Atrial Fibrillation

Management Strategies

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Atrial Fibrillation

- Estimated that 2.6 to 6.1 million people in the U.S. with Afib as of 2010
- By 2050 it is expected that Afib will affect nearly 5.6 to 12 million Americans
- The percentage of strokes attributable to afib increases steeply from 1.5% at 50-59 years of age to 23.5% at 80-89 years of age

Atrial Fibrillation Treatment Approach

- Rate Control vs Rhythm Control Strategies
- Integrated consideration:
  - Degree of symptoms
  - Likelihood of successful cardioversion
  - Presence of comorbidities
  - Candidacy for Afib ablation

Rhythm Control

- Improves cardiac hemodynamics
- Improves exercise tolerance
- Possibly reverses atrial dilatation
- Possibly improves quality of life

AFFIRM

Atrial Fibrillation Follow-up Investigation of Rhythm Management

- 4060 subjects age 65 or greater with afib randomized to strategy of rhythm control (cardioversion plus drugs) versus strategy of rate control (no attempt to restore sinus rhythm)
- No difference in rate of stroke or death between rate control and rhythm control strategies

Management of New-onset Afib Rate Control vs Rhythm Control

- General recommendations: Rate Control
  - Asymptomatic
  - Older patients
  - Minimally symptomatic with HTN or other co-morbidities
- General recommendations: Rhythm Control
  - Younger
  - Highly symptomatic
  - Few co-morbidities

Rate Control Strategy

- A number of Intrinsic and extrinsic factors affect ventricular rate
- Intrinsic AV nodal condition properties
- Underlying sympathetic and parasympathetic tone

Rate Control Strategy

- First line agents:
  - Beta Blockers
  - Calcium Channel Blockers
  - Effective both at rest and with exertion
  - IV forms
  - Caution with beta blockers and patients with reactive airway disease

Rate Control Strategy

- Digoxin
  - Rarely used as montherapy
  - Poorly effective in active settings
  - Heart failure and reduced LV function may make a good choice of therapy

Rate Control Strategy

- Amiodarone
  - IIA recommendation for those intolerant or unresponsive to other agents
  - Patients who do not tolerate Beta Blockers or Calcium Channel Blockers, such as patients with CHF may be good candidates

Rhythm Control Strategy

- Many physicians believe that an attempt at rhythm control should be made in most patients
- In general: younger patients with more severe symptoms and fewer co-morbidities a rhythm control strategy is appropriate. In older patients with structural heart disease, less likely to maintain SR and more likely to have side effects from antiarhythmic drugs, a rate control strategy would be reasonable

Rhythm Control Strategy

- Several antiarhythmic drugs have established efficacy in pharmacologic conversion of Afib to sinus rhythm
  - Flecainide
  - Propafenone
  - Dofetilide
  - Amiodarone

Amiodarone

- Patients with CAD, systolic or diastolic HF, amiodarone becomes drug of choice because of its decreased proarrhythmic effects compared to other antiarrhythmic agents
- Amiodarone more effective in maintaining sinus rhythm in Canadian Trial of Atrial Fibrillation (CTAF) and Sotalol Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T)

Dronedarone

- 2011 update to ACCF/AHA/HRS Afib guidelines add that it is reasonable to use dronaderone to reduce the probability that hospitalization will be required for patients with paroxysmal Afib or after cardioversion of persistent Afib
- Contradindicated in class IV HF or a recent episode of decompensated HF
- Not approved for patients with permanent AF
  - PACCAS study, 2 fold rise in death and 2 fold increase in strokes and heart failure hospitalizations

Sotalol

- Class III drug
- Monitor QTc
- Increased risk of QT prolongation and torsade de pointes
- Proarrhythmic effects increased in patients with CHF (unlike amiodarone and dofetilide)
- Hypokalemia should be corrected and avoided (prolongs QT)

Afib Risk Management

- Overall, approximately 15-25% of all strokes in U.S. can be attributed to Afib
- Benefits in terms of stroke prevention weighed against risk of serious bleeding

Afib and Stroke Risk

Risk Factors	Relative Risk
Prior Stroke/TIA	2.5
History of HTN	1.6
HF or reduced LV function	1.4
Advanced age	1.4
Diabetes	1.7
CAD	1.5

CHADS2 Score

- Cardiac Failure
- Hypertension
- Age > 75
- Diabetes
- Previous Stroke or TIA (2 points)

