

The Current Management of Atrial Fibrillation

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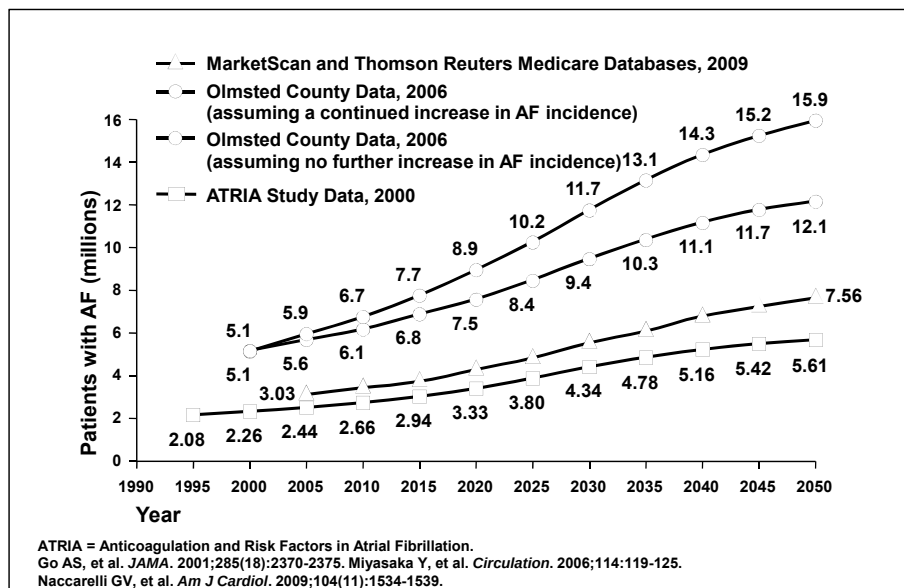
Disclosures

- **None**

Objectives

- Outline the 2015 treatment of atrial fibrillation
- Update on the oral anticoagulation therapy
- Pros and cons of the antiarrhythmic drugs (AADs) vs. ablative strategies

Projected Number of Patients with AF by 2050



Atrial Fibrillation: Costs to the Health Care System/ALOT!!

35% of arrhythmia hospitalizations

Average hospital stay = 5 days

Mean cost of hospitalization = \$18,800

Does not include:

Costs of outpatient cardioversions

Costs of drugs/side effects/monitoring

Costs of AF-induced strokes

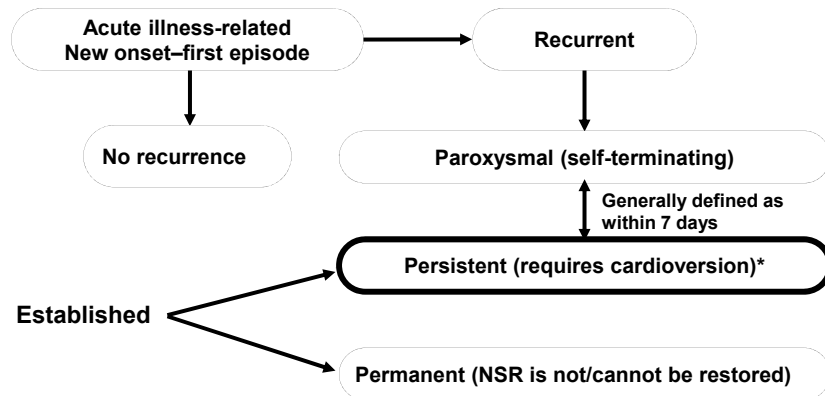
Estimated US cost burden 15.7 billion / year

What Are the Goals of AF Therapy?

- **Improve survival**
- **Reduce systemic thromboembolism**
 - **Stroke**
- **Reduce hospitalizations**
- **Improve symptoms**
- **Improve QoL**
- **Restore atrial function/reverse the remodeling process**

QoL = quality of life.

Classification of Patterns of AF

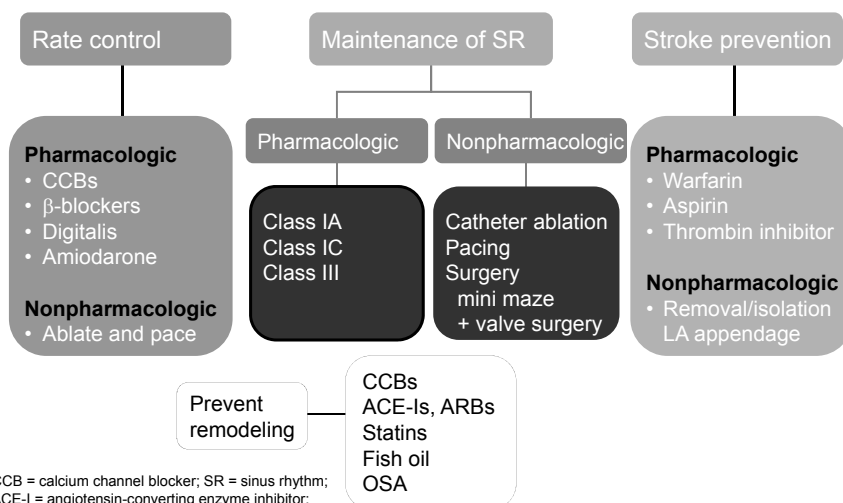


*Termination with pharmacologic therapy or DC cardioversion does not change the designation.

All forms can present with or without associated SHD

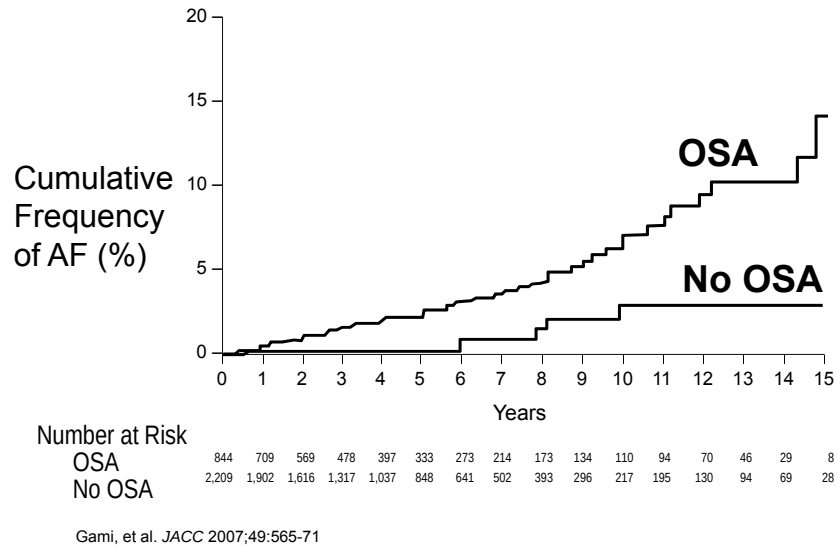
Fuster V, et al. *Circulation*. 2006;114(7):e257-e354.

AF: TREATMENT OPTIONS



CCB = calcium channel blocker; SR = sinus rhythm;
ACE-I = angiotensin-converting enzyme inhibitor;
ARB = angiotensin II receptor blocker; LA = left atrial.
Fuster V, et al. *J Am Coll Cardiol*. 2006;48(4):854-906. Prystowsky, *Am J Cardiol*. 2000;85:3D-11D.

Incidence of AF Based on Presence or Absence of OSA

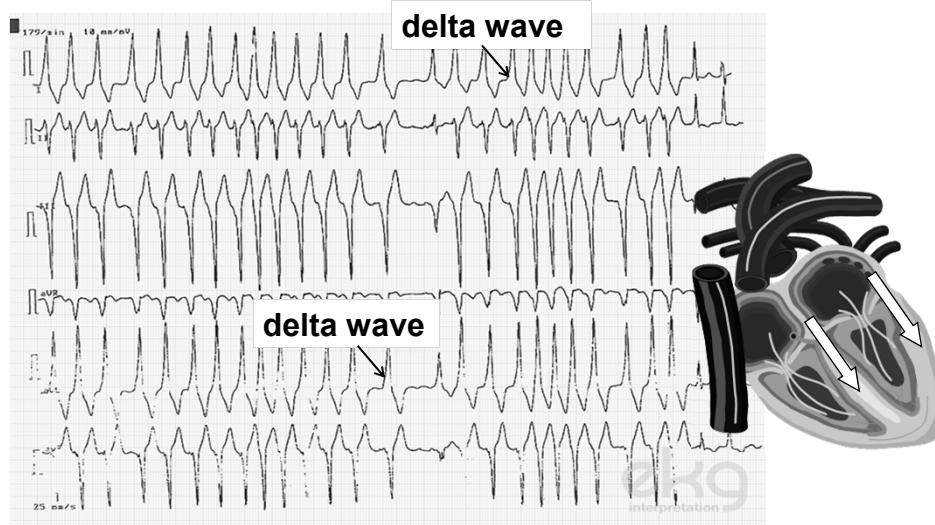


Acute Rate Control in AF with RVR

- IV beta blocker or calcium channel blocker.
 - Caution in *hypotension* & *CHF* Patients
- *Digoxin* and *amiodarone* should be used in
 - AF with RVR in CHF patient
 - AF with RVR in patient with hypotension

