Cleveland Clinic

# Atrial Fibrillation: Beyond the AFFIRM trial

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# Presentation Overview

- Review of the Basics
- The AFFIRM trial
- Stroke Prevention
- Rate Control
- Rhythm Control

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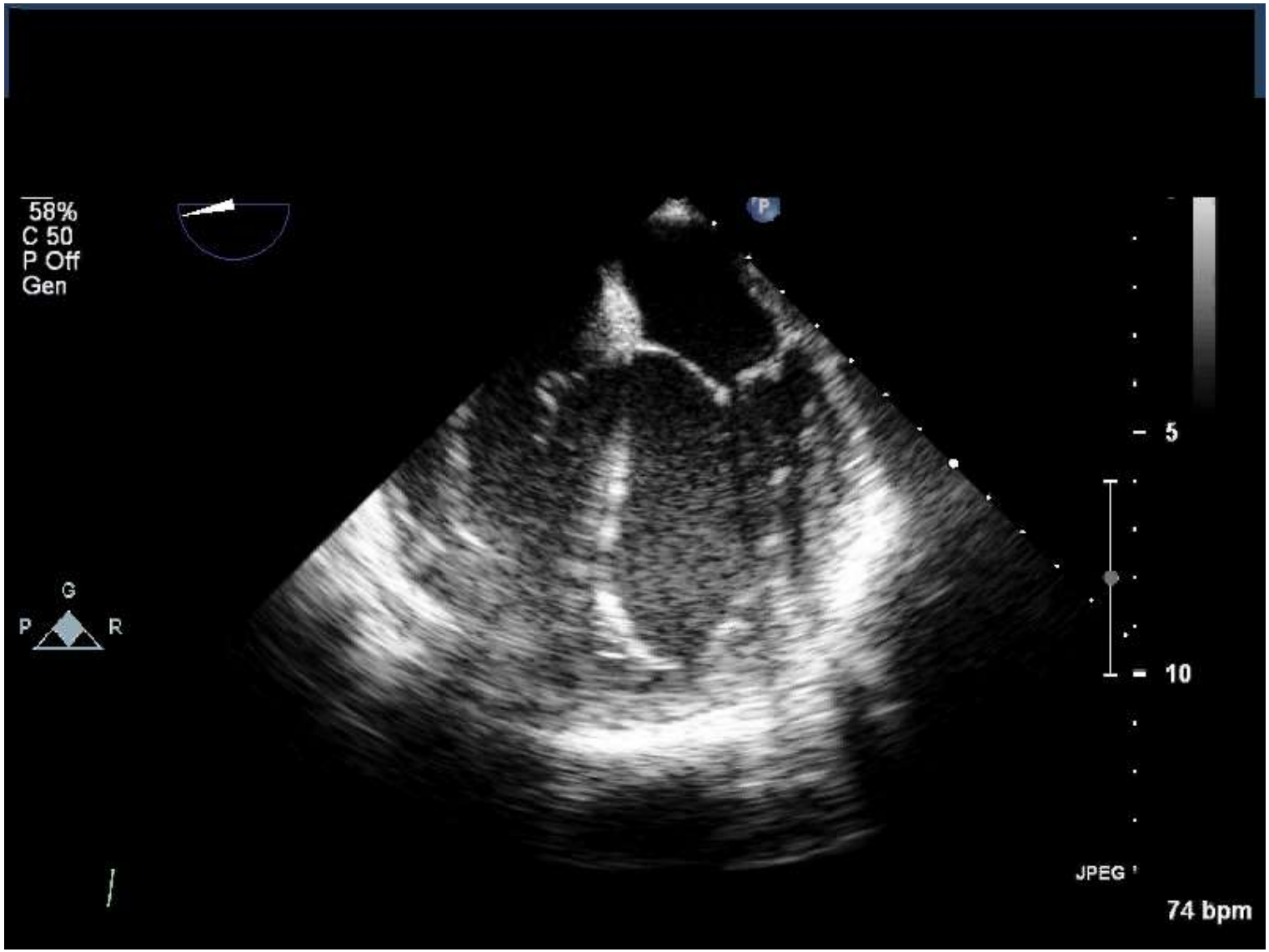
# 2011 Update on Definitions / Terminology

