ATRIAL FIBRILLATION: CURRENT STRATEGIES IN TREATMENT AND ANTICOAGULATION

Kevin McHale, D.O., F.A.C.C.
Pinnacle Health Cardiovascular Institute
Harrisburg, PA

Disclosures
• None

Goals
• Risk assessment/stratification in atrial fibrillation
• Determine proper treatment strategies
• Discuss target-specific (novel) oral anticoagulants
Introduction to Atrial Fibrillation

- Single most common cardiac arrhythmia
- <60yo, prevalence is 1%
- >80yo, prevalence increases to >8%
- More common in men (1.1%) than women (0.8%)
- Currently, an estimated 2.3 million United States adults have atrial fibrillation and >5.6 million by 2050

Pathogenesis

- AFib is usually associated with underlying heart disease
  - Atrial enlargement
  - Elevation in atrial pressure
  - Infiltration or inflammation of the atria
- Framingham Heart Study:
  - Left atrial enlargement was shown to precede and predispose to AFib
  - Ectopic foci are most often located near the pulmonary veins, occurring in 89% - 94% of cases.
  - Atrial premature beats appear to be most important as a trigger in patients with paroxysmal AFib who have normal or near-normal hearts.

Risk Factors/Causes

- Many other diseases/conditions associated with higher incidence of AFib:
  - Hypertensive heart disease:
    - 1.42-fold increase
  - Coronary artery disease:
    - Not common, although AFib occurs in 6-10% of patients with acute MI.
  - Valvular heart disease:
    - Mitral prolapse/regurgitation: 5% per year will develop AFib
    - Mitral stenosis (MS), mitral regurgitation (MR), and tricuspid regurgitation – 70%
    - MS and MR – 52%
    - Isolated MS – 29%
    - Isolated MR – 16%
Risk Factors/Causes

- Hypertrophic cardiomyopathy:
  - 10-28% incidence
- Congenital heart disease:
  - 20% of patients with atrial septal defect
- Venous thromboembolic disease
  - 10-14% of patients with PE develop AFib
- Chronic obstructive pulmonary disease

Risk Factors/Causes

- Peripartum cardiomyopathy
- Lupus myocarditis
- Pericarditis
- Obstructive sleep apnea
- Obesity
- Diabetes mellitus
- Metabolic syndrome
- Hypomagnesemia
- Hyperthyroidism
- Chronic kidney disease
- Cardiac and non-cardiac surgery
- Alcohol
- Caffeine
- Long-QT syndrome
- Vagal tone/autonomic dysfunction

Risk Factors/Causes

- The point is……..there are MANY causes of atrial fibrillation!
Classification

- First diagnosed AFib
  - First time AF in a patient regardless of duration of arrhythmia or presence and severity of symptoms
- Recurrent AFib
  - >/= 2 episodes of AFib
- Paroxysmal
  - Recurrent AFib that terminates spontaneously, possibly up to 7 days but usually <48 hours
- Persistent AFib
  - Sustained >7 days or requires termination by cardioversion
- Permanent AFib
  - Persistent >1yr
  - Cardioversion has failed or is foregone

Evaluation

- History & Physical
- Electrocardiogram
  - ? Need for Holter monitor if ECG shows sinus rhythm
- Echocardiogram
  - Look for structural heart disease
- Laboratory studies
  - TSH, magnesium
- Stress test
  - If ischemia is a concern

Clinical Case

- 67 y/o female patient
- PMH: HTN, DM, nephrolithiasis
- PSH: Hysterectomy, cholecystectomy
- Social Hx: 30 pack/yr smoker, quit 2010. No EtOH
- Family Hx: Father – lung cancer
- Medications: Lisinopril, HCTZ, Lantus, Humalog, aspirin
- Allergies: NKDA
- VS – 101/52, pulse 172, RR 24, O2 sat 96% RA
- General: Moderate distress
- Lungs: Clear, b/l
- Cardio: Irregularly irregular, tachycardic. No murmurs or rubs.
- Extremities: No clubbing or edema.
ECG

