Updates in the Management of Atrial Fibrillation

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Atrial Fibrillation

- Most common clinically significant cardiac arrhythmia
  - Affects ~2.2 million people in the US
  - Prevalence will rise as the population ages
- ~1 in 4 lifetime risk for patients older than 40 years
- Responsible for 15-20% of strokes

Objectives

- Rate vs. rhythm control
- Overview of antiarrhythmic strategies
- Risk stratification for stroke and antithrombotic treatment
- Newer anticoagulants

Goals of Therapy in Patients With AF

- Prevention of stroke (thromboembolism)
- Prevention of tachycardia-induced cardiomyopathy
- Symptom relief
- Primary prevention of other cardiovascular events
Treatment Strategies for AF

**Rate Control**
- Pharmacologic
  - Ca²⁺ blockers
  - β-blockers
  - Digitalis
  - Amiodarone
- Nonpharmacologic
  - Ablate and pace

**Maintenance of SR**
- Pharmacologic
  - Antiarrhythmic drugs:
    - Class IA
    - Class IC
    - Class III
- Nonpharmacologic
  - Catheter ablation
  - Pacing
  - Surgery
  - Implantable devices

**Stroke Prevention**
- Pharmacologic
  - Warfarin
  - Aspirin
  - Thrombin inhibitors
- Nonpharmacologic
  - Removal/isolation of LA appendage

**Rate Control**
- Should be part of initial therapy for AF
- Beta-blockers or nondihydropyridine calcium channel blockers are first-line agents
- Digoxin may be helpful in those with heart failure, who are sedentary, or as a 2nd drug
- AV node ablation can be considered if drug therapy fails

Rate vs. Rhythm
- Rhythm control not superior to rate control
- No differences in stroke rates or quality of life
  - Stroke rates: 5.5% with rate control and 7.1% with rhythm control (p=0.79)
- Does not obviate need for anticoagulation
  - Stroke events occurred mostly in patient off or sub-therapeutic on warfarin, regardless of rhythm
  - Trend towards worse outcomes with rhythm control, probably due to drug toxicity

Which of the following is most true?
1. Rhythm control with antiarrhythmic medications is superior to rate control
2. Rhythm control with cardioversion + antiarrhythmic medications is superior to rate control
3. Rate control is superior to rhythm control
4. Rate control and rhythm control have similar outcomes

AFFIRM Investigators, NEJM 2002
Strict vs. Lenient Rate Control

- Strict rate-control (resting heart rate < 80 bpm) had similar outcomes compared to lenient rate-control (resting heart rate < 110 bpm)
  - No difference in cardiovascular death, heart failure, stroke, bleeding, arrhythmias: 14.9% in strict and 12.9% in lenient
- Strict rate-control may not be beneficial unless heart rate symptomatic

Van Gelder et al, NEJM 2010

Which of the following is most true?

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2. Rhythm control with cardioversion + antiarrhythmic medications is superior to rate control
3. Rate control is superior to rhythm control
4. Rate control and rhythm control have similar outcomes

Rhythm Control

- Rhythm control recommended for *symptomatic* atrial fibrillation
- Can consider cardioversion with new onset atrial fibrillation
  - Most effective when initiated close to atrial fibrillation onset
- Antiarrhythmic medications
- Catheter ablation
Which of the following antiarrhythmics is considered first-line therapy for patients with AF and heart failure?

1. Flecainide
2. Sotalol
3. Amiodarone
4. Dronedarone

**Antiarrhythmic Drugs**

- Drug choice depends on clinical comorbidities and side-effect profile
- Class IC agents (flecainide, propafenone) amiodarone, sotalol, and dronedarone can be started as outpatients in patients with minimal underlying heart disease
  - “Pill in the pocket” approach for paroxysmal atrial fibrillation
- Amiodarone probably the most effective agent but limited by side-effects
  - Preferred antiarrhythmic in patients with heart failure

