Update on Current Perspectives and Management Options for Atrial Fibrillation

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March 20, 2015

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Patient Presentation

- 72 year old active male farmer and tow truck operator from Hemlock, NY
- Reports a 16 year history of heart racing, irregular heart beats and fatigue

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HEMLOCK LAKE

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HealthQuest™

Patient Support Program

QUESTRAN® LIGHT

(cholestyramine for oral suspension, USP)

	8-20	OUT	6:30 AM	IN 6:30 PM	12h
NEW	9-6	OUT	3:30 AM	IN 9:00 AM	5.5h
	9-17	OUT	2:30 AM	IN 10:00 AM	7.5h
	9-27	OUT	8:00 PM	9/28 IN 5:00PM	21h
NEW	10-10	OUT	11:00PM	10/11 IN 4:30PM	5.5h
	10-13	OUT	5:30AM	10/15 IN 11:30PM	54h
	10-22	OUT	5:30 AM	IN 10 AM	4.5h
	10-29	OUT	3:00 PM	10/30 IN 2:00PM	23h
NEW	11-1	OUT	7:30 PM	11/2 IN 9:00AM	16.5h
	11-20	OUT	7:00 PM	11/21 IN 2:30PM	19.5h
	11-23	OUT	7:00PM	11/24 IN 12:00PM	15h
NEW	12-1				

B-A507-1-91

For New Questran® or Questran® Light Patients

(cholestyramine for oral suspension, USP)

1-800-955-5222

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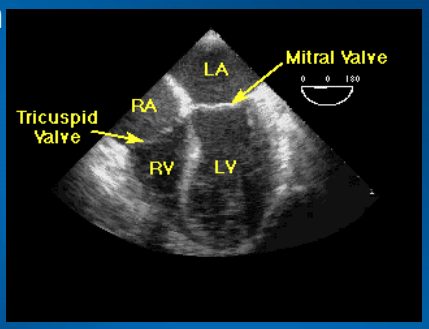
Past Medical History/Medications

- Hypertension
- Obesity
- Questionable obstructive sleep apnea
- No tobacco or ETOH history
- Current medications: Enalapril, Toprol XL, Nifedipine, Omeprazole, Allopurinol, and Indomethacin.

Echocardiogram

- Normal LVEF
- Left atrial size = 55 mm



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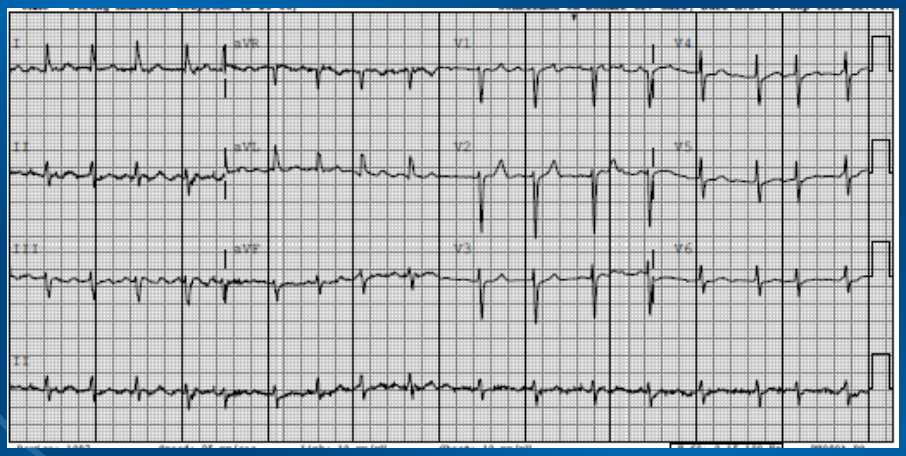
ECG



Diagnosis – Atrial Fibrillation

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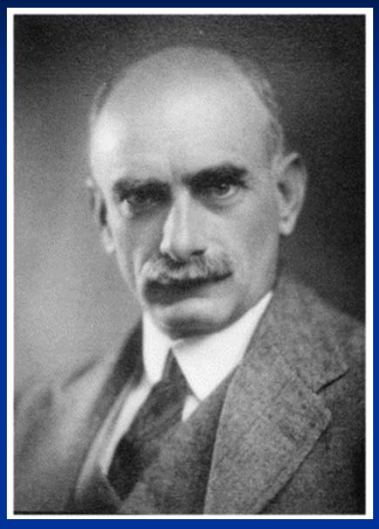
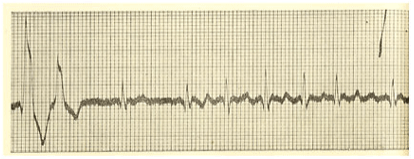
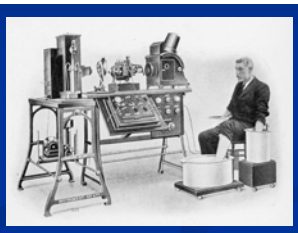
Sir Thomas Lewis



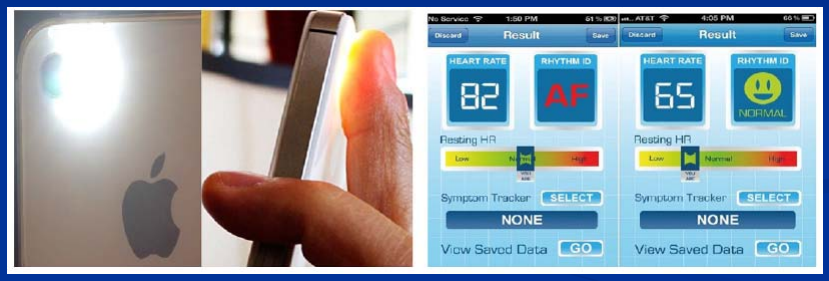
Lady Lewis's favorite picture of her husband





"Dear Professor Einthoven,
By this post I am sending you some curves, experimental and clinical. Please treat these curves I send as if they were your own."
London, 01/30/1910

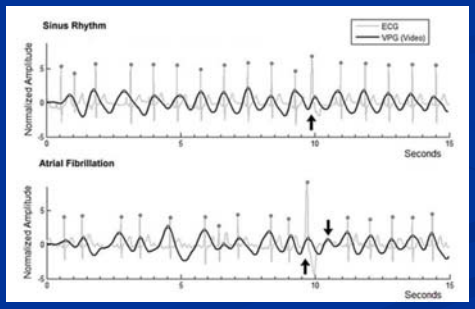
iPhone 4S for Detection of Atrial Fibrillation



McManus et al. Heart Rhythm 2013;10:314-319

Detection of Atrial Fibrillation Using Contactless Facial Video Monitoring

This technique uses a camera to record an individual's face and extract the subtle beat to beat variations of the skin color reflecting the cardiac pulsatile signal. In a group of adults referred for electrical cardioversion, we recorded the ECG and the video of the subjects' face prior and after the electrical cardioversion.



Couderc J, Hall B. Heart Rhythm 2015;12:195-201

ASSERT Trial

- One quarter of all strokes are of unknown cause
- Subclinical AF may be a common etiologic factor
- Pacemakers can detect subclinical episodes of AF
- Are subclinical episodes of AF detected by implantable devices associated with an increased risk of stroke?

Healey et al. N Engl J Med 2012;366:120-9

ASSERT Trial

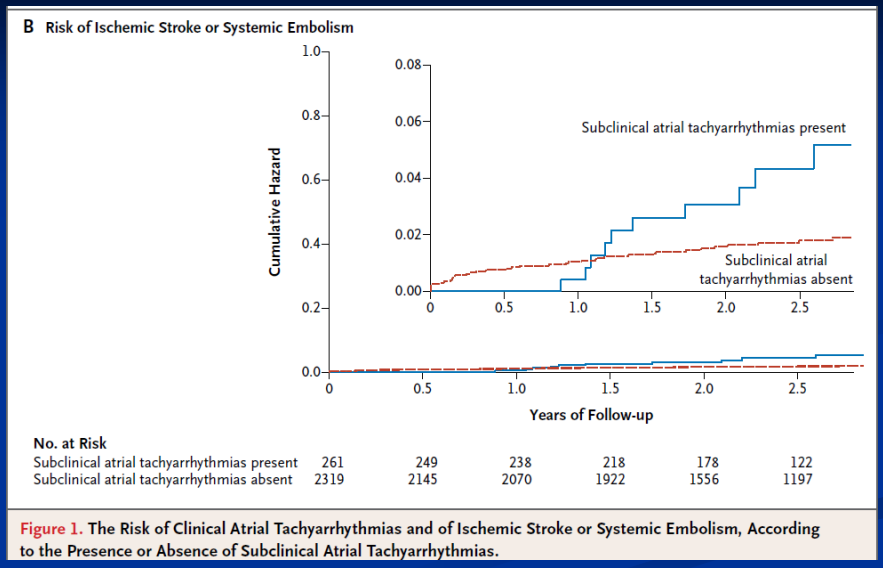


Figure 1. The Risk of Clinical Atrial Tachyarrhythmias and of Ischemic Stroke or Systemic Embolism, According to the Presence or Absence of Subclinical Atrial Tachyarrhythmias.

Healey et al. N Engl J Med 2012;366:120-9

ASSERT Trial Conclusions

- Subclinical AF was eight times as common as symptomatic AF
- The median time to detection of subclinical AF was 36 days
- Subclinical AF was independently associated with an increase by a factor of 2.5 in the risk of stroke

Healey et al. N Engl J Med 2012;366:120-9

How much AF is too much?

