Pharmacological Management of Atrial Fibrillation

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Advanced Practitioners for the River Region
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OBJECTIVES

- Understand treatment priorities in management of atrial fibrillation
- Review medications prescribed for rate control
- Recognize indications for anticoagulants
- Discuss antiarrythmic therapies

Definition

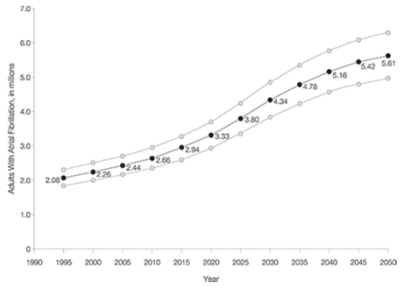
- Atrial fibrillation is a supraventricular tachyarrhythmia characterized by uncoordinated atrial activation resulting in compromised mechanical function.
- EKG characteristics:
  irregular R-R intervals
  absence of P waves

Prevalence

- Estimated 2.2 million in US alone
  1 in 25 age 60 or >
  1 in 10 age 80 or >
- Projected to increase to 5.6 million by 2050 with more than 50% of affected individuals 80 or older

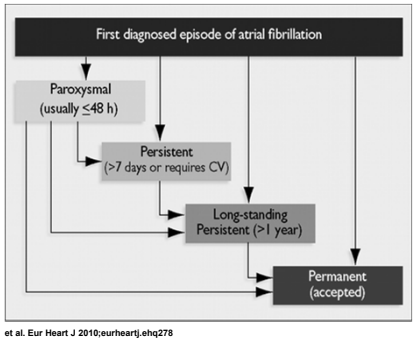
Go, A, et al. JAMA 2001;285:2370-75

Prevalence of AFib in the US is expected to increase upwards of 5.3 million by 2050



Go et al; JAMA 2001;285:2370-5

Different types of AF. AF = atrial fibrillation; CV = cardioversion.



et al. Eur Heart J 2010;eurheartj.ehq278

European Heart Journal

2006 ACC/AHA/ESC Guideline for Management of Patients with Atrial Fibrillation
2011 ACCF/AHA/HRS Atrial Fibrillation, Focused Update

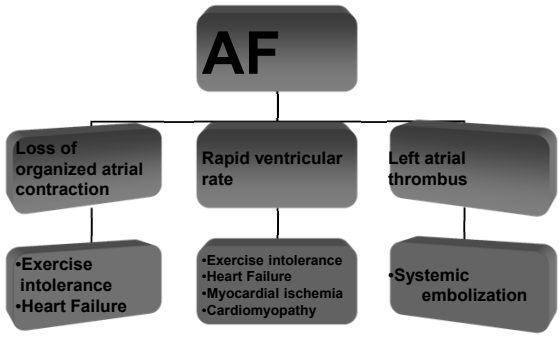
Treatment Goals:

Rate Control

Prevention of thromboembolic event

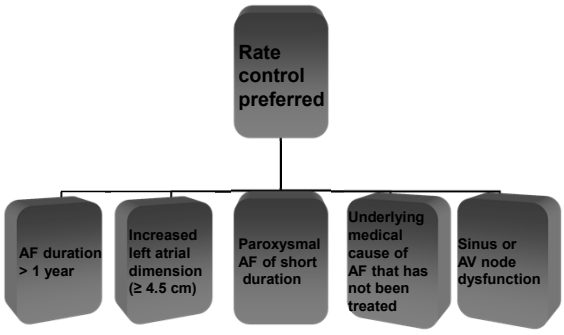
Maintenance of Sinus Rhythm

Major Consequences of AF



- Management Considerations
- Rate
- Duration
- Co morbidities
- Symptoms
- Structural abnormalities
  - LA size
  - LV size/function
  - Valvular disease
  - Ischemia

Candidates for Rate Control



AFFIRM Trial

- No survival advantage to rhythm control.
- Rhythm control patients were more likely to be hospitalized with adverse drug effects.
- Both groups had similar stroke risk (1% per yr)
  - Majority of strokes when warfarin stopped or INR subtherapeutic
  - Warfarin required long term even if sinus rhythm restored
- Torsades, bradycardic arrest more common with rhythm control.
- Typical patient: 69 yo man, no symptoms

