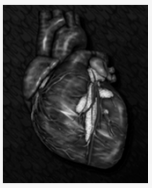
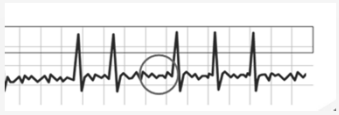
Pharmacy 451
Atrial Fibrillation





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RSS 2012

Session Objectives

1. To select appropriate therapy for acute ventricular rate control of AF
2. To select appropriate acute antithrombotic therapy for AF
3. To recognize antiarrhythmic agents that acutely convert AF to NSR
4. To understand the risks and benefits of RATE versus RHYTHM control strategies for chronic management of AF, and the 'preferred' initial strategy
5. To select appropriate therapy for chronic ventricular rate control for AF
6. To select appropriate chronic antiarrhythmic therapy for AF
7. To recognize important monitoring parameters for amiodarone therapy
8. To recognize when to avoid using dronedarone for AF
9. To recommend appropriate chronic antithrombotic therapy to prevent stroke in AF patients based on annual stroke risk, bleeding risk, cost, ease of administration, patient-specific factors

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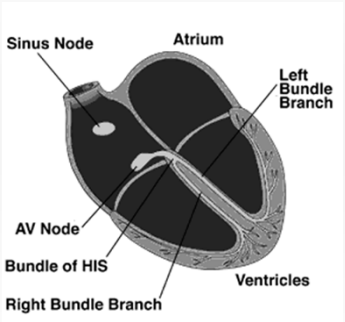
Normal Sinus Rhythm



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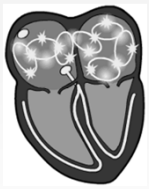
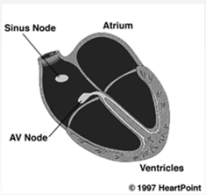
Definition of AF

- AF is an irregularly, irregular supraventricular arrhythmia with atrial rates of 350-450 bpm
- EKG: No p waves, irregular, narrow QRS





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Classification of AF

- First episode
- Paroxysmal
  → AF alternates with NSR, patient reverts spontaneously
- Persistent
  → AF alternates with NSR, patient requires treatment (electrical or pharmacological) to convert to NSR
- Permanent
  → Inability to convert to NSR with therapy

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Impact of Atrial Fibrillation

- Symptoms
  - Reduced exercise tolerance, weakness, fatigue, dizziness, lightheadedness, palpitations, chest pain, SOB, syncope. May be asymptomatic!
- Morbidity
  - Reduced EF, CO, CHF, hypotension
  - Valvular and non-valvular AF both increase stroke risk
  - Overall stroke rate is 4.5% / year
  - Higher in elderly (18% /yr), lower in 'lone' AF (1% /yr)
- Mortality
  - Independent risk factor post-stroke, post-MI, CHF

N Engl J Med 2001;344:1067-1078.

RSS 2012

Outcome Goals for AF

- Reduce symptoms
- Reduce morbidity
  - Improve heart function
  - Reduce incidence of stroke
  - Reduce emergency department visits
  - Reduce hospitalization rates
- Improve quality of life

- Reduce mortality
- Promote cost-effective therapy

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Specific Therapeutic Goals

1. Control or cure precipitating causes
2. Control rapid ventricular rate
3. Prevent thromboembolic complications
4. Convert AF to NSR
5. Reduce recurrences of AF by attempting to maintain NSR

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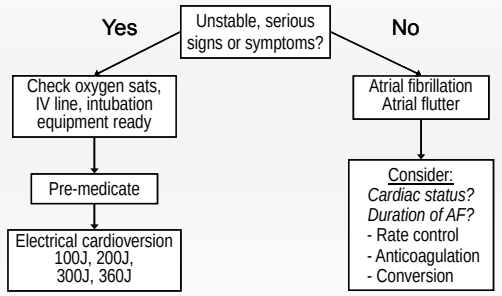
Approach to Acute AF



Adapted from Tachycardia Algorithm, Advanced Cardiac Life Support Guidelines Circulation 2010, 122:S729-S767.