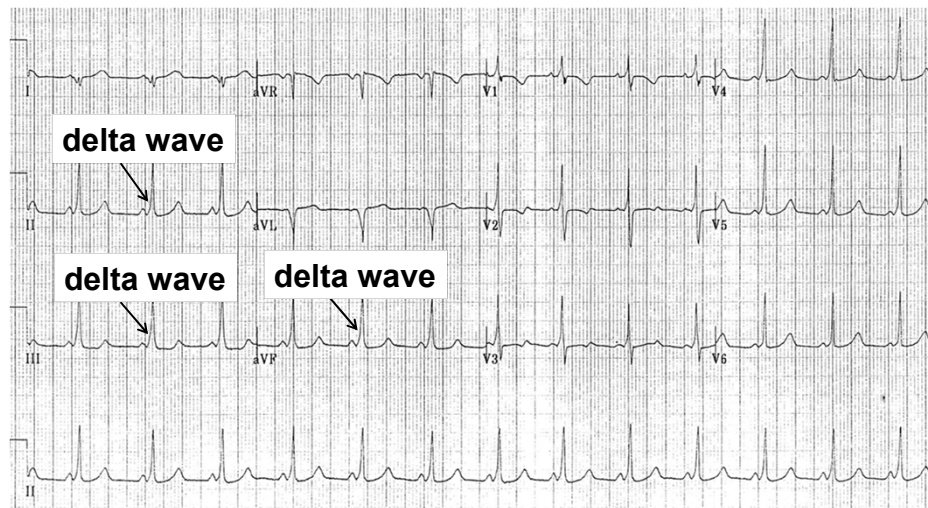
AF = atrial fibrillation; i.v. = intravenous.

AF with RVR & Pre-excitation (WPW)



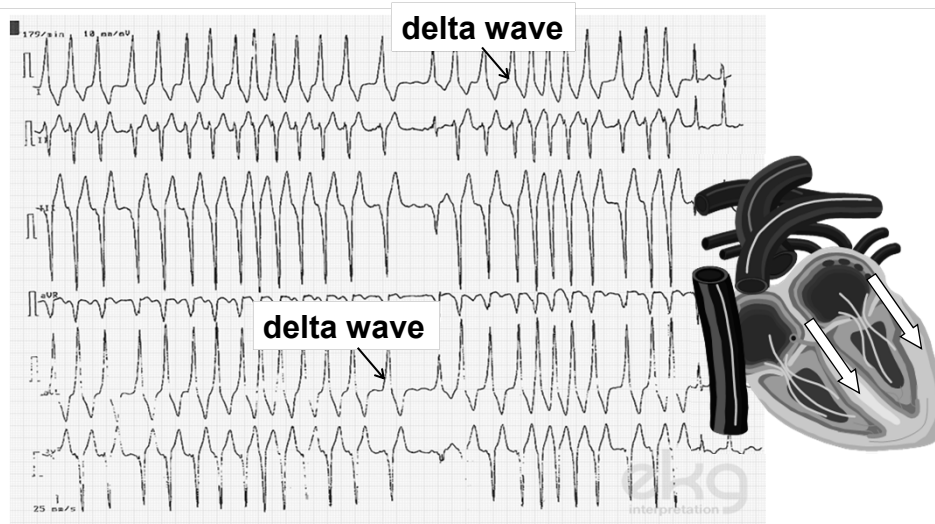
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AF with Pre-excitation (WPW)



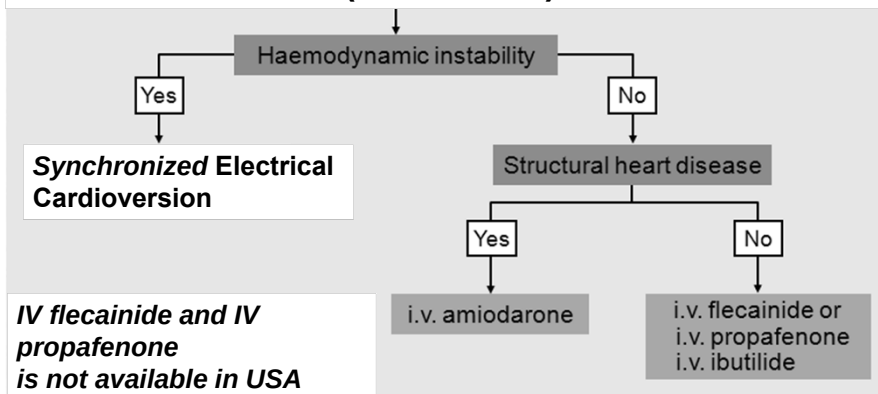
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AF with RVR & Pre-excitation (WPW)



**Avoid Beta blocker, CCB, Digoxin, adenosine
Procainamide or amiodarone or cardioversion**

Electrical conversion recent-onset AF (< 48 hrs)



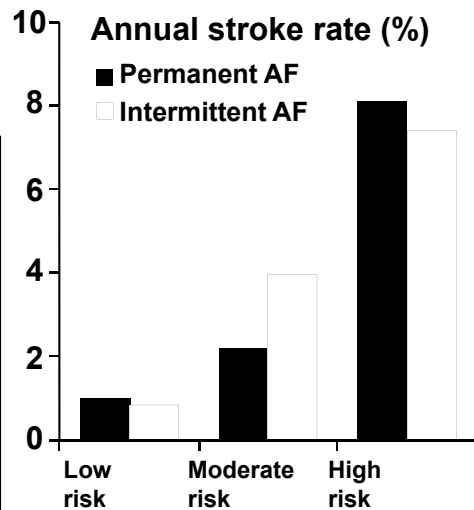
TEE Prior to Cardioversion (> 48 hr)

Ibutilide

- **Activates *slow inward Na* channels**
- **Risk of TdP: 1.7 to 8%**
- **Only IV**
- **Dose:**
 - **≥ 60 kg: 1mg over 10min**
 - **< 60 kg: 0.01mg/kg over 10min**
 - **May repeat once 10 min after 1st dose finished**
- ***Telemetry > 4 hr or until QTc at baseline***

Product Information: Corvert(R), ibutilide fumarate injection. Upjohn Company, Kalamazoo, MI, 2008

- **Stroke is the *most common* complication**
- **AF is an *independent* risk factor for stroke**
- **AF accounts for 15%**
- **Stroke risk *unchanged* regardless if the pt has a *little* or a *lot* of AF**
- **Stroke risk persists even in *asymptomatic* AF**
- **If *maintaining sinus rhythm* with medications, *stroke risk* still exists and is *unchanged***



CHADS₂ Score

Major Risks (2 pts):

Prior CVA / TIA

Systemic embolism

Non-Major Risks (1 pt):

CHF / LVEF ≤ 40%

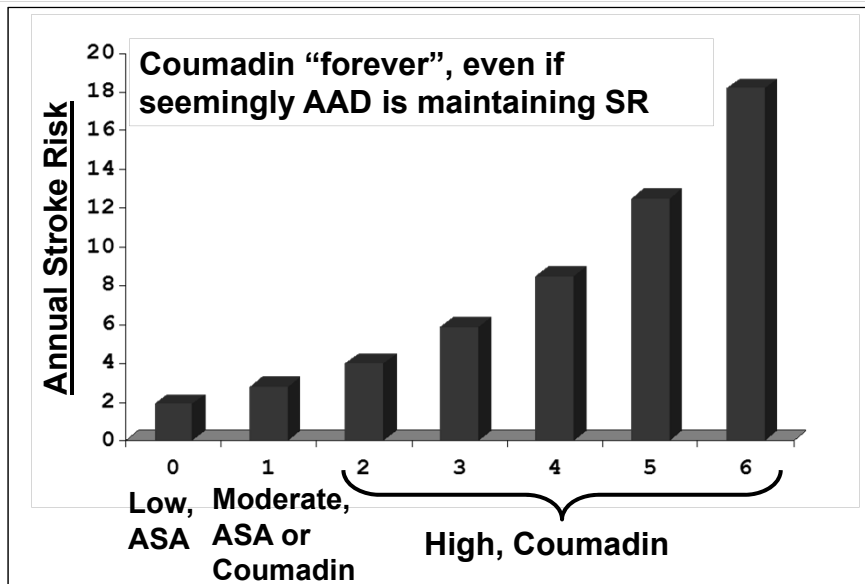
HTN

Age ≥ 75 yo

DM

Risk Factor	Score
Congestive HF	1
HTN	1
Age ≥ 75	1
DM	1
Stroke / TIA / TE	2
Maximum Score	6

Stroke Risk Related to CHADS₂ Score



CHA₂DS₂-VASc Score

Major Risks (2 pts):

Prior CVA / TIA

Systemic embolism

Age ≥ 75 yo

Non-Major Risks (1 pt):