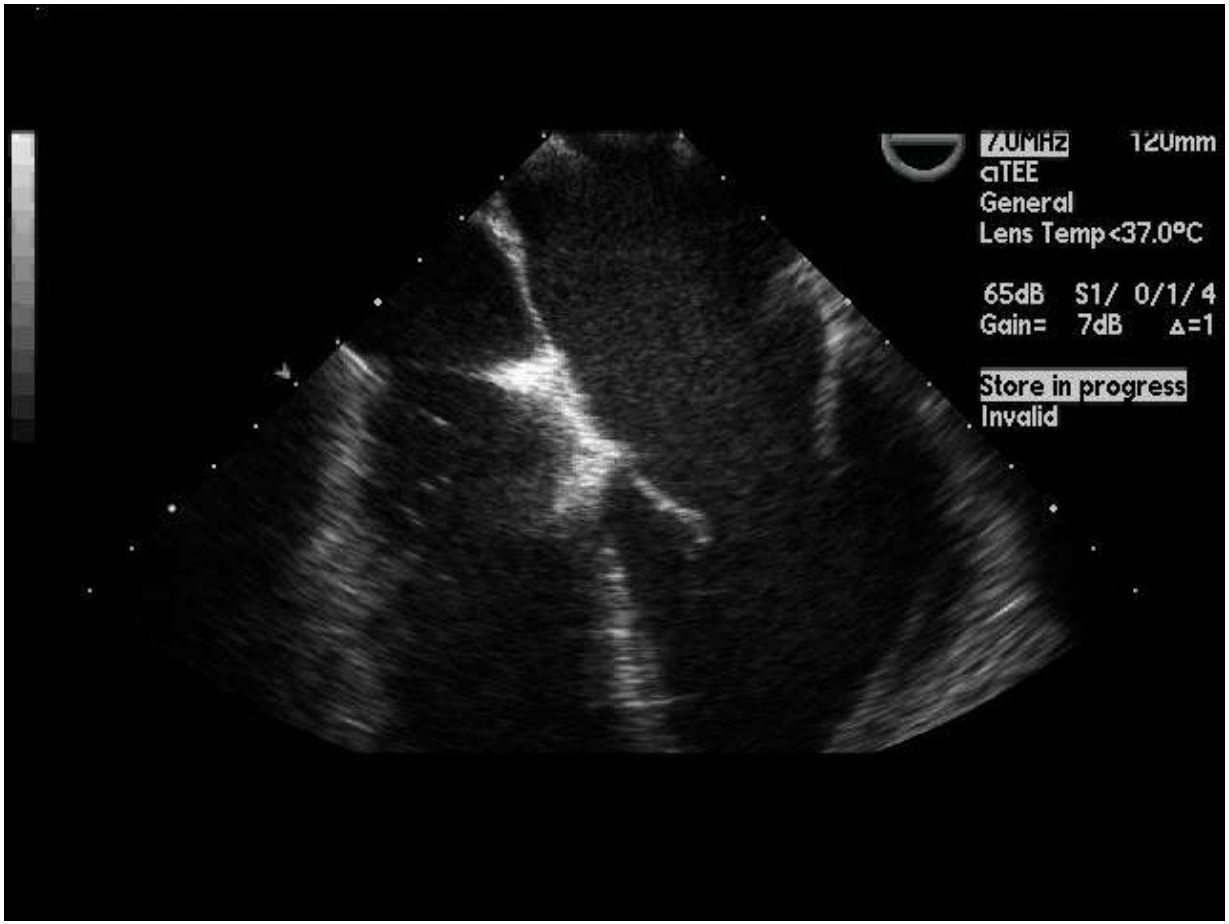
| | |
|---|---|
| • Atrial Fibrillation Episode | > 30 seconds in duration |
| • Paroxysmal | < 7 days or self-terminating |
| • Persistent | > 7 days or req cardioversion |
| • Long-standing persistent | > 1 year |
| • Permanent | Forgone or failed efforts to maintain sinus |

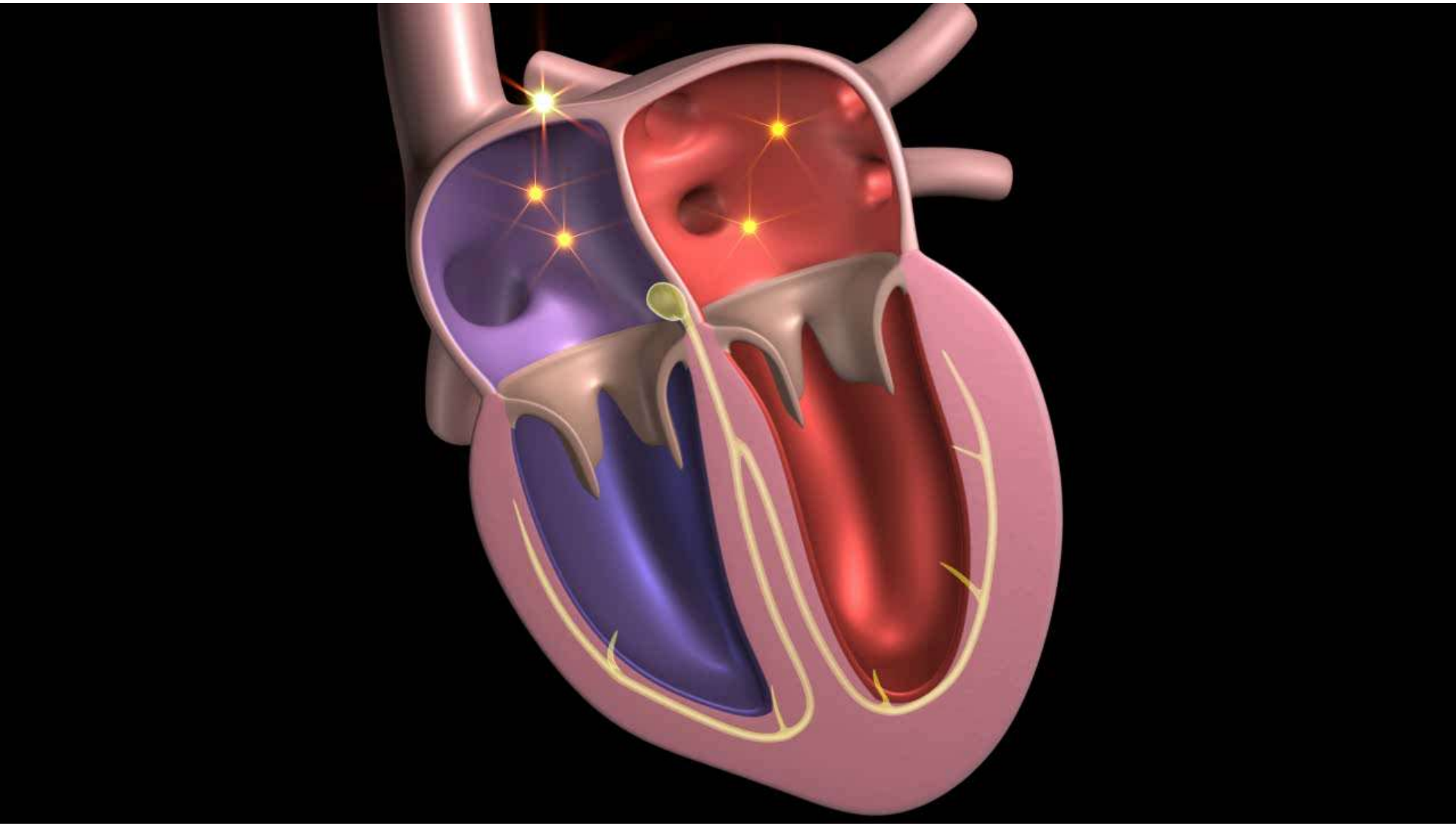
Atrial Fibrillation: Guidelines for Management *J Am Coll Cardiol* 2011; 57:101-98