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Acute Ventricular Rate Control

- Slower HR allows ventricles to fill better, improving cardiac hemodynamics
- May reduce AF symptoms, reduce ED treatment time, and prevent hospitalization
- Drugs MUST work to BLOCK AV Node
  - Beta blockers, CCBs, digoxin, amiodarone
- "Target" acute HR control controversial
  - Traditionally < 100 bpm, critically-ill < 120 bpm
  - Depends on symptoms and co-morbid diagnoses
- IV agents used if patient is symptomatic

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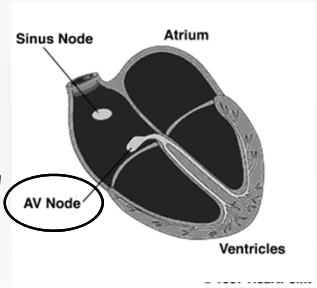
Acute Ventricular Rate Control

Rate Control Drugs
Beta blockers
Calcium blockers
Digoxin
Amiodarone



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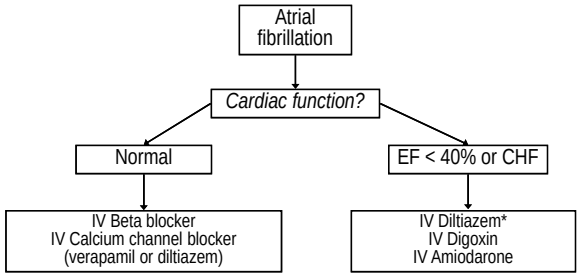
Acute Ventricular Rate Control



Adapted from Tachycardia Algorithm, Advanced Cardiac Life Support Guidelines Circulation 2010, 122:S729-S767. Can J Cardiol 2010; 27:38-46.

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Acute Antithrombotic Prophylaxis

- Blood stasis in fibrillating atria leads to clot formation inside atrial chambers
- Electrical, pharmacological, or spontaneous cardioversion to NSR may restore atrial contraction and eject clot (e.g. stroke)
- Risk of stroke during active cardioversion without antithrombotic therapy is:
  - 0.8% in AF ≤ 48 hours duration
  - 5.0% in AF > 48 hours duration
- Acute antithrombotic prophylaxis choice based on duration of AF episode, history of recurrence

Chest 2008;133(Suppl):546S-592S, Can J Cardiol 2010; 27:38-46.

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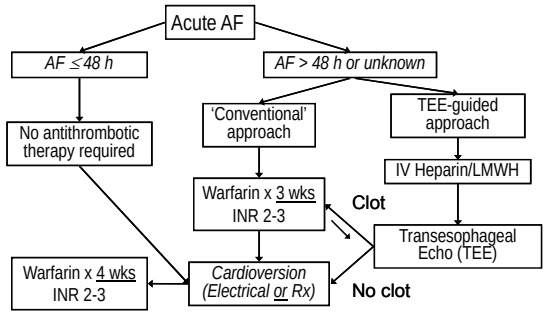
Acute Antithrombotic Prophylaxis



Chest 2008;133(Suppl):546S-592S.
Can J Cardiol 2010; 27:38-46. RSS 2013

Acute Conversion to NSR

- Electrical cardioversion or antiarrhythmic drugs can be used to acutely convert AF to NSR
- Conversion to NSR may reduce symptoms and improve cardiac hemodynamics by restoring atrial "kick", and eliminating the rapid ventricular response
- May reduce ED treatment time, and prevent hospitalization
- Drugs MUST act on ATRIAL TISSUE
  - Prolong atrial refractory period to convert AF to NSR
  - Class IA, IC, III antiarrhythmic drugs

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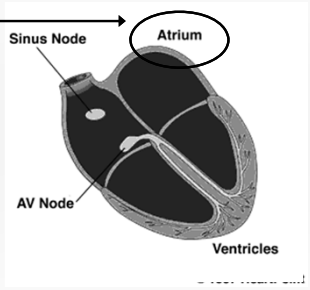
Acute Conversion to NSR

Antiarrhythmics

Class IA
- Quinidine
- Procainamide

Class IC
- Propafenone
- Flecainide

Class III
- Sotalol
- Amiodarone
- Ibutilide



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Acute Conversion to NSR

- More difficult to acutely convert some patients
  - Longer duration of AF
  - Larger left atrium
  - Low ejection fraction/clinical CHF
  - Mitral valve regurgitation
- Consider acute conversion for the following patients
  - Acute AF episode duration for ≤ 48h
  - First episode/paroxysmal AF, NOT persistent/permanent
  - Patients who remain symptomatic despite HR control
- Consider TEE-guided strategy or delayed cardioversion if AF episode > 48h

Can J Cardiol 2010; 27:38-46.