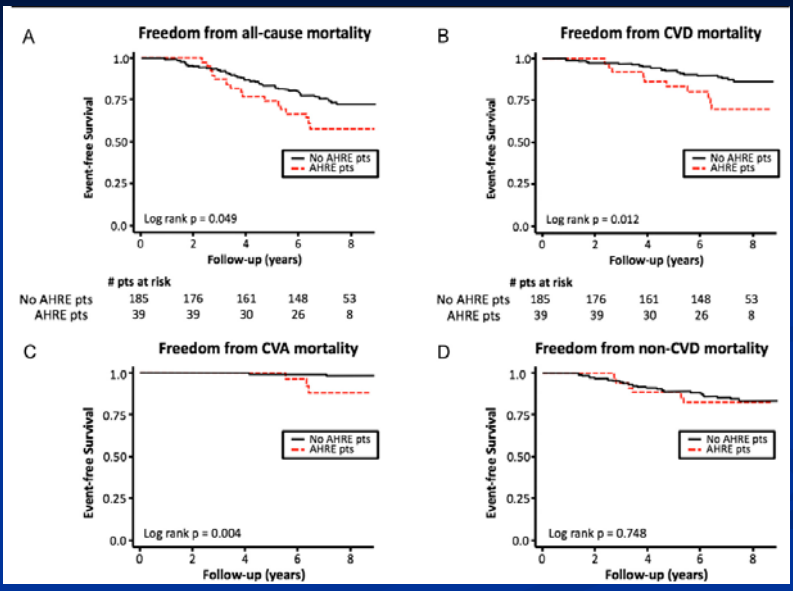
- Can we define a threshold for total AF burden and risk of stroke?
- Is all AF equal in terms of stroke risk or are shorter episodes of AF less risky?

Annualized thromboembolic event rate by AT/AF burden

AT/AF burden	Annualized rate (%/y)	Annualized rate excluding TIAs (%/y)
Zero	1.1	0.5
Low	1.1	1.1
High	2.4	1.8

Glotzer TV. American College of Cardiology 2008 Scientific Sessions; April 1, 2008; Chicago, IL.

Subclinical Atrial High Rate Episodes of ≥ 5 Minutes Pacemaker Detection



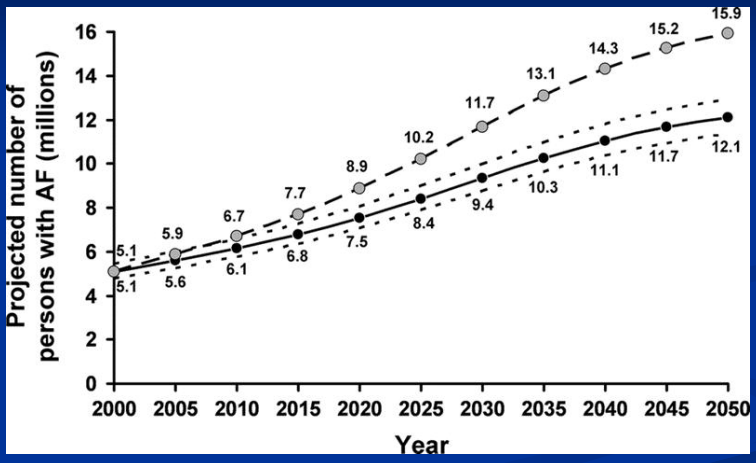
Gonzalez et al. Heart Rhythm 2014; 11:2214-2221

AF Definitions

- AF Episode: AF which has a duration of at least 30 seconds or if less than 30 s is present continuously throughout the ECG.
- Paroxysmal AF: recurrent AF that terminates within 7 days.
  AF episodes < 48 hrs terminated with CV are also paroxysmal.
- Persistent AF: AF which is sustained beyond 7 days, *or lasting > 48 hrs and less than seven days but necessitating CV.*
- Long standing persistent AF: Continuous AF of greater than 12 months duration.
- The term permanent AF is not appropriate in the context of patients undergoing ablation of AF as it refers to a group of patients where a decision has been made not to pursue restoration of sinus rhythm .

Heart Rhythm Society 2012 Expert Consensus Guidelines

Projected Number of Persons with AF in the United States Between 2000 and 2050



Miyasaka Y, et al. *Circulation* 2006;114:119-125.

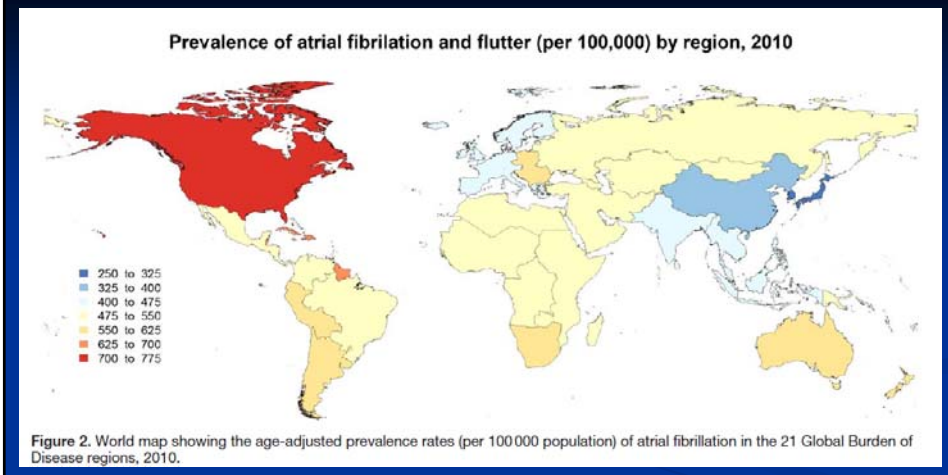
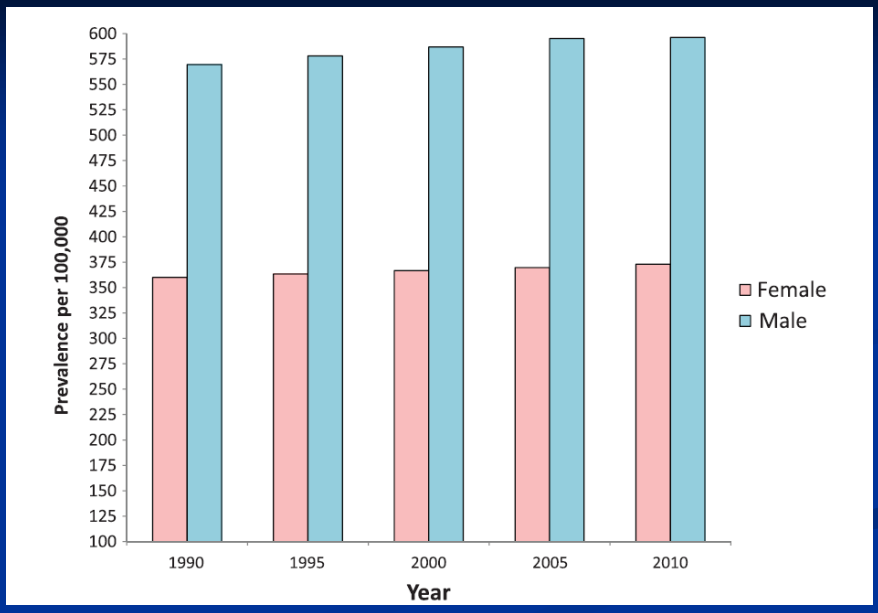


Figure 2. World map showing the age-adjusted prevalence rates (per 100 000 population) of atrial fibrillation in the 21 Global Burden of Disease regions, 2010.

Number of individuals with AF globally in 2010 – 33.5 million

Chugh et al. Circulation 2014;129:837-847.

Prevalence of AF. 1990 to 2010



Chugh et al. Circulation 2014;129:837-847

Mortality associated with AF

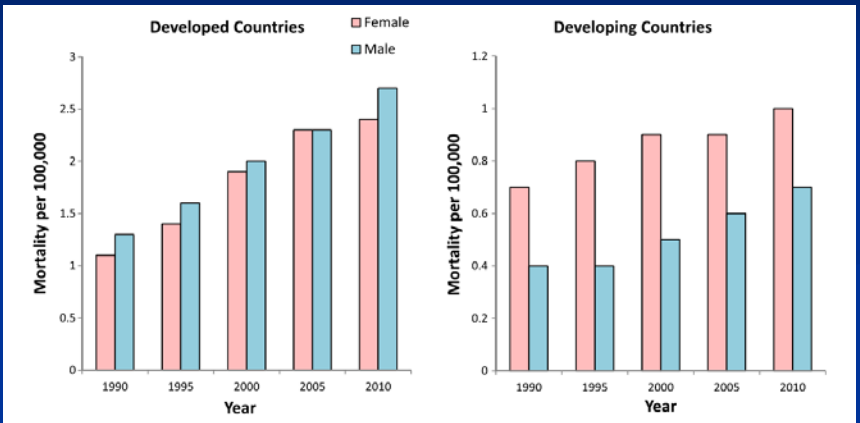
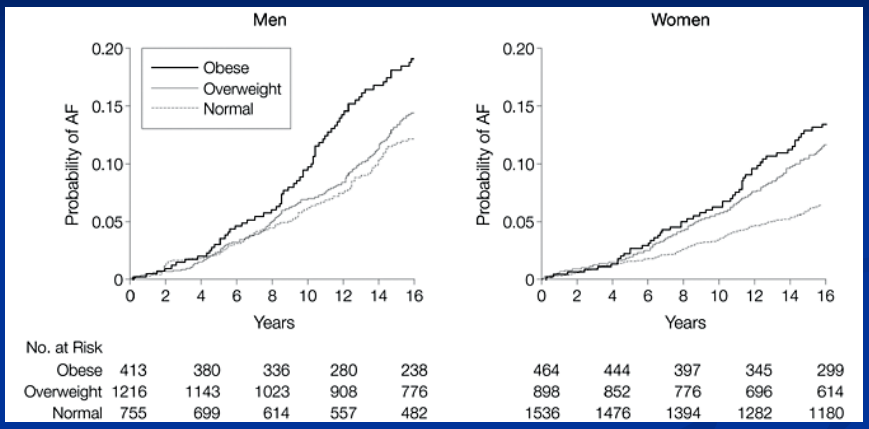


Figure 6. Mortality associated with atrial fibrillation (AF) stratified by sex and type of region (developed vs developing). Mortality associated with AF was higher in men and women in the developed regions. The significantly higher mortality in women in the developing regions is responsible for the overall higher AF-related mortality among women compared with men.