# Normal rhythm



# Atrial fibrillation





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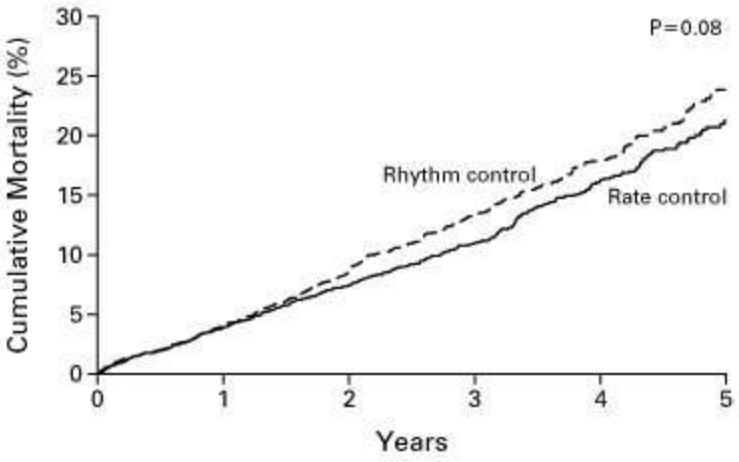
# The AFFIRM trial

- 4,060 patients randomized
- Rate control vs. rhythm control
- Endpoint = All cause mortality




| 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) |

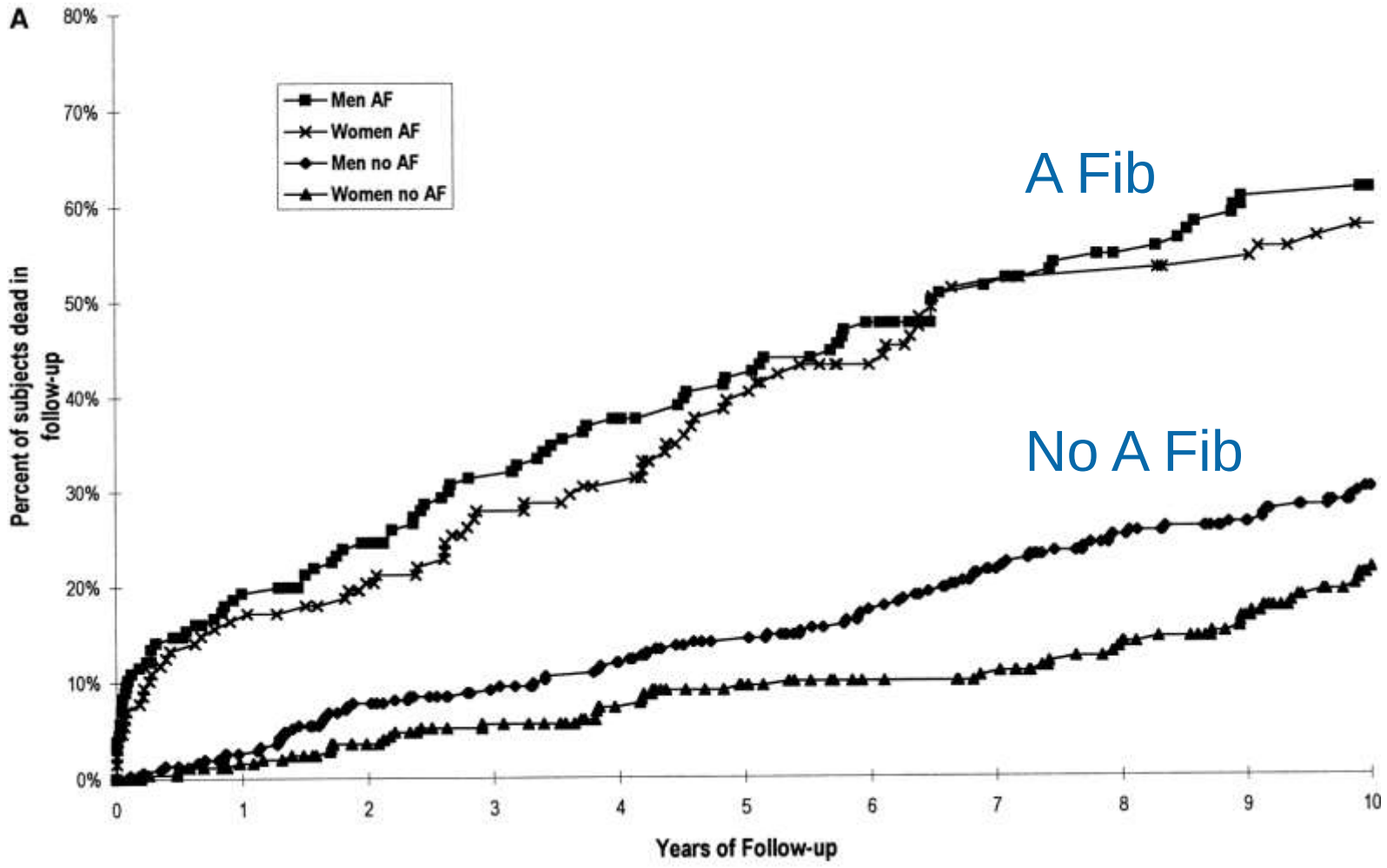
No survival advantage with DC cardioversions and anti-arrhythmic drugs

AFFIRM investigators, NEJM 2002; 347(23):1825-33.