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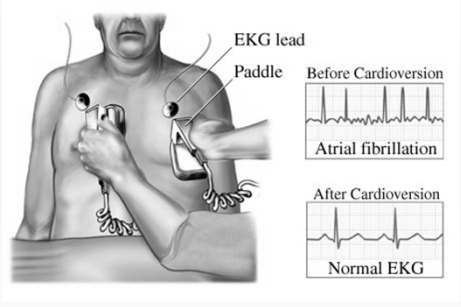
Electrical Conversion



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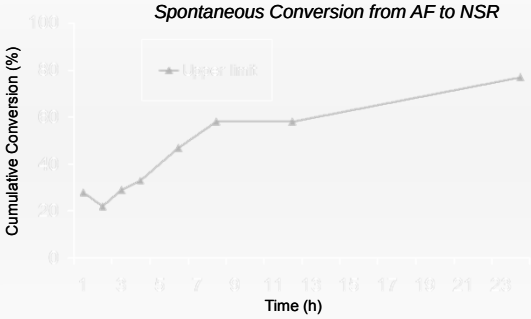
"Recent-onset AF"

Spontaneous Conversion from AF to NSR



Slavik RS, Tisdale JE, Borzak S. Prog Cardiovasc Dis 2001;44:121-152.

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Acute Conversion Regimens

- Ibutilide (IV) 1 mg IV over 10 mins, repeat x 1 prn
  - Contraindicated: history of Torsades de pointes, unstable angina, CHF, MI or CABG in past 6 months
- Procainamide (IV) 1 g IV over 30 mins, then 2 mg/min
  - Contraindicated: history of hypersensitivity,Torsades de pointes
- Propafenone (oral) 600 mg po single dose
  - Contraindicated: >80yo, unstable angina, MI in past 6 months, CHF ≥ NYHA class II, sick sinus syndrome
- Flecainide (oral) 300 mg po single dose
  - Contraindications as per propafenone

Note: *High-dose IV or oral amiodarone may convert AF, but conventional doses do not convert AF to NSR quickly in the acute setting. Oral sotalol NOT effective for acute conversion. Both amiodarone and sotalol effective for maintenance of NSR.

Prog Cardiovasc Dis 2001;44:121-152, Can J Cardiol 2010; 27:38-46.

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Optimal Long-term Strategy?

Rate control *Rhythm control*

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Optimal Long-term Strategy?

Randomized Controlled Trials

- Pharmacological Intervention in Atrial Fibrillation (PIAF)*
- Rate Control versus Electrical Cardioversion (RACE)
- Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM)*
- Strategies of Treatment of Atrial Fibrillation (STAF)
- How to Treat Chronic Atrial Fibrillation (HOT-CAFÉ)
- Atrial Fibrillation – Congestive Heart Failure (AF-CHF)*

Lancet 2000;356:1789-1794, N Engl J Med 2002;347:1834-1840, N Engl J Med 2002;347:1825-1833, J Am Coll Cardiol 2003;41:1690-1696, Chest 2004;126:476-486, N Engl J Med 2008;358:2667-2677.

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Pharmacological Intervention in AF (PIAF)

Design

- P, R, open-label pilot trial
- Inclusion: Age 18 - 75 yo, persistent AF ≥ 7 and < 360 days
- Exclusion: MI/CABG < 30d, unstable angina, class IV CHF, emboli in previous 3 months, safety exclusions
- Randomized allocation:
  - *Rate control* (diltiazem) vs. *rhythm control* (amiodarone)
  - All patients received warfarin INR 2.0 – 3.0
- Follow-up of 1.0 year
- Endpoints
  1º - Symptomatic improvement (dizziness, palpitations, SOB)
  2º - % NSR, HR, exercise tolerance, QOL, admissions, ADRs

Lancet 2000;356:1789-1794.

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Pharmacological Intervention in AF (PIAF)

Results	Diltiazem (n=125)	Amiodarone (n=127)	
Improved symptoms	61 %	55 %	
*NSR at 1 year	10 %	56 %	NNT = 2
HR Control	NS		
*Six minute walk test (m)	510	545	
Quality of Life (SF36)	NS		
*≥ 1 hospital admission	24 %	69 %	NNH = 2
*W/D due to ADRs	14 %	25 %	NNH = 9

** $p < 0.05$*

Lancet 2000;356:1789-1794.