CHF / LVEF $\leq 40\%$

HTN

DM

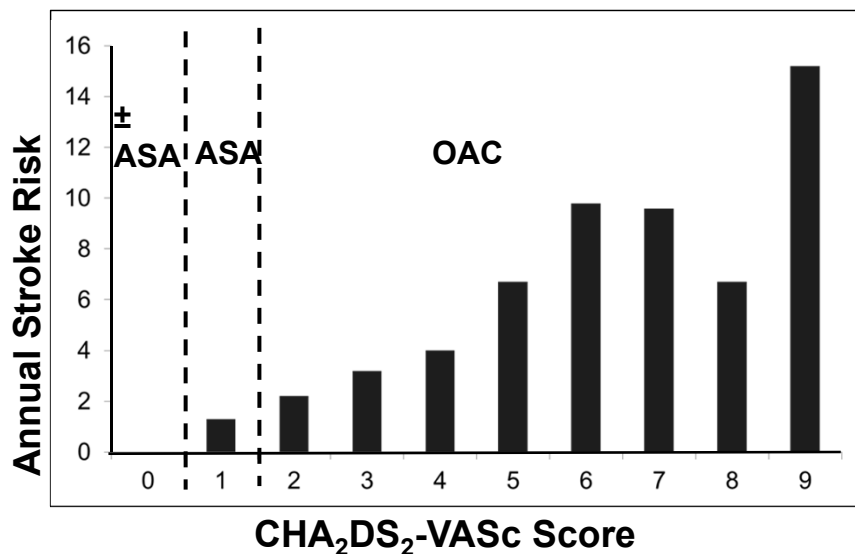
Female Sex

Age 65-74

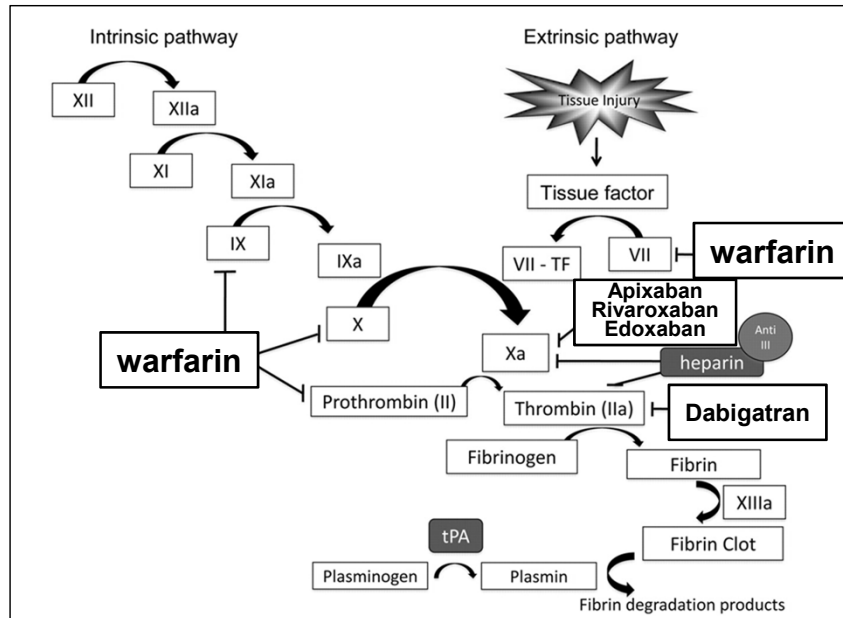
Vascular Disease

Risk Factor	Score
Congestive HF	1
HTN	1
Age ≥ 75	2
DM	1
Stroke / TIA / TE	2
Vascular Disease	1
Age 65 - 74	1
Sex (ie, female)	1
Maximum Score	9

Adjusted Annual Stroke Risk Using CHA₂DS₂-VASc Score n = 7329



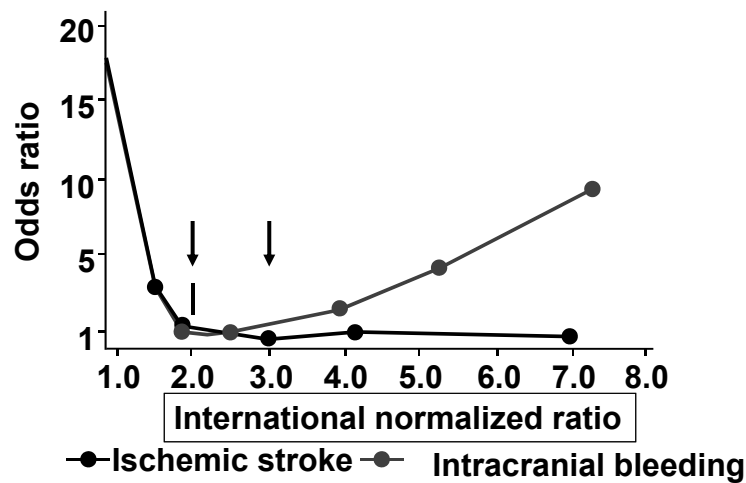
Camm AJ et al. Eur Heart J. 2010;31:2369-429.



Lazzaro M A , and Zaidat O O Neurology 2012;78:501-506

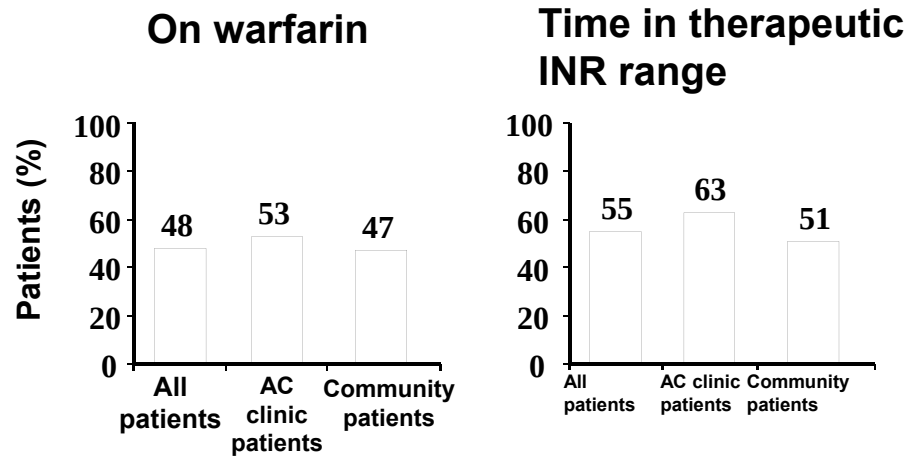
<http://www.neurology.org/content/78/7/501/F2.expansion.html>

Warfarin Risk/Benefit Balance INR Goal 2-3



Fuster V et al. Circulation. 2006;114:e257-e354.

Meta-analysis: 8 studies; 41,199 patient-yrs



Baker WL et al. J Manag Care Pharmacy. 2009;15:244-52.

Dabigatran

- RE-LY: dabigatran vs. warfarin
- RELY-ABLE: dabigatran vs. warfarin (extension)
- Brand Name Pradaxa

RE-LY: design

Noninferiority Trial

Randomized
Blinded/unblinded
(N = 18,113*)

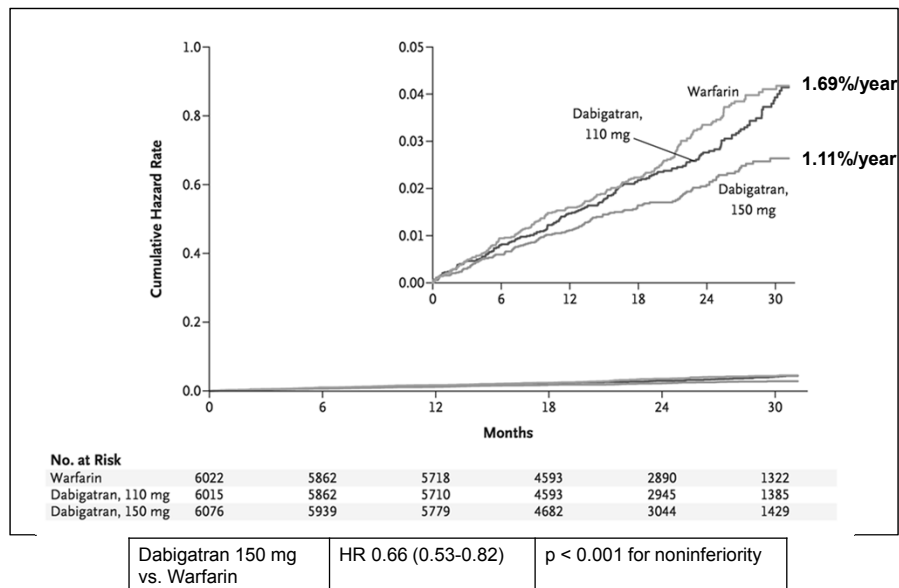
Dabigatran 150 mg
twice daily
(110 mg twice daily)

Warfarin
(target INR 2-3)

*N = 12,089 excluding
patients taking dabigatran
110 mg

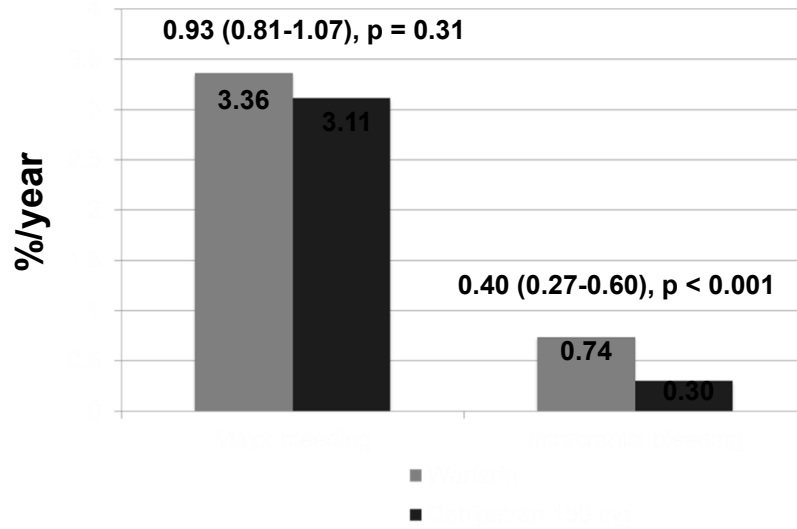
N Engl J Med 2011;365:981-92.

