FAQ's in Cardiology: Things that Make You Go Hmmmm…

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Vancouver Coastal Health Authority
November 21, 2008

Conflict of Interest

- I have no potential or actual conflicts of interest to declare

Objectives

- To review the indications for triple therapy (ASA, clopidogrel, warfarin) and evidence supporting the safety and efficacy of their use
- To review the role of "intensive" statin therapy
- To review how to use anti-arrhythmics SAFELY in patients who may benefit from rhythm control for atrial fibrillation (AF)
- To introduce methods of keeping afloat in the abundance of cardiology literature

Clinical Scenario #1
Warfarin, ASA and Clopidogrel: Three's a crowd?

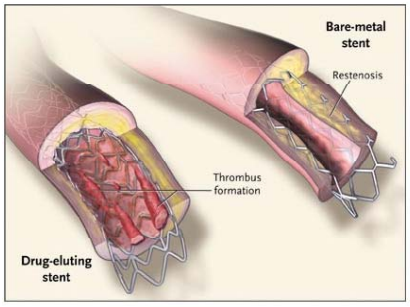
Clinical Scenario #1

- ID: AS, 83 y/o male
- RFA: Elective PCI for worsening CAD
- PMHx: HTN, CAD, AF, Recurrent Stroke
- Medications prior to procedure
  - Warfarin 4mg PO daily
  - Metoprolol 100mg PO BID
  - Ramipril 10mg PO DAILY
  - Simvastatin 40mg PO DAILY
- Medication Orders Post-Procedure
  - Warfarin 4mg PO daily
  - ASA 325mg PO daily
  - Clopidogrel 75mg PO daily x 12 months (for DES)
  - Continue metoprolol, ramipril and simvastatin

Questions to Contemplate…

- Is warfarin effective for preventing stent thrombosis?
- Is ASA + clopidogrel effective for stroke prophylaxis in AF?
- Is triple therapy effective?
  - What are the guidelines recommending?
  - Are the guidelines evidence-based?
- Is triple therapy safe?

Rationale for Drug-Eluting Stents: Stenosis vs. Thrombosis



Shuchman M. N Engl J Med. Nov 2006;355(19):1949-52

Predictors of Late Stent Thrombosis

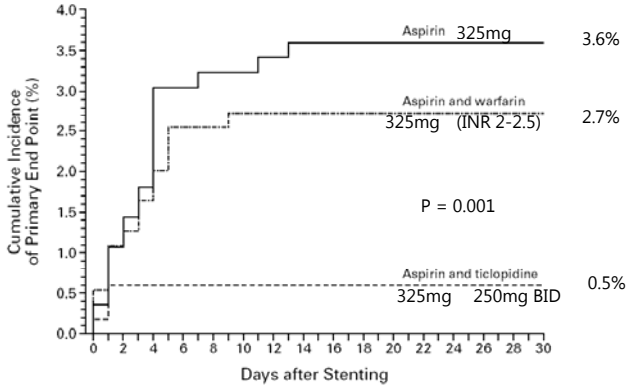
- Stenting of small vessels
- Multiple lesions
- Long stents
- Overlapping stents
- Ostial or bifurcation lesions
- Prior brachytherapy
- Suboptimal stent result
- Low ejection fraction
- Advanced age
- Diabetes mellitus
- Renal failure
- ACS
- Premature discontinuation of antiplatelet agents

King et al. J Am Coll Cardiol 2008; 51 (2): 1-38

Is warfarin effective in preventing stent thrombosis?

STARS

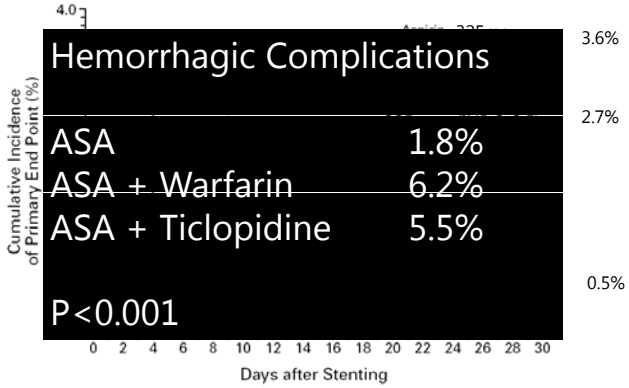
Leon MB et al. N Engl J Med 1998;339:1665-71



