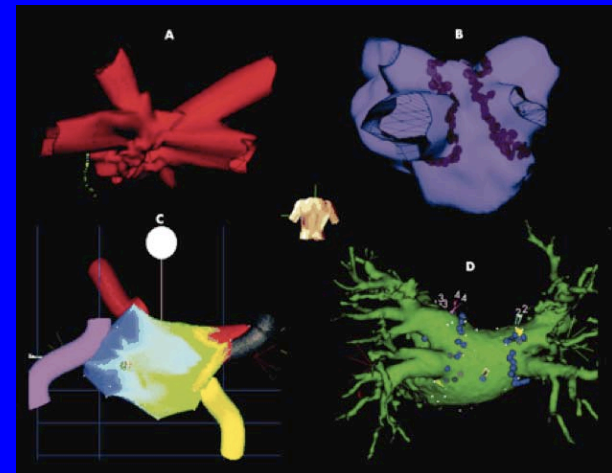
Transeptal Puncture



Intra-Cardiac Echocardiography (ICE)

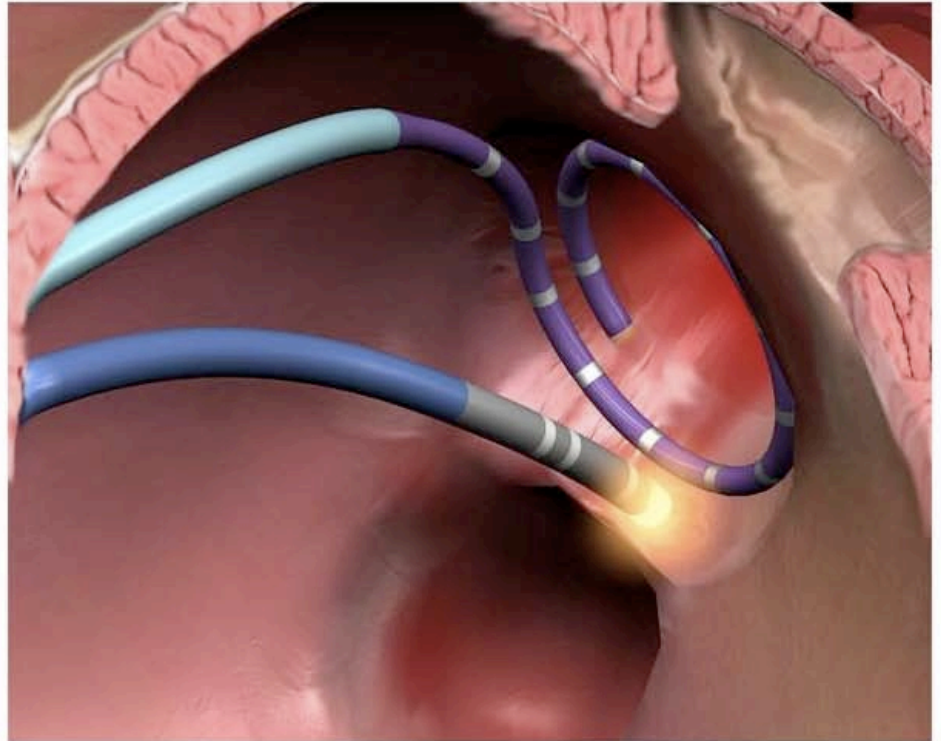
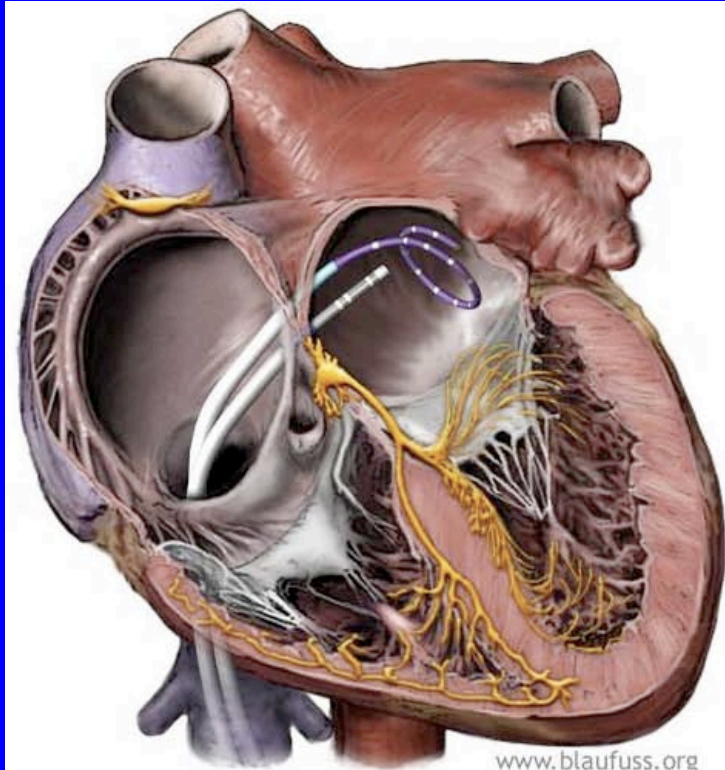