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Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM)

Design

- P, R, open-label multi-centre trial
- Inclusion: Age > 65 yo with paroxysmal AF, index episode within 12 wks, continuous for < 6 mos, no contras to 'rate' or 'rhythm' strategies or meds
- Exclusion: Failed cardioversion prior to randomization, other cardiac, medical, and non-medical contraindications
- Randomized allocation:
  - '*Rate control*' (Dig, BB, CCB, combo) with AV ablation/pacer prn vs. '*Rhythm control*' (amiodarone, disopyramide, flecainide, moricizine, procainamide, propafenone, quinidine, sotalol, dofetilide, or a combination based on study protocol)
  - All patients received warfarin INR 2.0 – 3.0, or ASA if NSR for ≥ 4 weeks
- Endpoint:
  1º - All cause mortality

N Engl J Med 2002;347:1825-1833.

RSS 2012

Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM)

Results	Rate (n=2027)	Rhythm (n=2033)	
All-cause mortality	25.9 %	26.7 %	p = 0.08
Composite endpoint	32.0 %	32.7 %	p = 0.33
*Hospitalizations	73.0 %	80.1 %	NNH=14
*Crossed-over	12.2 %	29.2 %	NNH=6
*Pulmonary	1.7 %	7.3 %	NNH=18
*Gastrointestinal	2.1 %	8.0 %	NNH=17
*Bradycardia	4.2 %	6.0 %	NNH=56
*QTc > 520 msec	0.3 %	1.9 %	NNH=63
*Bradycardic arrests	0.1 %	0.6 %	NNH=200
*Other ADRs	14.0 %	25.4 %	NNH=9

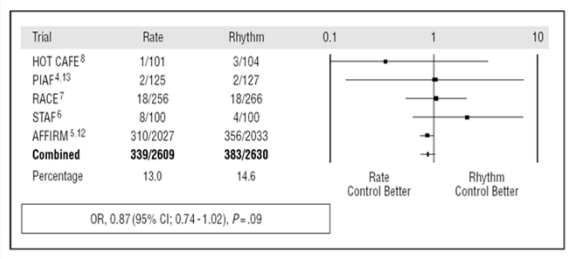
** p < 0.05*

N Engl J Med 2002;347:1825-1833.

RSS 2012

Optimal Long-term Strategy

Meta Analysis: All-cause mortality (p=NS), no benefit



Arch Internal Medicine 2005;165:258-262.

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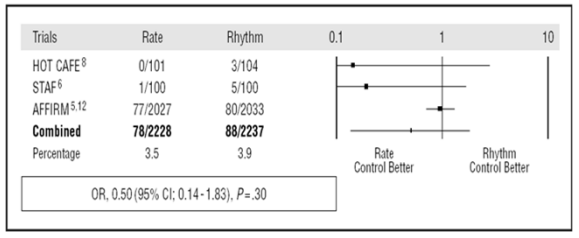
Optimal Long-term Strategy

Meta Analysis: Ischemic Stroke (p=NS), no benefit



Arch Internal Medicine 2005;165:258-262.

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AF-CHF Trial Results

Primary outcome

- Time to death: HR = 1.06 (0.86 to 1.30)

Secondary outcome

- Death any cause HR = 0.97 (0.80 to 1.17)
- Worsening CHF HR = 0.87 (0.72 to 1.06)
- Hospitalization 64% vs. 59% (p=0.06)

**More rhythm control patients hopsitalized in first year, more admits due to AF, more bradycardias*

- Quality of life Not reported
- Cost of therapy Not reported
- "Bad" Composite: HR = 0.90 (0.77 to 1.06)

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Optimal Long-term Strategy

- Rate control should be the preferred initial long-term strategy
- Consider trial of rhythm control for the following:
  - Patients who remain symptomatic with frequent and/or severe episodes despite rate control therapy

** Rhythm control did not improve outcomes in heart failure patients, and should not be initial strategy*

Can J Cardiol 2011;27:27-30.

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Chronic Ventricular Rate Control

- Therapeutic alternatives include beta blockers, calcium channel blockers, digoxin, amiodarone
- Many poorly-designed studies
- "Target" chronic HR control controversial
  - Recent data from RACE II trial comparing "strict" HR target of 80-110 versus "lenient" target> 110 bpm showed no difference in outcomes
  - Goal "target" HR should be less than 100 bpm, but should ideally depends on patient symptoms
- Agents from difference classes act synergistically
- Combination may be required for some patients

Can J Cardiol 2011;27:27-30, N Engl J Med 2010;362:1363-73.