RE-LY: stroke or systemic embolism



N Engl J Med 2011;365:981-92.

RE-LY: major bleeding



N Engl J Med 2011;365:981-92.

Rivaroxaban

- **ROCKET-AF: rivaroxaban vs. warfarin**
- **Brand name Xarelto**

ROCKET-AF: design

Noninferiority Trial
Randomized
Double-blind
Double-dummy
(N = 14 264)

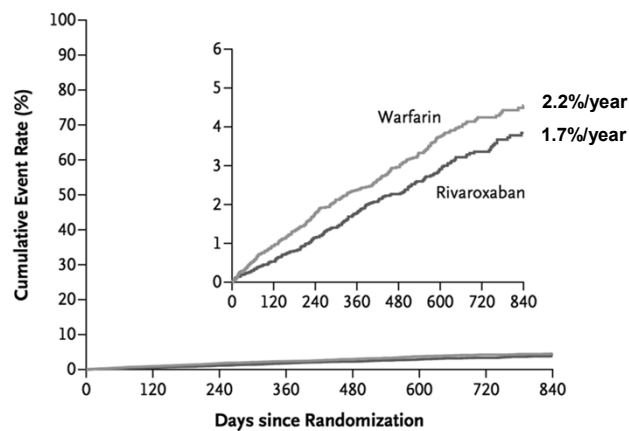
**Rivaroxaban 20 mg
 once daily
 (15 mg once daily*)**

**Warfarin
 (target INR 2-3)**

***CrCl 30-49 mL/min**

N Engl J Med 2011;365:883-91

ROCKET-AF: stroke or systemic embolism

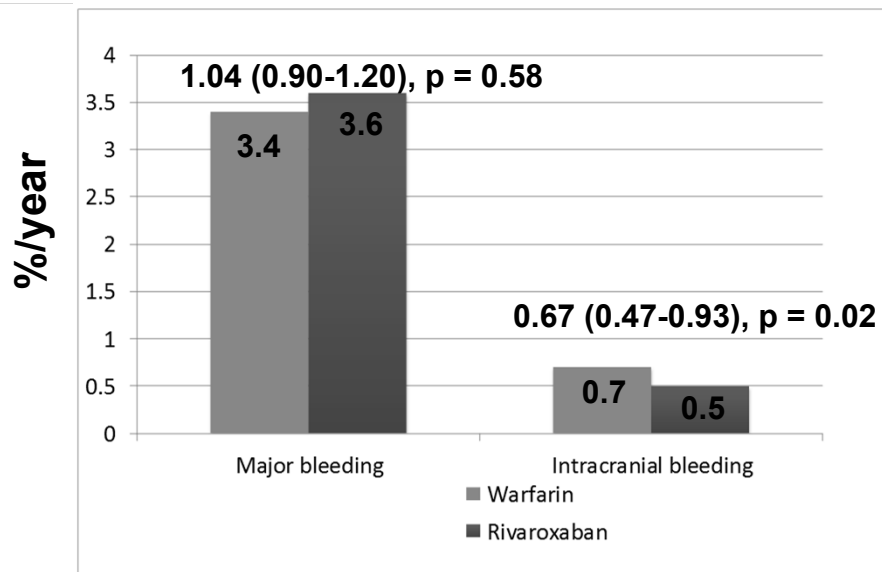


No. at Risk	
Rivaroxaban	6958 6211 5786 5468 4406 3407 2472 1496
Warfarin	7004 6327 5911 5542 4461 3478 2539 1538

Rivaroxaban vs. Warfarin	HR 0.79 (0.66-0.96)	p < 0.001 for noninferiority
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N Engl J Med 2011;365:883-91

ROCKET-AF: major bleeding



N Engl J Med 2011;365:883-91

Apixaban

- **AVERROES:** apixaban vs. aspirin
- **ARISTOTLE:** apixaban vs. warfarin
- **Brand name :** Eliquis

ARISTOTLE: design

Noninferiority Trial

Randomized,
Double blind
Double dummy
(N = 18,201)

Apixaban
5 mg twice daily
(2.5 mg twice daily*)

*age > 80 years, < 60
kg, SCr > 1.5 mg/dL
~ 4.7% of patients

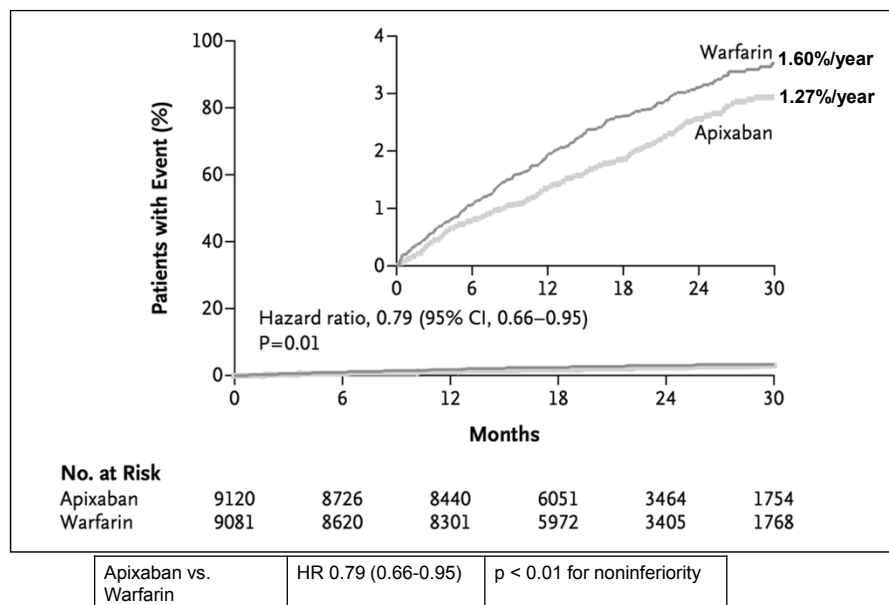
Warfarin
(target INR 2-3)

Previous use for > 30 days
~ 57% of patients

Mean time in therapeutic
range of 62.2%

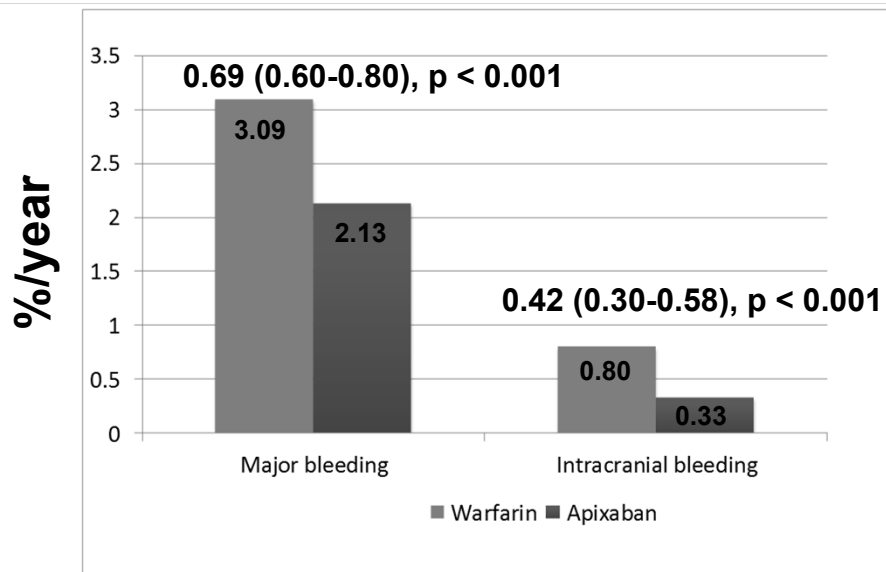
N Engl J Med 2011;365:981-92.

ARISTOTLE: stroke or systemic embolism



N Engl J Med 2011;365:981-92.

ARISTOTLE: major bleeding



N Engl J Med 2011;365:981-92.

Edoxaban

- **ENGAGE AF-TIMI**
- **Approved by FDA on 01/2015**

ENGAGE AF : design

Noninferiority Trial

Randomized
Double-blind
Double-dummy
(N = 21,105)

High Dose
Edoxaban 60
mg daily*

Low Dose
Edoxaban 30
mg daily*

Warfarin
(target INR 2-3)

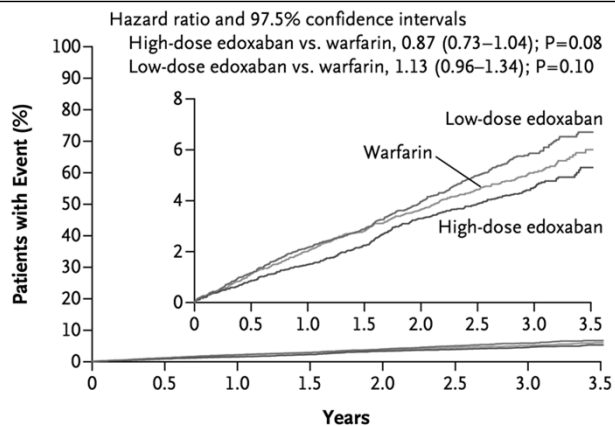
*Dose reduced by 50% if:

- CrCl 30-50 mL/min
- Weight < 60 kg
- Strong P-gp inhibitor

N Engl J Med 2013;369:2093-104.