Fluoroscopy

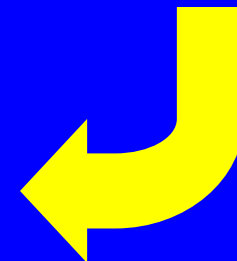
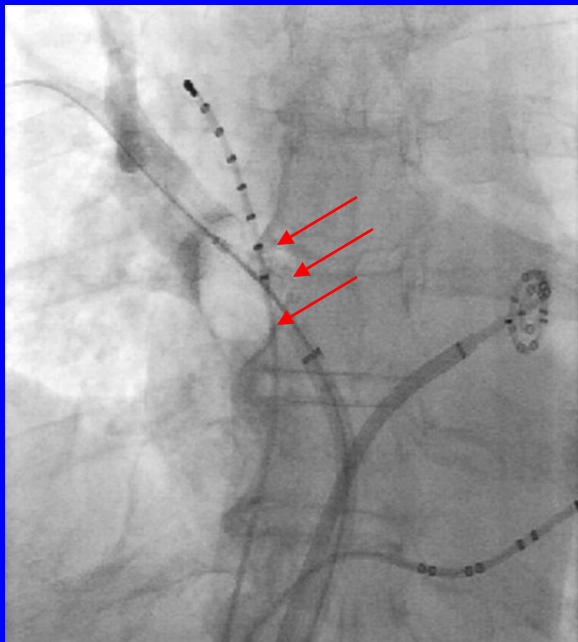
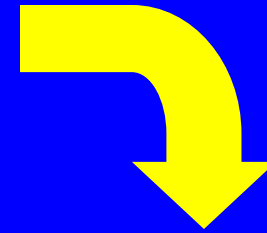


Electro-Anatomic Mapping

Pulmonary Vein Isolation



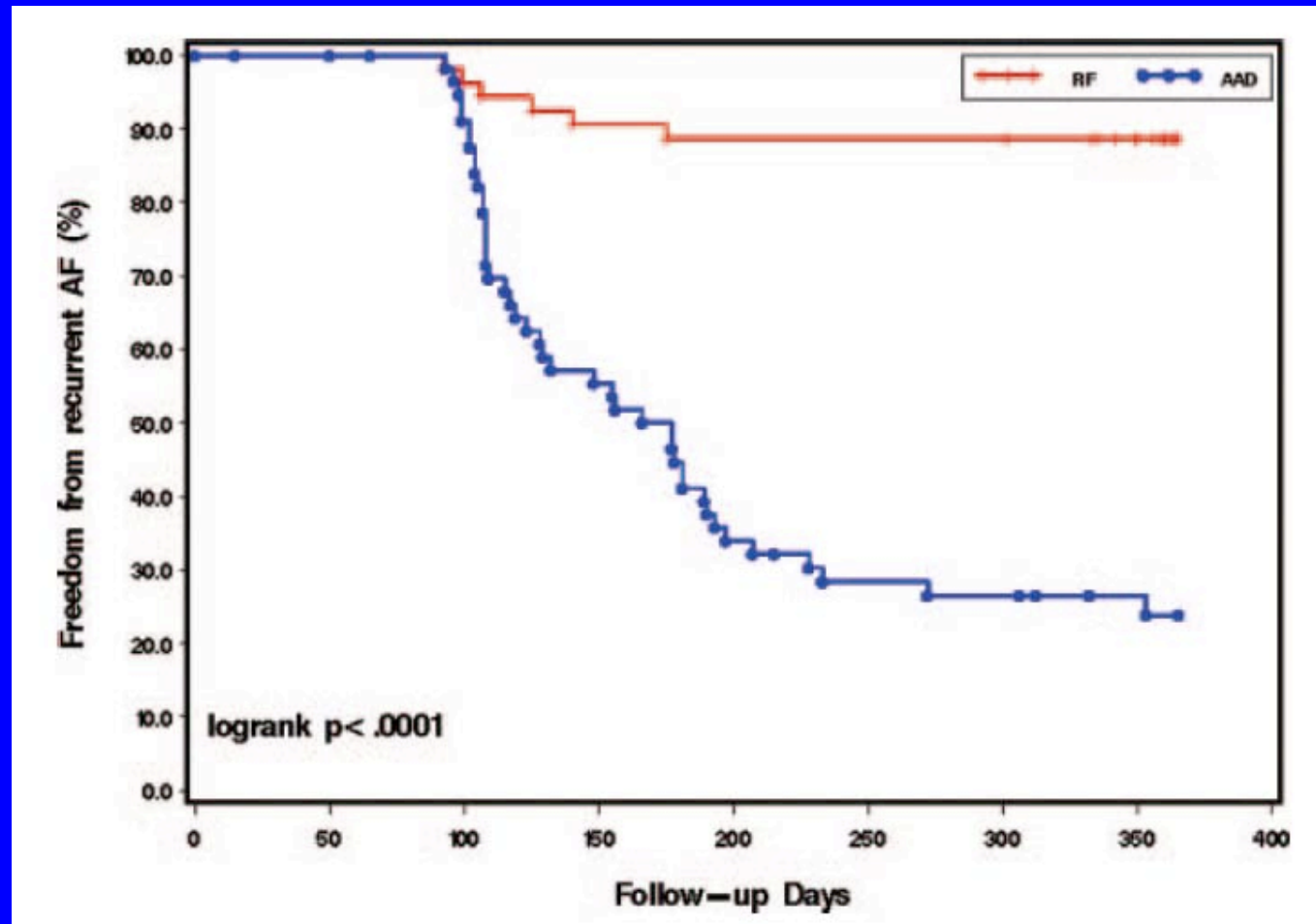
Arctic Front™ Cardiac CryoAblation Catheter