Olshansky,B. JACC.2004:43(7):1201-08

Acute management of RVR

Beta Blockers
- Metoprolol : 2.5 – 5 mg IV over 2 mins; may repeat x 3 doses
- Esmolol : 500 mcg/kg IV over 1 min then 50 mcg/kg/min IV gtt
- Propranolol: 0.15 mg/kg IV over 2 mins: may repeat in 2 mins

Calcium Channel Blockers
- Diltiazem: 0.25 mg/kg IV over 2 mins; rebolus prn 15 mins with 0.35mg/kg IV then gtt 5-15 mg/hr
- Verapamil: 0.075 to 0.15 mg/kg IV over 2 mins; Max dose 20 mg

Amiodarone: 150 mg IV over 10 mins; IV gtt 1 mg/min for 6 hrs then 0.5 mg/min for 18 hours

Digoxin: 2.5- 5mg IV followed by 0.25 mg q 6hr for total load of 1 mg

ACCF/AHA Pocket Guideline. 2011. Management Atrial Fibrillation

Long term rate control management

- Metoprolol: 25-100 mg twice daily
- Propranolol: 80-240 mg twice daily
- Diltiazem: 120-360 mg daily
- Verapamil: 120-360 mg daily
- Digoxin: 0.125-0.375 mg daily; reduce frequency for renal disease
- Amiodarone: 200 mg daily

Side Effects and Monitoring

Beta Blockers* and Calcium Channel Blockers++

- Excessive bradycardia, pauses, and heart block
- Hypotension
- Heart failure exacerbations
- Bronchospasm *
- Less severe symptoms include fatigue, dizziness, pedal edema(++) and constipation (++)

Digoxin

- Excessive bradycardia, pauses or heart block, ventricular arrhythmias
- Dig toxicity
- GI symptoms

Prevention of thromboembolic events

- 5 fold increase in risk of ischemic stroke and associated disability
- 15-20 % of all strokes are associated with atrial fibrillation
- Prior stroke or TIA is the stongest independent predictor of stroke risk

Fuster, v., Circulation.2006;114:700-752

How do we determine stroke risk ?

- CHADS2
  - **Congestive heart failure - 1pt**
  - **Hypertension - 1pt**
  - **Age > 75 - 1 pt**
  - **Diabetes - 1pt**
  - **Stroke or TIA - 2 pts**
  - **0 points – low risk** (1.2-3.0 strokes per 100 patient years)
  - **1-2 points – moderate risk** (2.8-4.0 strokes per 100 patient years)
  - **≥ 3 points – high risk** (5.9-18.2 strokes per 100 patient years)

(Gage, et al.: JAMA 2001)

Table 2—*The 2009 Birmingham Schema Expressed as a Point-Based Scoring System, With the Acronym CHA_2DS_2-VASc*

Risk Factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥ 75 y	2
Diabetes mellitus	1
Stroke/TIA/TE	2
Vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque)	1
Age 65-74 y	1
Sex **c**ategory (ie female gender)	1

Oleson, JB, et al. BMJ.2011;342:d124

Bleeding Risk – HAS-BLED Score

Letter	Clinical characteristic[a]	Points awarded
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (e.g. age >65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2
		Maximum 9 points

Pisters, R. Chest. 2010;138:1093-100

Stroke Risk

- Untreated – 4.5% annual rate of stroke
- Warfarin – decreased risk to 1.4% (60% men and 84% women)
- Aspirin – 44% risk reduction

- Anticoagulation therapy is approximately 50% more effective than aspirin therapy in stroke prevention
- Patients with contraindications or unreliable patients should consider aspirin therapy

Zipes,D. (2005). Braunwald's Heart Disease, 7th ed.

How about Clopidogrel + Aspirin ?

