Management of Atrial Fibrillation in 2013
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Epidemiology
- Most common arrhythmia in clinical practice
- 2.3 million people in North America
  - Average cost of $3600/patient/year
- Accounts for 1/3 of all hospitalizations for cardiac rhythm disturbances
- Prevalence: 0.4-1% in the general population and 8% in those older than 80 years

Why Is This Important?
- AF associated with an increased risk of stroke
- Six-fold increase in rate of ischemic stroke
- Rate of ischemic stroke in non-valvular AF approx 5%/year
- AF accounts for 15% of all strokes
- Associated with increased CHF and all-cause mortality


No financial disclosures
Atrial Fibrillation

- Work-Up
- Rate vs. Rhythm Control
- Treatment Options
- Anti-coagulation
- Future Treatment Options and What’s New

Case I

- 55 yo woman being seen for a new patient visit. Asymptomatic.
- PMH: HTN (untreated)
- PE: 150/80, HR 125 Irregularly irregular

The EKG…

What Work-Up Does She Need?

1) TSH
2) ECHO
3) r/o MI with troponins
4) 1 and 2
5) All of the above
What Work-Up Does She Need?
- Complete history and physical
- PIRATES

Secondary Causes of AF
- PIRATES – secondary causes
  - Pericarditis
  - Pulmonary/pulmonary embolism
  - Ischemia
  - Rheumatic heart disease
  - Atrial myxoma
  - Thyrotoxicosis
  - Ethanol
  - Sepsis

What Work-Up Does She Need?
- Complete history and physical exam
- Pulmonary/pulmonary embolism
- Ischemia
- Ethanol
- Sepsis

Secondary Causes of AF
- Other Secondary Causes
  - Obesity – likely due to LA dilatation
  - Smoking
  - Familial
  - Inflammation
- Treat Underlying Etiology

What Work-Up Does She Need?

- ECHO
  - Rheumatic heart disease
  - Atrial myxoma
  - The real reason...
    - LVH
    - Occult valvular disease
    - Occult pericardial disease


What Work-Up Does She Need?

- Complete history and physical exam
- TTE
- EKG
- CXR
- Associated labs
  - TSH, (CBC, renal and hepatic function)
- Other tests based on history...ex: event monitor


What Work-Up Does She Need?

1) TSH
2) ECHO
3) r/o MI with troponins
4) 1 and 2
5) All of the above

Classification

- Recurrent: 2 or more episodes
- Paroxysmal: arrhythmia terminates spontaneously
- Persistent: sustained beyond 7 days and is not self-terminating
- Permanent: cardioversion has failed (or been foregone)
- Lone: patients <60 years without clinical/EKG evidence of cardiopulmonary disease (incl htn)
Case I

- 55 yo woman being seen for a new patient visit. Asymptomatic.
- PMH: HTN (untreated)
- PE: 150/80, HR 125 Irregularly irregular

What is the Next Step for Our Case?

What should be our goal in treatment?
1) Convert her to sinus rhythm
2) Rate-control
3) Stroke prevention
4) #1 and #3
5) #2 and #3

Hemodynamic Consequences of AF

- Loss of atrial mechanical function
- Atrial fibrosis, loss of atrial muscle mass
- Irregular ventricular response
- Elevated HR
- Results in:
  - Reduction in diastolic filling, stroke volume, CO
  - Risk of cardiomyopathy (chronic > 130 bpm)
  - Asymptomatic afib 12X more common...

Rate or Rhythm?

- AFFIRM Study
  - Randomized 4070 patients with AF to rate-control vs. rhythm-control, F/U 3.5 years
  - Rate-control = coumadin
  - Rhythm-control = cardioversion/meds/coumadin
  - No difference in survival, stroke or QOL
  - Trend towards increased survival in rate-control (P = .08)
  - Pts ≥ 65 yrs and pts without h/o CHF had better outcomes with rate-control therapy
  - More thrombotic events in rhythm arm

AFFIRM Investigators, NEJM, 2002;347
Rate or Rhythm?