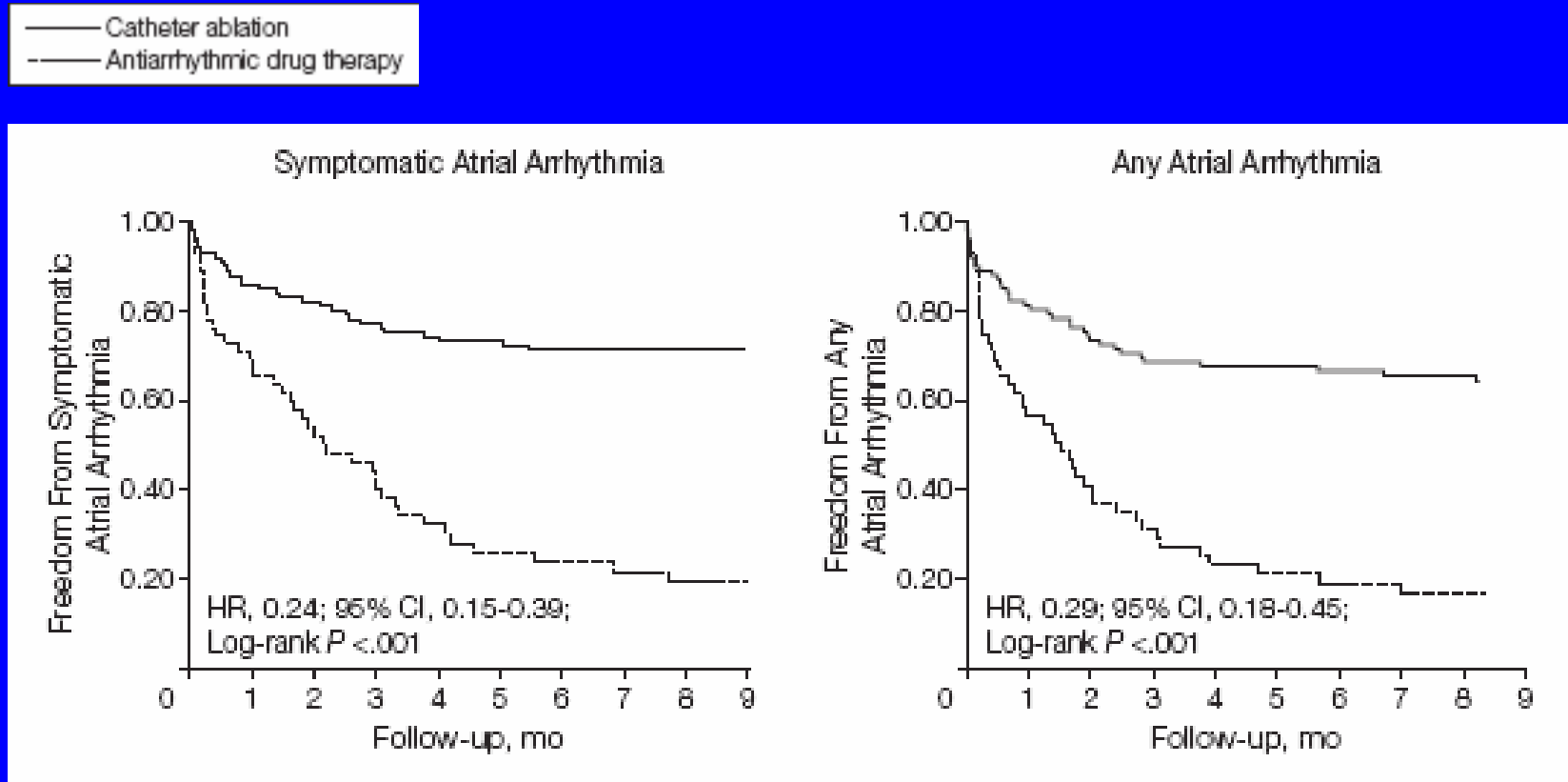
Ablation Does Reduce Atrial Fibrillation

112 PAF Patients
Randomized to
Ablation vs AADs

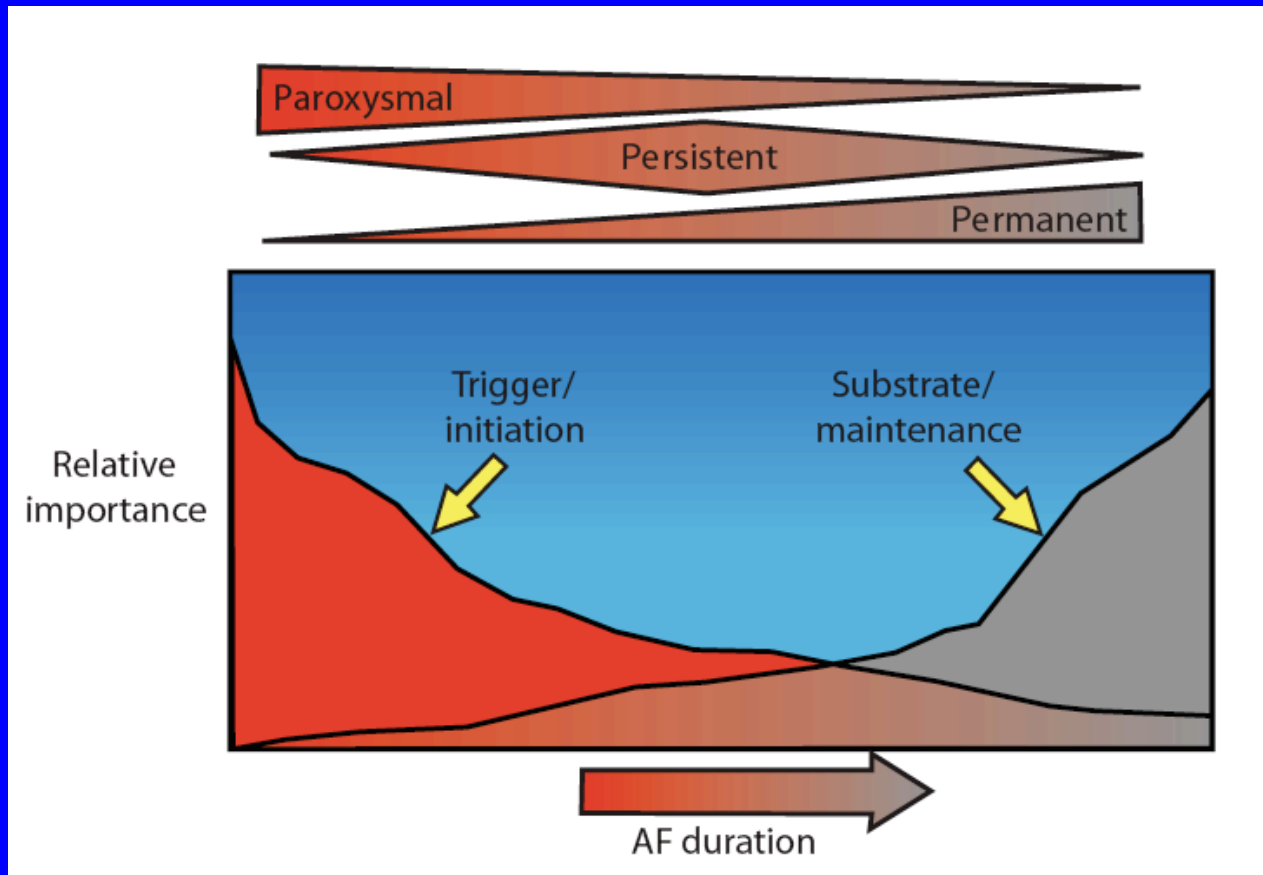
1 yr AF Freedom
AADs – 23%
Ablation – 89%