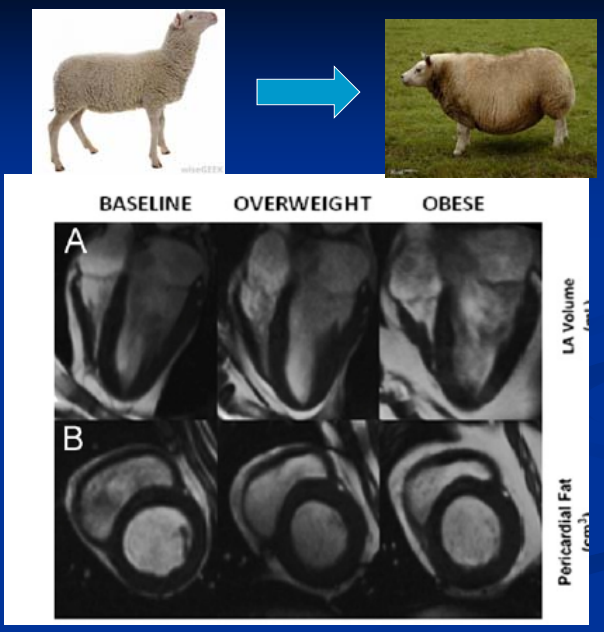
Cumulative Hazards of Developing AF in Men and Women by Baseline Body Mass Index Category



Normal <25
Overweight 25 to <30
Obese ≥ 30

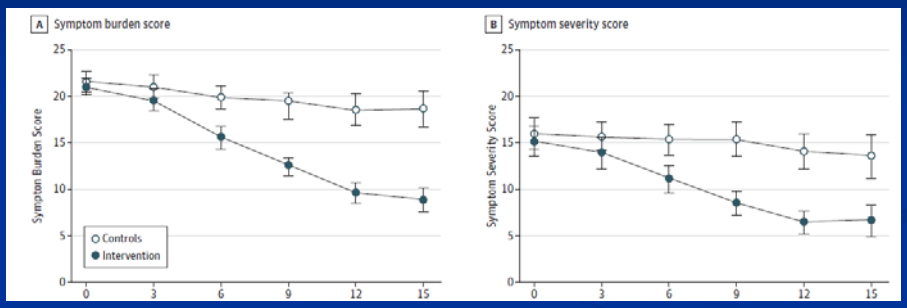
Wang T, et al. JAMA 2004;292:2471-2477.

Obesity Induced Progressive Atrial Structural and Electrical Remodeling



Hany et al. Heart Rhythm 2013;10:90-100.

Effect of Weight Reduction and Cardiometabolic Risk Factor Management on Symptom Burden and Severity in Patients With Atrial Fibrillation



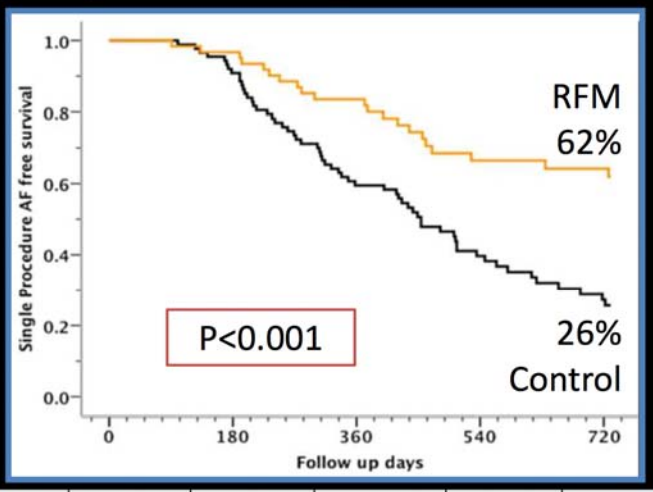
Abed et al. JAMA 2013;310(19):2050-2060.

ARREST -AF

- 165 patients after first AF ablation
- BMI>27 and one risk factor (HTN, DM, OSA, abnormal lipids)
- Active treatment group – weight loss management strategies, treatment of hyperlipidemia, glucose intolerance, HTN and OSA. Tobacco and ETOH use also aggressively targeted.

Pathak et al. JACC 2014; 64:2222-31.

Single procedure AF free survival

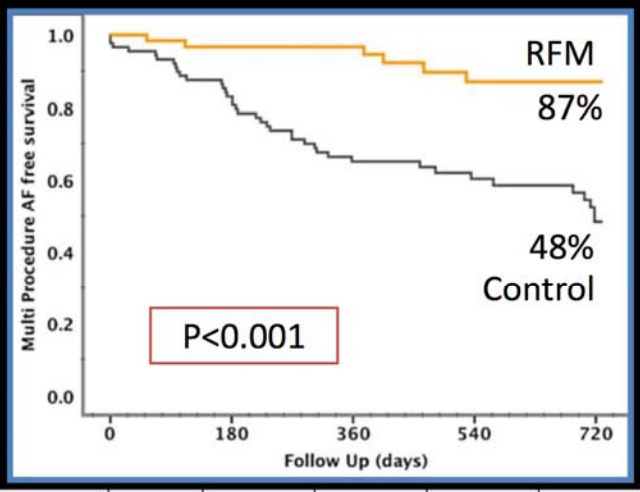


Days	0	180	360	540	730
RFM	61	59	48	33	27
Control	88	72	51	36	23

Multi procedure AF free survival

Control

No. of Procedure:
- 1: 37 (43%)
- ≥2: 49 (57%)

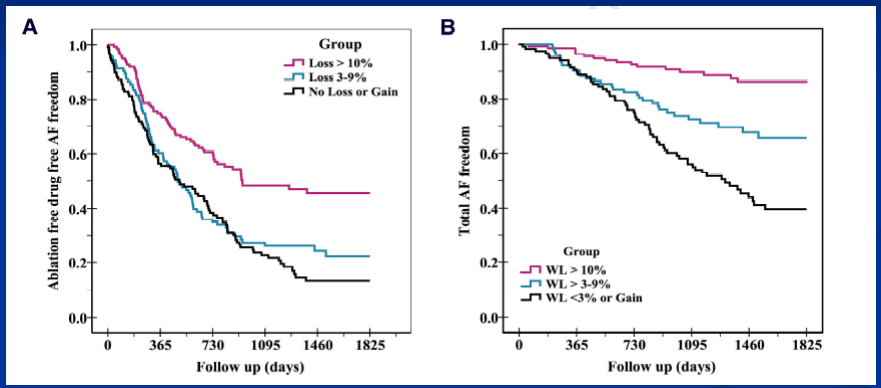


RFM

No. of Procedure:
- 1: 34 (54%)
- ≥2: 29 (46%)

Days	0	180	360	540	730
RFM	61	55	46	32	25
Control	88	72	51	36	23

The Greater the Weight Loss – The Greater the Decrease in AF

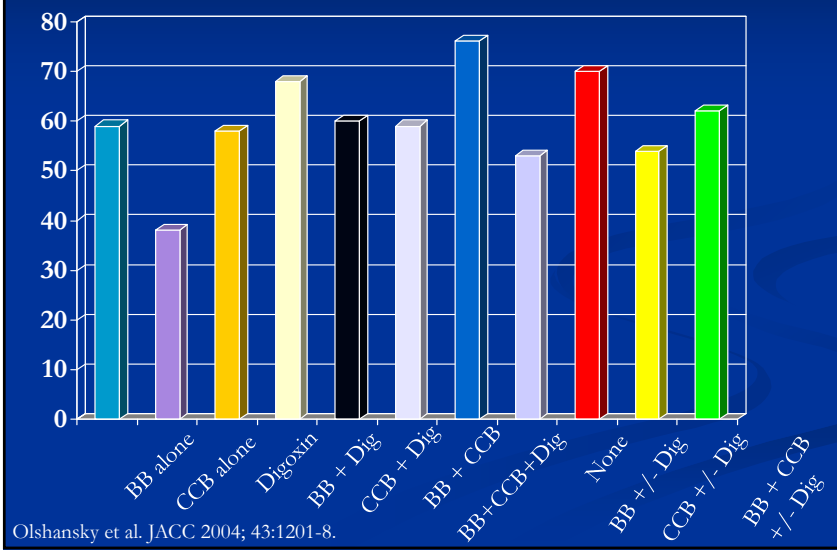


Pathak et al. Journal of the American College of Cardiology (2015), doi: 10.1016/j.jacc.2015.03.002.

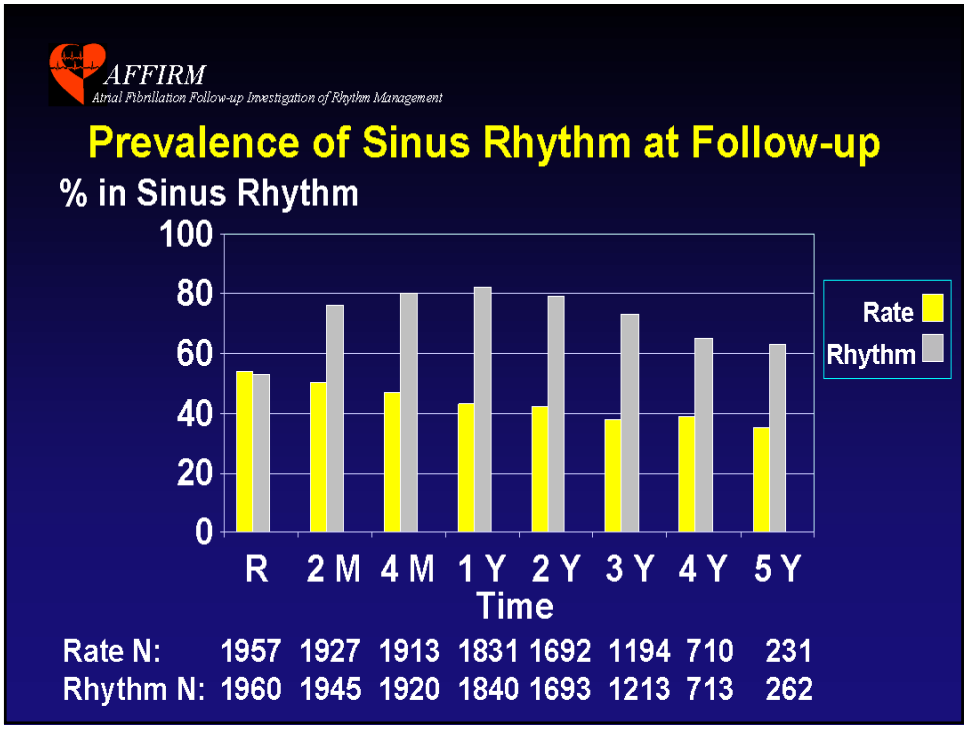
Treatment Options?