**Dronedarone**

- New antiarrhythmic approved in 2009
- Less effective than amiodarone, but may have somewhat fewer side-effects
- Avoid in patients with heart failure
- Drug-drug interactions
  - Digoxin, statins
  - QT interval prolongation or CYP3A4 inducers
  - May potentiate nodal blockade when used with beta-blockers/calcium channel blockers
- Case reports of hepatotoxicity; should monitor LFTs during initiation of therapy

**Catheter Ablation**

- May be useful for symptomatic atrial fibrillation or if antiarrhythmic medications do not control rhythm
- Outcomes are not well described for older patients or those with heart failure
- Many people go back into atrial fibrillation
  - Highest relapse rate is within the first year

Piccini et al, JACC 2009; 2011 ACCF/AHA/HRS Guidelines
Sinus Rhythm after First Catheter Ablation

Weerasooriya et al. JACC 2011

Maintenance of Sinus Rhythm

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1. Flecainide
2. Sotalol
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A 70 y/o man presents with atrial fibrillation.
He has a history of hypertension, asthma,
peripheral arterial disease, and diabetes.
What is his CHADS$_2$ stroke risk score?

1. CHADS$_2$ = 1
2. CHADS$_2$ = 2
3. CHADS$_2$ = 3
4. CHADS$_2$ = 4
5. CHADS$_2$ = 5

CHADS$_2$ Risk Scheme For Stroke

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent congestive heart failure</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age $\geq$75 years</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>History of stroke or transient ischemic attack (TIA)</td>
<td>2</td>
</tr>
</tbody>
</table>

CHADS$_2$ Risk Score and Stroke Rates

<table>
<thead>
<tr>
<th>CHADS$_2$Score</th>
<th>Stroke Rate per 100 p-yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.9</td>
</tr>
<tr>
<td>1</td>
<td>2.8</td>
</tr>
<tr>
<td>2</td>
<td>4.0</td>
</tr>
<tr>
<td>3</td>
<td>5.9</td>
</tr>
<tr>
<td>4</td>
<td>8.5</td>
</tr>
<tr>
<td>5</td>
<td>12.5</td>
</tr>
<tr>
<td>6</td>
<td>18.2</td>
</tr>
</tbody>
</table>

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He has a history of hypertension, asthma,
peripheral arterial disease, and diabetes.
What is his CHADS$_2$ stroke risk score?

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5. CHADS₂ = 5

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8<sup>th</sup> ACCP Guidelines

<table>
<thead>
<tr>
<th>Stroke Risk</th>
<th>Recommended Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (&lt;1%/yr)</td>
<td>CHADS₂ = 0 Aspirin 75 to 325 mg</td>
</tr>
<tr>
<td>Intermediate (1-4%/yr)</td>
<td>CHADS₂ = 1 Warfarin or Aspirin</td>
</tr>
<tr>
<td>High (&gt;4%/yr)</td>
<td>CHADS₂ ≥ 2 Warfarin</td>
</tr>
</tbody>
</table>

8<sup>th</sup> ACCP Consensus Statement, Chest 2008.

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Warfarin

- The most commonly used oral anticoagulant
- Reduces risk of atrial fibrillation-related stroke by 64%
- Recommended International Normalized Ratio (INR) range: 2.0 – 3.0

Warfarin works … but what about bleeding?

Falls and Intracranial Hemorrhage
- Relatively little data on falls and ICH
- Oldest patients generally excluded from studies
- Some observational data:

<table>
<thead>
<tr>
<th>Fall Risk</th>
<th>ICH Rate</th>
<th>Stroke Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>2.8%</td>
<td>13.7%</td>
</tr>
<tr>
<td>Not high</td>
<td>1.1%</td>
<td>6.9%</td>
</tr>
</tbody>
</table>


Falls and Intracranial Hemorrhage
- Assessed effect of warfarin on combined outcome of stroke, major hemorrhage, MI in patients at high fall risk

<table>
<thead>
<tr>
<th>CHADS2</th>
<th>HR [95%CI]</th>
<th>Recommended Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 1</td>
<td>0.98 [0.6-1.7]</td>
<td>Aspirin or none</td>
</tr>
<tr>
<td>2 - 6</td>
<td>0.75 [0.6-0.9]</td>
<td>Anticoagulation</td>
</tr>
</tbody>
</table>


You start your patient on warfarin. Over the next 6 months however, his INRs have been difficult to control. He wants to know whether he can stop warfarin. What do you recommend?