Success of Ablation Compared to Anti-Arrhythmic Drugs

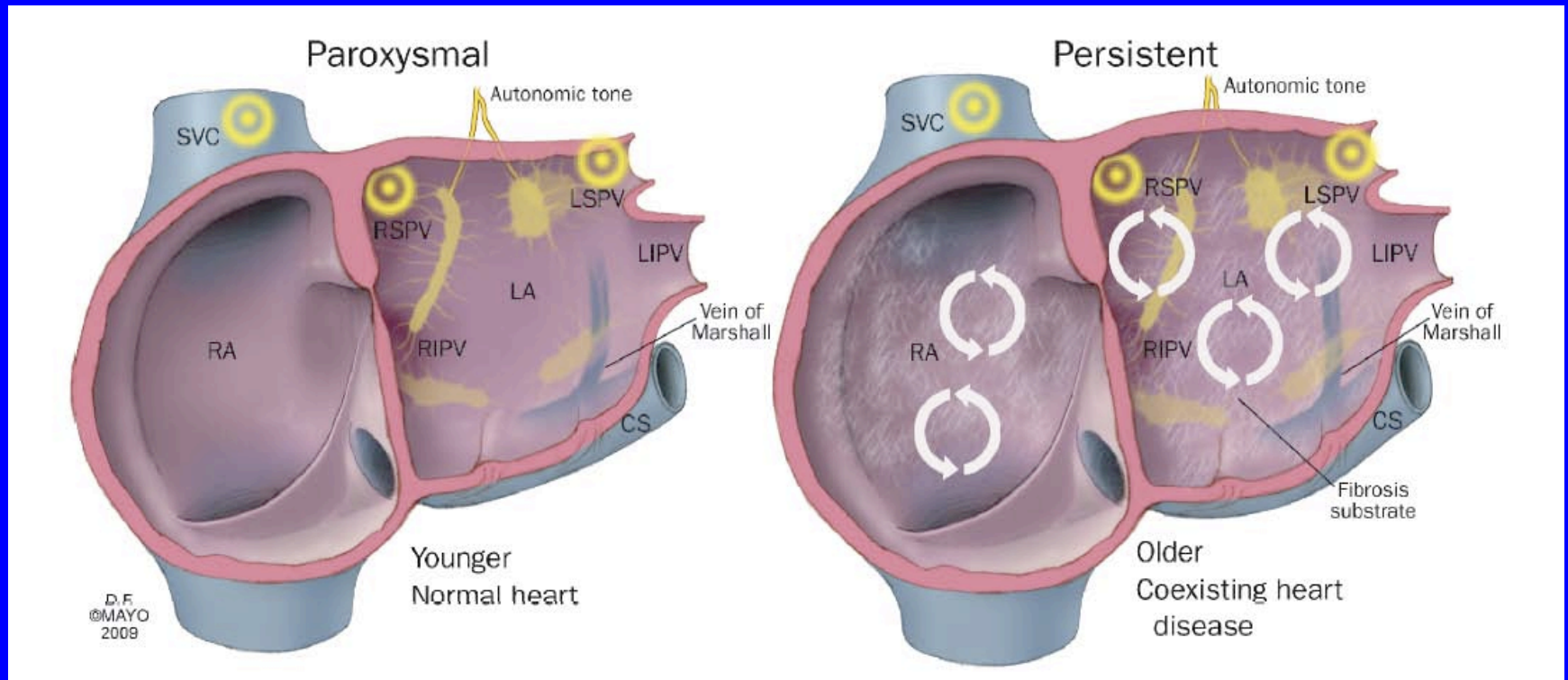


Pulmonary Veins vs Atrial Myocardial Contribution

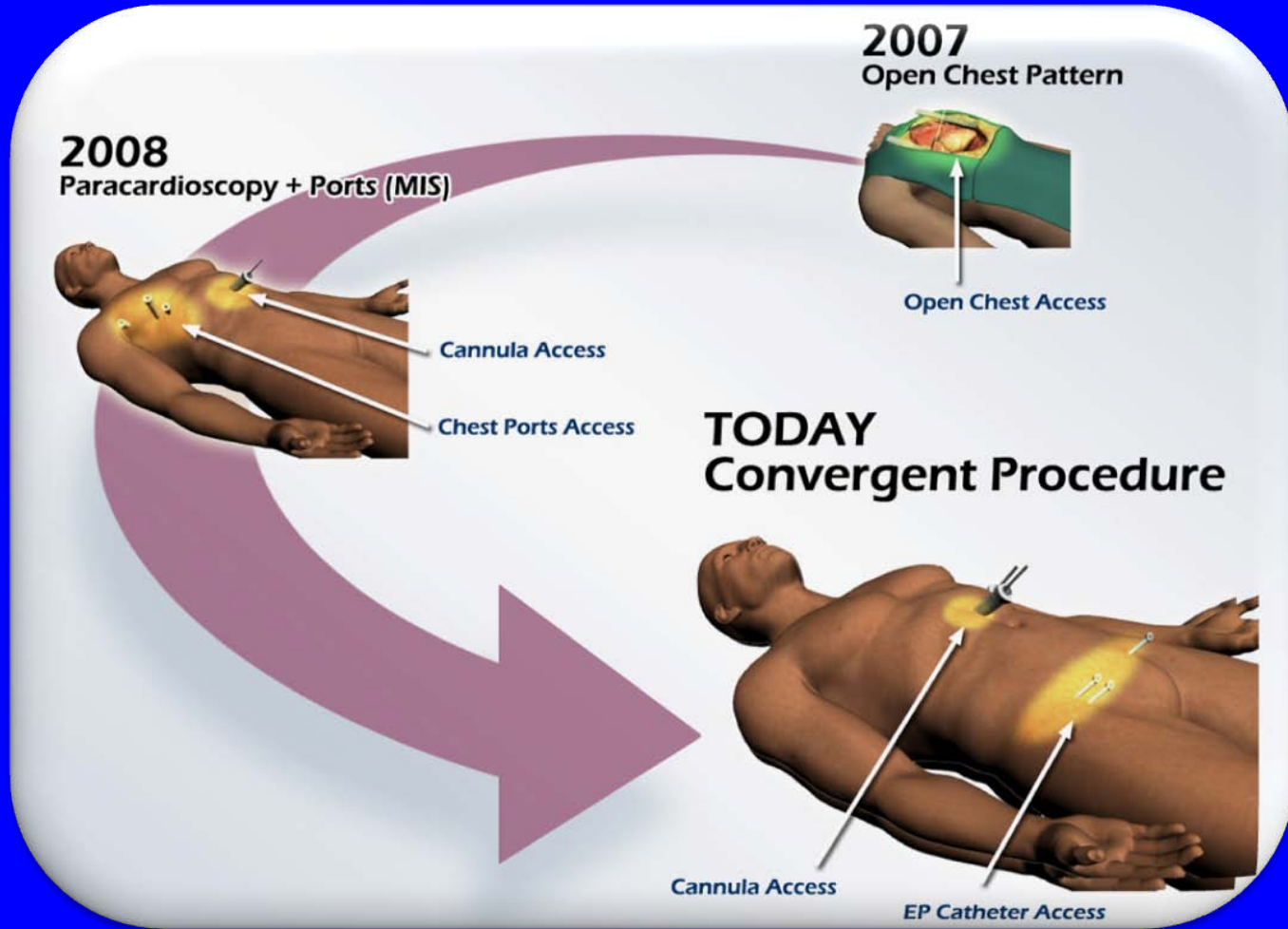


As Atrial Fibrillation Becomes More