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Chronic Ventricular Rate Control

Summary

- Digoxin, BB, CCB all control resting HR
- Digoxin is less effective in younger patients, and does not control exercise-induced HR
- Digoxin may be an option in elderly patients with CHF who cannot tolerate BB
- BB and CCB control resting and exercise HR
- CCB or digoxin may improve exercise tolerance, BB may worsen exercise tolerance
- Choose agent based on patient demographics, co-morbid diseases, medications, and cost

Journal of Family Practice 2000;49:47-59.

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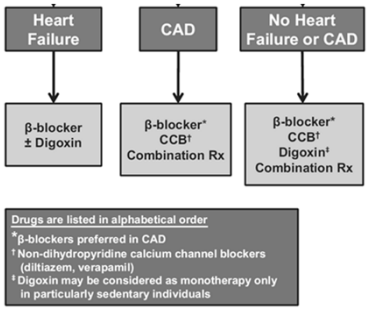
Chronic Ventricular Rate Control



Can J Cardiol 2012;28:125-136.

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Diltiazem

Indication:	AV nodal blocking agent for acute and chronic ventricular rate control of AF
Dose:	IV: 0.25 mg/kg (20 mg) IV, repeat in 15 mins with 0.35 mg/kg (25 mg) IV. IV infusion of 5-15 mg/hr
	Oral: 30 mg-90 mg po tid-qid, SR, CD form*
ADRs:	Headache, dizziness, lightheadedness, fatigue, bradycardia, heart block, hypotension, exacerbation of CHF, peripheral edema, GERD, constipation
Monitor:	Patient symptoms, baseline EKG, lytes, LFTs, CBC
	Vitals, P/E at each visit, prn EKG
Caution:	Avoid in CHF (IV use safe in class I-III), heart block or SSS, WPW, wide complex tachycardia

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Metoprolol

Indication:	AV nodal blocking agent for acute and chronic ventricular rate control of AF
Dose:	IV: 5 mg IV q 5 mins x 3, then 5-15 mg IV q6h prn
	Oral: 25 mg bid – 200 mg po bid, SR form*
ADRs:	Fatigue, depression, insomnia/nightmares, headache, dizziness, blurred vision, bradycardia, heart block, hypotension, exacerbation of CHF and asthma, N/V/D, ↓ exercise tolerance, masks hypoglycemic symptoms in diabetics, cold extrem.
Monitor:	Patient symptoms, baseline EKG, lytes, LFTs, CBC
	Vitals, P/E at each visit, prn EKG
Caution:	Avoid in uncontrolled CHF, heart block/SSS, asthma, WPW, wide complex tachycardia

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Digoxin

- Mechanism of Action
  - Inhibits Na/K/ATPase pump, to increase intracellular Ca concentrations, also potentiates vagal tone on AV node
  - (+) inotropic agent
  - Delayed onset of activity (> 3 hours in RCTs)
- Dose
  - Total loading dose usually 15mg/kg (about 1.0 mg)
  - Loading dose is divided at q2-3h intervals to avoid dose-related toxicities. Eg 0.5mg – 0.25 mg – 0.25 mg
  - Maintenance dose determined by *body weight & renal function*
  - Loading and maintenance doses can be given IV or po

"Therapeutic" Range: 1.0 – 2.6 nmol/L (0.8-2.0 mcg/L)

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Digoxin

- Adverse effects
  - Fatigue, weakness, confusion, agitation, psychosis, seizures
  - Color distrubances, photophobias, halos, headache
  - AV nodal block (additive with other agents), almost any proarrhythmia
  - Anorexia, abd pain, N/V/D
  - ↑ K+ is biggest metabolic risk
- Monitoring
  - Question patient for CNS, GI toxicities, etc.
  - Vital signs (BP, HR) and EKG (rhythm) at each visit
  - Watch PR interval on lead II (<0.20 sec) for heart blocks
  - Routine electrolytes, urine output, SCr

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Digoxin

- Indications for a digoxin serum concentration
  - Suspected toxicity
  - Suspected drug interaction
  - Marked changes in renal function
  - Investigate lack of response
  - Assess compliance
- Serum concentrations
  - Must be taken > 12-24 hours after the dose
  - Levels taken prior to steady state (<10 days) of no value except to confirm suspected pre-admission clinical toxicity
  - Levels of no use in overdose situation if Digibind® given