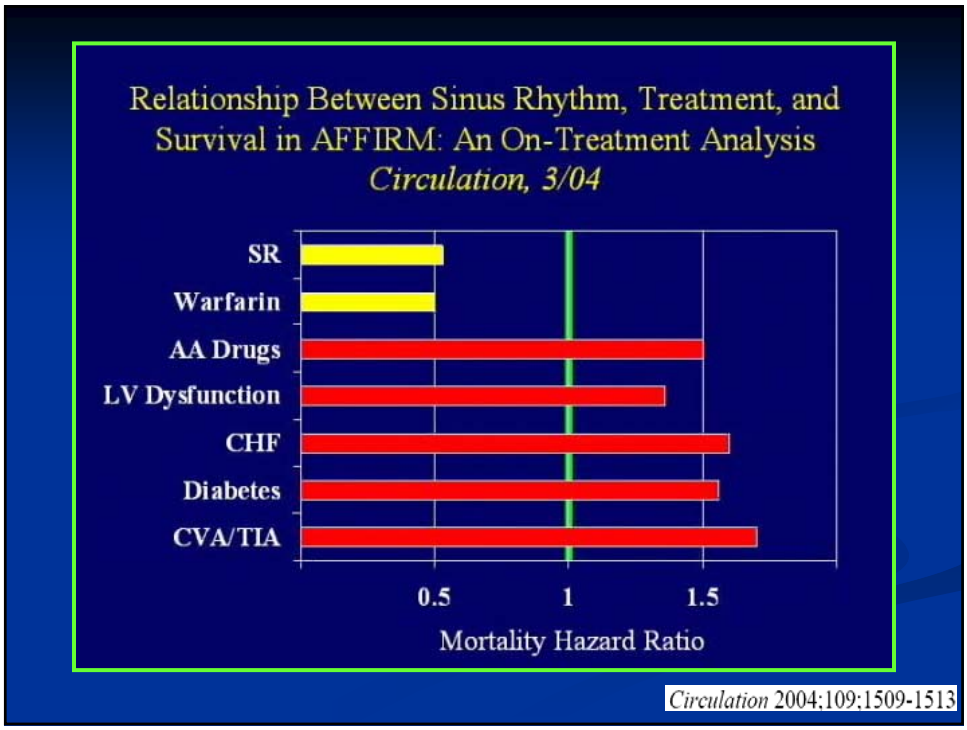
- Rate control
  - Includes pacemaker insertion with AVN ablation
- Rhythm control
  - Cardioversion
  - Antiarrhythmic drugs
  - Ablation therapy
- Anticoagulation – None, ASA, Warfarin, Dabigatran, Rivaroxaban, Apixiban

Overall Successful Rate Control Affirm Trial



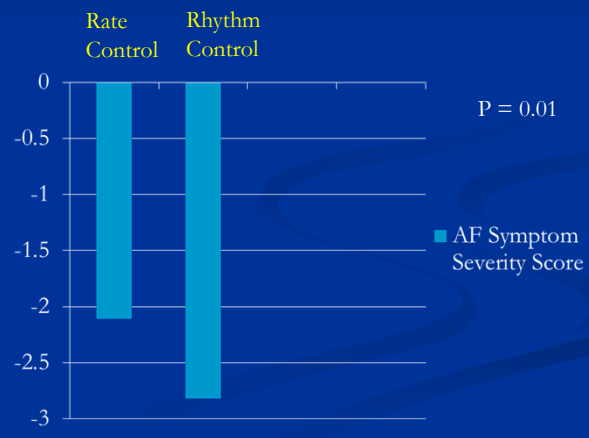
Olshansky et al. JACC 2004; 43:1201-8.


AFFIRM
Atrial Fibrillation Follow-up Investigation of Rhythm Management
Prevalence of Sinus Rhythm at Follow-up
% in Sinus Rhythm
100
80
60
40
20
0
Rate
Rhythm
R 2 M 4 M 1 Y 2 Y 3 Y 4 Y 5 Y
Time
Rate N: 1957 1927 1913 1831 1692 1194 710 231
Rhythm N: 1960 1945 1920 1840 1693 1213 713 262


Relationship Between Sinus Rhythm, Treatment, and Survival in AFFIRM: An On-Treatment Analysis
Circulation, 3/04
SR
Warfarin
AA Drugs
LV Dysfunction
CHF
Diabetes
CVA/TIA
0.5
1
1.5
Mortality Hazard Ratio
Circulation 2004;109:1509-1513

RECORD – AF Trial

- 2439 Patients with recent onset AF diagnosed less than one year
- Randomized to rate or rhythm control and evaluated health related quality of life over one year.



Ha et al. Circ Cardiovasc Qual Outcomes 2014

Lenient versus Strict Rate Control in Patients with Atrial Fibrillation

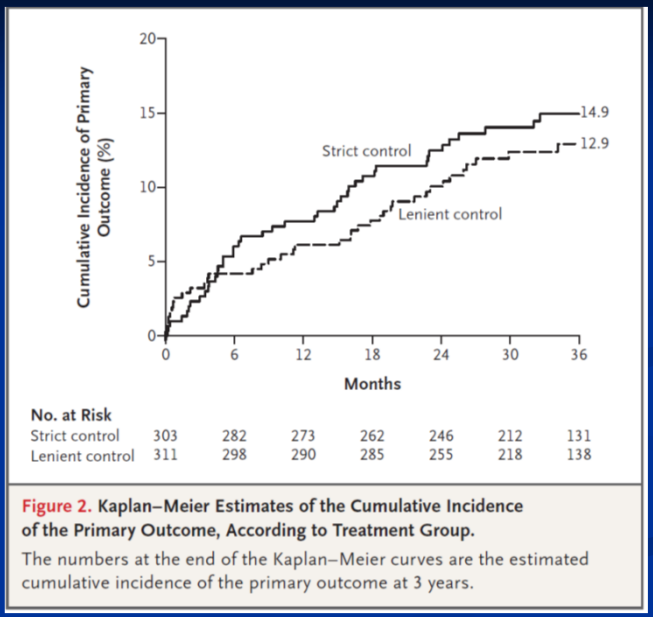


Figure 2. Kaplan–Meier Estimates of the Cumulative Incidence of the Primary Outcome, According to Treatment Group.
The numbers at the end of the Kaplan–Meier curves are the estimated cumulative incidence of the primary outcome at 3 years.

Gelder et al. N Engl J Med 2010;362:1363-41.

Increased Mortality Associated With Digoxin in Patients With AF

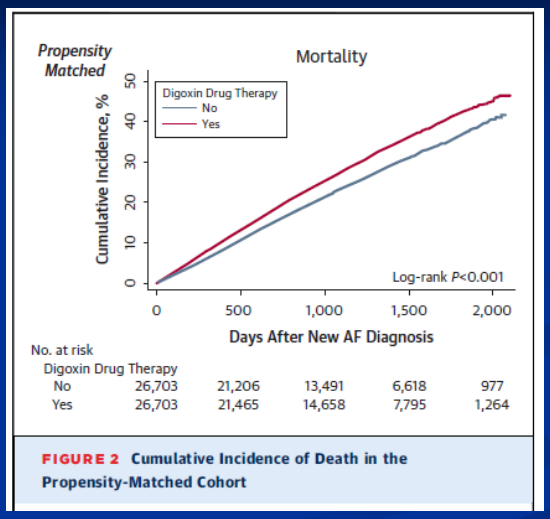
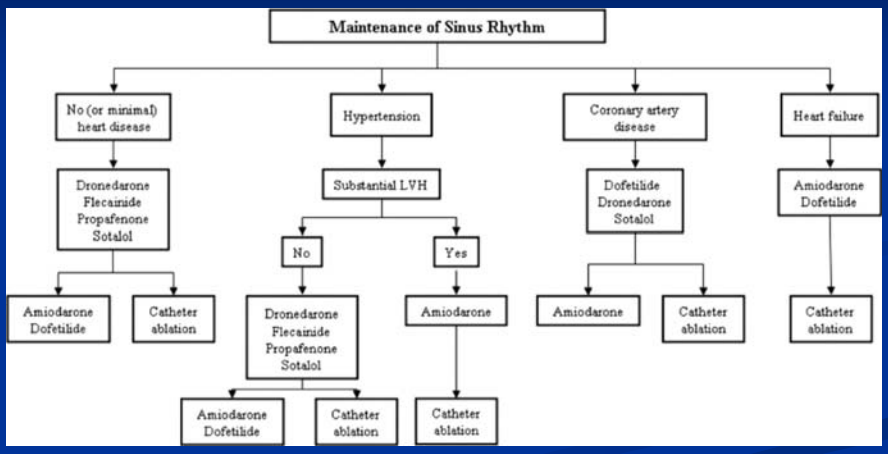


FIGURE 2 Cumulative Incidence of Death in the Propensity-Matched Cohort

Turakhia et al. JACC 2014;64:660-8.

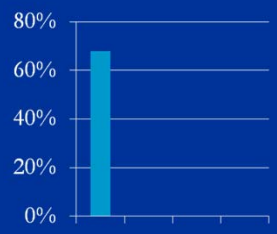
Therapy to maintain sinus rhythm in patients with recurrent paroxysmal or persistent atrial fibrillation



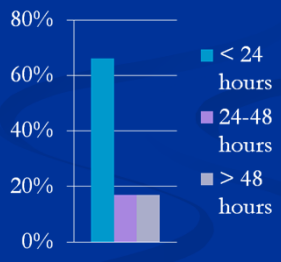
Wann, L. S. et al. J Am Coll Cardiol 2011;57:223-242

Is Cardioversion Always Necessary For New Onset AF?