Persistent, the Relative Contribution of the Pulmonary Veins Decreases as the Role of the Atrial Myocardium Increases

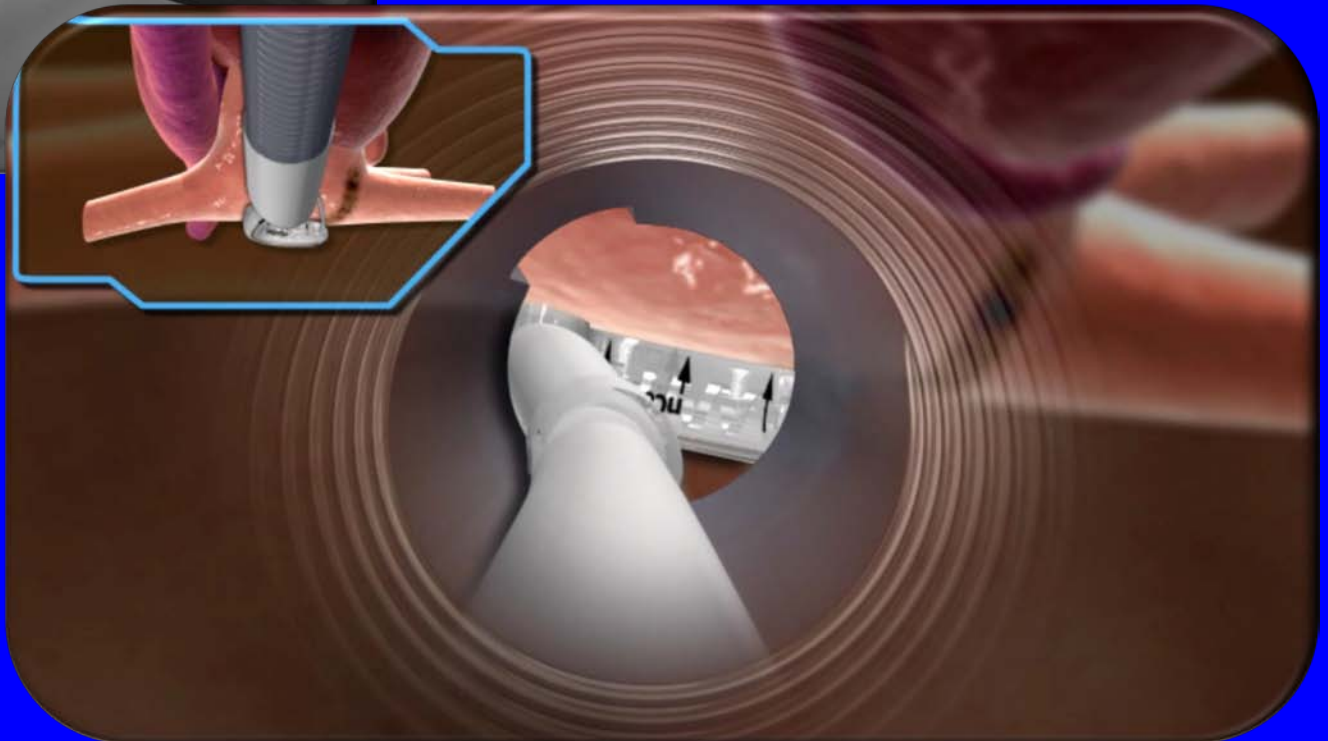
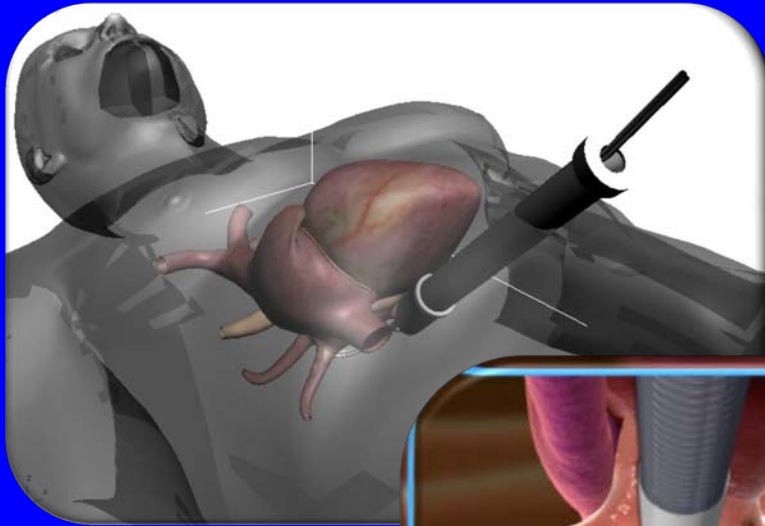
Natural History of Atrial Fibrillation