1°: stent thrombosis, death, revascularization, non-fatal MI

STARS

Leon MB et al. N Engl J Med 1998;339:1665-71



1°: stent thrombosis, death, revascularization, non-fatal MI

2007 ACC/AHA/SCAI PCI Guidelines: Clopidogrel

JACC 2008; 51(2):172-209

ALL post-PCI stented patients should be on ASA indefinitely plus…

- DES:
  - clopidogrel 75mg DAILY x AT LEAST 12 months (if not high risk of bleeding) – Class I (LOE B)
- BMS:
  - clopidogrel 75mg DAILY x AT LEAST 1 month (ideally up to 12 months), unless patient is at increased risk of bleeding – Class I (LOE B)

Is ASA + clopidogrel effective in preventing vascular events in AF?

Safety & Efficacy of ASA + Clopidogrel in AF

Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial

The ACTIVE Writing Group on behalf of the ACTIVE Investigators*

Summary

Background Oral anticoagulation therapy reduces risk of vascular events in patients with atrial fibrillation. However, long-term monitoring is necessary and many patients cannot achieve optimum anticoagulation. We assessed whether clopidogrel plus aspirin was non-inferior to oral anticoagulation therapy for prevention of vascular events.

Methods Patients were enrolled if they had atrial fibrillation plus one or more risk factor for stroke, and were randomly allocated to receive oral anticoagulation therapy (target international normalised ratio of 2·0–3·0; n=3371) or clopidogrel (75 mg per day) plus aspirin (75–100 mg per day recommended; n=3335). Outcome events were adjudicated by a blinded committee. Primary outcome was first occurrence of stroke, non-CNS systemic embolus, myocardial infarction, or vascular death. Analyses were by intention-to-treat. This study is registered with ClinicalTrials.gov, number NCT00243178.

Results The study was stopped early because of clear evidence of superiority of oral anticoagulation therapy. There were 165 primary events in patients on oral anticoagulation therapy (annual risk 3·93%) and 234 in those on clopidogrel plus aspirin (annual risk 5·60%; relative risk 1·44 (1·18–1·76; p=0·0003). Patients on oral anticoagulation therapy who were already receiving this treatment at study entry had a trend towards a greater reduction in vascular events (relative risk 1·50, 95% CI 1·19–1·80) and a significantly (p=0·03 for interaction) lower risk of major bleeding with oral anticoagulation therapy (1·30; 0·94–1·79) than patients not on this treatment at study entry (1·27, 0·85–1·89

Lancet 2006; 367: 1903–12

See Comment page 1877

*Members listed at end of paper

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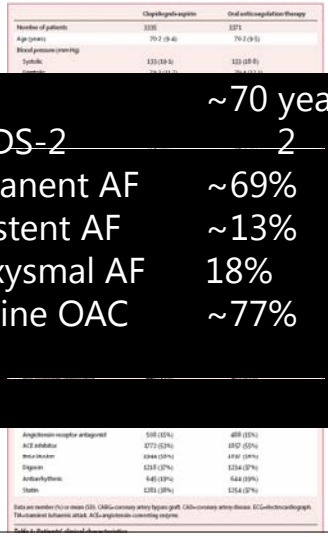
ACTIVE-W

Lancet 2006; 367: 1903–12

Objective	To assess whether clopidogrel + ASA as NON-INFERIOR to oral anticoagulation (OAC) for prevention of vascular events in patients w/ AF at "high" risk of stroke
Design	Randomized, OL
Population N=6706	• Patients w/ AF, eligible and willing to take OAC • At least one of the following: Age ≥ 75y, treated for HTN, previous stroke/TIA or non-CNS systemic embolus, LV dysfunction, peripheral arterial disease • if Age = 55-74 years and none of the above, must have DM or CAD
Intervention	Clopidogrel 75mg/d + ASA 75-100mg/d) vs. OAC (INR 2-3)
Outcomes	1°: stroke, non-CNS systemic embolism, MI or vascular death 2°: bleeding (major, severe, minor); individual endpoints