# Why go beyond the AFFIRM trial?

- Rate ≠ Rhythm control for all
- Rhythm control strategies continually improving
- Special populations
  - Coronary artery disease
  - Heart failure
  - Valvular heart disease

# Coronary Disease, Atrial Fibrillation and Mortality: The Framingham Heart Study




Benjamin, et. al. *Circulation* 1998; 98:946-952

# Quality of Life: Rhythm ≠ Rate control for all

- Quality of life improvements with sinus rhythm
  - Thrall et. al. *Am J Med* 2006
- Post hoc analysis of AFFIRM
  - More symptomatic heart failure in the rate control group
  - Patients less symptomatic in sinus rhythm (Guglin et. al. *Heart Rhythm* 2010)
- Conflicting data from post hoc analyses of AFFIRM and other trials

# Heart Failure

- Improvement in symptoms, LV systolic function, and chamber dimensions after catheter ablation
  - Hsu et. al. *NEJM* 2004

- No reduction in all-cause mortality with routine rhythm control strategy
  - Roy et. al. *NEJM* 2008

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# Stroke Prevention: Beyond the AFFIRM trial

- Improvements in Risk Stratification
  - $CHA_2DS_2$ VASc scoring system
- Novel anticoagulants
  - Dabigatran (Pradaxa)
  - Rivaroxaban (Xarelto)
  - Apixaban (Eloquis)

# Estimating the Risk of Stroke

**Table 2.** Risk of Stroke in National Registry of Atrial Fibrillation (NRAF) Participants, Stratified by $CHADS_2$ Score*

| $CHADS_2$ Score | No. of Patients (n = 1733) | No. of Strokes (n = 94) | NRAF Crude Stroke Rate per 100 Patient-Years | NRAF Adjusted Stroke Rate, (95% CI)† |
|---|---|---|---|---|
| 0 | 120 | 2 | 1.2 | 1.9 (1.2-3.0) |
| 1 | 463 | 17 | 2.8 | 2.8 (2.0-3.8) |
| 2 | 523 | 23 | 3.6 | 4.0 (3.1-5.1) |
| 3 | 337 | 25 | 6.4 | 5.9 (4.6-7.3) |
| 4 | 220 | 19 | 8.0 | 8.5 (6.3-11.1) |
| 5 | 65 | 6 | 7.7 | 12.5 (8.2-17.5) |
| 6 | 5 | 2 | 44.0 | 18.2 (10.5-27.4) |

*$CHADS_2$ score is calculated by adding 1 point for each of the following conditions: recent congestive heart failure, hypertension, age at least 75 years, or diabetes mellitus and adding 2 points for having had a prior stroke or transient ischemic attack. CI indicates confidence interval.
†The adjusted stroke rate is the expected stroke rate per 100 patient-years from the exponential survival model, assuming that aspirin was not taken.

$CHADS_2$ Score:

| | |
|---|---|
| +1 | Heart failure |
| +1 | High blood pressure |
| +1 | Age ≥ 75 years old |
| +1 | Diabetes |
| +2 | Prior stroke or mini-stroke (TIA) |

- AF strokes twice as likely fatal than non-AF strokes
- AF-related stroke recurrence double that of non-AF strokes

Gage, et. al. *JAMA* 2001; 285:2864-2870

Miller, et. al. *Stroke* 2005; 36:360-366

## $CHA_2DS_2$ VASc

| | | |
|---|---|---|
| +1 | Heart failure | +1 Diabetes |
| +1 | Hypertension | +2 Stroke / TIA |
| +2 | Age ≥ 75 yrs | +1 Vascular dz. |
| +1 | Age 65-74 yrs | +1 Female gender |

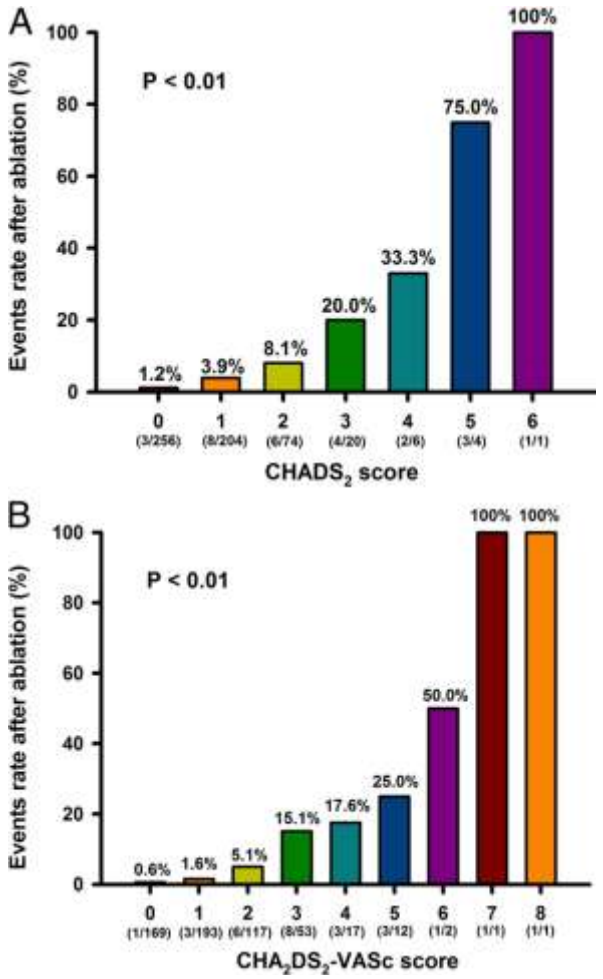


Table 6—*Stroke or Other TE at 1 Year Based on the 2009 Birmingham ($CHA_2DS_2$-VASc) Scoring System*