- AFFIRM Study…the Caveats…
  - No symptomatic patients
  - Average age of enrollees: 70 yrs
  - Only 63% of patients in control arm in sinus rhythm

AFFIRM Investigators, NEJM, 2002;347

Rate or Rhythm for CHF Patients

- Patients: 1376 patients with h/o afib, EF<35%, sx of CHF
- Intervention: RCT rate vs. rhythm
- Outcome: time to death from CV causes, followed 37 months
- Results
  - 27% in rhythm-control group died from CV causes
  - 25% in rate-control group died from CV causes
  - HR 1.06
  - Other outcomes similar (CVA, worse CHF, all-cause mortality)


Rate Control

- Previous goal HR: 60-80 bpm at rest; 90-115 bpm during exercise
- No evidence getting HR <80 vs. <110 any better for mortality
- No benefit to strict control (if no sx and EF>40%)

Van Gelder IC et al. NEJM 2010;362

Rate Control

- What do I use?
  - First choice: beta-blockers or calcium-channel blockers
  - Don't give if Wolf-Parkinson-White or other accessory pathways
  - OK to combine nodal-blocking agents
  - Digoxin is second-line as it does not control HR during exercise

Rhythm vs. Rate…Bottom Line

- Highly symptomatic or unstable: rhythm control
- If minimal symptoms: rate control is safe and appropriate (maintain goal HR <110)
- Anticoagulation therapy should be continued regardless of the strategy (rhythm vs. rate)

What About Cardioversion?

- Electrical cardioversion preferred
  - Most effective if within 7 days of AF onset
  - Requires conscious sedation or anesthesia
- Most thrombi in atrial fibrillation arise from the LA appendage
- Cardioversion can reduce LA appendage function
- Peri-cardioversion period is particularly pro-thrombotic
  - Regardless of mode of cardioversion

Electrical Cardioversion

- If AF < 48 hrs, can safely undergo cardioversion without anticoagulant therapy
  - Must be documented!
- If AF > 48 hrs (or unknown duration) OR high-risk for stroke (h/o stroke/TIA, mechanical heart valve), then 2 choices:
  - Anti-coagulate X 3 weeks (therapeutic INR) before cardioversion
  - TEE to r/o clot
- Anti-coagulate for at least 4 weeks afterward
  - Anti-coagulate also for those who would not normally require coumadin

Cardioversion – Thrombus Risk

- Other factors besides LA clot may affect stroke risk
  - Age
  - DM
  - LA flow velocity
  - HTN
- One study showed intra-atrial thrombus has been detected by TEE in 15% of patients with AF < 72 hours duration
- No difference in thrombus risk between electrical and pharmacologic cardioversion

Fuster et al. ACCF/AHA/HRS Practice Guidelines. J. Am Coll Cardiol 2011
Pharmacologic Cardioversion – Stable Patients

- Pharmacologic cardioversion in AF < 7 days
  - Type 1C
    - Flecainide
    - Propafenone
  - Type III
    - Dofetilide
    - Ibutilide
- Pharmacologic cardioversion in AF > 7 days
  - Proven efficacy: dofetilide, ibutilide, amiodarone

The Next Step...

55 yo woman being seen for a new patient visit.
Asymptomatic.
PMH: HTN (untreated)
PE: 150/80, HR 125 Irregularly irregular

Does she need anti-coagulation?
1) Yes, with coumadin
2) Yes, with ASA
3) Yes, with coumadin and ASA
4) Yes, with dabigatran (pradaxa)
5) No

Key Point...

- A rhythm control strategy does not negate the need for anticoagulation therapy
- Assuming anticoagulation is indicated

Risk/Benefits of Coumadin

- Pooled analysis from five primary prevention trials in non-valvular AF
- Annual rate of stroke 4.3% in control group
- 1.4% risk of stroke in the warfarin group
- 20% of subjects >75 yrs; excluded pts at risk for bleed
- Need to consider warfarin risks
  - Symptomatic intracranial hemorrhage 0.4% with warfarin; 0.2% in control
  - Major bleeding: 2.2% with warfarin; 0.9% in control

**What About Aspirin?**
- Two randomized trials evaluated the use of ASA (75mg, 325mg) in primary stroke prevention
- Pooled data: Risk of stroke with ASA 4.2%; risk of stroke in controls 6.4%
- ASA may be better in preventing non-cardioembolic strokes and non-disabling strokes


**Secondary Prevention of Stroke**
- Risk of stroke with warfarin 3.1%; placebo 10%
- Risk of stroke with ASA (300mg) 7.7%

  EAFT Study Group, Lancet, 1993

**Anti-Platelets vs. Coumadin?**
- ACTIVE-W trial
  - 3335 patients with AF and at least 1 other risk factor for stroke
  - ASA + clopidogrel vs. coumadin
  - Outcomes: stroke, non-CNS systemic embolus, MI or vascular death
  - Stopped early because of superiority of warfarin in preventing vascular events (166 events vs. 234 events). Warfarin even better for those who entered the study already taking it.