Echocardiogram
- Atrial size
- Ventricular function
- Possible evaluation for presence of thrombus (though not sensitive)

Treatment Strategies
- Initial diagnosis vs. established diagnosis
- AFib treatment MUST address 2 main points:
  - Prevention of systemic embolization (CVA)
  - Rate control vs. rhythm control
- Most patients who present will have symptoms due to rapid ventricular rate
- Controlling heart rate will generally improve symptoms substantially
### Rate Control vs. Rhythm Control

- **AFFIRM Trial** - Randomly assigned 4060 patients with recurrent AF to:
  - Rate control (using digoxin, beta blocker, and/or calcium channel blocker) and anticoagulation with warfarin.
  - Rhythm control with the most effective antiarrhythmic drug, ± warfarin.
- 3.5 years later, there was a trend toward lower all-cause mortality with rate control (21.3 versus 23.8 percent).
- There was no difference between the two groups in the incidence of cardiac death, arrhythmic death, or deaths due to ischemic or hemorrhagic stroke.
- Two subgroups had a significant reduction in mortality with rate control: those without a history of heart failure and those aged 65 years or older.

### AFFIRM Trial (continued)

- The number of patients requiring hospitalization during follow-up was significantly lower in the rate control group than in the rhythm control group (73 versus 80 percent).
- There was no significant difference in any other endpoints, i.e. death, ischemic stroke, anoxic encephalopathy, major bleeding, cardiac arrest, or quality of life.

### RACE Trial

- The RACE trial enrolled 522 patients (mean age 68) with recurrent persistent AF or atrial flutter less than one year in duration who had required one to two cardioversions within the prior two years.
- Successful rate control was HR < 100 bpm & no symptoms.
- Initial therapy for rhythm control was sotalol (later amiodarone and then cardioversion if failed to stay in SR).
RACE Trial

- Significantly fewer patients were in SR in the rate control group.
- There was an almost significant trend toward a lower incidence of cardiovascular death, heart failure, thromboembolism, bleeding, pacemaker placement, and antiarrhythmic drug side effects with rate control (17.2 versus 22.6 percent with rhythm control).
- There were no significant differences in quality of life between the rate and rhythm control groups, a finding similar to that in AFFIRM.

Rate Control vs. Rhythm Control

Patient is Now Rate Controlled
Approach to Anticoagulation

• Who needs oral anticoagulation?
• First, assess patient's probability of thromboembolic event
  • CHADS Score
  • CHADS VASc Score

CHADS₂, CHA₂DS₂ VASc

CHADS₂ -> CHA₂DS₂ VASc

CHADS₂ Score Patients (n = 172) Adjusted stroke rate % / year
0 129 0.9
1 463 2.0
2 523 4.0
3 300 5.9
4 255 6.5
5 98 12.5
6 5 18.2

CHADS₂ VASc Score Patients (n = 137) Adjusted stroke rate % / year
0 1 0
1 422 1.5
2 1050 3.2
3 1708 3.8
4 1178 4.0
5 1159 0.7
6 879 9.6
7 284 9.8
8 82 6.7
9 14 15.2

CHADS₂, CHA₂DS₂ VASc

CHADS₂ -> CHA₂DS₂ VASc

CHADS₂ Risk Score CHADS₂ VASc Risk Score
CHF or LVEF < 40% 1
Hypertension 1
Age > 75 2
Diabetes 1
Stroke/TIA 2
The reclassification
Vascular Disease 1
Age 65-74 1
Female 1

Applying CHADS\(_2\) or CHA\(_2\)DS\(_2\)-VASc

- Among patients with atrial fibrillation at **moderate to high risk** of thromboembolic events (CHADS\(_2\) or CHA\(_2\)DS\(_2\)-VASc score ≥2), warfarin significantly reduces the incidence of clinical stroke at an acceptable risk of bleeding compared to placebo.
- The benefit to risk ratio from oral anticoagulation in patients at **low risk** (CHA\(_2\)DS\(_2\)-VASc score of 0 or 1, or a CHADS\(_2\) score of 0), has not been well studied.