Trial STOPPED early on August 25th, 2005 due to higher event rates on ASA + clopidogrel (Median f/u duration = 1.28y)

HIDE



Age	~70 years
CHADS-2	2
Permanent AF	~69%
Persistent AF	~13%
Paroxysmal AF	18%
Baseline OAC	~77%

ACTIVE-W

Lancet 2006; 367: 1903–12

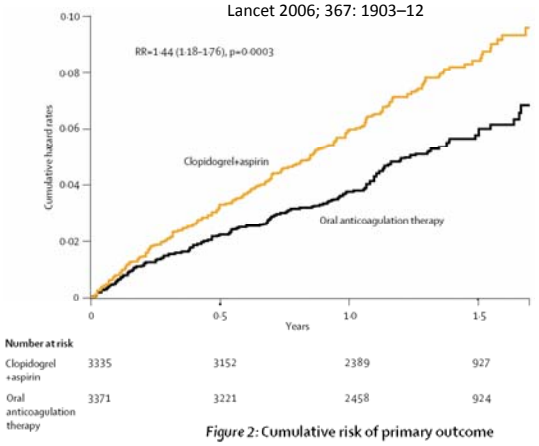


Figure 2: Cumulative risk of primary outcome

1° Outcome: CVA, Non-CNS systemic embolus, MI, or vascular death

ACTIVE-W

Lancet 2006; 367: 1903–12

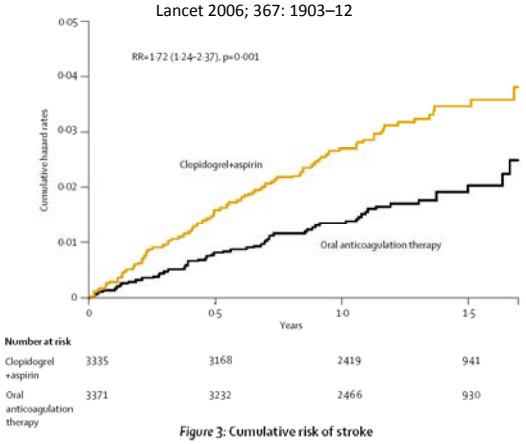


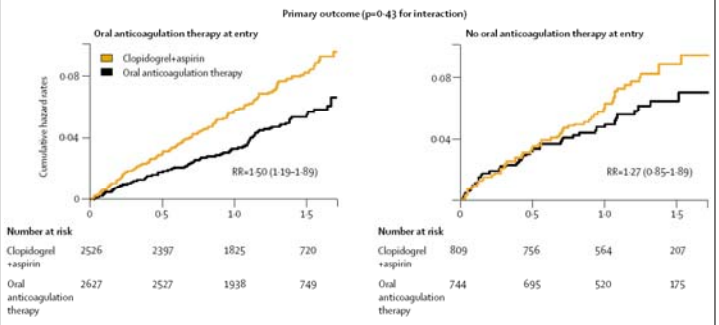
Figure 3: Cumulative risk of stroke

	Clopidogrel+aspirin vs oral anticoagulation	
	RR (95% CI)	p
Composite of stroke, non-CNS embolus, myocardial infarction, vascular death	1·44 (1·18–1·76)	0·0003
Non-CNS embolus	4·66 (1·58–13·8)	0·005
Myocardial infarction	1·58 (0·94–2·67)	0·09
Stroke	1·72 (1·24–2·37)	0·001
Ischaemic	2·17 (1·51–3·13)	<0·0001
Haemorrhagic	0·34 (0·12–0·93)	0·036
Stroke severity		
Non-disabling	2·49 (1·42–4·37)	0·002
Disabling	1·47 (0·98–2·20)	0·06
Fatal	0·93 (0·45–1·94)	0·85
Total mortality	1·01 (0·81–1·26)	0·91
Vascular death	1·14 (0·88–1·48)	0·34
Non-vascular death	0·76 (0·50–1·15)	0·20
Haemorrhage		
Major (includes severe and fatal)	1·10 (0·83–1·45)	0·53
Severe	1·09 (0·78–1·52)	0·62
Fatal	0·64 (0·25–1·66)	0·36
Minor	1·23 (1·09–1·39)	0·0009
Total	1·21 (1·08–1·35)	0·001
Net benefit		
Primary outcome and major bleed	1·41 (1·19–1·67)	<0·0001
Primary outcome, major bleed, and death	1·31 (1·12–1·54)	0·0008