1. Stop warfarin and start aspirin
2. Stop warfarin and start aspirin + clopidogrel
3. Stop warfarin and start dabigatran
4. Obtain genetic testing to help figure out his optimal dose and advise him to continue warfarin

Genotype-guided Warfarin Dosing
- Two haplotypes related to warfarin response
  - CYP2C9 (cytochrome P450 enzyme, which metabolizes warfarin)
  - VKORC1 (Vitamin K epoxide reductase complex, required to regenerate vitamin K)
- Warfarin dosing algorithms using genotyping + clinical factors can predict 50-60% of the variability in warfarin dosing
- However, not yet clear whether incorporating genetic testing significantly improves patient outcomes

Alternatives to Warfarin?

- Antiplatelet agents
- Direct thrombin inhibitors
- Factor Xa inhibitors

Aspirin

- Compared to placebo, aspirin reduces stroke risk by 22%
  - Considerably less effective than warfarin
- BAFTA Trial: randomized older patients (mean age 81.5 years) to warfarin vs. aspirin
  - Warfarin more effective
  - Bleeding rates were similar (1.4% per year on warfarin, 1.6% on aspirin)

Compared to placebo, aspirin reduces stroke risk by 22% compared to placebo, aspirin reduces stroke risk by 22% compared to placebo, aspirin reduces stroke risk by 22% compared to placebo, aspirin reduces stroke risk by 22% compared to placebo, aspirin reduces stroke risk by 22% compared to placebo, aspirin reduces stroke risk by 22% compared to placebo, aspirin reduces stroke risk by 22% compared to placebo, aspirin reduces stroke risk by 22%

Aspirin + Clopidogrel More Effective Than Aspirin Alone in Non-Warfarin Candidates

- Clopidogrel + Aspirin Less Effective than Warfarin for Stroke Prevention
  - Clopidogrel + aspirin
  - Oral anticoagulation therapy
  - RR = 1.72 (1.24-2.37)

- Aspirin + Clopidogrel More Effective Than Aspirin Alone in Non-Warfarin Candidates
  - Clopidogrel + aspirin
  - Aspirin
  - HR = 0.72 (0.62-0.84)

Hart et al., Ann Intern Med 2007; Mant et al., Lancet 2007


ACTIVE A Trial: Connolly SJ, et al. NEJM 2009
New and Investigational Agents for Stroke Prevention in AF

- **Direct thrombin inhibitors**
  - Dabigatran (RE-LY): FDA approved for prevention of stroke and blood clots in patients with AF (10/19/10)

- **Direct factor Xa inhibitors**
  - Rivaroxaban (ROCKET AF)
  - Apixaban (ARISTOTLE)
  - Edoxaban (ENGAGE-AF)
  - Betrixaban (EXPERT)
  - YM150 (ONYX-2)

- **Indirect Xa inhibitors**
  - Idraparinux (BOREALIS-AF)

- **Indirect inhibitors (eg, odiparcil)**

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Newer Anticoagulants

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>Thrombin</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
</tr>
<tr>
<td><strong>Time to effect</strong></td>
<td>2 hrs</td>
<td>2.5-4 hrs</td>
<td>3 hrs</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>14-17 hrs</td>
<td>9-13 hrs (older pts)</td>
<td>8-15 hrs</td>
</tr>
<tr>
<td><strong>Monitoring</strong></td>
<td>Not needed</td>
<td>Not needed</td>
<td>Not needed</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>Twice daily</td>
<td>Once daily</td>
<td>Twice daily</td>
</tr>
<tr>
<td><strong>Bioavailability</strong></td>
<td>5%-6%</td>
<td>60%-80%</td>
<td>50%-85%</td>
</tr>
<tr>
<td><strong>Renal excretion</strong></td>
<td>80%</td>
<td>33%</td>
<td>25%</td>
</tr>
<tr>
<td><strong>Drug interactions</strong></td>
<td>PPI and P-gp inhibitors</td>
<td>Potent CYP3A4 inhibitors</td>
<td>Potent CYP3A4 inhibitors</td>
</tr>
</tbody>
</table>