  Active Writing Group. Lancet, 2006;367(9526)

**Anti-Coagulation**
- Bottom line…anticoagulation with warfarin superior to ASA and superior to ASA + clopidogrel. Effective in the prevention of primary and secondary stroke.

  Active Writing Group. Lancet, 2006;367(9526)
Who Needs Anti-Coagulation in AF?

- CHADS2 used as accurate predictor of stroke
  - 1 point each for:
    - CHF (or reduced systolic function)
    - Htn
    - Age ≥ 75 years
    - Diabetes
  - 2 points for:
    - History of stroke or TIA
  - 0 pts: no treatment; ≥1 pt: anticoagulation
  - Problem: doesn’t account for other stroke RF


Who Needs Anti-Coagulation in AF?

- For low-risk patients CHA2DS2-VASc outperformed CHADS2
  - CHF/LV dysfunction = 1 pt
  - Htn = 1 pt
  - Age ≥75 yrs = 2 pts
  - DM = 1 pt
  - Stroke/TIA/Thromboembolism = 2 pts
  - Vascular Disease (prior MI, PVD) = 1 pt
  - Age 65-74 yrs = 1 pt
  - Sex category (female) = 1 pt

Olsson JB et al. BMJ, 2011;342

Anticoagulation...Who Needs It?

- CHA2DS2-VASc
  - Stroke rate (%/year based on cohort data)
    - 0 points: 0
    - 1 point: 1.3
    - 2 points: 2.2
    - 3 points: 3.2
    - 4 points: 4.0
    - 5 points: 6.7
    - 6 points: 9.8
    - 7 points: 9.6
    - 8 points: 6.7
    - 9 points: 15.2

Lip GY et al. Stroke, 2010;41(12).

Anticoagulation...Who Needs It?

- CHA2DS2-VASc
  - No benefit of oral anticoagulation if patients low-risk (score=0)
  - No treatment vs. ASA 81-325mg daily
  - Neutral or positive benefit of anticoagulation for score ≥1
    - Score of 1: ASA or anticoagulation (anticoagulation preferred)
    - Score ≥2: anticoagulation
Back to Our Case…

- 55 yo woman being seen for a new patient visit. Asymptomatic.
- PMH: HTN (untreated)
- PE: 150/80, HR 125 Irregularly irregular
- CHA²DS²-VASc score = 2 points; CHADS² score=1
- Offer anticoagulation

Anti-Coagulation Special Considerations

- What about my 85 yo patient who falls?
  - Predisposition to falling not considered a contraindication for warfarin
- What about my patient with a remote h/o GIB?
  - Risk of recurrent bleeding 1.2%
  - Resolved peptic ulcer disease bleeding (with H. Pylori testing/treatment) not a contraindication for warfarin


Anti-Coagulation Special Considerations

- What are absolute contraindications to warfarin?
  - Bleeding diathesis
  - Thrombocytopenia (<50K)
  - Untreated or poorly-controlled htn (> 160/90)
  - Non-compliance with INR monitoring
- Relative contraindications
  - Significant ETOH use, NSAID use without PPI, activities predisposing to trauma


Anti-Coagulation Special Considerations

- What about stopping anti-coagulation for a procedure?
  - Mechanical heart valve → heparin (UFH vs LMWH)...most of the time…
  - Non-valvular AF
    - High-risk (CHADS 5 or 6) → heparin
    - Medium-risk (CHADS 3 or 4) → heparin full or low-dose
    - Low-risk (CHADS 1 or 2) → ok to stop coumadin for <1 week

**Prediction for Major Bleeding Risk – HAS-BLED**

- HAS-BLED risk scheme for AF
  - Hypertension
  - Abnormal renal function
  - Abnormal liver function
  - h/o Stroke/TIA
  - Bleeding history
  - Labile INR
  - Elderly (age>65 yrs)
  - Drugs (NSAIDs/steroids) or alcohol* concomitantly

**HAS-BLED Risk Classification**

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**What if warfarin is contraindicated?**

- ACTIVE-A Trial
  - 7554 patients with a/fib at increased stroke risk, warfarin “unsuitable”
  - RCT clopidogrel (75mg) + ASA vs. placebo + ASA
  - Outcome: stroke, MI, embolism, vascular death
  - Median f/u 3.6 years
  - Vascular events clopidogrel 6.8% vs. 7.6% (RR 0.89; CI 0.81-0.98)
  - Mostly due to stroke reduction (2.4% vs. 3.3%)
  - Major bleeding 2% vs. 1.3% (RR 1.57; CI 1.29-1.92)