Table 2: Primary and secondary outcomes

ACTIVE-W

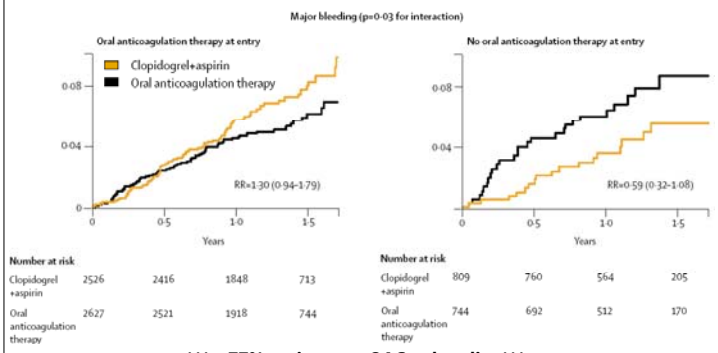
Lancet 2006; 367: 1903–12



*****~ 77% patients on OAC at baseline*****

ACTIVE-W

Lancet 2006; 367: 1903–12



*****~ 77% patients on OAC at baseline*****

ACTIVE-W: Limitations & Conclusions

Lancet 2006; 367: 1903–12

- Author's Conclusion:
  - *"OAC is superior to clopidogrel + ASA for prevention of vascular events with AF at high risk of stroke, especially in those already taking OAC"*
- Limitations
  - ~77% on OAC at baseline
    - Favours OAC due to improved tolerability and INR control
    - Unclear benefit and safety of OAC in patients not previously on OAC (at study entry)
  - INR at least therapeutic (≥ 2.0) 79% of time
    - INR = 2-3: 64% of time
    - INR > 3 = 15% of time

Safety & Efficacy of Triple Therapy

Evidence for Triple Therapy

Hermosillo AJ and Spinler SA. Ann Pharmacother 2008; 42: 790-805

- No randomized controlled trials to date
- Based on case series, observational studies and case-controlled studies of patients undergoing PCI
- Conflicting data
  - Bleeding
    - zero to 3-6 fold ↑
  - Clinical benefit
    - No benefit to reductions in death, MI, revascularization, stent thrombosis, hospitalization

2007 PCI Recommendations	2007 COR and LOE
Antiplatelet Agents/Anticoagulants: Warfarin	
1. Managing warfarin to an INR equal to 2.0 to 3.0 for paroxysmal or chronic atrial fibrillation or flutter is recommended, and in post-MI patients when clinically indicated (e.g., atrial fibrillation, left ventricular thrombus).	*I (A)*
2. Use of warfarin in conjunction with aspirin and/or clopidogrel is associated with an increased risk of bleeding and should be monitored closely.	*I (B)*
3. In patients requiring warfarin, clopidogrel, and aspirin therapy after PCI, an INR of 2.0 to 2.5 is recommended with low dose aspirin (75 mg to 81 mg) and a 75-mg dose of clopidogrel.	***I (C)***

King et al. J Am Coll Cardiol 2008; 51 (2): 1-38

PCI Focused Update

2007 Focused Update of the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention

Circulation

American Heart Association. Learn and Live.

Questions to Contemplate…

- Is warfarin effective for preventing stent thrombosis? - NO
- Is ASA + clopidogrel effective for stroke prophylaxis in AF? – NO (not in patients previously on warfarin)
- Is triple therapy safe or effective?
  - Not sure
  - Will be answered in future - WARSTENT
- When is triple therapy indicated?
  - Post-PCI w/ stent insertion PLUS strong indication for warfarin (moderate to high risk AF, LV thrombus, thromboembolic disease, prosthetic heart valve) with low risk of bleed

Clinical Scenario #2: Getting Intense with Statin Therapy

Clinical Scenario #2

- ID: HS, 55 y/o male
- CC: retrosternal chest pain radiating to LEFT arm
- Past Medical History: HTN, obesity, cholesterol (unknown)
- Medications (prior to admission):
  - Ramipril 10mg PO DAILY
- Diagnosis: ST-Elevation MI
- Management in Hospital:
  - ASA 160mg chewed STAT, then 81mg PO DAILY
  - Enoxaparin 30mg IV x 1, then 1mg/kg SC q12h
  - Tenecteplase IV x 1
  - Clopidogrel 300mg PO x 1, then 75mg DAILY
  - Metoprolol 100mg PO BID
  - Ramipril 10mg PO DAILY
  - Other Medications???