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RE-LY Trial: Dabigatran vs. Warfarin

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran 110 mg (n = 6015)</th>
<th>Dabigatran 150 mg (n = 6076)</th>
<th>Warfarin (n = 6022)</th>
<th>Dabigatran 110 mg vs Warfarin</th>
<th>Dabigatran 150 mg vs Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Annual Rate</strong></td>
<td>Stroke 1.4%</td>
<td>1.0%</td>
<td>1.6%</td>
<td>RR 0.92 0.7-1.1</td>
<td>0.41 0.64 0.5-0.8 &lt; .001</td>
</tr>
<tr>
<td></td>
<td>Death 3.8%</td>
<td>3.6%</td>
<td>4.1%</td>
<td>RR 0.91 0.8-1.0</td>
<td>0.13 0.88 0.8-1.0 0.05</td>
</tr>
</tbody>
</table>

Dabigatran vs. Warfarin

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran 110 mg</th>
<th>Dabigatran 150 mg</th>
<th>Warfarin</th>
<th>Dabigatran 110 mg vs Warfarin</th>
<th>Dabigatran 150 mg vs Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Annual Rate</td>
<td>Annual Rate</td>
<td>Annual Rate</td>
<td>RR 95% CI</td>
<td>P Value</td>
</tr>
<tr>
<td>Major Bleeds</td>
<td>2.7%</td>
<td>3.1%</td>
<td>3.4%</td>
<td>0.80</td>
<td>0.69-0.93</td>
</tr>
<tr>
<td>Intracranial Hemorrhage</td>
<td>0.2%</td>
<td>0.3%</td>
<td>0.7%</td>
<td>0.31</td>
<td>0.20-0.47</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>0.7%</td>
<td>0.7%</td>
<td>0.5%</td>
<td>1.35</td>
<td>0.98-1.87</td>
</tr>
</tbody>
</table>


Dabigatran

- At least similar in efficacy to warfarin for AF
- May have lower rates of intracranial hemorrhage
- Associated with a slight increase in risk of myocardial infarction
- FDA approved doses: 150mg BID and 75mg BID dosing (for CrCl < 30)
- More costly than warfarin
- No way to monitor or reverse anticoagulant effect

When Should I Prescribe Dabigatran?

- Patients who have difficulty remaining in a therapeutic INR range on warfarin
- Do not have renal insufficiency
- Can be adherent to twice a day dosing
- Can afford dabigatran

ROCKET-AF Trial: Rivaroxaban vs. Warfarin

<table>
<thead>
<tr>
<th>Rivaroxaban 20mg (n = 7081)</th>
<th>Warfarin (n = 7090)</th>
<th>Rivaroxaban vs. Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Annual Rate</td>
<td>Annual Rate</td>
</tr>
<tr>
<td>Vascular death, stroke, embolism</td>
<td>3.1</td>
<td>3.6</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>1.3</td>
<td>1.4</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>0.4</td>
<td>0.7</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>3.6</td>
<td>3.4</td>
</tr>
</tbody>
</table>

Rivaroxaban
- Similar efficacy and safety compared to warfarin
- Not yet approved for use in the US
- Once daily dosing
- Hepatically-cleared (might be able to use in renal insufficiency)
- Also no effective way to monitor or reverse anticoagulant effect

You start your patient on warfarin. Over the next 6 months however, his INRs have been difficult to control. He wants to know whether he can stop warfarin. What do you recommend?

1. Stop warfarin and start aspirin
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Summary
- Rate control and rhythm control have similar outcomes
  - May not require strict rate control
- Consider rhythm control for symptomatic patients
  - Choice of therapy depends on patient characteristics and side-effect profile
- Antithrombotic therapy should be guided by risk stratification
- Warfarin is more effective than antiplatelet agents
  - Net benefit of warfarin increases with older patients at higher stroke risk
- Newer anticoagulants (dabigatran, rivaroxaban) may become viable alternatives to warfarin
Bibliography


Bibliography