RSS 2012

Chronic Antiarrhythmic Therapy

- Chronic antiarrhythmic therapy is not indicated after a single episode of AF, or infrequent, asymptomatic AF
- Quinidine, disopyramide, propafenone, flecainide, sotalol, amiodarone, and dronedarone are more effective than placebo at maintaining NSR
- In general, amiodarone may delay recurrences of AF better than other agents, but may have more ADEs
- Agent selection depends on co-morbid conditions (HT, CAD, heart failure, etc.), medications, ADE profile

Can J Cardiol 2011;27:27-30.

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Dronedarone – Summary

- Effective at controlling heart rate in AF/AFL
- Prolongs time to first recurrence of symptomatic AF in a population primarily without HF (83%)
- Increases mortality in population of admitted HF patients with NHYA class II (40%), III (56%), IV (4%)
- Prolongs time to "first" hospitalization due to a CV event (NNT = 14) in pts with history of paroxysmal/persistent AF, but few patients had HF: NHYA class II (17%), III (4%), and few had EF < 45% (12%)
- Increases risk of rash, N/V/D, QTc prolongation, creatinine increase, drug interactions, WD due to ADEs

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Dronedarone – Summary

- Dronedarone has not been compared directly to propafenone, flecainide or sotalol
- Dionysis trial (2010): Dronedarone 400 mg po bid versus amiodarone 600 mg po daily x 28 days, then 200 mg daily in patients with AF > 72 hrs (6 months)
- "Failure" defined as EKG recurrence or D/C due to ADR

Outcomes	Dronedarone	Amiodarone	HR (95% CI)	NNH (95% CI)
"Failure"	74 %	53 %	1.6 (1.3 to 2.0)	3 (2 to 7)
D/C due to AF	21 %	6 %	3.9 (2.2 to 6.8)	7 (4 to 15)
D/C due to ADR	10 %	13 %	NS	NS

J Cardiovasc Electrophysiol 2010;21:597-605.

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Dronedarone – New Risks

- FDA Warning (Jan 2011)
  - Reports of acute liver toxicity, transplantation, deaths
- FDA Warning (July 2011)
  - Report of 'PALLAS' study, increased risk of stroke, hospitalization for heart failure, CV death
- Do not use dronedarone for AF patients with heart failure, rate control for permanent AF, or patients at risk of liver toxicity

http://www.fda.gov/Drugs/DrugSafety/ucm240011.htm
http://www.fda.gov/Drugs/DrugSafety/ucm264059.htm
N Engl J Med (10.1056/NEJMoa1109867) – Published online Nov 14, 2011

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Chronic Antiarrhythmic Therapy

Population	First Choice	Alternatives
No co-morbidity, or HT alone	Propafenone Flecainide Sotalol Dronedarone?	Amiodarone [1]Dofetilide
Coronary artery disease (Stable, post-ACS or PCI)	Sotalol Amiodarone	[1]Dofetilide
Heart failure	Amiodarone	[1]Dofetilide

[1]Dofetilide available special access in Canada, restricted to electrophysiologists

RSS 2012

Propafenone

Indication: Class IC antiarrhythmic for acute conversion of AF, maintenance of NSR

Dose: Acute conversion: 600 mg po single dose
Maintenance of NSR: 150 mg – 300 mg po tid

ADRs: Fatigue , headache, anxiety, dizziness, blurred vision, proarrhythmia (bradycardia, heart block, atrial flutter, ventricular tachycardia), hypotension, exacerbation of CHF and asthma, metallic taste, N/V/D, rare agranulocytosis

Monitor: Patient symptoms, baseline EKG, lytes, LFTs, CBC
Vitals, EKG, P/E at each visit

Caution: Avoid medications that can prolong QTc interval, interaction with digoxin, drop dig by 25-50%

RSS 2012

Sotalol

Indication: Class III antiarrhythmic only for maintenance of NSR

Dose: 80 mg – 160 mg po bid

ADRs: Fatigue, depression, insomnia/nightmares, headache, dizziness, blurred vision, proarrhythmia (bradycardia, heart block, TdP), hypotension, exacerbation of CHF and asthma, metallic taste, N/V/D, masks hypoglycemic symptoms in diabetics, cold extremities