Questions to Contemplate…

- Which statin to choose?
- What dose to choose?
  - Is "intensive statin" therapy necessary?
    - What is "intensive statin" therapy?
    - What are the comparative efficacies of"intensive statin" therapy?

"Intensive Statin Therapy"

"Possible" Definitions	Clinical Trial	Population
Simvastatin 80mg/day	A-to-Z	Post-ACS
Atorvastatin 80mg/day	PROVE IT-TIMI 22 TNT IDEAL REVERSAL SPARCL	Post-ACS Stable CAD Stable CAD Stable CAD CVA/TIA
Rosuvastatin 20 to 40mg/day	ASTEROID METEOR JUPITER	Stable CAD Low CV Risk Healthy (↑ hsCRP)
Reduction of LDL-C < 2.0mmol/L		

Effects of Statins on LDL-C and HDL-C

STELLAR Trial. Am J Cardiol 2003; 92: 152-160

LDL-C Effect	Prava	Simva	Atorva	Rosuva
10mg	-20.1%	-28.3%	-36.8%	-45.8%
20mg	-24.4%	-35.0%	-42.6%	-52.4%
40mg	-29.7%	-38.8%	-47.8%	-55.0%
80mg		-45.8%	-51.1%	

HDL-C Effect	Prava	Simva	Atorva	Rosuva
10mg	3.2%	5.3%	5.7%	7.7%
20mg	4.4%	6.0%	4.8%	9.5%
40mg	5.6%	5.2%	4.4%	9.6%
80mg		6.8%	2.1%	

Considerations when Selecting "Intensive" Statin Therapy

- Simvastatin
  - Simva 80mg = Simva 20mg; ↑ADRs with higher dose (A-to-Z - ACS)
- Atorvastatin
  - studies compare to placebo or "lower" intensity statin
    - Atorva 80mg > Prava 40mg (PROVE IT-TIMI 22 – ACS; REVERSAL – CAD)
    - Atorva 80mg > Atorva 10mg (TNT – stable CAD)
    - Atorva 80mg = Simv 20mg (IDEAL – stable CAD; may reduce MI and revascularization)
    - Atorva 80mg > Placebo (SPARCL – Stroke)
  - Less effect on HDL when dose ≥ 40mg/day
- Rosuvastatin
  - Limited trials demonstrating benefit in hard clinical outcomes
    - JUPITER – Rosuva 20mg > Placebo (LOW risk patients with normal cholesterol levels but elevated highly sensitive C-reactive protein)

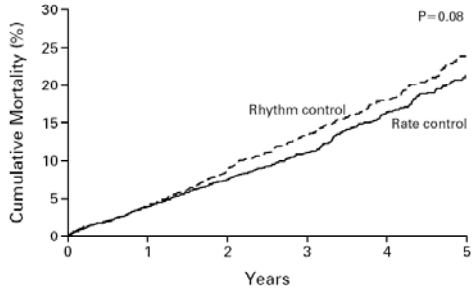
What We Don't Know…

- Is Atorvastatin 80mg or Rosuvastatin 20 - 40mg better than…
  - Simvastatin 40mg/day
  - Atorvastatin 20 or 40mg/day
  - Rosuvastatin 5 or 10mg/day

  …in reducing hard clinical outcomes?
- Should we be aiming for lipid targets (LDL-C or TC:HDL-C) or be using study regimens?

Using Antiarrhythmic Agents Safely for Maintenance of Sinus Rhythm in Atrial Fibrillation

RATE vs. RHYTHM



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)

Figure 1. Cumulative Mortality from Any Cause in the Rhythm-Control Group and the Rate-Control Group.
Time zero is the day of randomization. Data have been truncated at five years.