**What if warfarin is contraindicated?**

- Bottom line…
  - Lessened stroke risk almost off-set by increased bleeding risk (but not quite)
  - AF Guidelines: Could consider in patients at high-risk for stroke who can’t take warfarin (**but consider dabigatran first**)
  - Need to ensure not at high-risk for bleeding

Wann et al. JACC, 2011;57(2).
**New Oral Anticoagulants**

**Oral Xa Inhibitors**
- Rivaroxaban
- Apixaban

**Oral IIa Inhibitor**
- Dabigatran

**Mechanism**
- DTI Anti-Xa Anti-Xa

**Renal Metabolism**
- Dabigatran: 80%
- Rivaroxaban: 30-60%
- Apixaban: 25%

**Approval Status**
- Nonvalvular Afib
- DVT Prevention
- DVT and PE treatment

**T ½ Hours**
- Dabigatran (Pradaxa): 12-17
- Rivaroxaban (Xarelto): 5-9
- Apixaban (Eliquis): 8-15

**CYP3A4**
- Dabigatran: ---
- Rivaroxaban: Yes
- Apixaban: Yes

**Substrate of p-glycoprotein**
- Yes: Dabigatran
- Yes: Rivaroxaban
- ---: Apixaban

**Antidote**
- None: Dabigatran, Rivaroxaban, Apixaban

**Monitoring**
- Dabigatran: PTT
- Rivaroxaban: Anti Xa
- Apixaban: Anti Xa

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**Dabigatran**

- AF Guidelines: recommended as an alternative to warfarin for prevention of stroke and systemic thromboembolism (non-valvular AF)
- Recommended by American College of Chest Physicians instead of warfarin
- Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY)
  - 18,113 patients with afib and stroke risk (CHADS2 score mean 2.1)
- RCT Dabigatran vs. warfarin
  - Dabigatran 110mg or 150mg BID (blinded) vs. unblinded adjusted warfarin

**Dabigatran**

**RE-LY Study**
- Primary outcome: stroke or embolism, F/U 2 years
  - 1.69% warfarin
  - 1.53% for 110mg dabigatran (non-inferior)
  - 1.11% for 150mg dabigatran (superior)
- Rate of major bleeding
  - 3.36% warfarin
  - 2.71% dabigatran 110mg
  - 3.11% dabigatran 150mg (p-value NS)

**Caveats…**
- Dyspepsia/gastritis
- GI bleeding increased with dabigatran
- Increased MI's in dabigatran groups (RR 1.38; CI 1.0-1.91 for high-dose)
- Valvular AF excluded
- Warfarin 64% in therapeutic range
- As effective as coumadin post-cardioversion

**Oral direct thrombin inhibitor**
- Pros: No INR monitoring, fewer dietary/drug interactions
- Cons: BID, $200/one month supply, no antidote (is dialyzable), renally cleared
- Dosing: 150mg BID if CrCl>30 (75mg BID if CrCl 15-30). Not for CrCl<15
- Substrate of transporter p-glycoprotein
  - P-gp inducers (St. John’s wart, rifampin) decrease levels
  - P-gp inhibitors (ketoconazole) increase levels

**Starting Dabigatran**
- Baseline labs: CBC, Cr, PTT (LFTs)
- Patient Education med guide
- Monitoring
  - Adherence
  - Adverse effects (GI)
  - Bleeding/Stroke
- Follow-Up
  - 2 weeks
  - 1 month
  - 3 months
  - Continue monthly check-in
Rising Concerns with Dabigatran…
- Dec 7, 2011 FDA launches investigation into bleeding reports with pradaxa
- Meta-analysis: more coronary events
  - 30,514 patients
  - OR 1.33 (CI 1.03-1.71) for MI or ACS

Uchino K and Hernandez AV. Arch of Intern Med, 2012

Rivaroxaban (Xarelto)
- Direct Xa inhibitor
- Once daily dosing
  - 20mg qhs if CrCl >50
  - 15mg if CrCl 15-50
- Approved July 2011 for prevention of DVTs in knee/hip arthroplasty patients
- Approved Nov 2011 for non-valvular atr fibrillation
- Beware CYP3a4 inhibitors: diltiazem, amiodarone, verapamil