CHADS2 Score

CHADS2 Score	Adjusted Stroke Rate (%)
0	1.9%
1	2.8%
2	4.0%
3	5.9%
4	8.5%
5	12.5%
6	18.2%

CHADS2-VASc Score

- Adds Vascular Disease and Sex into formula
- Can be estimated with online calculator
- Better at predicting high risk and low risk subjects

CHADS2 Score and Therapy Recommendations

Risk Score	Recommended Therapy
No risk factors	ASA 81-325 mg
1 moderate risk factor	ASA 81-325 mg or Warfarin
2 or greater	Warfarin (INR 2-3)

Risk Factors

- Hi risk factors: prior CVA, TIA or systemic embolization
- Risk factors of unknown signficance:
  - Female sex
  - Age 65-74
  - CAD
  - Thyrotoxicosis

Warfarin for Stroke Prevention

- At least 4 large trials have clearly demonstrated that anticoagulation with warfarin decreases risk of stroke by 50-80%
- Warfarin superior to Clopidogrel or ASA/Clopidogrel in prevention of stroke in higher risk patients
- Once again, stroke risk vs bleeding risk needs to be considered

Electrical Cardioversion

- Urgent Cardioversion:
  - Hemodynamically unstable
  - Severe dyspnea
  - Chest pain
  - Pre-excited Afib

DC Cardioversion

- Delivery of electrical current that is synchronized to QRS complexes
- Monophasic or biphasic forms
- Sedation
- Success rate > 75%
- Most important complication is embolization, if <48 hrs generally safe to proceed, if >48 hrs TEE guided or 3-4 weeks of anticoagulation recommended
- Stunning of atrium and stasis can occur despite SR, therefore 4 weeks of anticoagulation is recommended

DC Cardioversion

- Other potential complications:
  - Pulmonary edema
  - Hypotension
  - Myocardial dysfunction
  - Skin burns

DC Cardioversion Paddle/Patches

- Anterolateral (Ventricular Apex and Right infraclavicular
- Anterior-Posterior (Sternum and left Scapular)
- One study A-P position increased efficacy

Pharmacologic Cardioversion

- "Pill-in-the-Pocket" approach
  - Flecainide 300 mg (>60 kg) 200 mg (<60 kg)
  - Propafenone 600 mg (>60 kg) 450 mg (<60 kg)
- Sotalol
  - Inpatient monitoring
  - Patients with no heart disease, with QTc < 450 ms and normal electrolytes could be started as outpatient
- Ibutilide (Corvert)
  - 1 mg (>60 kg) over 10 min and repeat if necessary
- Amiodarone, flecainide , ibutilide, propafenone or sotalol alone or in combination with DC cardioversion

Atrial Fibrillation Catheter Ablation

- 2011 ACCF/AHA/HRS AF Guidelines
  - It is recommended as an alternative to pharmacologic therapy to prevent recurrent paroxysmal afib in significantly symptomatic patients with little or no structural hear disease or pulmonary disease (Class 1, evidence level A)
  - It is reasonable at a treatment for symptomatic persistent Afib
  - Catheter ablation may be reasonable as a treatment for symptomatic paroxysmal Afib in patients with structural heart disease

Afib Catheter Ablation

- Afib catheter ablation may be superior to AV nodal ablation and biventricular pacing in heart failure patients but is technically difficult and more demanding

Catheter ablation vs minimally invasive surgical ablation

- Boersma et al found that patients with AF who had a dilated left atrium and hypertension or who failed prior AF ablation, surgical ablation was superior in achieving freedom for left atrial arrhythmias after 12 months of followup; however procedural adverse event rate was significantly higher with surgical ablation, primarily postoperative pneumothorax, major bleeding and an increased need for a permanent pacemaker

New Medical and Device Based Rhythm Control Strategies

- Renin-angiotensin system antagonists
- Statins
- Single and dual site atrial pacemakers to prevent AF
- Atrial defibrillators
- New surgical and catheter based therapies to compartmentalize the atria and localize focal triggers

Stroke Prevention

- Warfarin
- Dabigatran (Pradaxa)
- Rivaroxaban (Xarelto)
- Apixaban (Eliquis)
- ASA
- Clopidogrel

Risk of Bleeding

- ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation Study)
- 5-Point risk factor stratification scheme
  - Anemia
  - Severe Renal Diseas
  - Age
  - Prior Bleeding
  - Hypertension