| $CHA_2DS_2$-VASc Score | No. | Number of TE Events | TE Rate During 1 y (95% CI) | TE Rate During 1 y, Adjusted for Aspirin Prescription,[a] % |
|---|---|---|---|---|
| 0 | 103 | 0 | 0% (0-0) | 0 |
| 1 | 162 | 1 | 0.6% (0.0-3.4) | 0.7 |
| 2 | 184 | 3 | 1.6% (0.3-4.7) | 1.9 |
| 3 | 203 | 8 | 3.9% (1.7-7.6) | 4.7 |
| 4 | 208 | 4 | 1.9% (0.5-4.9) | 2.3 |
| 5 | 95 | 3 | 3.2% (0.7-9.0) | 3.9 |
| 6 | 57 | 2 | 3.6% (0.4-12.3) | 4.5 |
| 7 | 25 | 2 | 8.0% (1.0-26.0) | 10.1 |
| 8 | 9 | 1 | 11.1% (0.3-48.3) | 14.2 |
| 9 | 1 | 1 | 100% (2.5-100) | 100 |
| Total | 1,084 | 25 | *P* Value for trend 0.003 | |

Lip, et. al. *Chest* 2010; 137(2):263-72

Chao, et. al. *JACC* 2011; 59(23): 2380-5

# Warfarin (Coumadin)

- Antagonist for Vitamin K dependent clotting factors
- Pros
  - Established safety profile over decades of clinical use
  - Readily reversible with Vitamin K (1mg IV, 10mg PO)
  - Quickly overcome by transfusing fresh frozen plasma
  - Cheap (1 month supply $13.99 on drugstore.com)
  - Used for both valvular and non-valvular AF
- Cons
  - Nuisance bleeds very common (bruising, nose bleeds, etc.)
  - Need for PT/INR monitoring (Goal INR 2-3)
  - Strict dietary consistency needed (green leafy vegetables)
  - Drug interactions (amiodarone, bactrim, azithromycin, etc.)
  - Typically 3-5 days to become therapeutic

# Dabigatran (Pradaxa)

- Direct thrombin inhibitor
- Pros
  - ‘Non-inferior’ to warfarin for stroke prevention
  - Does not require PT/INR monitoring
  - Lower major bleeding (2.7%/year vs. 3.4%/year with warfarin)
  - ‘One dose for all’ 150mg twice daily (controversial concept)
- Cons
  - GI side effects and bleeding
  - No pharmacologic reversal agent available
  - Expensive (1 month supply $245.99 on drugstore.com)
  - FDA approval limited to non-valvular AF

RE-LY trial. *New England Journal of Medicine* 2009; 361(12)

# Rivaroxaban (Xarelto)

- Direct Factor Xa inhibitor
- Pros
  - ‘Non-inferior’ to warfarin for stroke prevention
  - Once daily dosing 20mg, no monitoring required
  - Slightly lower risk of intracranial hemorrhage and fatal bleeding
- Cons
  - Very new to the market – only FDA approved November 2011
  - Expensive (~$200/month by GoodRx.com)

ROCKET AF trial. *New England Journal of Medicine* 2011; 365(10)

# Apixaban (Eliquis)

- Direct Factor Xa Inhibitor
- Pros
  - Superiority to warfarin in major bleeding (2.13% vs. 3.09% per year
  - Slight decrease in mortality at ~2 yrs (3.52% vs. 3.94%)
  - Hemorrhagic stroke lower (0.24% vs. 0.47% per year)
- Cons
  - Newest kid on the block yet; FDA approved Dec 2012
  - Twice daily dosing (5mg); Renal dose 2.5mg
  - Non-valvular AF indication
  - Expensive (no pricing info yet available on drugstore.com)

ARISTOTLE trial. *New England Journal of Medicine* 2011; 365(11)

# Anticoagulation Intolerant Patients

- Aspirin is better than nothing at all (81mg – 325mg)
- Aspirin / clopidigrel (plavix) is superior to aspirin alone (ACTIVE A trial)
- Warfarin is superior to aspirin / clopidigrel (plavix) combination (ACTIVE W trial)

ACTIVE A trial. *New England Journal of Medicine* 2009; 360:2068-78.

ACTIVE W trial. *Lancet* 2006; 367 (9526):1903-12.

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# Rate Control: Beyond the AFFIRM trial

- In AFFIRM, goal was resting HR <80 and <110 with moderate exercise (Considered Strict rate control)

- In RACE II trial, goal resting HR <110 / min for patients with normal LV systolic function (Lenient rate control)

- Lenient rate control non-inferior and more convienient (fewer outpatient visits) EXCEPT in certain scenarios (e.g., mitral stenosis, heart failure)

RACE II trial. *New England Journal of Medicine* 2010; 362(15):1363-73.

# B-Blockers

- Slows down AV nodal conduction
- Common side effects: Bradycardia, fatigue, depressed mood, loss of libido, erectile dysfunction, shortness of breath
- Bronchospasm in Asthma/COPD and worsening claudication for patients with PAD

# Calcium channel blockers

- Slows down AV nodal conduction (NDHP)
- Common side effects: Bradycardia, constipation, fatigue, hypotension (particularly orthostatic)
- No concern for bronchospasm in COPD / emphysema

# Digoxin

- Use as an adjunct to a calcium channel blocker or B-blocker
- Contraindicated as a solo agent for rate control
- Beware of renal disease and drug interactions (lots of them)
- Dose 0.125mg – 0.25mg PO daily
- Beware of those dig toxic rhythms (both fast and slow)
- Low potassium = Increased digoxin effect!