Spontaneous conversion in patients with AF of less than 72 hours in duration

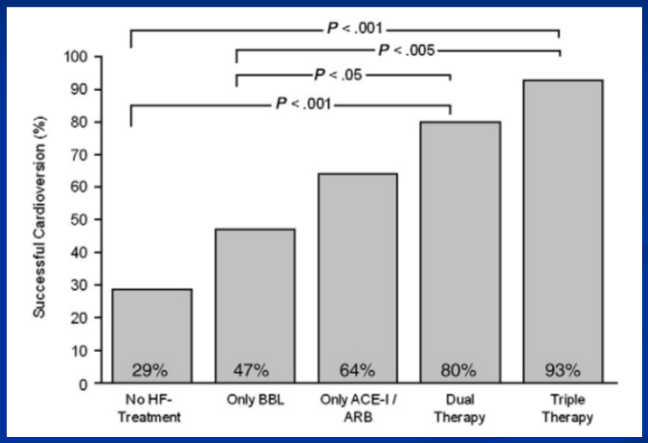


Duration of AF in patients with Spontaneous conversion



JACC 1998;31:588.

Cardioversion in a Heart Failure Population (Mean EF = 32%)



Boldt et al. Am Heart J. 2008;155:890-895.

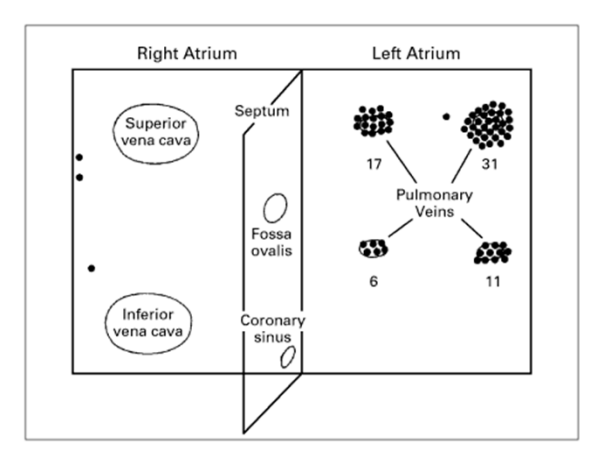
Cardioversion Key Points

- Everyone gets heparin before cardioversion
- Give 4 weeks of oral anticoagulation after cardioversion unless both true:
  - Episode clearly less than 48 hours
  - No stroke risk present
- If AF > 48 hours, either 3 weeks OAC or perform TEE, and 4 weeks of OAC after CV
- Treat atrial flutter like atrial fibrillation

Catheter Ablation of Atrial Fibrillation

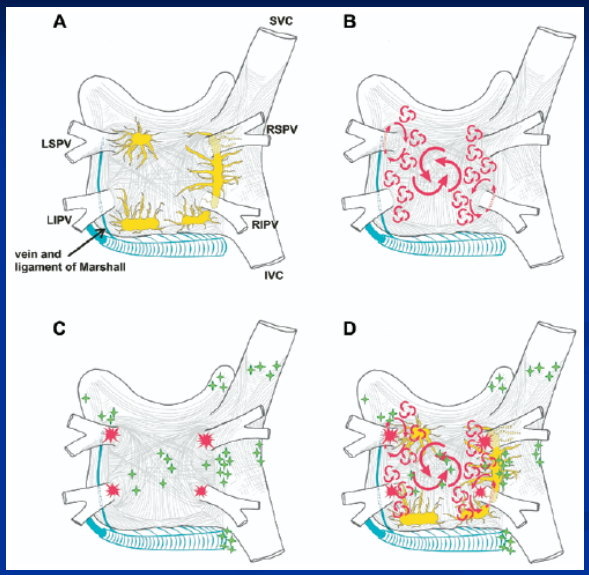
- Over the past decade, radiofrequency catheter ablation (RFA)of atrial fibrillation (AF) has evolved from an experimental procedure to an important treatment option for many patients.
- Although AF ablation is performed worldwide, its proper place in the treatment algorithms remains subject to debate.
- Reported success rates for AF ablation have varied widely from 29% to 85%
- There have been very few, prospective, randomized multi-center clinical trials performed that compare the relative efficacy of catheter ablation versus AAD therapy

Foci Triggering AF



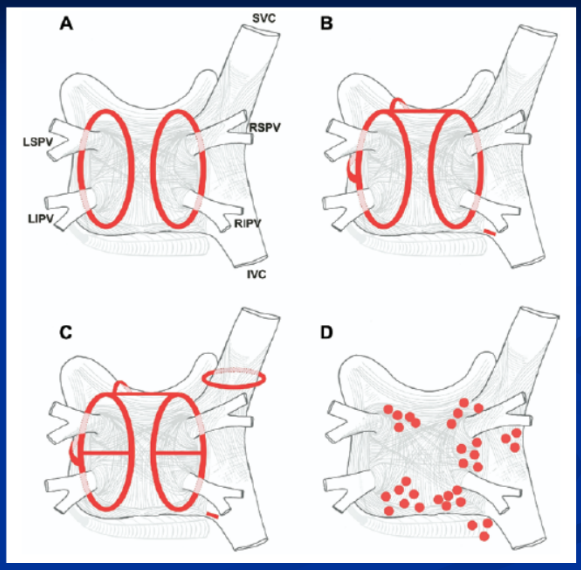
Haissaguerre et al. *NEJM* 1998; 339:659-66.

Mechanisms of Atrial Fibrillation



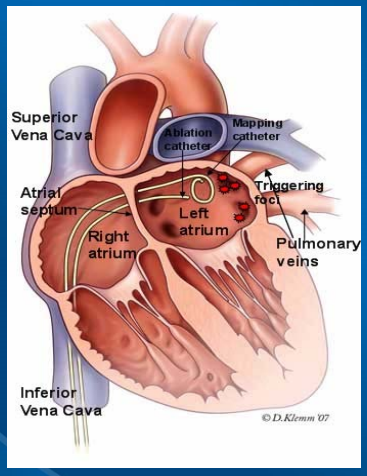
Calkins et al. Heart Rhythm 2007;4:816-861

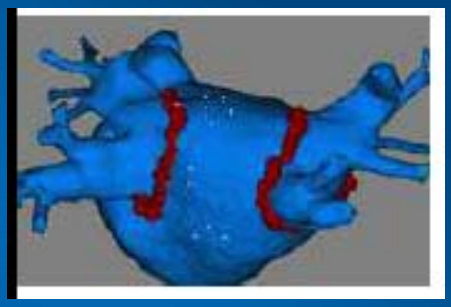
Common Lesion Sets Employed in AF Ablation



Calkins et al. Heart Rhythm 2007;4:816-861

Atrial Fibrillation Ablation





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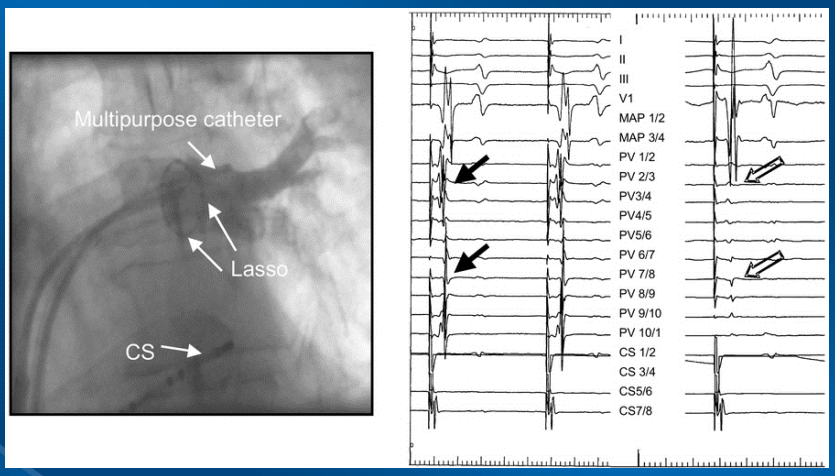
Segmental Pulmonary Vein Ablation



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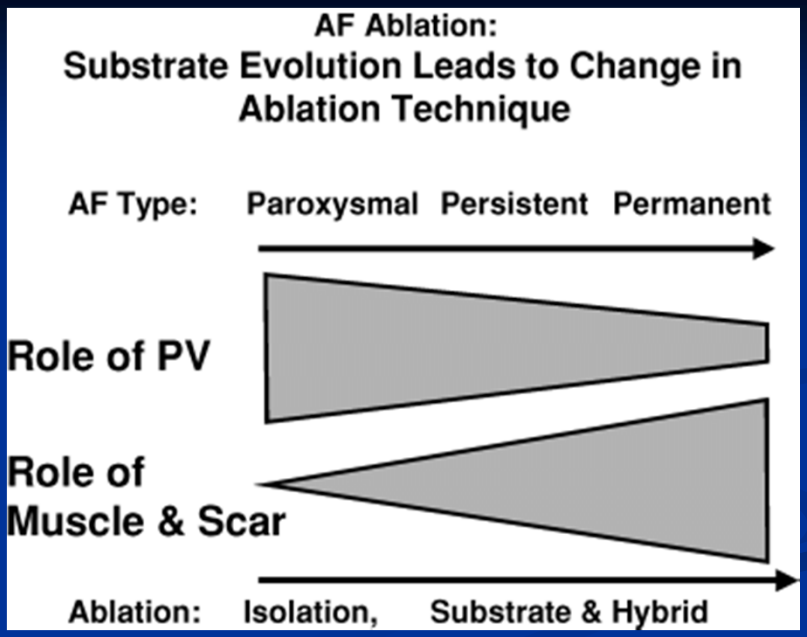
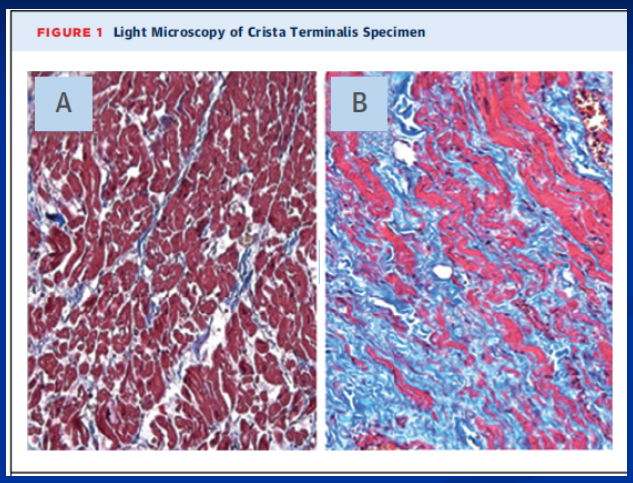
Karch et al. Circulation 2005;111:2875-2880.