Rivaroxaban
- ROCKET AF trial
  - 14,264 non-valvular atr fibrillation pts at high risk for stroke (mean CHADS2=3.5)
  - Randomized: rivaroxaban 20mg/d or 15mg/d vs. warfarin
  - Endpoint: stroke or systemic embolism
  - Non-inferior to warfarin in AF patients
    - 1.7% rivaroxaban vs. 2.2% warfarin
    - Bleeding rates overall equal but statistically fewer intracranial and fatal bleeding with rivaroxaban (more GIB)
    - Low rate of therapeutic INR (58%)  
  

The Next Step…
55 yo woman being seen for a new patient visit. Asymptomatic, 55/80, HR 125 Irregularly irregular
CHA2DS2-VASc score = 2 points; CHADS2 score=1

Does she need anti-coagulation?
1) Yes, with coumadin
2) Yes, with ASA
3) Yes, with coumadin and ASA
4) Yes, with dabigatran
5) No
Apixaban

- Factor Xa inhibitor
- ARISTOTLE Trial
  - 18,201 afib patients with 1 additional risk factor for stroke (mean CHADS₂=2.1)
  - Randomized, double-blind apixaban 5mg BID (2.5mg BID in select pts) vs. warfarin
  - Outcomes: stroke, systemic embolism
  - Apixaban superior to warfarin in primary outcome
    - Lower mortality and less bleeding
  - Approved Dec 2012


What’s “In” and What’s “Out”?

What’s “Out”---Dronedarone

- Approved July 2009 for low-to intermed-risk pts with AF
- Similar to amiodarone but noniodinated, thus no thyroid/pulm toxicity
- Athena Trial:
  - 4628 pts with afib
  - Outcome: First hospitalization due to CV events or death
  - 31.9% dronedarone vs. 39.4% in placebo group (HR 0.76; CI 0.69-0.84)
  - Reduction mostly due to afib hospitalization (no difference in death rate)

Hohnloser SH et al. NEJM, 2009;360.

Dronedarone in CHF

- ANDROMEDA trial
- Patients with symptomatic CHF RCT dronedarone vs. placebo
  - Stopped early due to increased mortality in dronedarone group
  - Mostly worsened CHF


Dronedarone in High-Risk Permanent Afib

- 3236 patients >65 yrs with at least 6 mo h/o permanent afib and risk factors for major vascular events
- Dronedarone vs. placebo
- Outcome: stroke, MI, systemic embolism, death from CV causes
- Study stopped early for safety reasons (more stroke, CV deaths, CHF)
- Post marketing reports of hepatocellular injury
- Bottom line…would avoid dronedarone in CAD/CHF pts

Connolly SJ et al. NEJM, 2011;365;24
What’s New?--Ablation

- Paroxysmal AF primarily emanates from the pulmonary veins
  - Less effective than ablation for SVT, a-flutter
- Updated guidelines: ablation recommended (in experienced center) for pts with symptomatic, paroxysmal AF who have failed drug treatment

Wann et al. JACC, 2011;57(2).

Future Directions

- Edoxaban
  - Studied in ENGAGE study
  - Edoxaban vs. warfarin
  - Awaiting results
- Obliteration of left atrial appendage
  - Where 90% of thrombi form

Recap…Current Guidelines

- Paroxysmal
  - Anticoagulate; treat if symptoms
- Persistent
  - Anticoagulate, rate control
  - Can then decide whether to accept permanent AF vs. antiarrhythmic drug therapy +/- cardioversion
- Recurrent paroxysmal
  - Anticoagulate, rate control
  - If disabling symptoms, antiarrhythmic meds and ablation if this fails

Current Guidelines…To Maintain Sinus Rhythm

- No heart disease→ flecainide, propafenone or sotolol (dronedarone)
  - If no response→ amiodarone/or dofetilide or ablation
- If heart disease→ dofetilide or sotolol (dronedarone)
  - If no response→ amiodarone or ablation
- If CHF→ amiodarone or dofetilide
  - If no response→ ablation

Fuster et al. JACC/AHA/ESC Practice Guidelines. JACC, 2006;48(4).
Current Guidelines…To Maintain Sinus Rhythm

- Hypertension with LVH → amiodarone
  - If no response → ablation
- Hypertension and NO LVH → flecainide, propafenone, sotalol (amiodarone)
  - If no response → amiodarone or dofetilide or ablation


Thank You!!