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# Drugs for the Non-Electrophysiologist

- Amiodarone
- Dronedarone (Multaq)
- Sotalol (Betapace)*

* QT prolonging effect -- should be started in the hospital on monitor

# Drugs used by the Electrophysiologist

- Class Ic drugs: Flecainide (Tambacor), Propafenone (Rhythmol)
- Class Ia drugs: Procainamide (IV only), Disopyramide (Norpace), Quinidine
- Class III drugs: Sotalol (Betapace), Dofetilide (Tikosyn), Ibutilide (IV use only, a pure cardioversion drug)

# Choice of drug by underlying heart condition:

- No structural heart disease:
  - Flecainide, Propafenone, Sotalol, Dronedarone
- Hypertension and ‘substantial’ LVH
  - Amiodarone
- Coronary artery disease / heart failure
  - Amiodarone, dofetilide, sotalol, dronedarone (except NYHA class IV)

# Exclusions / Precautions:

- Impaired Renal function
  - Sotalol, Dofetilide
- Liver dysfunction
  - Amiodarone, Flecainide (partially liver metabolized)
- QT prolonging drugs – can cause torsades
  - Sotalol, Dofetilide >> Amiodarone
- NYHA functional class IV heart failure
  - Dronedarone

# Common side effects

Flecainide: Dizziness

Propafenone: Dizziness, metallic taste, bronchospasm (slow metabolizers)

Disopyramide: Urinary retention, blurred vision, constipation, ataxia, tremor, pupil dilation, increased body temp – avoid in pts with BPH, myasthenia gravis and glaucoma

Procainamide: Nausea, Lupus-like reaction, Agranulocytosis

Amiodarone: Nausea, Pulmonary fibrosis, Hepatitis, Thyroid (hyper and hypo), Photosensitivity, Ocular deposits

→ Major adverse event rate with amiodarone is 2% per year

# Don’t forget about CYP and P-glycoprotein

- CYP 2C19: Metabolizes warfarin. Inhibited by amiodarone
- CYP 3A4: Metabolizes amiodarone, dofetilide, dronedarone, diltiazem, verapamil.  Inhibited by grapefruit juice, ketoconazole.
- CYP 2D6: Metabolizes propafenone, metoprolol, carvedilol, flecainide.  Inhibited by quinidine and SSRIs
- P-Glycoprotein: Substrates digoxin, dofetilide, verapamil, dabigatran.  Inhibited by grapefruit juice, amiodarone, dronedarone, cyclosporine, verapamil and quinidine.

# Pregnancy

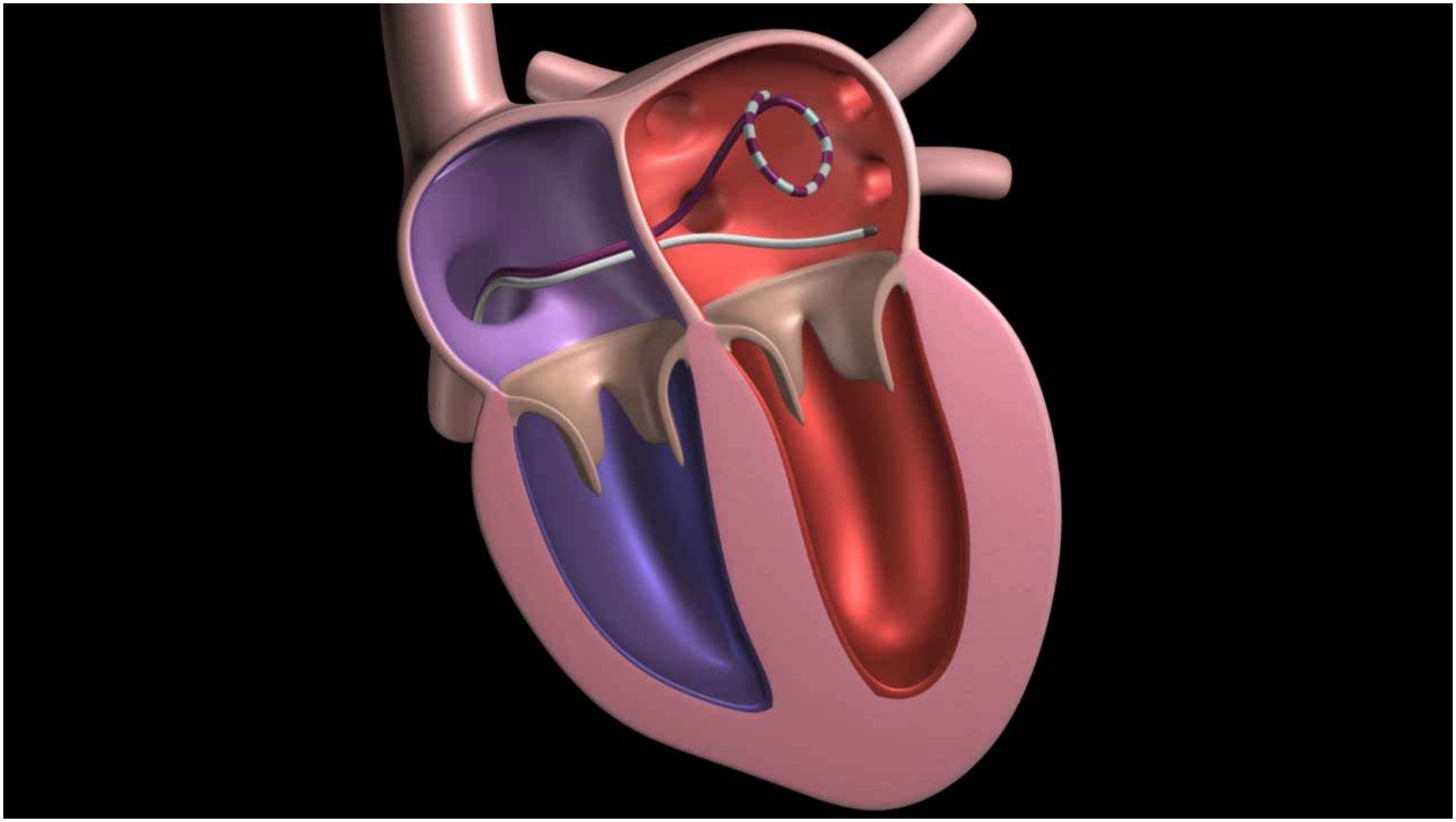
Sotalol is the ONLY class B drug, but is excreted in breast milk.