AF Ablation: Substrate Evolution Leads to Change in Ablation Technique



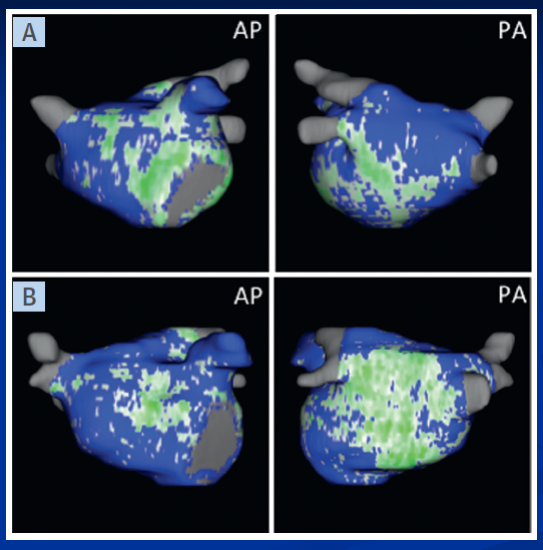
Spinelli et al. PACE 2006;29:523-537.

Sinus Rhythm Persistent AF



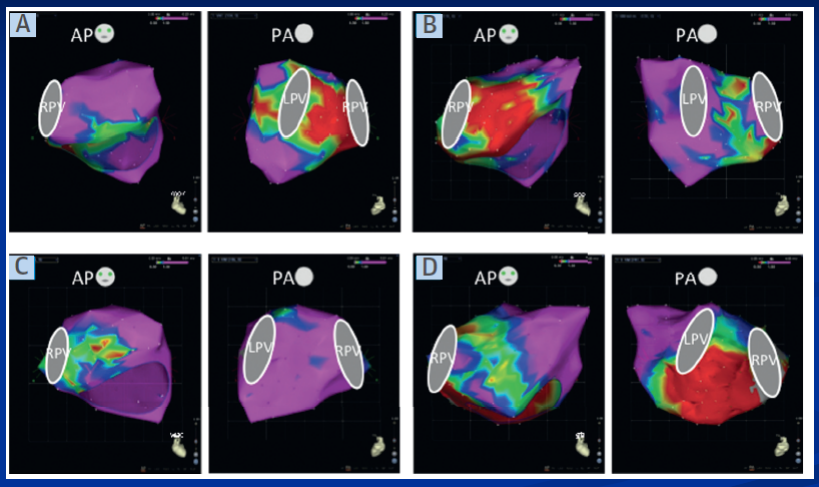
Kottkamp et al. JACC 2015;65:196-206.

Delayed Enhancement MRI

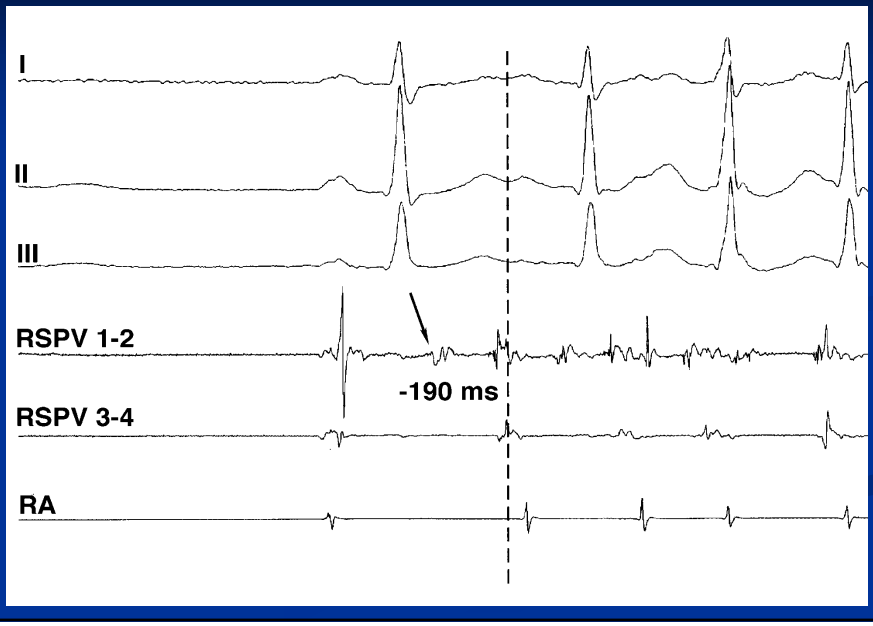


Kottkamp et al. JACC 2015;65:196-206

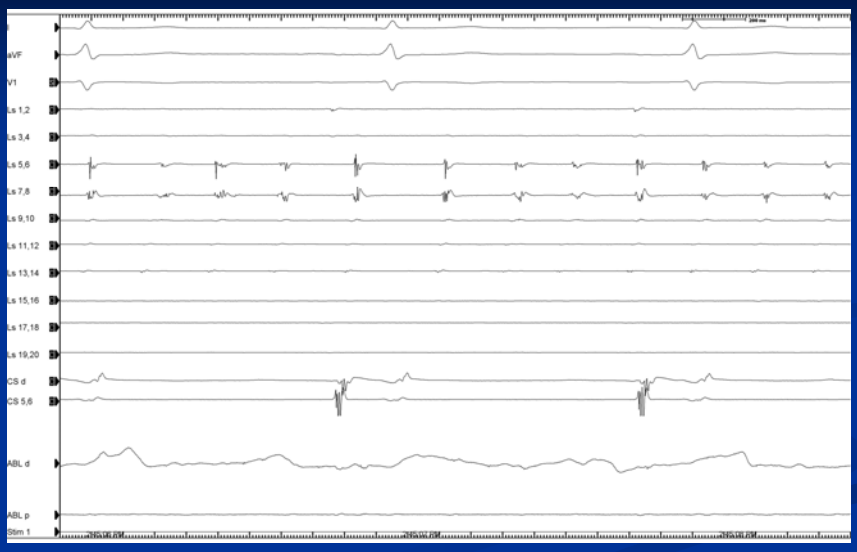
Voltage Mapping Showing Variable Localization of LA Fibrosis



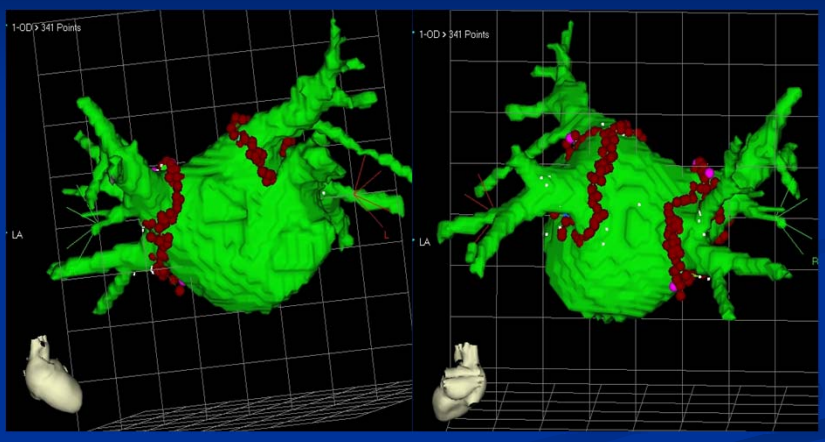
AF Trigger From RSPV



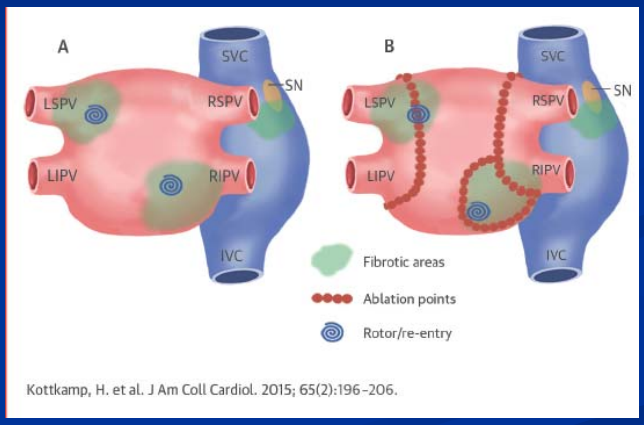
50 yo male with AF



3D Merge with CT or MRI



Regional Substrate Localization and Individualized Ablation

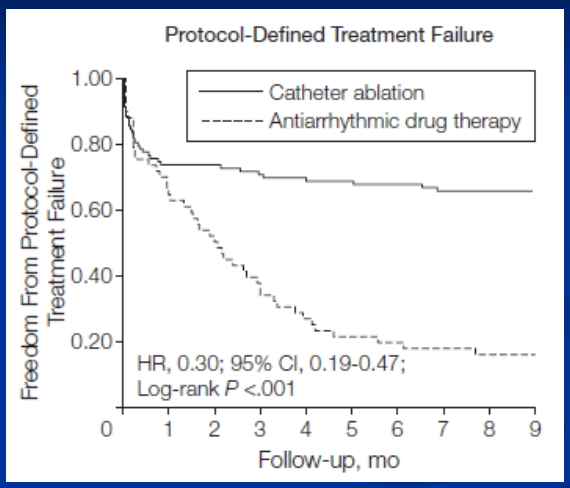


Kottkamp, H. et al. J Am Coll Cardiol. 2015; 65(2):196-206.