AFFIRM Investigators. NEJM 2002;347:1825-1833

RATE vs. RHYTHM

Torsade de pointes:
0.2% vs. 0.8% p=0.007

~~PEA or Bradycardia or other rhythm:~~
<0.1% vs. 0.6% p=0.01

Hospitalization after baseline: 76.6% vs. 73% p<0.001

↑ ADRs (prolonged QT, ↓HR, GI, Resp)

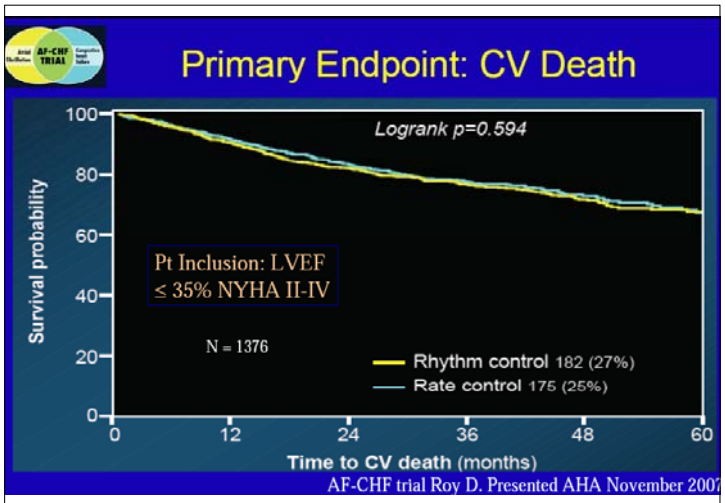
Time zero is the day of randomization. Data have been truncated at five years.

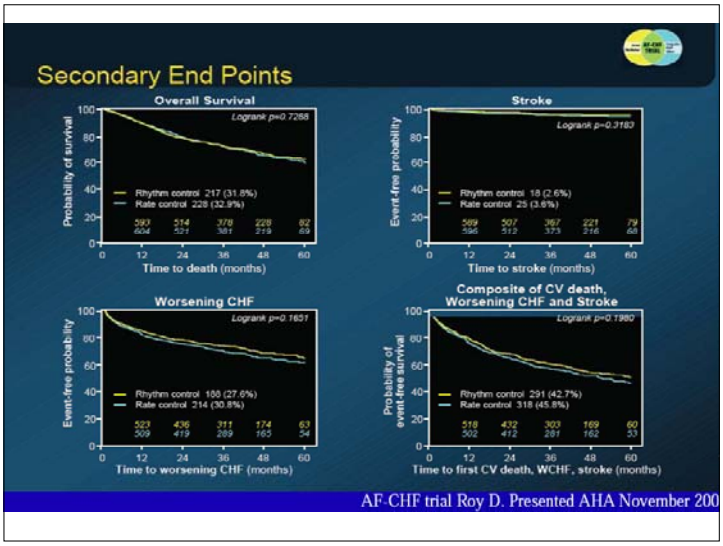
AFFIRM Investigators. NEJM 2002;347:1825-1833

Favours Rate Control	Favours Rhythm Control
Persistent AF	Paroxysmal AF
Recurrent AF	1st episode AF
Less symptomatic	More symptomatic
> 65 years of age	< 65 years of age
Hypertension	No hypertension
~~No Hx CHF~~	~~Hx CHF~~
Previous antiarrhythmic drug failure	No previous antiarrhythmic drug failure
Patient preference	

Canadian Cardiovascular Society

Kerr CR, Roy D et al. CCS Consensus Conference 2004 Atrial Fibrillation





When Rhythm Control Might be Considered

In patients who…

- Have troublesome symptoms related to paroxysmal AF or recurrent AF after cardioversion
- Are able tolerate antiarrhythmic drugs
- Have a good chance of remaining in sinus rhythm over an extended period
  - e.g. young patients without organic heart disease or hypertension, a short duration of AF, and normal LA size

***DISCONTINUE antiarrhythmic therapy if…

- No symptomatic improvement and/or
- Patient experiences adverse effects

JACC 2006; 48 (4): e149-246

Assessing Efficacy: Recurrence ≠ Failure

- Any recurrence of AF may seem intolerable to some patients
- Other patients with recurrent AF may choose to continue antiarrhythmic therapy because…
  - episodes of AF become less frequent, briefer, or less symptomatic
  - ↓ in arrhythmia burden may constitute therapeutic success for some patients

JACC 2006; 48 (4): e149-246

Goals of Therapy of Antiarrhythmic Therapy in AF

- To maintain sinus rhythm
- To suppress symptoms
- To improve exercise capacity and hemodynamic function
- To prevent tachycardia-induced cardiomyopathy
- To make AF episodes less frequent, briefer or less symptomatic
- To prevent thromboembolism???