# Amiodarone

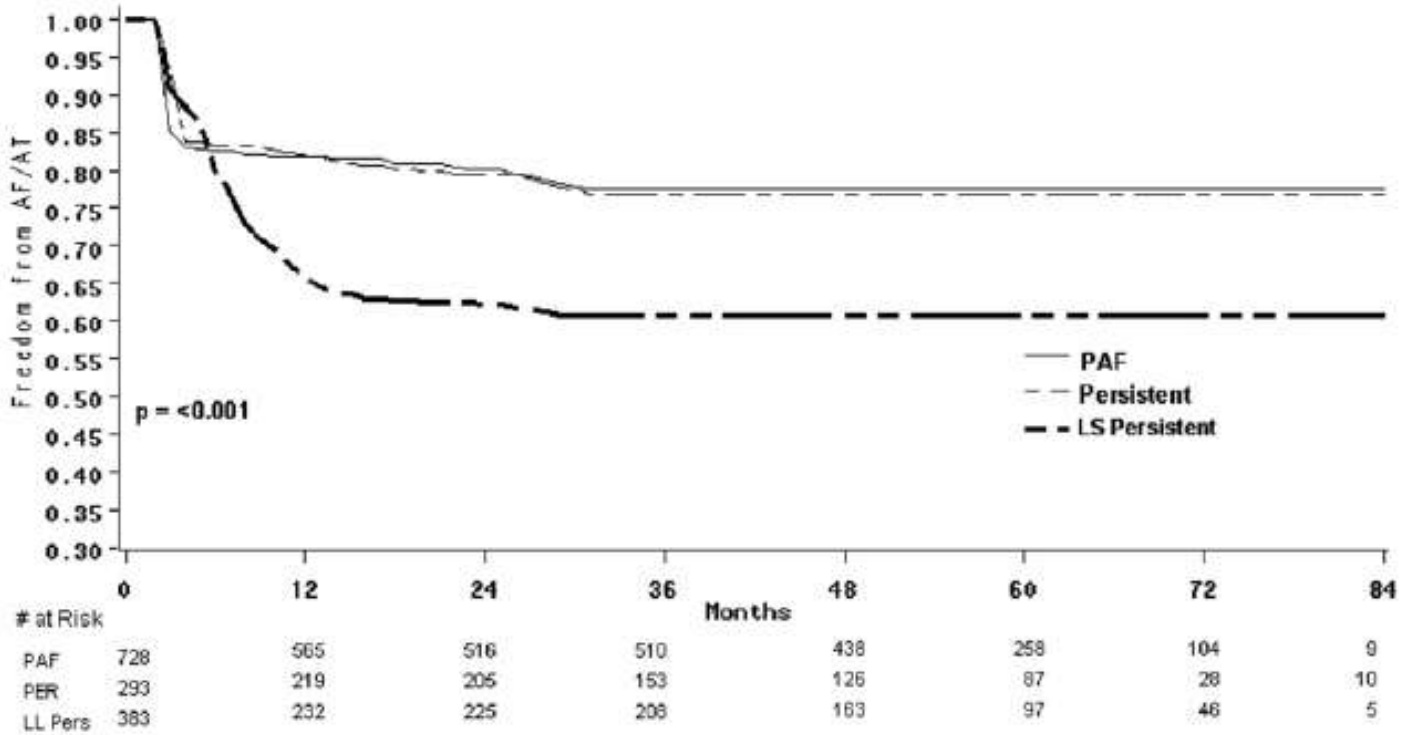
- Great short term drug; bread-and-butter for post-op AF
- Load 10 grams orally, then 200mg daily maintenance dose. My regimen is Amiodarone 400mg BID x 10 days, 400mg QD x 5 days, then 200mg daily.
- Amiodarone 150mg IV bolus, then 1mg/min x 6 hours, then 0.5mg/min x 18 hours
- Efficacy rates 60-70% at 1 year
- Prolongs QT – not a problem when by used itself – but when mixed with other QT prolonging drugs

# Procedure Treatments

- Cardioversion –
  - Therapeutic anticoagulation: 3 weeks prior and 4 weeks post
  - TEE guided DC cardioversion, therapeutic anticoagulation that day
- Surgical based treatments
  - Open heart surgery / MAZE procedure
  - Mini-MAZE procedure / pulmonary vein isolation
  - Left atrial appendage removal or clipping
- Catheter ablation
  - Pulmonary vein isolation
  - AV nodal ablation plus a pacemaker