Prospective Randomized Clinical Trials Comparing PVI alone vs. AAD to prevent AF recurrence

Acronym Reference	Patients	Study design	End-points	Findings
APAF (1 center) Pappone C et al. [80]	198 Pts (mean age 56 years) Drug-refractory paroxysmal AF 6 weeks blanking period	CPVA + CTI/MI vs. untested AAD PPP: 1.1	- **AA recurrence** *(ECGs, 24h HM, daily TTM and symptom-triggered recordings)* - **Hospitalization**	- **1-Yr atrial arrhythmias free survival** *86% in the CPVA group vs. 22% in the AAD group (p<0.001)* - **Cardiovascular Hospitalization** *7 times more frequent in the AAD group vs. CPVA group (p<0.001)*
RAAFT (3 centers) Wazni et al. [79]	70 Pts (mean age 53 years) Paroxysmal AF: 95% 2 months blanking period First line therapy	ICE guided PVI vs. AAD Single procedure PPP: 1.0	- **AF recurrence** *(ECGs, 24h HM, 1 month event loop recorder, Log of symptoms and TTM)* - **Hospitalization** - **QOL** (*SF-36) at 6 months*	- **1-Yr AF free survival** *87% in the PVAI group vs. 37% in the AAD group (p<0.001)* - **Hospitalization** *54% in the AAD group vs. 9% in the PVAI group (p<0.001)* - **QOL** Significantly better in the PVAI group (p<0.001)
A4 (4 centers) Jais et al. [73]	112 Pts (mean age 51 years) Paroxysmal AF 3 months blanking period	PVI + CTI ± linear lesion vs. untested AAD up to 3 procedures PPP: 1.8	- **AA recurrence** *(ECGs, 24h HM)* - **QOL** *(SF-36)* - **Exercise capacity** *(Treadmill; max HR, workload, METs)*	- **1-Yr atrial arrhythmias free survival** *89% in the PVAI group vs. 23% in the AAD group (p<0.0001)* - **AF burden** *Greatest reduction in pts randomized to PVAI.(p=0.0001)* - **QOL, symptoms and Exercise capacity** *Improved more after PVAI than AAD therapy (p<0.001)*
Thermo-cool AF (19 centers) Wilber D et al. [81]	167 Pts (mean age 55 years) Paroxysmal AF 3 months blanking period.	PVI ± CTI, left atrial lines & CFAEs vs. untested AAD up to 3 procedures PPP: 1.1	- **AA recurrence** *(ECGs, 24h HM, TTM and symptom-triggered recordings)* - **QOL** (*SF-36)*	- **1-Yr atrial arrhythmias free survival** *63% in the CA group vs. 17% in the AAD group (p<0.0001)* - **QOL and symptoms** *Improved significantly more after PVAI than AAD therapy (p<0.001)*

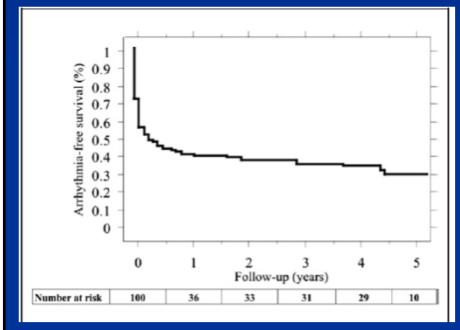
Comparison of Antiarrhythmic Drug Therapy and Radiofrequency Catheter Ablation in PatientsWith Paroxysmal Atrial Fibrillation



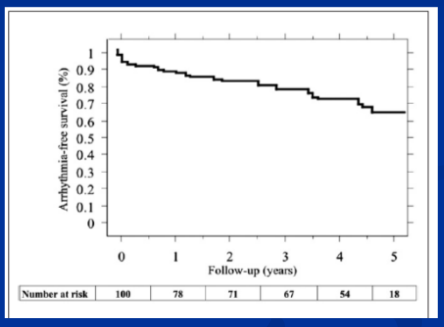
Wilber et al. JAMA 2010;303:333-340.

Long Term Follow-up of Atrial Fibrillation Ablation

Single Procedure Success

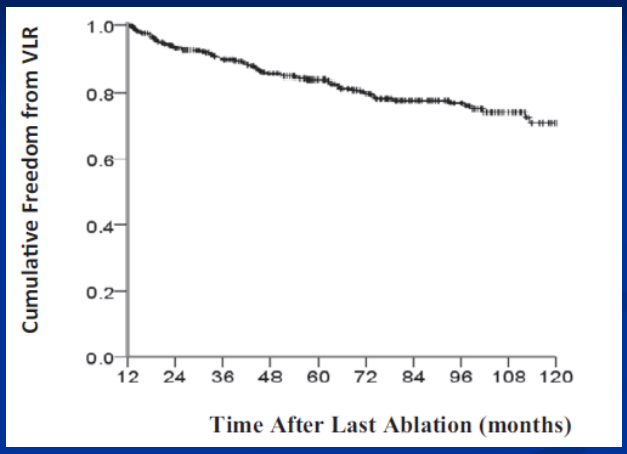


Multiple Procedure Success



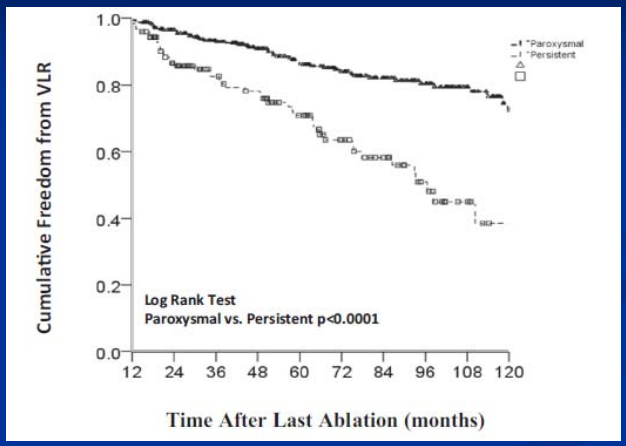
Weerasooriya et al. JACC 2011;57:160-6

Very Long-Term Outcome after Initially Successful Catheter Ablation of AF



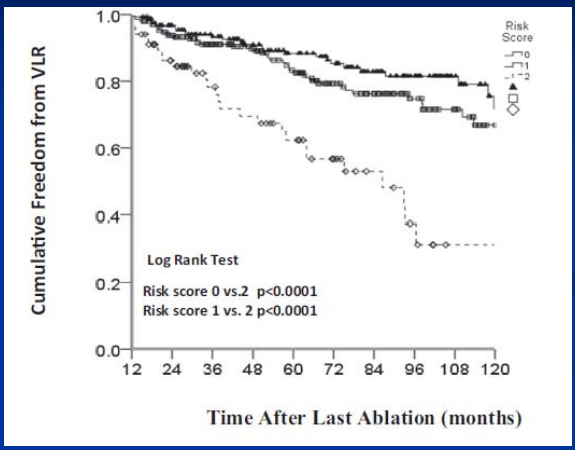
Steinberg et al. Heart Rhythm 2014; 11:771-776.

Paroxysmal vs Persistent AF Patients



Steinberg et al. Heart Rhythm 2014; 11:771-776

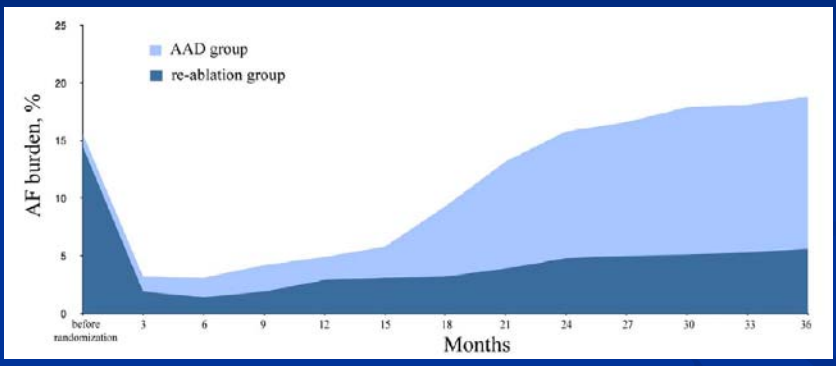
Very Long-Term Outcome after Initially Successful Catheter Ablation of AF



Risk Factors:
- HTN
- Persistent AF

Steinberg et al. Heart Rhythm 2014; 11:771-776

Drug Therapy vs. Reablation after Initial Failed Ablation



Pokushalov et al. Circ Arrhythm Electrophysiol. 2013; 6:754-760.

New Technologies for Atrial Fibrillation Ablation
Stereotaxis Magnetic Catheter Manipulation

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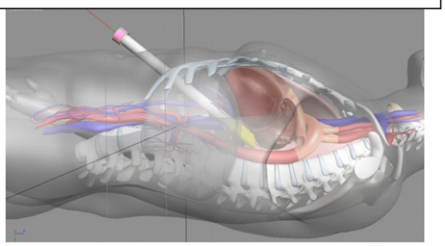
Hybrid Approach to AF Ablation - Convergent Procedure

Transdiaphragmatic Pericardioscipic Access



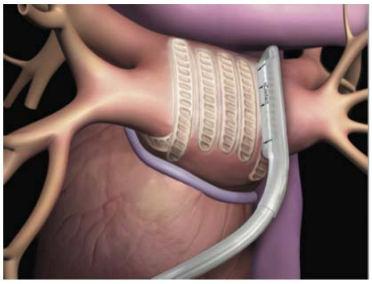


Figure 2: Depiction of the ablation catheter and typical epicardial lesion set.

Causes of death in 32 569 patients from 162 centers

Causes of death	n (%)
Early death (within 30 d)	
• Tamponade	7 (21.8)
• Atrioesophageal fistula	5 (15.6)
• Stroke	3 (9.4)
• Massive pneumonia	2 (6.3)
• 1 event each of MI, pulmonary vein perforation, irreversible torsades de pointes, septicemia, sudden respiratory arrest, acute pulmonary vein occlusion, hemothorax, and anaphylaxis	1 (3.1)
Late death (after 30 d)	
• Stroke	2 (6.3)
• 1 event each of tracheal compression of subclavian hematoma, acute respiratory distress syndrome, esophageal perforation from TEE probe, tamponade with subsequent cardiac arrest in prior stroke, and intracranial bleeding under anticoagulation therapy in prior stroke	1 (3.1)

TEE=transesophageal echocardiography

Cappato R et al. *J Am Coll Cardiol* 2009; 53: 1798-1803.