JACC 2006; 48 (4): e149-246

Safe use of Antiarrhythmics in AF: Considerations

- Initiating prescriber
- Patient Co-Morbidities and Risk Factors
- Drug Profile
  - Efficacy
  - Safety
  - Adverse Reactions and Contraindications

Patient Characteristics	First Line	Second Line	Alternative Choices
Structurally Normal Hearts	• Propafenone (IC) • Flecainide (IC) • Sotalol (III)	•Amiodarone (III)	•Disopyramide (IA) •Dofetilide (III)
Structurally Abnormal Hearts			
CAD with normal LV function	•Sotalol (III)	•Amiodarone (III)	•Dofetilide (III) •Propafenone (IC)
LV Dysfunction	•Amiodarone (III)	•Dofetilide (III)	
Hypertension w/LVH	•Sotalol (III) •Amiodarone (III) •Propafenone (IC) •Flecainide (IC)		

Kerr CR, Roy D et al. CCS Consensus Conference 2004 Atrial Fibrillation

Canadian Cardiovascular Society

Patient Characteristics	First Line	Second Line
No (or minimal) heart disease)	• Propafenone (IC) • Flecainide (IC) • Sotalol (III)	•Amiodarone (III) •Dofetilide (III)
Heart Disease		
Hypertension (no LVH)	•Propafenone (IC) • Flecainide (IC) • Sotalol (III)	•Amiodarone (III) •Dofetilide (III)
Hypertension (LVH)	•Amiodarone (III)	
CAD	•Sotalol (III) •Dofetilide (III)	•Amiodarone (III)
Heart Failure	•Amiodarone (III) •Dofetilide (III)	

JACC 2006; 48 (4): e149-246

ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation) Developed in Collaboration With the European Heart Rhythm Association and the Heart Rhythm Society

Valentin Fuster, Lars E. Ryden, David S. Cannom, Harry J. Crijns, Anne B. Curtis, Kenneth A. Ellenbogen, Jonathan L. Halperin, Jean-Yves Le Heuzey, G. Neal Kay, James E. Lowe, S. Bertil Olsson, Eric N. Prystowsky, Juan Luis Tamargo, and Samuel Wann

JACC Journal of the American College of Cardiology

Class IA Agents: Things you should know…

(Procainamide, Disopyramide, Quinidine)

- Monitor ECG for prolonged QTc (Torsade de pointes)
  - QT prolongation NOT dose dependent (can occur a therapeutic and sub-therapeutic doses)
- Avoid drugs or conditions that may prolong QT
  - Drugs: quinolones, macrolides, antipsychotics, etc…
  - Conditions: LVH, hypokalemia
- Control ventricular rate w/ BB or CCB before using IA agent
  - May convert AF to slow flutter rate; slow flutter rate may conduct 1:1 → rapid ventricular conduction with a wide complex QRS

Class IC Agents: Things you should know…

(Flecainide, Propafenone, Moricizine)

- Monitor ECG
  - Prolongs PR interval and widens QRS complex
  - Does NOT cause TdP
  - May cause sustained monomorphic ventricular arrhythmias
- Control ventricular rate w/ BB or CCB before using IC agent for long-term maintenance
  - May convert AF to slow flutter rate; slow flutter rate may conduct 1:1 → rapid ventricular conduction with a wide complex QRS
- AVOID in heart failure
  - May depress LV function
- AVOID in ischemic heart disease
  - May increase mortality in post-MI patients
    - Cardiac Arrhythmia Suppression Trial (CAST)

Class III Agents: Things you should know…

(Sotalol, Amiodarone, Dofetilide)