N Engl J Med 2011;365:981-92.

ENGAGE AF: stroke or systemic embolism

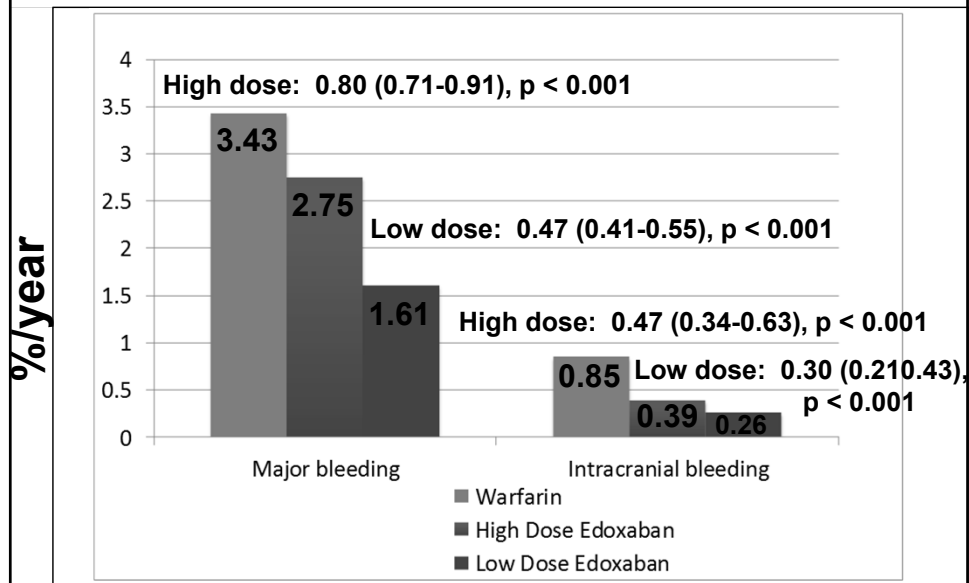


No. at Risk

Warfarin	7036	6798	6615	6406	6225	4593	2333	536
High-dose edoxaban	7035	6816	6650	6480	6283	4659	2401	551
Low-dose edoxaban	7034	6815	6631	6461	6277	4608	2358	534

N Engl J Med 2013;369:2093-104.

ENGAGE AF: major bleeding



N Engl J Med 2013;369:2093-104.

Edoxaban

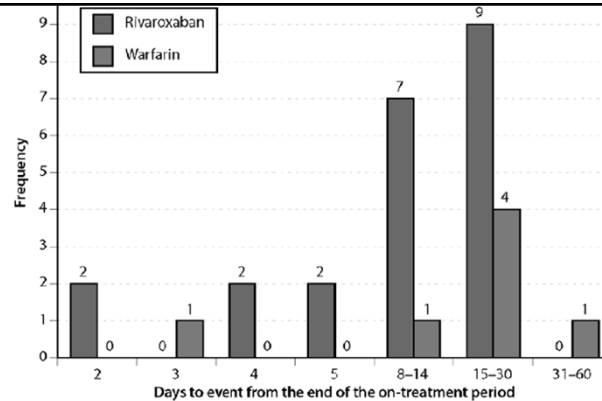
- Edoxaban blood levels are lower in patients with better renal function
- Reduced efficacy in non-valvular AF in patients with creatinine clearance > 95 ml/min
- Assess creatinine clearance, before initiating therapy

$$\text{CrCL} = (140 - \text{age}) \times (\text{weight in kg}) \times (0.85 \text{ if female}) / (72 \times \text{creatinine in mg/dL}).$$

SAVAYSA (edoxaban). [package insert]. Daiichi Sankyo, Inc Revised January 2015.

Early discontinuation

Black Box Warning:
**“Premature discontinuation of any
 anticoagulant...
 increases the risk of thrombotic events”**



N Engl J Med 2011;365:883-91 (supplementary

US Food and Drug Administration. Advisory Committee briefing. Available at: <http://www.fda.gov/>

Summary of AF Data (vs. Warfarin)

	Dabigatran 150 mg (Pradaxa®)	Rivaroxaban (Xarelto®)	Apixaban (Eliquis®)	Edoxaban (Savaysa®)
Stroke and Systemic Embolism	Reduced	Equal	Reduced	Equal
Major Bleeding	Equal	Equal	Reduced	Reduced
Intracranial Hemorrhage	Reduced	Reduced	Reduced	Reduced
Gastrointestinal Bleeding	Increased	Increased	Equal	Equal (Reduced with 30 mg)

In RE-LY, ROCKET-AF, and ENGAGE-AF, patients with CrCl < 30 mL/min were excluded.

In ARISTOTLE, patients with CrCl < 25 mL/min were excluded.

FDA-Approved NOACs Indications

	Dabigatran (Pradaxa®)	Rivaroxaban (Xarelto®)	Apixaban (Eliquis®)	Edoxaban (Savaysa®)
Prevent Stroke and Systemic embolism in non-valvular AF	✓ (Approved 10/2010)	✓ (Approved 11/2011)	✓ (Approved 12/2012)	✓ (Approved 1/2015)
VTE Treatment	✓ (Approved 4/2014)	✓ (Approved 11/2012)	✓ (Approved 8/2014)	(Applied for FDA approval 1/2014)
VTE Secondary Prevention	✓ (Approved 4/2014)	✓ (Approved 11/2012)	✓ (Approved 8/2014)	
VTE Prevention after hip and knee replacement surgery		✓ (Approved 7/2011)	✓ (Approved 3/2014)	

AF = atrial fibrillation

VTE = venous thromboembolism, including deep vein thrombosis, pulmonary embolism



2014 AHA guidelines Risk-Based Antithrombotic Therapy

Recommendations	COR	SPE
Prior stroke, TIA, or CHA2DS2-VASc score ≥ 2 , oral anticoagulants are recommended. Options include:	I	B
1- Warfarin	I	A
2- Dabigatran, rivaroxaban, or apixaban	I	B
3- Direct thrombin or factor Xa inhibitor recommended if unable to maintain therapeutic INR	I	C
Reevaluate the need for anticoagulation at periodic intervals (pt might develops HTN...)	I	C

COR: Class of recommendations

SPE: strength of the evidence

2014 AHA guidelines Risk-Based Antithrombotic Therapy

Recommendations	COR	SOE
Warfarin recommended for mechanical heart valves	I	B
Direct thrombin inhibitor dabigatran should not be used with a mechanical heart valve	III	B
Direct thrombin & factor Xa inhibitor are not recommended in patients with AF and <u>end-stage CKD (CrCl <15 mL/min) or on dialysis</u>	III	C
Evaluate renal function before initiation of direct thrombin or factor Xa inhibitors, and reevaluate when clinically indicated and at least annually	I	B

COR: Class of recommendations
SPE: strength of the evidence

Exclusion for use of NOAC?

- Concurrent use of dronedarone, carbamazepine, phenytoin, ketoconazole, itraconazole, HIV protease inhibitors, rifampin
- Oncology patients
- Morbid obesity
- Concurrent MI, ASA/Plavix (triple therapy)
- Concurrent high risk thrombosis? (lupus anticoagulant disorder)
- Past hx GI bleed – avoid dabigatran / rivaroxaban?
- Advanced age – consider apixiban?

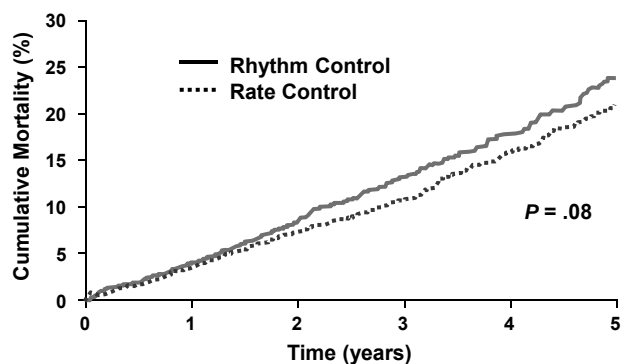
Reversal Agents

- **Andexanet Alfa is Designated as Factor Xa Inhibitor Antidote**

Reversal Agents

- **Idarucizumab is a humanized *antibody fragment*, or Fab *Immediate reversal* of the anticoagulant effect of *dabigatran***

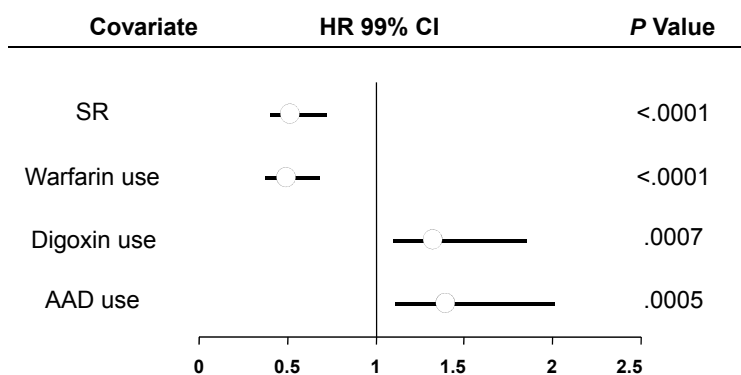
AFFIRM: Primary Endpoint All-Cause Mortality



	Number of Deaths	Number (%)				
Rhythm	0	80 (4)	175 (9)	257 (13)	314 (18)	352 (24)
Rate	0	78 (4)	148 (7)	210 (11)	275 (16)	306 (21)

AFFIRM = Atrial Fibrillation Follow-up Investigation of Rhythm Management.
The AFFIRM Investigators. *N Engl J Med.* 2002;347(23):1825-1833.