HEMORR2HAGES

- Hx of bleeding 2 points
- Hepatic or renal dz 1 pt
- Alcohol abuse 1 point
- Malignancy 1 point
- Age > 75 1 point
- Reduced platelet count or ASA therapy 1 pt
- HTN 1 point
- Anemia 1 point
- Genetic predisp. 1 point
- Excessive fall risk 1 point
- Stroke 1 point

- Bleeding event per 100 patient-years
  - 0 points- 1.9%
  - 1 point- 2.5%
  - 2 points-5.3%
  - 3 points-8.4%
  - 4 points-10.4%
  - 5 points-12.3%

2011 ACCF/AHA/HRS Guidelines

- If warfarin not to be used, adding clopidogrel to ASA may be considered

Dabigatron
Pradaxa

- Class 1b: Treatment considered useful/effective based on single randomized trial
- May be used as alternative to warfarin for prevention of stroke and systemic embolus in patients with paroxysmal or permanent atrial fibrillation
- Direct Thrombin Inhibitor

RE-LY

- 18,000 patients with Afib
- Randomized to 1 of 3 arms
  - 1. Adjusted dose warfarin
  - 2. Dabigatron 110 mg bid
  - 3. Dabigatron 150 mg bid
- Dabigatron 110 mg was noninferior to warfarin to primary efficacy endpoint of stroke or systemic embolization
- Dabigatron 150 mg was significantly more effective than warfarin or Dabigatron 110 mg

RE-LY
Bleeding

- Major bleeding occurred significantly less often with Dabigatron 110 mg than warfarin
- Dabigatron 150 mg had similar bleeding to warfarin

Patients not a candidate for Dabigatron

- Prosthetic Heart Valves
- Hemodynamically significant valvular heart disease
- Renal Failure: CrCl < 15 ml/min
- Advanced Liver Disease

Dabigatron Administration

- Capsule (do not crush, chew or break)
- < 18 years of age: safety and efficacy not established
- Missed dose: take as soon as possible on same day; skip dose if cannot be taken at least 6 hrs before next scheduled dose. Do not double dose to make up for a missed dose

Dabigatron
Renal impairment

- > 30 ml/min 150 mg bid
- Moderate (30-50 ml/min) plus P-Glycoprotein inhibitor (ie. Dronaderone, ketoconazole) decrease to 75 mg bid
- Severe (15-30 ml/min) decrease to 75 mg bid
- < 15 ml/min or dialysis: No data available

Dose Conversion

Warfarin/Heparin/Lovenox to Dabigatron

- Discontinue warfarin and initiate Dabigatron when INR < 2.0
- IV Heparin: initiate at time of discontinuing IV heparin
- SQ Lovenox: give 0-2 hrs before next dose

Dose Conversion
Dabigatron to Warfarin

- CrCl > 50 ml/min: start warfarin 3 days before d/c of Dabigatron
- Cr Cl 30-50 ml/min: start warfarin 2 days before d/c of Dabigatron
- CrCl 15-30 ml/min: start warfarin 1 day before d/c of Dabigatron
- CrCl < 15 ml/min: no recommendations

Dose Conversion

Parenteral Anticoagulation from Dabigatron

- CrCl > 30 ml/min: wait 12 hrs after last dose
- CrCl < 30 ml/min: wait 24 hrs after last dose

Rivaroxaban
Xarelto

- Factor Xa inhibitor
- Oral bioavailability
- Rapid onset of action

ROCKET AF

- Multinational trial
- Double blind
- Over 14,000 patients
- Rivaroxaban vs warfarin
- Noninferior to warfarin in prevention of stroke and thromboembolism
- Intracranial hemorrhage and fatal bleeding less in Rivaroxaban arm
- Note: only 57.8% optimal INR in warfarin arm

EINSTEIN Trial

- Compare safety and efficacy of Rivaroxaban with standard therapy
- 3,449 patients with DVT
- Rivaroxaban or Enoxaparin/Warfarin
- Duration: 3, 6 or 12 months – physician discretion
- Primary efficacy outcome: symptomatic recurrent venous thromboembolism
- Primary safety outcome: composite of major bleeding and clinically relevant nonmajar bleeding

EINSTEIN results
NEJM Dec. 23, 2010

- Rivaroxaban had noninferior efficacy with respect to primary outcome 2.1% vs 3.0%
- Primary safety outcome 8.1% in each group
- In continued-treatment study, Rivaroxaban had superior efficacy 8 (1.3%) events vs 42 (7.1%) events. Four patients in Rivaroxaban group had nonfatal major bleed versus none in other group.