- Monitor ECG for prolonged QTc (Torsade de pointes)
  - QT prolongation is usually dose dependent
  - Lower propensity of TdP with amiodarone
- Avoid drugs or conditions that may prolong QT
  - Drugs: quinolones, macrolides, antipsychotics, etc…
  - Conditions: Hypokalemia
- Monitor Electrolytes…especially K+ and Mg++
- Monitor renal function and adjust dose for renally eliminated drugs (sotalol, dofetilide)
- Avoid sotalol if LVH or HF, severe renal impairment and in patients at high risk (elderly women on diuretics)
- Dofetilide NOT available in Canada (initiated in hospital -3d)

Monitoring for Amiodarone

Bickford CL. JMCP 2006; 12:3: 254-59

Adverse Effect	Incidence	NASPE Recommendations (2000)
LFT elevation (>3x ULN) Hepatitis	4-50% <3%	Liver Function Test: Baseline and q6 mos
Pulmonary Toxicity	2-17%	CXR: Baseline, then q12 months Pulmonary Testing (PFT with D_LCO: Baseline, then PFTs PRN
Hyperthyroidism Hypothyroidism	2-10% 1-22%	TSH: Baseline then q 6 mos

D_LCO = carbon monoxide diffusing capacity

2006 ACC/AHA Guideline Recommendations: Maintenance of Sinus Rhythm

Class I

- **Before initiating antiarrhythmic drug therapy, treatment of precipitating or reversible causes of AF is recommended. *(Level of Evidence: C)***

Class III

- **Antiarrhythmic therapy with a particular drug is not recommended for maintenance of sinus rhythm in patients with AF who have well-defined risk factors for proarrhythmia with that agent. *(Level of Evidence: A)***
- **Pharmacological therapy is not recommended for maintenance of sinus rhythm in patients with advanced sinus node disease or AV node dysfunction unless they have a functioning electronic cardiac pacemaker. *(Level of Evidence: C)***

JACC 2006; 48 (4): e149-246

Class IIa

- **Pharmacological therapy can be useful in patients with AF to maintain sinus rhythm and prevent tachycardia-induced cardiomyopathy. *(Level of Evidence: C)***
- **Infrequent, well-tolerated recurrence of AF is reasonable as a successful outcome of antiarrhythmic drug therapy. *(Level of Evidence: C)***
- **Outpatient initiation of antiarrhythmic drug therapy is reasonable in patients with AF who have no associated heart disease when the agent is well tolerated. *(Level of Evidence: C)***
- **In patients with lone AF without structural heart disease, initiation of propafenone or flecainide can be beneficial on an outpatient basis in patients with paroxysmal AF who are in sinus rhythm at the time of drug initiation. *(Level of Evidence: B)***
- **Sotalol can be beneficial in outpatients in sinus rhythm with little or no heart disease, prone to paroxysmal AF, if the baseline uncorrected QT interval is less than 460 ms, serum electrolytes are normal, and risk factors associated with class III drug–related proarrhythmia are not present. *(Level of Evidence: C)***
- **Catheter ablation is a reasonable alternative to pharmacological therapy to prevent recurrent AF in symptomatic patients with little or no LA enlargement. *(Level of Evidence: C)***

JACC 2006; 48 (4): e149-246

Keeping Afloat in the Abundance of Literature in Cardiology

US Resources

- Theheart.org – daily updates on what's new and exciting in the world of cardiology
- American College of Cardiology: http://www.acc.org/qualityandscience/clinical/statements.htm - current evidence based guidelines
- American Heart Association: http://www.americanheart.org – excellent source for patient information on disease states
- National Heart, Lung and Blood Institute: http://www.nhlbi.nih.gov/ - excellent source for patient information on disease states
- http://www.incirculation.net/whatswhat/ - website with trial summaries (service provided by Astra Zeneca)
- e-TOC (NEJM, JAMA, Lancet)

Canadian Resources

- Canadian Cardiovascular Society: http://www.ccs.ca/home/index_e.aspx
- Canadian Hypertension Society: http://www.hypertension.ca/ - find current Canadian guidelines on hypertension
- CSHP – Cardiology PSN
- Canadian Cardiovascular Pharmacist Network (CCPN)
- RX Files: http://www.rxfiles.ca/rxfiles/modules/druginfoindex/druginfo.aspx - several useful charts summarizing pharmacotherapy and landmark trials for different disease states