Monitor: Patient symptoms, baseline EKG, lytes, SCr, CBC
Vitals, EKG, P/E at each visit

Caution: Avoid for AF if CrCl < 40 ml/min, avoid in CHF, asthma, heart block, history of prolonged QTc, TdP, avoid meds/conditions that can prolong QTc interval

RSS 2012

Amiodarone

Indication: Class III antiarrhythmic only for maintenance of NSR

Dose: Atrial PO: 600-800 mg/d x 4 weeks, then maintenance of 100-200 mg/d

ADRs: Fatigue, weakness, dizziness, ataxia, tremor, insomnia, corneal microdeposits, optic neuritis, blurred vision, dry eyes, hypo/hyperthyroidism, allergic pneumonitis, pulmonary fibrosis, bradycardia, heart block, TdP (rare), hypotension, exacerbation of CHF (rare), anorexia/N/V, asymptomatic ↑ LFTs, rare hepatitis, photosensitivity, blue-grey skin discoloration, phlebitis

RSS 2012

Amiodarone

Monitoring Plan

Baseline: History (including medications), vitals, P/E, EKG, ophthalmologic exam, CXR, pulmonary fxn tests, electrolytes, SCr, LFTs, thyroid fxn tests

Each visit: Question by system on signs/symptoms of ADRs, symptoms of AF, changes in drug therapy, check vitals and perform targeted physical exam

Lab tests: EKG at each visit (q 3 months), LFTs and thyroid function q 6 months, ophthalmologic exam and CXR q 12 months

Principles: Use lowest effective dose, many ADRs dose-related watch for DRUG INTERACTIONS!!

RSS 2012

Chronic Antithrombotic Prophylaxis

- All forms of AF seem to increase risk of stroke (i.e. paroxysmal, persistent, permanent)
- Antiarrhythmic therapy does NOT always prevent AF recurrences, does NOT protect against stroke
- Indicated for either RATE CONTROL or RHYTHM CONTROL strategies
- Screen all patients, choice between ASA, ASA plus clopidogrel, WARFARIN or DABIGATRAN or RIVAROXABAN based on risk factors for stroke, bleeding, etc.

(Dr. Loewen's lecture on Stroke)

RSS 2012

Chronic Antithrombotic Prophylaxis

- Warfarin confers ~ 66% relative risk reduction and provides protection against all stroke, ischemic stroke, disabling or fatal stroke, and systemic emboli
- Warfarin increases the risk of major extracranial bleeding and possibly ICH compared to placebo
- Patients with risk factors for bleeding (> 80 yo, previous stroke/TIA) will also receive the most absolute benefit from warfarin
- Risk of bleeding in elderly patients with history of "falls" is generally over-estimated

RSS 2012

Chronic Antithrombotic Prophylaxis

- BAFTA trial published in 2007 in elderly patients (> 75 yr) showed lower stroke rates with warfarin with no increased bleeding risk compared to ASA
- Observational data suggests INR, stroke, and bleeding rates are similar to clinical trial data
- Compared to ASA, warfarin has a larger relative risk reduction for stroke, and a small or no increase in major extracranial bleeding
- ASA may confer ~ 22% relative risk reduction for stroke

RSS 2012

Chronic Antithrombotic Prophylaxis

- Warfarin is more effective for stroke prevention than ASA/clopidogrel combination
- ASA/clopidogrel provides ~ 44% relative risk reduction for stroke in patients "ineligible or unwilling" to take warfarin, but slso increases rates of major and severe bleeding vs. ASA alone, and is no safer than warfarin in patients in whom use of warfarin is a concern due to bleeding risk

RSS 2012

Chronic Antithrombotic Prophylaxis

- Dabigatran (Pradax®)
  - Direct anti-IIa inhibitor, "RELY" trial
- Rivaroxaban (Xarelto®)
  - Direct anti-Xa inhibitor, "ROCKET-AF" trial
- Apixaban (Eliquis®)
  - Direct anti-Xa inhibitor, "ARISTOTLE" trial
- Non-inferior to warfarin at preventing stroke, similar or lower bleeding rates, no INR monitoring required, reduce dose/avoid for renal dysfunction, drug interactions

N Engl J Med 2009;361:1-13, N Engl J Med 2010;363:1875-1877.
N Engl J Med 2011;365(11):883-891.
N Engl J Med 2011;365(11):981-92.