ORIGINAL ARTICLE

Effect of Clopidogrel Added to Aspirin in Patients with Atrial Fibrillation

The ACTIVE Investigators*

ABSTRACT

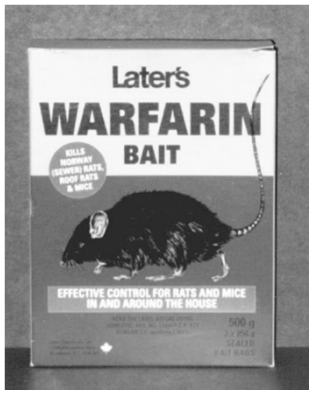
BACKGROUND

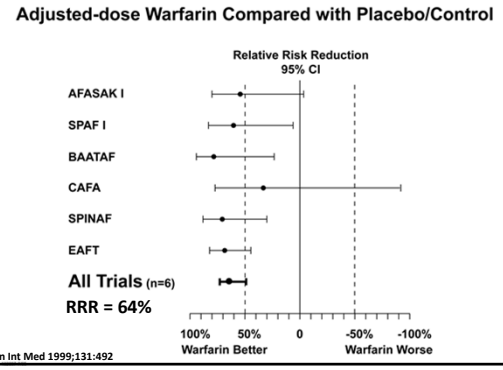
Vitamin K antagonists reduce the risk of stroke in patients with atrial fibrillation but are considered unsuitable in many patients, who usually receive aspirin instead. We investigated the hypothesis that the addition of clopidogrel to aspirin would reduce the risk of vascular events in patients with atrial fibrillation.

METHODS

A total of 7554 patients with atrial fibrillation who had an increased risk of stroke and for whom vitamin K–antagonist therapy was unsuitable were randomly assigned to receive clopidogrel (75 mg) or placebo, once daily, in addition to aspirin. The primary outcome was the composite of stroke, myocardial infarction, non–central nervous system systemic embolism, or death from vascular causes.

N Engl J Med online publication March 31, 2009





Hart Ann Int Med 1999;131:492

Warfarin

- 5-15 mg q hs
- Onset 36-72 hours
- Peak effect 5-7 days
- INR goal 2.0-3.0
- Follow INR closely, every 3-4 days with dosage adjustments or initiation of new drug therapy, i.e. antibiotics, amiodarone
- In US maximal monitoring period usually 4 weeks
- Home monitoring currently done weekly
- Avoid high bolus doses as can produce hypercoagulable state
- Educate patients related to dietary issues/potential drug interactions/ monitoring for bleeding abnormalities
- Reverse with Vitamin K if high risk or active bleeding, preoperatively, or INR >10

Recommendations - Antithrombotic

- 5. We suggest, that when OAC therapy is indicated, most patients should receive dabigatran in preference to warfarin. In general, the dose of dabigatran 150 mg po bid is preferable to a dose of 110 mg po (exceptions discussed in text).

(Conditional recommendation. High Quality Evidence).

RELY

- Dabigatran 110 mg twice daily
  - Equal to warfarin in stroke prevention
    - Warfarin 1.69%/yr – dabigatran (110mg) 1.53%/yr
  - Less bleeding than warfarin
    - Warfarin 3.36%/year – dabigatran (110mg) 2.71%/yr
- Dabigatran 150 mg twice daily
  - More effective than warfarin in stroke prevention
    - Dabigatran (150mg) 1.11%/yr
  - Equivalent bleeding to warfarin

less hemorrhagic stroke than warfarin

Connolly, S. NEngJMED.2009;361(12):1139-51

Dabigatran

- 150 mg BID / 75 mg BID - Cr CL 15-30/ do not use if <15
- Half life of drug is 12-17 hours
- 80% excreted by kidneys
- Assess renal function prior to initiation
- No routine monitoring necessary
- DO NOT RELY ON INR AS IT IS INACCURATE. If necessary check aPTT or ECT to assess for activity.
- Avoid with Rifampin. Caution with dronaderone
- No specific reversal agent available.
- Discontinue drug 1-2 days preoperatively with normal renal function, 3-5 days if CrCl <50 ml/min
- FDA investigation of post-market reports of serious bleeding events

REVIEW ARTICLE

ONLINE FIRST

Dabigatran Association With Higher Risk of Acute Coronary Events

Meta-analysis of Noninferiority Randomized Controlled Trials

Ken Uchino, MD; Adrian V. Hernandez, MD, PhD

Background: The original RE-LY (Randomized Evaluation of Long-term Anticoagulant Therapy) trial suggested a small increased risk of myocardial infarction (MI) with the use of dabigatran etexilate vs warfarin in patients with atrial fibrillation. We systematically evaluated the risk of MI or acute coronary syndrome (ACS) with the use of dabigatran.