# Single procedure outcomes: Cleveland Clinic




Bhargava M, et al. *Heart Rhythm* 2009;6:1403–1412

# Outcomes, cont.

| Study | Year | Patients | Age, y | Parox, % | SHD, % | Tool(s) | End Point | AF Free (Off Drugs), % | Follow-Up, d |
|---|---|---|---|---|---|---|---|---|---|
| Ouyang et al[37] | 2004 | 41 | 63±9 | 100 | NA | CARTO | PV Isolat'n | 76* | 178 |
| Haissaguerre et al[38] | 2004 | 70 | 53±8 | NA | 43 | Fluoro | PV Isolat'n | 79 | 210 |
| Mansour et al[40] | 2004 | 40 | 55±10 | 80 | 13 | CARTO | PV Isolat'n | 75 | 330 |
| Marrouche et al[41] | 2003 | 259 | 54±11 | 51 | 21 | ICE | PV Isolat'n | 87† | 347 |
| Oral et al[39] | 2003 | 40 | 54±11 | 100 | 3 | CARTO | EGM Red'n | 88 | 365 |
| Pappone et al[36] | 2003 | 589 | 65±9 | 69 | 6 | CARTO | EGM Red'n | 79 | 861 |
| Total | | 1039 | | | | | | 81.0 | |

Verma A, et. al *Circulation* 2005 112: 1214

# Complications: National Data

| Event | Approximate Incidence |
|---|---|
| Pro-arrhythmia | 5 - 25% |
| Thrombo-embolism | 5 – 7% |
| Groin Hematoma / fistula | 4% / 1% |
| Cardiac tamponade | 2 – 6 % |
| Phrenic nerve injury | 0.5% |
| Pulmonary vein stenosis | 0.3 % (previously up to 38%) |
| Esophageal injury / fistula | 0.25% |

Calkins, et. al. HRS/EHRA/ECAS Consensus Statement. *Heart Rhythm* 2007

# Complications: Cleveland Clinic

| Event | Approximate Incidence |
|---|---|
| Major complications | 2-3% |
| Stroke | 0.5% |
| Cardiac tamponade | 1% |
| Pulmonary vein stenosis | 1% |
| Esophageal injury | <1% |
| Vascular complications | 1-2% |

Heart and Vascular Outcomes, 2010. www.clevelandclinic.org

# AV nodal ablation + Biventricular Pacing: Improved Mortality Outcomes in Heart Failure

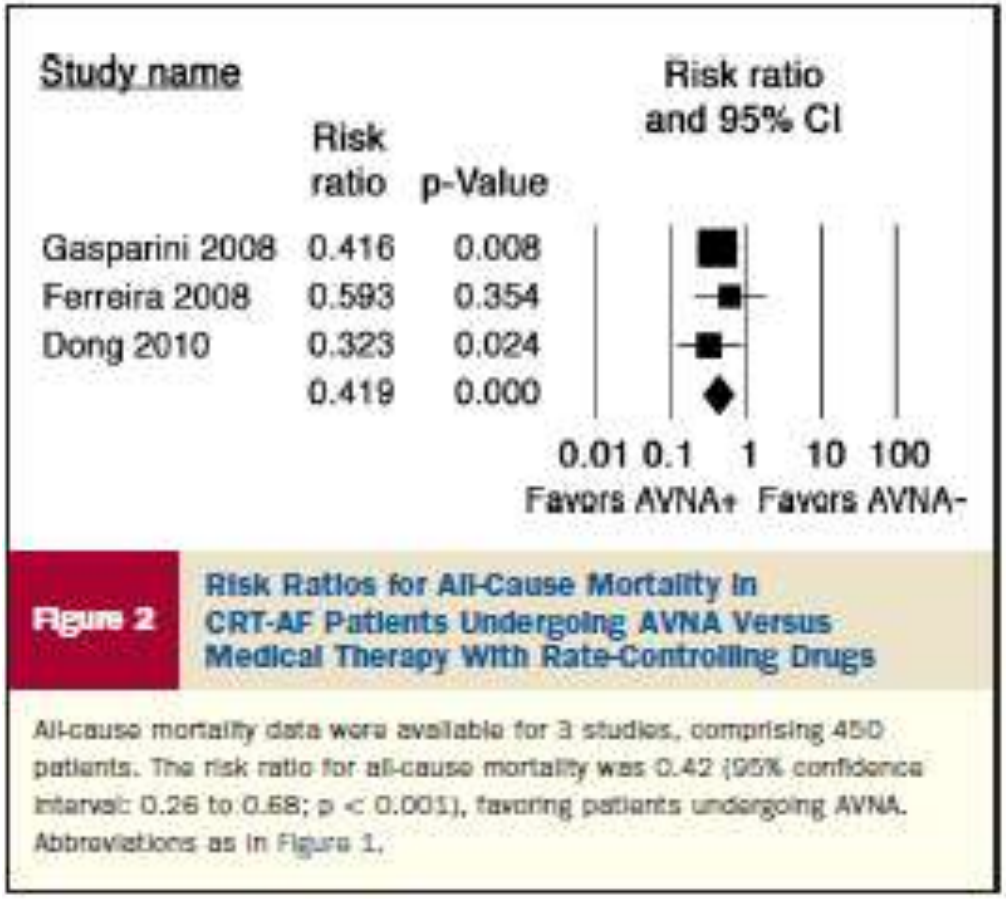



**Figure 2** **Risk Ratios for All-Cause Mortality in CRT-AF Patients Undergoing AVNA Versus Medical Therapy With Rate-Controlling Drugs**

All-cause mortality data were available for 3 studies, comprising 450 patients. The risk ratio for all-cause mortality was 0.42 (95% confidence interval: 0.26 to 0.68; $p < 0.001$), favoring patients undergoing AVNA. Abbreviations as in Figure 1.

Ganesan et. al. *J Am Coll Cardiol* 2012