RSS 2012

Chronic Antithrombotic Prophylaxis

- All NOACs non-inferior to warfarin for prevention of stroke or systemic embolism
- DAB 150 BID and APIX are superior to warfarin
- All NOACs have lower rates of ICH
- Some have lower life threatening bleeding (DAB 110 BID, RIV), major bleeding (DAB 110 BID, APIX)
- DAB has higher withdrawal due to SAEs, dyspepsia All NOACs have a higher acquisition cost than warfarin, slight differences between agents
- NOACs not easily reversed for bleeding/OR

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Chronic Antithrombotic Prophylaxis

- Risk factor stratification using validated instruments and patient decision aids are required to promote individualized, patient-centered therapy
- Although there are many tools available, the $CHADS_2$ instrument is conservative, easy to use, and provides an annual numerical risk of stroke, rather than providing general descriptions of risk as "low", "moderate", or "high"

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Predictive Index for Stroke

$CHADS_2$

Risk Factor	Score
Congestive Heart Failure	1
Hypertension	1
Age ≥ 75	1
Diabetes Mellitus	1
Stroke/TIA/ Thromboembolism	2
Maximum Score	6

Patients (n = 1733)	Adjusted Stroke Rate (%/yr) 95% CI	$CHADS_2$ Score
120	1.9 (1.2 to 3.0)	0
463	2.8 (2.0 to 3.8)	1
523	4.0 (3.1 to 5.1)	2
337	5.9 (4.6 to 7.3)	3
220	8.5 (6.3 to 11.1)	4
65	12.5 (8.2 to 17.5)	5
5	18.2 (10.5 to 27.4)	6

Bleeding Risk – HAS-BLED Score

Letter	Clinical Characteristic	Points
H	Hypertension	1
A	Abnormal Liver or Renal Function 1 point each	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (age > 65 yr)	1
D	Drugs or Alcohol 1 point each	1 or 2
		Maximum 9 points

Pisters R et al. Chest. 2010 Nov;138:1093-100

Major bleeding at 1y using HAS-BLED

HAS-BLED* score	Number of patients	Number of bleedings	Bleeds per 100 patient years
0	798	9	1.13
1	1286	13	1.02
2	744	14	1.88
3	187	7	3.74
4	46	4	8.70
5	8	1	12.50
6	2	0	0.0
7	---	---	---
8	---	---	---
9	---	---	---
Total	3,071	48	*P value for trend .007*

*Adapted from Chest 2010;138;1093-1100, Ann Hematol 2011;90:1191–1200. (*Not recommended for practice!)*

RSS 2012

Summary – Major Bleeding Risk

- Age > 65 yo (> 75 yo?)
- Previous major bleed
- Previous stroke
- Liver dysfunction
- Renal dysfunction
- Hypertension (SBP > 160)
- Labile INR (TTR < 60%, INR > 4)
- Antiplatelet agents
- Alcohol
- Drug interactions

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Summary – Stroke Prophylaxis

- Risk factors for stroke = HF, HT, DM
- $CHADS_2$ score = 3
- Annual risk for stroke = 5.9%
- Incorporate patient values and preferences into decision-making on choice of regimen:
  - Annual stroke risk
  - Major bleeding risk
  - Cost
  - Ease of administration (lifestyle, lab, logistics)
  - Patient specific factors (co-morbidities such as other disease states, organ function, drug interactions)

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Summary - Stroke Prophylaxis

Outcome	No Rx	ASA	ASA/Clop	Warf	DAB 110 MG BID	RIV	APIX	DAB 150 MG BID
Stroke (RRR)	0 %	**22%**	**44%**	**66%**	**66%**	**66%**	**74%**	**79%**
Annual risk	**5.9 %**	**4.6 %**	**3.3 %**	**2.0%**	**2.0%**	**2.0%**	**1.5%**	**1.2 %**
Major bleed	**0.6 %**	**1.1 %**	**3.8 %**	**3.8%**	**3.0%**	**3.8%**	**2.6%**	**3.8 %**
Cost (Acq)	0	$22	$1059	*$233	$1121	$1263	$1263	$1121
Ease of admin	++++	+++	++	+	+	++	++	+
Patient factors	++++	+++	++	+	+	++	++	+

**Acquisition costs for warfarin includes 16 INR tests annually.*

www.vhpharmsci.com/sparc

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