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Our Patient

**CHADS\(_2\) -> CHA\(_2\)DS\(_2\)-VASc**

<table>
<thead>
<tr>
<th>CHADS(_2) Risk</th>
<th>Score</th>
<th>CHA(_2)DS(_2)-VASc Risk</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF</td>
<td>1</td>
<td>CHF or LVEF ≤ 40%</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥ 75</td>
<td>1</td>
<td>Age ≥ 75</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
<td>Diabets</td>
<td>1</td>
</tr>
<tr>
<td>Stroke or TIA</td>
<td>2</td>
<td>Stroke/TIA/Thromboembolosis</td>
<td>2</td>
</tr>
</tbody>
</table>

**CHADS\(_2\) Score**

<table>
<thead>
<tr>
<th>CHADS(_2) Score</th>
<th>Patients (n=120)</th>
<th>Adjusted stroke %/year</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>120</td>
<td>1.9</td>
</tr>
<tr>
<td>1</td>
<td>463</td>
<td>2.6</td>
</tr>
<tr>
<td>2</td>
<td>52</td>
<td>4.0</td>
</tr>
<tr>
<td>3</td>
<td>33</td>
<td>5.9</td>
</tr>
<tr>
<td>4</td>
<td>225</td>
<td>6.5</td>
</tr>
<tr>
<td>5</td>
<td>68</td>
<td>12.5</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>18.2</td>
</tr>
</tbody>
</table>

**CHA\(_2\)DS\(_2\)-VASc Score**

<table>
<thead>
<tr>
<th>CHA(_2)DS(_2)-VASc Score</th>
<th>Patients (n=732)</th>
<th>Adjusted stroke %/year</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>463</td>
<td>1.6</td>
</tr>
<tr>
<td>2</td>
<td>956</td>
<td>3.2</td>
</tr>
<tr>
<td>3</td>
<td>1528</td>
<td>3.3</td>
</tr>
<tr>
<td>4</td>
<td>1718</td>
<td>4.5</td>
</tr>
<tr>
<td>5</td>
<td>1799</td>
<td>6.7</td>
</tr>
<tr>
<td>6</td>
<td>37</td>
<td>9.8</td>
</tr>
<tr>
<td>7</td>
<td>14</td>
<td>15.2</td>
</tr>
</tbody>
</table>

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“Atrial Fibrillation: Current Strategies in Treatment and Anticoagulation”
Kevin J. McHale, D.O.

POFPS 41st Annual CME Symposium
August 5-7, 2016
Warfarin or Target-Specific Oral Anticoagulants?

- Drawbacks to Warfarin:
  - Narrow therapeutic range
  - Slow onset of action
  - Slow offset of action (long duration of action, long elimination half life)
  - Multiple drug and dietary interactions
  - Monitoring required to maintain in therapeutic range
  - Difficult to manage for invasive procedures
  - Impaired quality of life for the patient
  - Labor intensive for health care provider
  - Under-use of therapy due to fear of adverse events and complexity of management

Target-Specific Oral Anticoagulants

- Direct thrombin (Factor IIa) inhibitor
  - Dabigatran (Pradaxa)
- Factor Xa inhibitors
  - Rivaroxaban (Xarelto)
  - Apixaban (Eliquis)
  - Edoxaban (Savaysa)
Mechanism of Action

Target-Specific Oral Anticoagulants

- Advantages of the newer oral anticoagulants include:
  - Convenience (no requirement for routine testing of the INR)
  - A small reduction in the risk of intracranial hemorrhage
  - Less susceptibility to dietary and drug interactions

- Disadvantages include:
  - In some cases, lack of an approved antidote/reversing agent
  - Potential need for dose adjustment in patients with chronic severe kidney disease
  - Lack of easily available monitoring of blood levels and compliance
  - Higher cost
  - Potential that unanticipated side effects will subsequently become evident.