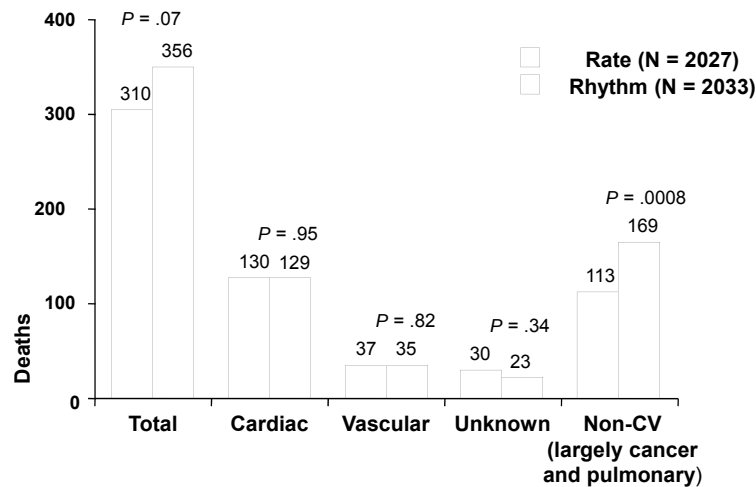
AFFIRM Results: Additional Analysis



The toxicity of AADs (mainly amiodarone) counterbalanced the benefits of SR

HR = hazard ratio; CI = confidence interval; LVEF = left ventricular ejection fraction.
Corley SD, et al. *Circulation.* 2004;109:1509-1513.

AFFIRM: Cause-Specific Mortality



CV = cardiovascular.
Steinberg JS, et al. *Circulation*. 2004;109:1973-1980.

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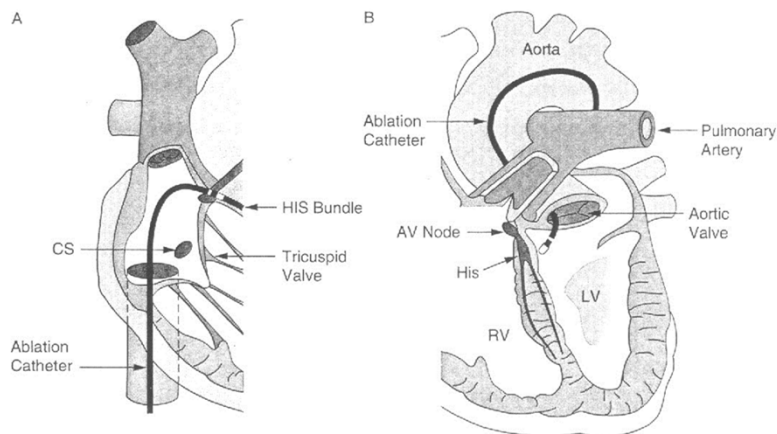
Long-term Rate Control in AF

- Resting HR < 110 bpm (RACE II)
- Stircker HR < 80 bpm / <110bpm (mod exercise)
- Adequate rate control is critical to avoid tachycardia-mediated cardiomyopathy
- 24 hour Holter monitor.

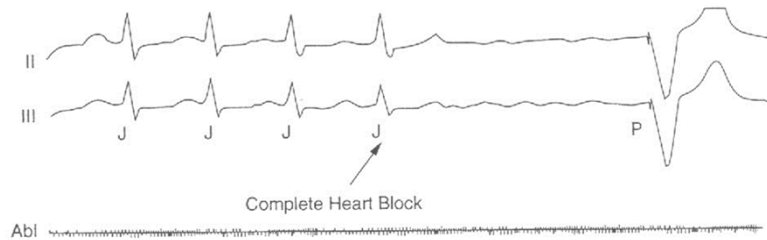
AV node ablation in AF patients

1. Rate *can not be controlled* by medications.
2. *Intolerance* for anti-arrhythmic drugs (AAD)
3. Catheter ablation or surgical intervention *is not indicated*, failed or rejected by patients.
4. *Tachycardia induced* cardiomyopathy (1-3)
5. Pacemaker has to be *implanted first*.

AV node ablation in AF patients

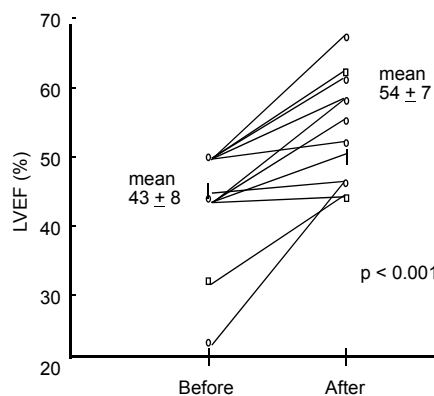


AV node ablation in AF patients

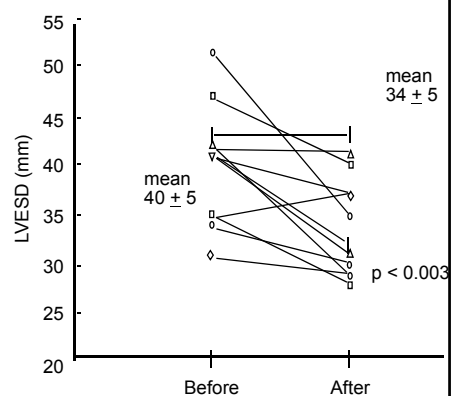


- **Anticoagulation *is needed* if not contra-indicated.**
- **Pacemaker *regulate heart rate***

Objective Benefits of AV nodal Ablation



A Left ventricular ejection fraction (%)



B Left ventricular end systolic diameter (mm)

Rodriguez LM. Am J Cardiol. 1993;72:1137-1141.

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Rhythm Control Strategy

- Anti-arrhythmic drugs or ablation to *restore SR*.
- The aim is *not* to restore SR *and* discontinue anticoagulation.
- *Needs anticoagulation* if indicated by CHADS2 or CHA2DS2-Vasc score

Benefits of Sinus Rhythm

- *Reduce symptoms and improve QoL*
- *Improve ejection fraction and reduce HF in patients with SHD*
- *Reduce LA size*
- *Reduce CV morbidity and mortality (may be patient- and therapy-specific)*

SHD = structural heart disease.
Mitchell AR. *BMJ*. 2009;339:b3174. Cha YM, et al. *Circulation*. 2004;109(23):2839-2843.

Antiarrhythmic Classification Vaughn Williams

Class I: fast Na⁺ blocker

- Class IA- Procainamide, quinidine, disopyramide
- Class IB- Lidocaine, mexilitine (*ventricle*)
- Class IC- Propafenone, flecainide
- Class II- Beta-blockers
- Class III (K⁺ blocker) *sotalol* and *dofetilide*
- Class IV- Calcium-channel blockers

Amiodarone, ibutilide and dronedarone

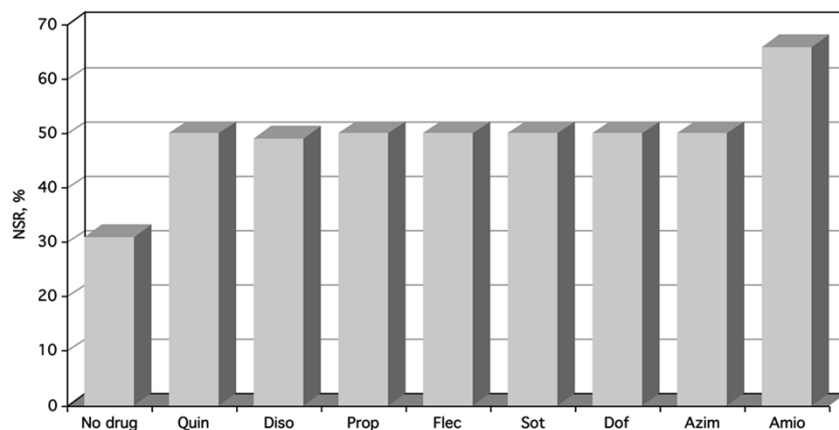
Rhythm Control for AF: Commonly Used Oral Antiarrhythmic Drugs

Class IA	Class IC	Class III
Quinidine	Propafenone	Sotalol
Procainamide	<u>Propafenone SR</u>	Amiodarone
Disopyramide	<u>Flecainide</u>	Dofetilide

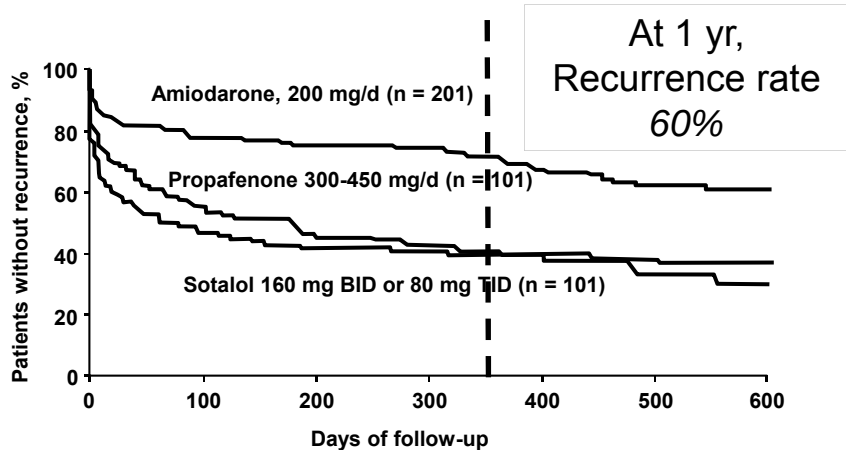
Procainamide, disopyramide, and amiodarone *are not* FDA-approved for treatment of AF.