Methods: We searched PubMed, Scopus, and the Web of Science for randomized controlled trials of dabigatran that reported on MI or ACS as secondary outcomes. The fixed-effects Mantel-Haenszel (M-H) test was used to evaluate the effect of dabigatran on MI or ACS. We expressed the associations as odds ratios (ORs) and their 95% CIs.

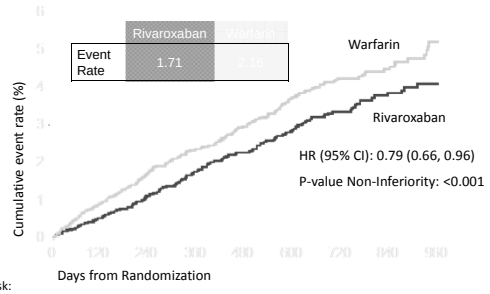
Results: Seven trials were selected (N = 30 514), including 2 studies of stroke prophylaxis in atrial fibrillation, 1 in acute venous thromboembolism, 1 in ACS, and 3 of short-term prophylaxis of deep venous thrombosis. Control arms included warfarin, enoxaparin, or placebo administration. Dabigatran was significantly associated with a higher risk of MI or ACS than that seen with agents used in the control group (dabigatran, 237 of 20 000 [1.19%] vs control, 83 of 10 514 [0.79%]; OR_{M-H}, 1.33; 95% CI, 1.03-1.71; $P = .03$). The risk of MI or ACS was similar when using revised RE-LY trial results (OR_{M-H}, 1.27; 95% CI, 1.00-1.61; $P = .05$) or after exclusion of short-term trials (OR_{M-H}, 1.33; 95% CI, 1.03-1.72; $P = .03$). Risks were not heterogeneous for all analyses ($I^2 = 0\%$; $P \geq .30$) and were consistent using different methods and measures of association.

Conclusions: Dabigatran is associated with an increased risk of MI or ACS in a broad spectrum of patients when tested against different controls. Clinicians should consider the potential of these serious harmful cardiovascular effects with use of dabigatran.

Arch Intern Med.
Published online January 9, 2012.
doi:10.1001/archinternmed.2011.1666

Primary Efficacy Outcome

Stroke and non-CNS Embolism



No. at risk:

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

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

Patel,M. N Eng JMed. 2011;365:883-891

Rivaroxaban

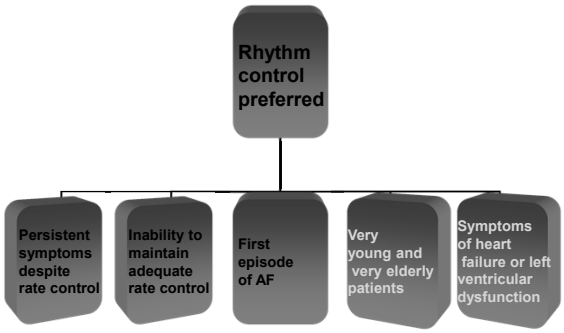
- 20 mg once daily with evening meal; 15 mg if CrCl 15-50 mL/min
- Elimination half life 5-9 hours in 20-49 yo and 11-13 hours in elderly
- 66% renally excreted
- Food increases bioavailability with maximum concentrations in 2-4 hrs
- Avoid with P-glycoproteins and strong CYP3A4 inhibitors
- No routine monitoring
- No specific antidote.
- Prothrombin complex concentrate(PCC), activated PCC or recombinant factor VIIa may reverse; not dialyzable
- Discontinue 24 hours preoperatively
- Indicated for DVT prophylaxis post hip, knee surgery at dose 10 mg/day
- Rocket AF Trial Bleeding risks :

	Xarelto n=7111	Warfarin n=7125
Major Bleed	395	386
Critical Organ	91	133
GI	221	140

New anticoagulants

- Short half life – less bleeding
  - Subtherapeutic if misses one or two doses
- Lack of need for routine monitoring
  - No standard available test to asses if anticoagulated
- Generally safer than warfarin
  - No antidote
  - ??? Dabigatran
- Cost of medication
  - Overall cost of care

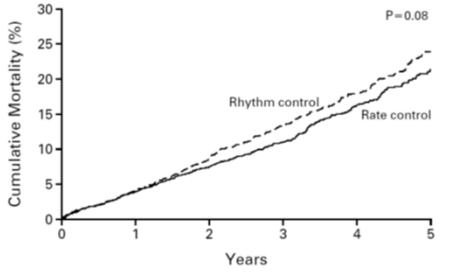
Candidates for Rhythm Control



Theoretical Benefit of Rhythm Control

- Improved hemodynamics
- Relief of symptoms
- Improved exercise tolerance
- Reduced risk of stroke
- Avoidance of anticoagulants