Approved Uses

- Prevention of thromboembolism (stroke) in non-valvular atrial fibrillation
- Treatment of deep venous thrombosis and/or pulmonary embolism
- Prophylaxis for DVT and/or PE
Dabigatran (Pradaxa)

The NEW ENGLAND JOURNAL of MEDICINE

Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., Michael D. Ezekowitz, M.A., Khurana, M.D., D.P.H., Salim Yusuf, F.R.C.P., D.P.H.,
John V. Alexander, M.D., James O’Gorman, M.D., F.R.C.P., Ameeta Maraj, M.D., James Pogue, M.D., Paul A. Kelly, Ph.D.,
Filippo Thieneke, B.A., Joonas Sonninen, M.D., Susan Wang, Ph.D., Mario Alings, M.D., Ph.D., Denis Koster, M.D.,
Jon-Thu, M.D., Rafael Ding, M.D., Baud E. Lewis, M.D., Harold Darius, M.D., Hans Christoph Steiner, M.D., Ph.D.,
Campbell D. Jones, M.D., Lars Wallentin, M.D., Ph.D., and the RE-LY Steering Committee and Investigators.

RE-LY Trial - Overview

- In a large, randomized trial, two doses of the direct thrombin inhibitor dabigatran were compared with warfarin in patients who had atrial fibrillation and were at risk for stroke.
- At 2 years, the 110-mg dose of dabigatran was found to be noninferior, and the 150-mg dose superior, to warfarin with respect to the primary outcome of stroke or systemic embolism.
RE-LY Trial: Conclusion

- In patients with atrial fibrillation, dabigatran given at a dose of 110 mg was associated with rates of stroke and systemic embolism that were similar to those associated with warfarin, as well as lower rates of major hemorrhage.
- Dabigatran administered at a dose of 150 mg, as compared with warfarin, was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage.
- Current recommended dosage is 150mg bid or 75 mg bid for creatinine clearance 15-30.

Rivaroxaban (Xarelto)

ROCKET AF Trial - Overview

- In this trial, 14,264 patients with atrial fibrillation were randomly assigned to receive either rivaroxaban or warfarin.
- In a per-protocol, as-treated analysis, rivaroxaban was noninferior to warfarin with respect to the primary end point of stroke or systemic embolism.
Cumulative Rates of the Primary End Point (Stroke or Systemic Embolism)

Cumulative Rates of the Primary End Point During Treatment

Primary End Point of Stroke or Systemic Embolism

Table 2. Primary End Point of Stroke or Systemic Embolism. *

<table>
<thead>
<tr>
<th>Study Population</th>
<th>Nonvitamin</th>
<th>Warfarin</th>
<th>Hazard Ratio [95% CI]</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients</td>
<td>No. of Events</td>
<td>Rate [per 100 patient-years]</td>
<td></td>
</tr>
<tr>
<td>Non-protocol, as-treated population</td>
<td>2058</td>
<td>138</td>
<td>1.7</td>
<td>1984</td>
</tr>
<tr>
<td>Safety, as-treated population</td>
<td>2058</td>
<td>138</td>
<td>1.7</td>
<td>1984</td>
</tr>
<tr>
<td>Intention-to-treat population</td>
<td>2058</td>
<td>138</td>
<td>1.7</td>
<td>1984</td>
</tr>
<tr>
<td>During treatment</td>
<td>158</td>
<td>1.7</td>
<td>240</td>
<td>2.2</td>
</tr>
<tr>
<td>After discontinuation</td>
<td>50</td>
<td>4.7</td>
<td>98</td>
<td>6.3</td>
</tr>
</tbody>
</table>

* The median follow-up period was 595 days for the nonvitamin group, 627 days for warfarin, and 365 days for the intention-to-treat population. Hazard ratios are for the nonvitamin group as compared with the warfarin group. The primary analysis was performed in the intention-to-treat population during treatment. Follow-up in the intention-to-treat population continued until notification of study termination.
Rates of Bleeding Events