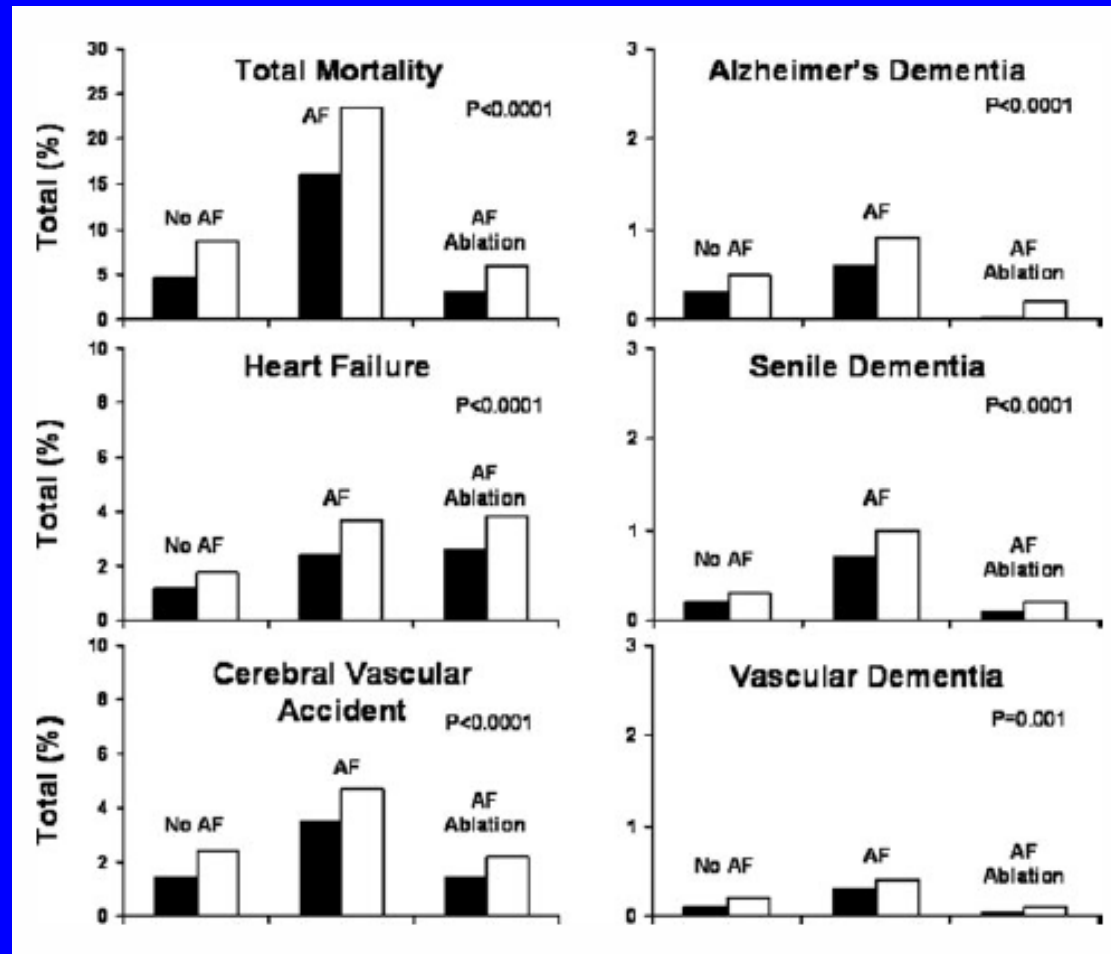
Convergent Hybrid Procedure



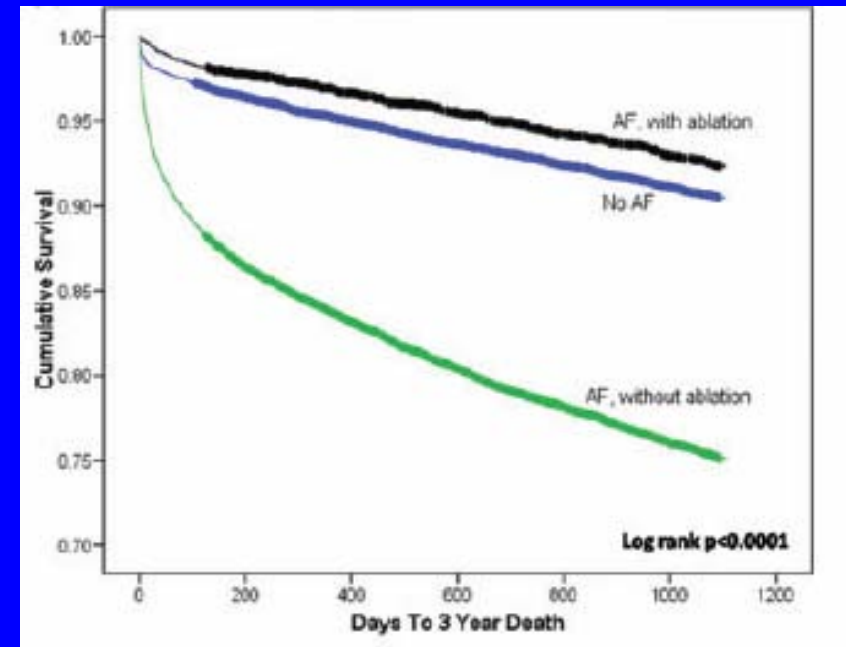
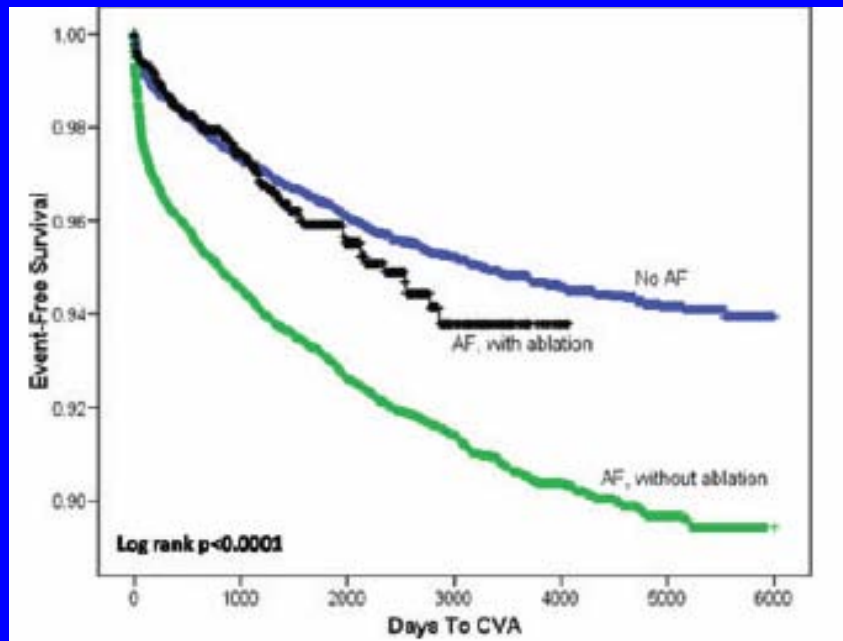