Cumulative all-cause mortality: rhythm control vs. rate control



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)

N Engl J Med 2002;347:1825

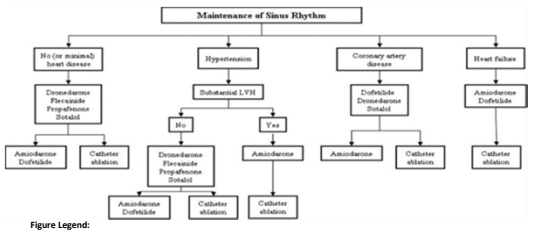


Figure Legend:

Therapy to maintain sinus rhythm in patients with recurrent paroxysmal or persistent atrial fibrillation. Drugs are listed alphabetically and not in order of suggested use. The seriousness of heart disease progresses from left to right, and selection of therapy in patients with multiple conditions depends on the most serious condition present. LVH indicates left ventricular hypertrophy.

Pharmacologic Cardioversion

- Less than 7 days duration:
  - Dofetilide
  - Flecainide
  - Ibutilide
  - Propafenone
  - Amiodarone

  More than 7 days
  - Amiodarone
  - Ibutilide

Pill-in-the-Pocket

- A "pill-in-the-pocket" approach allows patients to self-administer an oral dose of anti-arrhythmic agent when symptoms of AF recur (Class IIa).
- Propafenone and flecainide have been the most rigorously evaluated for this strategy.
- Patients considered for a pill-in-the-pocket approach should be maintained on rate control agents and have no evidence of structural heart disease or conduction system abnormalities.

Pharmacologic Cardioversion

- Class III agents
- Ibutilide- 1 mg IV over 10 mins and repeat after 10 mins if AF persists
  - Weight adjusted dose for <60 kg
  - Half life 2-12 hrs; mean termination of AF time 30 minutes
  - Risk of TdP up to 8%, also monitor for hypotension, bradycardia at least 4 hrs after administration
  - Correct K+ and Mag levels prior to administration
  - Contraindicated in patients with prolonged QT, severe structural heart disease, heart failure and sinus node dysfunction

Rhythm Control

- IC agents:
- Flecainide- 50 mg q 12 hours and may increase to max 300 mg/day
  - Half life 7-22 hrs; peaks at 1.5-3hrs; adjust dosage if CrCl <10mg/dl
  - Prolong R-R and QRSD, less likely the QTc
  - Monitor EKG for QRS lengthening, bradycardia and AV block
  - Avoid in structural heart disease
  - SE include dizziness, visual disturbances, dyspnea
  - Correct K+ and Mag deficiency
  - Pill in pocket method

Rhythm Control

- IC agents:
- Propafenone-150-300 mg q 8 hrs and may increase to max 1200 mg/day
  - Half life 10-32 hrs; peaks in 2-3 hrs
  - Monitor EKG for QRS lengthening and AV block
  - Less proarrhythmic than flecainide
  - Avoid in CHF, structural heart disease
  - SE include N/V and unusual taste
  - Pill in pocket method

Rhythm Control

- Class III agents:
- Sotalol- 80 mg BID to max dose of 160 mg BID; CrCl 40-60 mg/dl 80 mg once a day; CrCl <40 do not use; preferable to initiate in hospital
  - Half life 12 hrs; peaks at 2.5-4 hrs
  - Monitor EKG for bradycardia, heart block, QT prolongation (stop or decrease dosage if QTc >500 ms)
  - Correct K+ and magnesium abnormalities
  - Avoid in active bronchospastic lung disease
  - SE include fatigue, dizziness and lightheadedness, weakness and dyspnea

Rhythm Control

- Class III agents:
- Sotalol- 80 mg BID to max dose of 160 mg BID; CrCl 40-60 mg/dl 80 mg once a day; CrCl <40 do not use; preferable to initiate in hospital
  - Half life 12 hrs; peaks at 2.5-4 hrs
  - Monitor EKG for bradycardia, heart block, QT prolongation (stop or decrease dosage if QTc >500 ms)
  - Correct K+ and magnesium abnormalities
  - Avoid in active bronchospastic lung disease
  - SE include fatigue, dizziness and lightheadedness, weakness and dyspnea