EINSTEIN

- Conclusion: Rivaroxaban offers a simple, single drug approach to the short-term and continuous treatment of venous thrombosis that may improve the benefit-to-risk profile of anticoagulation

EINSTEIN-PE

- Compare safety and efficacy of Rivaroxaban with standard therapy
- 4,832 patients with confirmed PE
- Rivaroxaban or Enoxaparin/Warfarin
- Treatment duration: 3, 6 or 12 months – physician discretion
- Primary efficacy outcome: symptomatic recurrent venous thromboembolism
- Primary safety outcome: composite of major bleeding and clinically relevant nonmajor bleeding

EINSTEIN-PE results
NEJM April 05, 2012

- Rivaroxaban was noninferior to standard therapy with 50 events in Rivaroxaban group versus 44 events in the standard-therapy group
- Principal safety outcome occurred in 10.3% of Rivaroxaban group and 11.4% of those in standard-therapy group
- Major bleeding observed in 1.1% of Rivaroxaban group and 2.2% of standard-therapy group

EINSTEIN-PE

- Conclusion: A fixed-dose regimen of Rivaroxaban alone was non-inferior to standard therapy for the initial and long-term treatment of pulmonary embolism and a potentially improved benefit-risk profile

Rivaroxaban (Xarelto) Dosing

- DVT prophylaxis
  - Knee replacement: 10 mg daily for 12 days
  - Hip replacement: 10 mg daily for 35 days
- DVT and PE Treatment
  - 15 mg q12 hrs for 21 days then 20 mg daily for 6 months
- Nonvalvular Afib
  - 20 mg daily for with evening meal

Rivaroxaban (Xarelto)
Discontinuation for surgery/procedure

- Stop Rivaroxaban at least 24 hrs before procedure
- Restart after surgery/procedure as soon as adequate hemostasis is established
- Consider parenteral drug if unable to take PO

Switching

- Warfarin to Rivaroxaban
- D/C warfarin and start rivaroxaban as soon as INR below 3.0

Rivaroxaban to warfarin

No clinical data available

INR measurements made during coadministration may not be useful

One approach: start coumadin and parenteral agent at the time next dose of Rivaroxaban would have been taken

Rivaroxaban (Xarelto)
Administration

- Forms: 10 mg, 15 mg and 20 mg tablets
- 15 and 20 mg tablets may be crushed and mixed with applesauce or food. Dose should be immediately followed with food

Rivaroxaban (Xarelto)
Dosing Modifications

- Renal impairment
  - CrCl > 50 ml/min 20 mg daily with evening meal
  - CrCl 15-50 ml/min 15 mg daily w/ evening meal
  - Cr Cl < 15 ml/min avoid use
- Avoid use in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment or with any hepatic disease with associated coagulopathy

Apixaban
Eliquis

- Factor Xa inhibitor
- Approved Dec. 2012 for stroke prevention treatment of patients with nonvalvular AFib

ARISTOTLE

Apixaban for Reduction in Strokes and Other Thromboemoblic Events

- Apixaban versus Warfarin
- Nonvalvular Afib with at least 1 risk factor for stroke
- Apixaban superior to warfarin in preventing stroke with less bleeding and lower mortality

AVERROES

Apixaban versus Actysalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment

- Apixaban versus ASA in patient when warfarin therapy was considered unsuitable
- Stopped early because significant reduction in stroke and systemic embolism compared to ASA
- Modest increase in bleeding in Apixaban arm

Apixaban
Eliquis

- Nonvalvular Afib patients
- Indicated to reduce risk of stroke and systemic embolism associated witn nonvalvular afib
- 5 mg bid

Apixaban (Eliquis) Dosage Modifications

- Coadministration with strong dual inhibitors of CYP3A4 and P-gp: decrease dose to 2.5 mg PO BID
- Decrease dose to 2.5 mg PO BID in patients with at least 2 of following characteristics: Age > 80, weight < 60 kg or serum creat > 1.5 mg/dl
- CrCl < 15 mg/min: No data available
- Hepatic impairment
  - Mild: No dosage adjustment required
  - Mod: No recommendations avalable
  - Severe: No recommendations available

Cost Considerations

- Warfarin 30 days cost
- Pradaxa 30 day cost
- Xarelto 30 day cost
- Eliquis 30 day cost

- $17
- $317
- $304
- $298

Cost Considerations

- Commercial Insurance patients with multiple programs to reduce costs
- Cost of Prothrombin Time/INR $28 for lab and $19 draw fee to patient or insurance carrier