Fatality Rates According to Type of Complication

Complication	Death/Overall Events (n)	Rate (%)
Tamponade	7/331	2.3
Atrioesophageal fistula	5/7	71.4
Massive pneumonia	2/2	100.0
Peripheral embolism		
Stroke	3/59	5.1
Myocardial infarction	1/3	33.3
Torsades de pointes	1/1	100.0
Septicemia (3 weeks after procedure)	1/3	33.3
Sudden respiratory arrest	1/1	100.0
Acute pulmonary vein occlusion of both lateral veins	1/6	16.7
Internal bleeding (includes hemothorax, subclavian hematoma, and extrapericardial pulmonary vein perforation)	3/21	14.3
Anaphylaxis	1/6	16.7
Acute respiratory distress syndrome	1/1	100.0
Esophageal perforation from intraoperative TEE probe	1/1	100.0
Intracranial bleeding under oral anticoagulation therapy in prior stroke	1/4	25.0

TEE = transesophageal echocardiographic.

Cappato et al. J Am Coll Cardiol 2009; 53: 1798-803

Ablation vs. Rate Control for Persistent AF in Heart Failure

Change in peak oxygen consumption

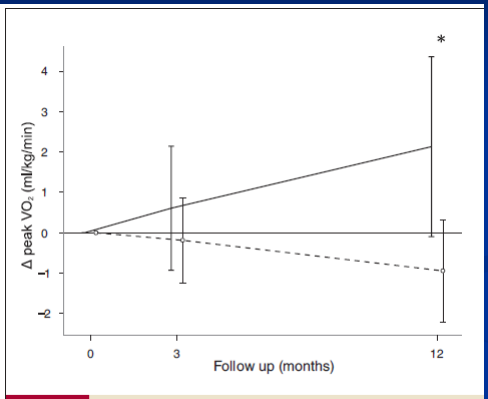


Figure 2 Primary Endpoint: Summary Data

Solid line = ablation

Dashed line = rate control

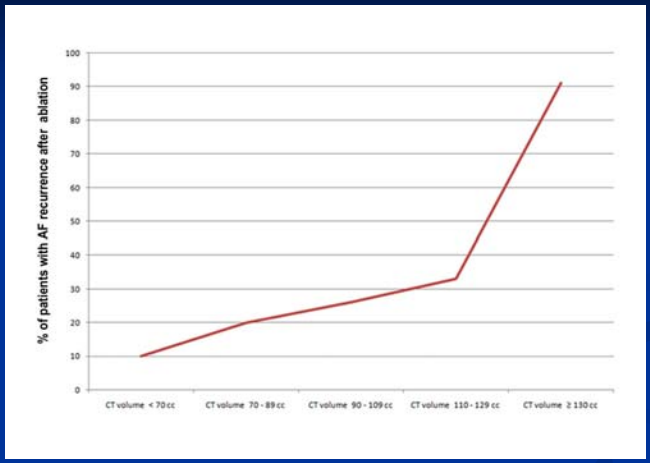
Jones et al. JACC 2013;61:1894-903.

Predictors of Success After Ablation For Atrial Fibrillation

- Left atrial volume
- Duration of AF history

Figure 2.

Failure rate after AF ablation depending on left atrial volume by CT.



- As shown in the ROC analysis, the frequency of AF recurrence after ablation increases as left atrial volume increases. The recurrence rate increase is 10 % in patients with small atria with volumes < 70 cc and increases to over 33% in patients with left atrial volumes between 110-129 cc. A left atrial volume over 130 cc as measured by CT appears to function as a threshold. Failure rate in patients with a volume of 130 cc or larger had an AF recurrence rate of more than 90 %.

Patient Selection for AF Ablation

Variable	Yes →	Probably not
Symptoms	Highly symptomatic	Minimally symptomatic
Class I and III drugs failed	>1	0
AF type	Paroxysmal	Long-standing persistent
Age	Younger (<70)	Older (>70)
LA size	Smaller (<50 mm)	Larger (>50 mm)
Ejection Fraction	Normal	Reduced
CHF	No	Yes
Other cardiac disease	No	Yes
Pulmonary disease	No	Yes
Sleep apnea	No	Yes
Obesity	No	Yes
Prior stroke/TIA	No	Yes

Back to our patient

- Started on Sotalol and then Tikosyn (Antiarrhythmic drugs) but continued to have symptomatic episodes of atrial fibrillation
- Decided to proceed with ablation therapy

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Effect of Yoga on Arrhythmia Burden in Paroxysmal Atrial Fibrillation

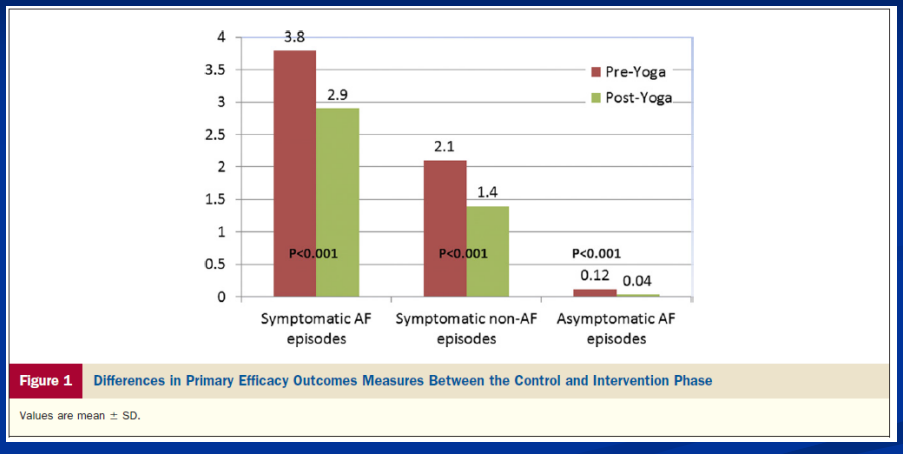


Figure 1 Differences in Primary Efficacy Outcomes Measures Between the Control and Intervention Phase

Values are mean ± SD.

Lakkireddy et al. JACC 2013;11:1177-82.

Omega-3 Fatty Acids for the Prevention of Recurrent Atrial Fibrillation

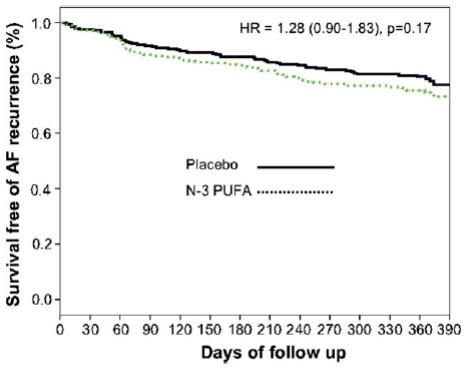
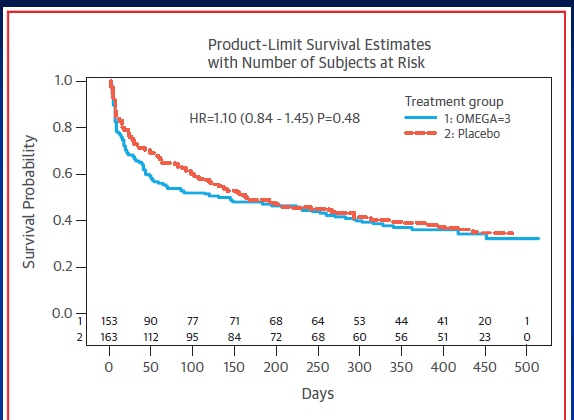


Figure 2 Primary Efficacy Endpoint

Time to first recurrence of symptomatic atrial fibrillation (AF). HR = hazard ratio; n-3 PUFA = polyunsaturated fatty acids.

Macchia et al. JACC 2013;4:463-8.

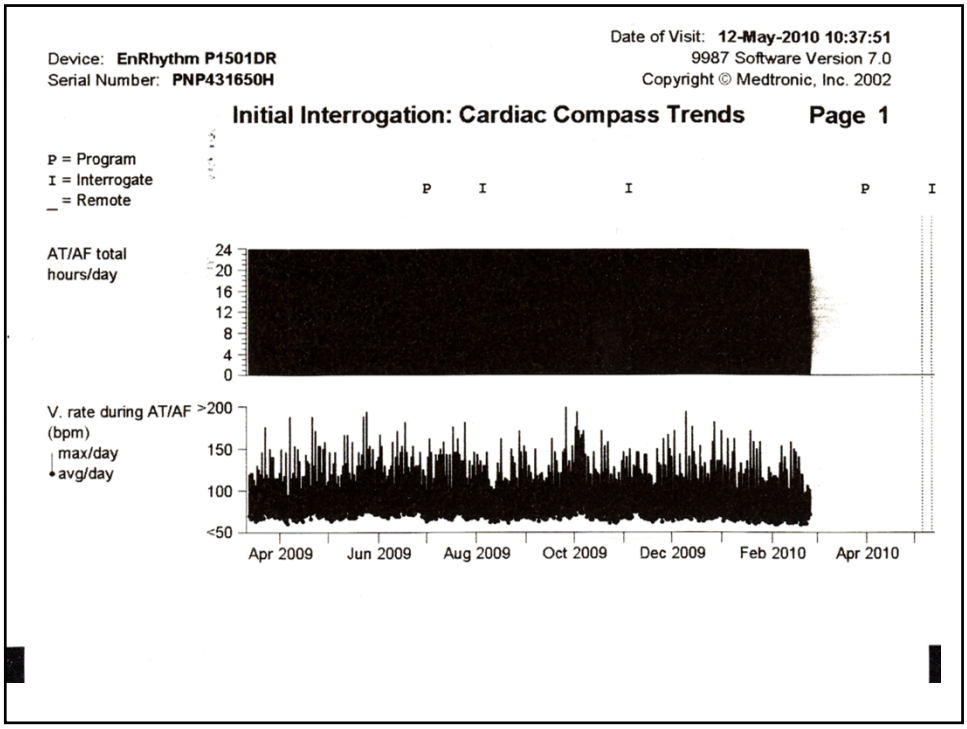
Fish Oil for the Reduction of Atrial Fibrillation



CENTRAL ILLUSTRATION Time to First Symptomatic or Asymptomatic Atrial Fibrillation

AF = atrial fibrillation; HR = hazard ratio.

Nigam et al. JACC 2014; 64: 1441-8.



Center For Atrial Fibrillation at URMC

Burr Hall, MD

275-4775