Miller and Zipes. In: Braunwald, et al (eds). *Heart Disease*. 6th ed. 2001.

AF Efficacy: Maintaining NSR $\geq$ 6 Months



Canadian Trial of AF Medications Rarely Provide Long Term Efficacy



Roy, et al. NEJM, 2000.

AF Antiarrhythmic Therapy

- **Treatment goals**
 - ↓ frequency of recurrences
 - ↓ duration of recurrences
 - ↓ severity of recurrences
 - Not to abolish every episode
- *Safety is primary concern*
- Minimize risk of *pro-arrhythmia*

Factors Which Influence Ventricular Pro-arrhythmia Risk

- Hypokalemia, hypomagnesemia
- Long QT at baseline
- CHF / Decreased EF
- Ventricular hypertrophy
- Bradycardia
- Female gender
- Reduced drug metabolism or clearance
- *Amiodarone has lowest risk*

Antiarrhythmic Therapy ORGAN TOXICITY

- **Examples:**
 - **Lupus, agranulocytosis, thrombocytopenia, optic neuritis, pulmonary fibrosis, hepatitis, etc.**
- **Negligible:**
 - *Dofetilide, flecanide, propafenone, sotalol*
- **High:**
 - *Amiodarone, procainamide, quinidine*

Sotalol- Baseline Assessment

- **QT interval (EKG)**
 - **Contraindicated: QT >450 ms**
- **Avoid in:**
 - **Asthma/COPD**
 - **Overt CHF**
 - **Long QT syndromes**
 - **Severe bradycardia**
 - **2nd or 3rd degree block**

Dofetilide- Drug Interactions

- **Contraindicated**
 - Cimetidine
 - *Trimethoprim (including Bactrim)*
 - Ketoconazole
 - *Verapamil*
 - Prochlorperazine
 - Megestrol
 - *HCTZ*
- **Avoid if possible Any drug that prolongs QT interval**
 - Tricyclic antidepressants
 - Phenothiazines
 - *Metformin*
 - (fluoroquinolones, macrolides)

Amiodarone

- **Multiple channel blockade**
 - K, Na, Beta, Ca, Alpha
- **Effective for most arrhythmias**
- **Drawbacks: toxicity, drug interactions**
- **Comparatively more effective than other AARx**

Amiodarone- Drug Interactions

Drug	Effect	Action
Digoxin	↑	↓ Digoxin by 50%
Warfarin	↑	↓ Warfarin by 30 to 50%
Simvastatin	↑	Avoid >20mg/day
Lovastatin	↑	Avoid >40mg/day
Cyclosporine	↑	Check levels

Amiodarone Monitoring- OSU Ross Heart Hospital Antiarrhythmic Clinic Protocol

Frequency	Test
Baseline	CXR, ECG, LFT, PFT, TFT
Q6 Months	ECG, LFT, TFT
Q12 Months	CXR, PFT
PRN	Ophthalmology

Adapted from: Goldschlager N, et al. Heart Rhythm 2007;4:1250-9

Amiodarone and Dronedarone

Less thyroid and lung toxicity

Iodine molecules were removed from the
amiodarone chemical structure

Sun W, et al, Circulation 1999;100:2276-2281

Liver toxicity and the concern in CHF in patient who are taking Dronedarone?

Liver toxicity
Acute liver failure
and worsening of heart failure

were reported during
post marketing Multaq therapy

Dronedarone: Labeling Changes

- **6 Label changes in 2011**
 - **Liver injury**
 - **New/worsening CHF**
 - **↑ INR with warfarin**
 - **Reports of interstitial lung disease**
 - **↑ Serum Creatinine beyond initiation**
 - **Updated Black Box Warning and warnings regarding use in permanent AF**

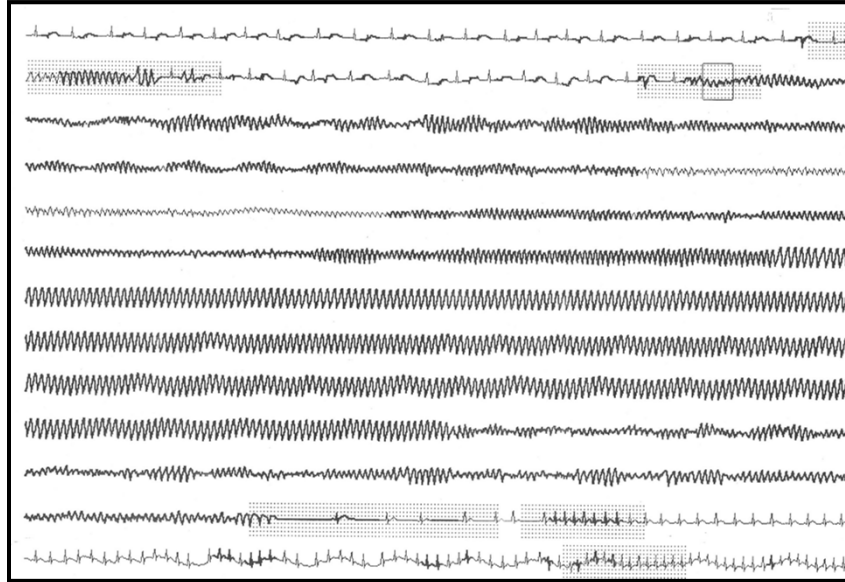
Accessed 1/11/2012

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist

Comorbidities to Avoid/Adjust AADs

CAD / MI	CHF	Hepatic Failure	Renal Failure
Class IC	Class I (especially IC) Dronedarone	Class I Amiodarone Dronedarone	Dofetilide Sotalol Flecainide Disopyramide

Drug-Induced Proarrhythmia - Torsades



Indications for Catheter AF Ablation

- **Symptomatic AF refractory or intolerant to at least 1 class I or III AAD**
- **Selected symptomatic patients with HF and/or reduced ejection fraction**
- **As an alternative to device implantation to support AAD therapy in bradycardic patients**
- **Presence of an LA thrombus is a contraindication to catheter ablation of AF**

Calkins H, et al. *Heart Rhythm*. 2007;4(6):816-861.

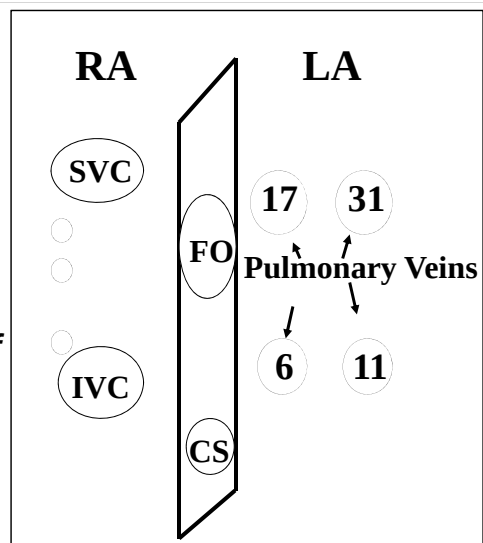
Beginnings of “Non Drug” Therapies for AFib

- Minneapolis Feb 1999
- Haisseguerra – Bordeaux, France
- Designed a *circular catheter* to map the pulmonary veins
- “Pulmonary Vein Isolation”
 - Atrial muscle bundles span the *transition zone* from the pulmonary veins into the atria – trigger for AFib

Focal Origin of Atrial Fibrillation

Hassaiguerre M, NEJM, 1998

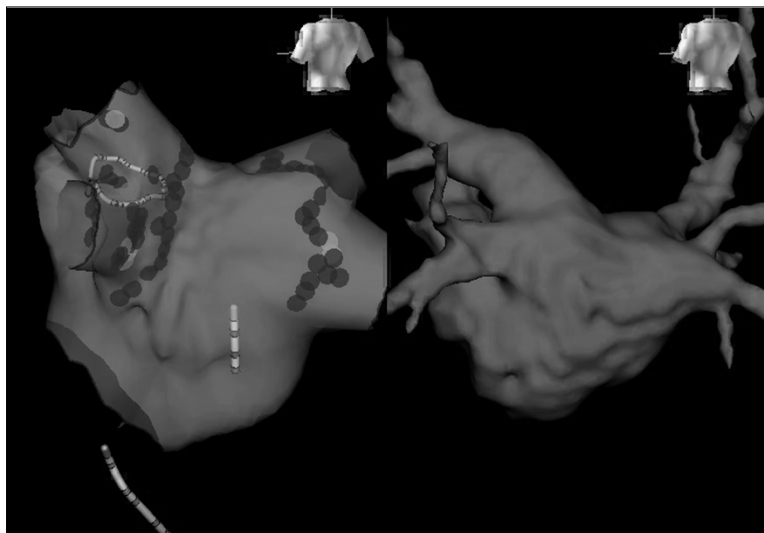
- 94% of AF triggers from Pulmonary Veins
- “90 – 95% of all AF is initiated by PV ectopy”
- Pulmonary vein isolation is the target of the RF ablation or cryo-ablation