Epicardial Access



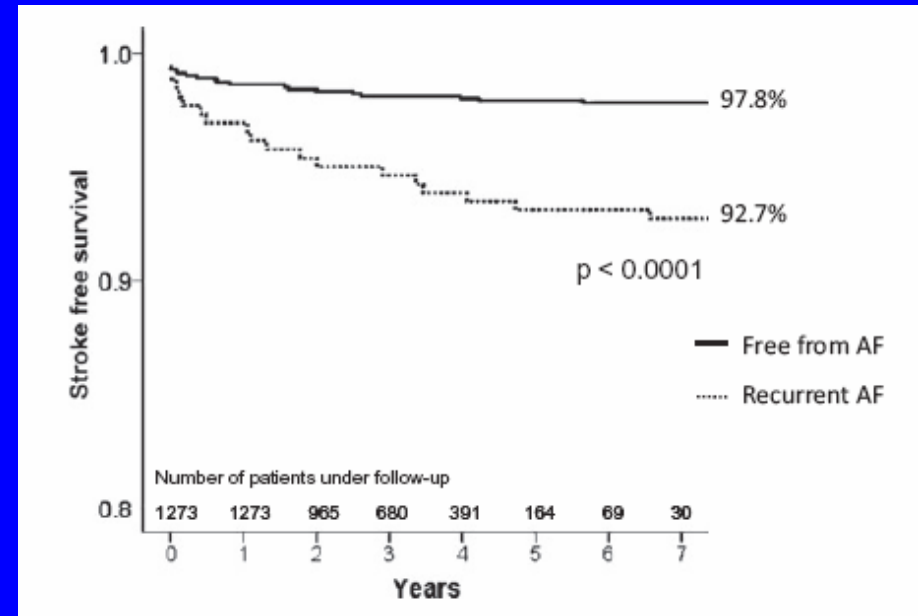
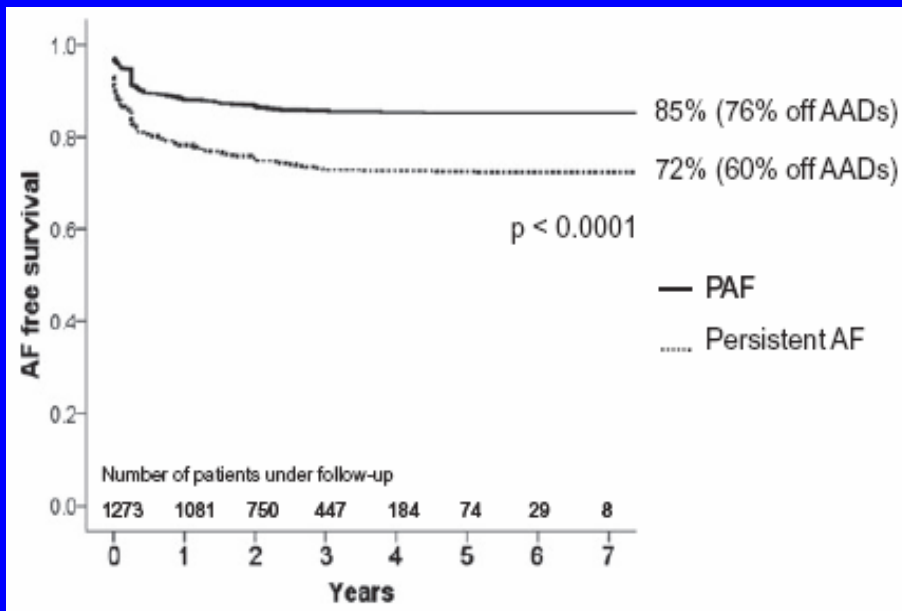
Atrial Fibrillation Ablation Reduces Dementia and Stroke