Rhythm Control

- Class III agents:
- Amiodarone-800 mg/day po for 2 weeks then 200-400 mg daily for 3-6 mos then 100-300 mg/day maintenance dosage. May be initiated as an IV dosage
  - Half life 15-142 days, average 58 days with onset in 3 days to 3 weeks
  - Monitor EKG for bradycardia, heart block, QT prolongation (low risk TdP)
  - IV may cause hypotension
  - Monitor thyroid, pulmonary and liver function (lab testing q 6 mos)
  - Higher doses associated with GI upset i.e. nausea and vomiting
  - SE include pulmonary toxicity, hyper- (2%) or hypothyroidism (8%), tremors, neuropathy or myopathy, optic neuritis or corneal deposits, photosensitivity or blue gray skin discoloration

Rhythm Control

- Amiodarone (continued):
  - Increases risk of bleeding on warfarin. Decrease the warfarin by 1/3 with initiation of therapy and increase INR surveillance.
  - Increases digoxin level so decrease digoxin dose by ½ on initiation of therapy
  - Avoid with doses of simvastatin >20 mg/day
  - Multiple studies have demonstrated amiodarone as superior to other agents for cardioversion and maintenance of sinus rhythm.
  - Suitable and preferable in patients with severe LV dysfunction

Side Effects and Monitoring

Amiodarone

- Hypotension, heart block, bradycardia
- Proarrythmia
- Pulmonary toxicity
- Hypo/hyperthyroidism
- Abnormal LFTs
- Corneal deposits
- Tremor
- GI intolerance
- Skin discoloration

Consider baseline CXR, PFTs, LFTs, TFTs with routine monitoring

Rhythm Control

- Class III agents:
- Dronaderone – 400 mg BID
  - Half life 24 hours and metabolized by liver; increased absorption with food
  - Increases mortality in heart failure and severe LV dysfunction
  - Monitor EKG for QT prolongation, bradycardia, heart block, SSS
  - Rare cases of liver toxicity reported
  - Most common SE are GI
  - Contraindicated in Permanent AF, NYHA Class IV HF or Class II-III with recent decompensation requiring hospitalization, sever liver impairment.
  - Decrease digoxin dosage by ½ .
  - Avoid with simvastatin, potent CYP3A4 inhibitors

Revised EU Labeling for Dronedarone Contraindications

- **Hypersensitivity to the active substance or to any of the excipients**
- **Second- or third- degree atrioventricular block, complete bundle branch block, distal block, sinus node dysfunction, atrial conduction defects, or sick sinus syndrome (except when used in conjunction with a functioning pacemaker).**
- **Bradycardia < 50 beats/min**
- **Permanent atrial fibrillation (AF) with an AF duration 6 months (or duration unknown) and attempts to restore sinus rhythm no longer considered by the physician**
- **Patients in unstable hemodynamic conditions**
- **History of, or current heart failure or left ventricular systolic dysfunction**
- **Patients with liver and lung toxicity related to the previous use of amiodarone**
- **Coadministration of potent cytochrome P450 3A4 inhibitors, such as ketoconazole, itraconazole, voriconazole, posaconazole, telithromycin, clarithromycin, nefazodone, and ritonavir.**
- **Medicinal products inducing torsades de pointes, such as phenothiazines, cisapride, bepridil, tricyclic antidepressants, terfenadine, and certain oral macrolides (such as erythromycin); class I and III antiarrhythmics (see section 4.5)**
- **QTc Bazett interval 500 ms**
- **Severe hepatic impairment**
- **Severe renal impairment (creatinine clearance < 30 mL/min)**

Arrhythmia & EP theheart.org Medscape

Summary

- Multiple factors contribute to treatment decisions for atrial fibrillation
- An expected increase in prevalence ensures all providers will be involved in these treatment decisions and follow up
- Rate control to assure hemodynamic stability and decrease long term complications is a top priority
- Anticoagulation or antiplatelet therapy effectively decreases the major risk of stroke, adding their own inherent risks
- Restoring sinus rhythm, achieved with antiarrhythmic therapy, potentially increases hospitalizations and mortality rates related to cardiovascular disease