Prior to RF ablation we need

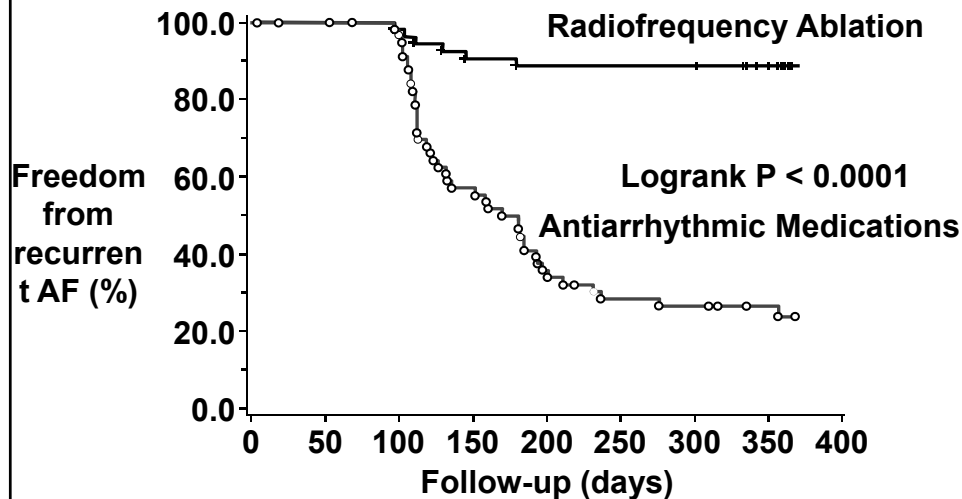
- TEE to rule out LAA thrombus
- Cardiac CT/ MRI to assess:
 - The pulmonary vein anatomy
 - Adjacent structure next to the posterior wall “the esophagus”

Atrial Fibrillation Ablation Atrial Shell and Cardiac CT



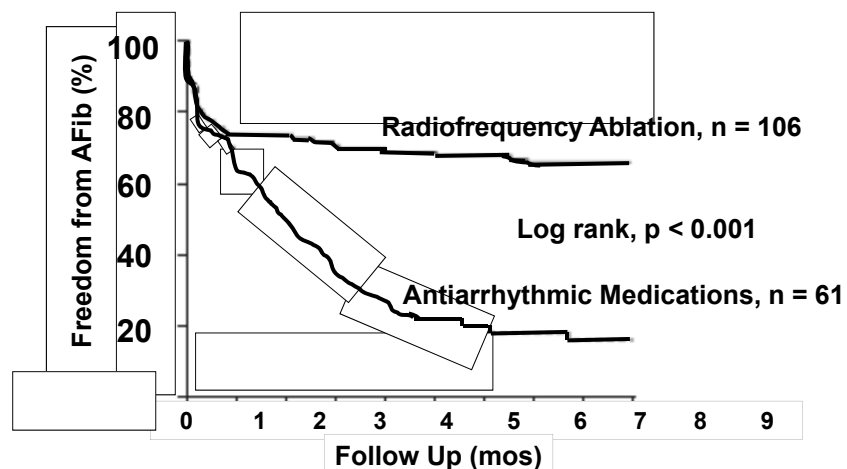
A4 study: Catheter Ablation vs Anti-Arrhythmic drug therapy for PAF

Jais P, Macle L, Daoud E, *Circulation*. 2008
Paroxysmal AF resistant to ≥ 1 AAD, n = 112



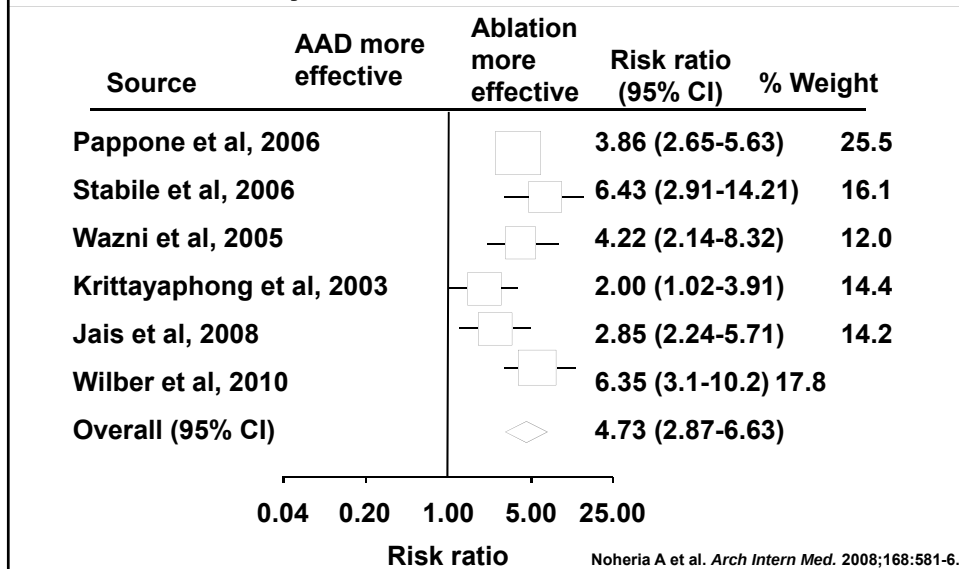
Comparison of Antiarrhythmic Drug vs. RF Ablation in Patients With Paroxysmal AFib Randomized Controlled Trial

D. Wilber, MD, C. Pappone, MD, F. Marchlinski, MD, A. Natale, MD,
L. Macle, MD, E. Daoud, MD, H. Calkins, MD; *JAMA*, 2010



Catheter Ablation vs Antiarrhythmic Drug Therapy for AF

Meta-analysis of 4 randomized clinical trials



Complications, OSU Experience

- Major complications 1.4%
 - Pericardial Effusion/Tamponade
 - Stroke
 - Vascular access complication
 - Phrenic nerve injury
- No deaths
- No inadvertent damage to the esophagus

Atrial Fibrillation: Ablation vs Drug Rx.

Ablation

80% success

PV stenosis

AE fistula

TIA/CVA

PV stenosis

AE fistula

Drug Rx.

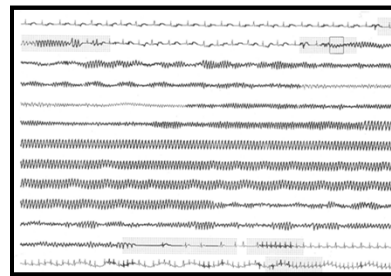
50% success

Proarrhythmia

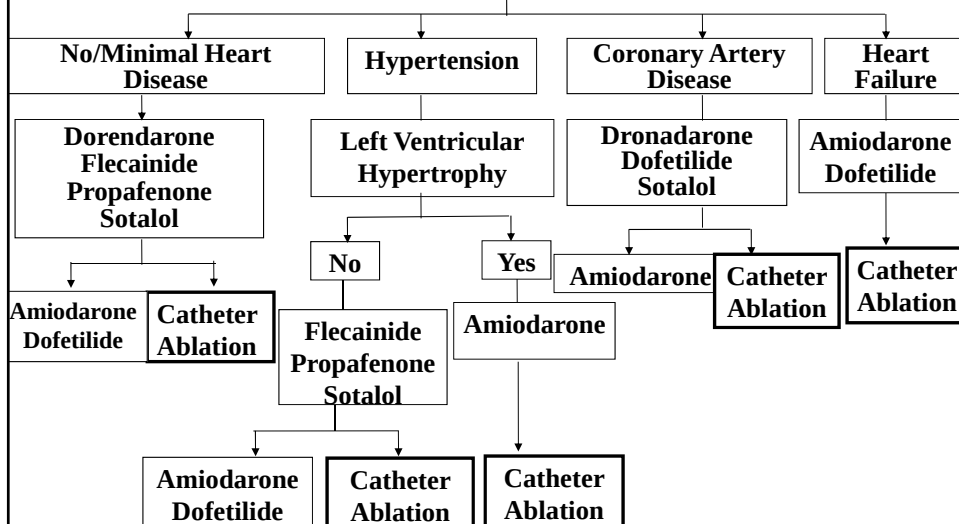
End Organ Toxicity

Pick Your Poison

Torsades



Maintenance of Sinus Rhythm



Conclusion

- AF is a common disease that is increasing in prevalence
- Decision regarding *Rate control strategy* Vs. *Rhythm control strategy* and *antithrombotic therapy* are patient specific.
- Anticoagulation is essential in AF patients with risk markers, *regardless of any restoration of SR*
- Guidelines provide *recommendations* for the management of patients with AF