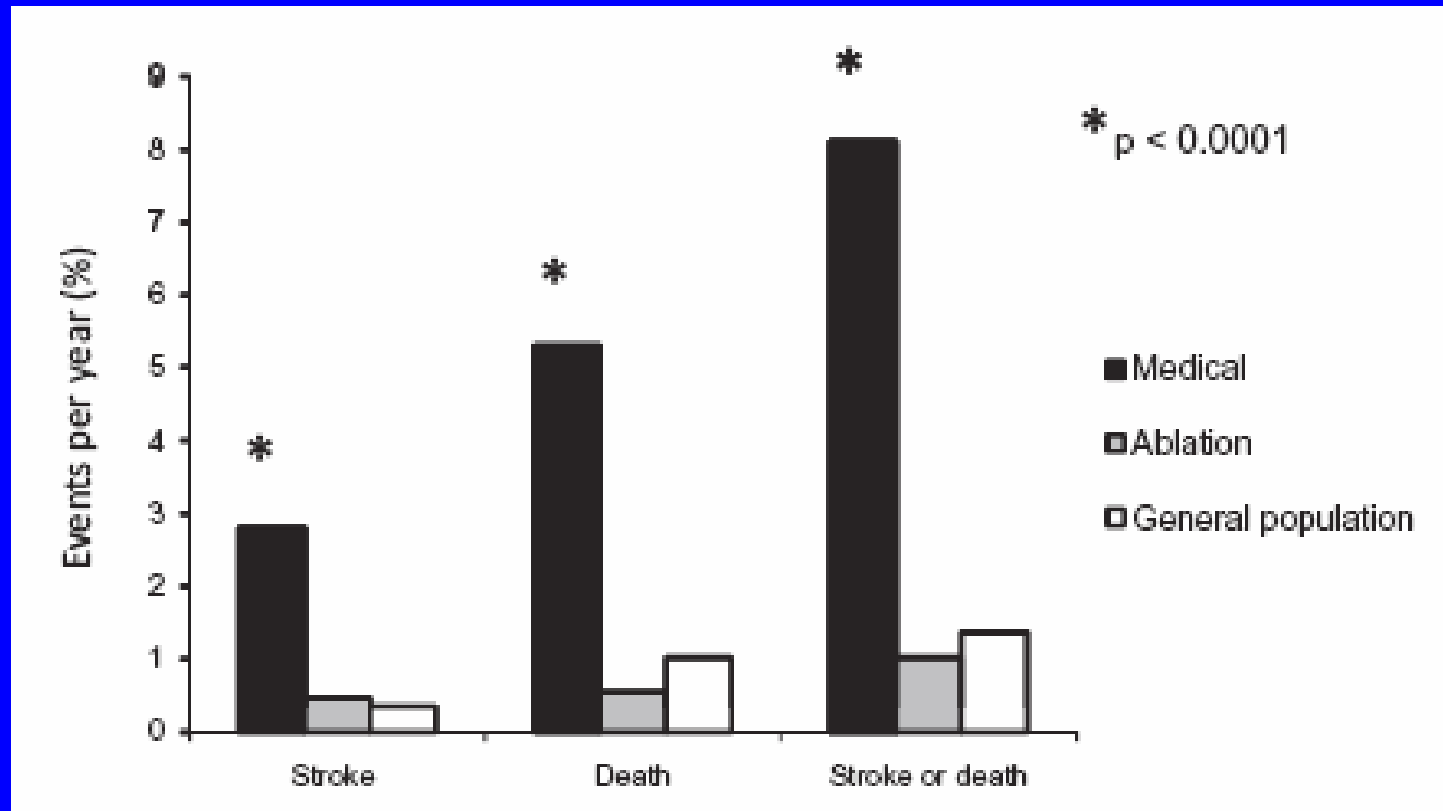
Atrial Fibrillation Ablation Reduces Dementia and Stroke



Maintenance of Sinus Rhythm with Ablation Reduces Stroke Risk



Maintenance of Sinus Rhythm with Ablation Reduces Stroke Risk



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