<table>
<thead>
<tr>
<th>Table 1. Rates of Bleeding Events.†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>Principal safety and percent major and minor nonmajor bleeding</td>
</tr>
<tr>
<td>Major bleeding</td>
</tr>
<tr>
<td>Transfusion</td>
</tr>
<tr>
<td>Mortality</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
</tr>
<tr>
<td>Extracranial hemorrhage</td>
</tr>
</tbody>
</table>

† All analyses of rates of bleeding are based on the first event in the safety population during treatment.

Conclusions – ROCKET AF

- In patients with atrial fibrillation, rivaroxaban was noninferior to warfarin for the prevention of stroke or systemic embolism.
- There was no significant between-group difference in the risk of major bleeding, although intracranial and fatal bleeding occurred less frequently in the rivaroxaban group.
**ARISTOTLE Trial - Overview**

- The oral direct factor Xa inhibitor, apixaban, was compared with warfarin in atrial fibrillation.
- Apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and lowered mortality.

**Kaplan–Meier Curves for the Primary Efficacy and Safety Outcomes**

**Efficacy Outcomes**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Apixaban Group (n=2,056)</th>
<th>Warfarin Group (n=2,048)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome: stroke or systemic embolism</td>
<td>253 (12.3%)</td>
<td>265 (12.9%)</td>
<td>0.99 (0.94-1.04)</td>
<td>0.51</td>
</tr>
<tr>
<td>Stroke</td>
<td>199 (9.7%)</td>
<td>208 (10.2%)</td>
<td>0.95 (0.86-1.04)</td>
<td>0.27</td>
</tr>
<tr>
<td>Ischemic or unclear type of stroke</td>
<td>161 (8.3%)</td>
<td>175 (8.6%)</td>
<td>0.95 (0.84-1.07)</td>
<td>0.42</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>161 (8.0%)</td>
<td>171 (8.4%)</td>
<td>0.96 (0.85-1.09)</td>
<td>0.38</td>
</tr>
<tr>
<td>Ischemic or unclear type of stroke</td>
<td>161 (8.3%)</td>
<td>175 (8.6%)</td>
<td>0.95 (0.84-1.07)</td>
<td>0.42</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>17 (0.8%)</td>
<td>17 (0.8%)</td>
<td>0.97 (0.40-2.36)</td>
<td>0.93</td>
</tr>
</tbody>
</table>

**Other secondary outcomes:**

- Stroke, systemic embolism, or death from any cause: 763 (37.5%) vs. 764 (37.8%) (p=0.02)
- Hemorrhagic stroke: 75 (3.7%) vs. 82 (4.0%) (p=0.09)
- Stroke, systemic embolism, or death from any cause: 763 (37.5%) vs. 764 (37.8%) (p=0.02)
- Pulmonary embolism or deep vein thrombosis: 7 (0.3%) vs. 9 (0.4%) (p=0.33)
Bleeding Outcomes and Net Clinical Outcomes

<table>
<thead>
<tr>
<th>Table 1. Bleeding Outcomes and Net Clinical Outcomes.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcomes</strong></td>
</tr>
<tr>
<td>------------</td>
</tr>
<tr>
<td>Primary safety outcomes (ITM major bleeding)</td>
</tr>
<tr>
<td>Adverse events</td>
</tr>
<tr>
<td>Major or clinically relevant minor bleeding</td>
</tr>
<tr>
<td>DEFRO stroke or systemic embolism</td>
</tr>
<tr>
<td>TIM major bleeding</td>
</tr>
<tr>
<td>Defro minor bleeding</td>
</tr>
<tr>
<td>Non-cardiac outcomes</td>
</tr>
<tr>
<td>Stroke, systemic embolic, or major bleeding</td>
</tr>
<tr>
<td>Stroke, systemic embolic, or major bleeding, or major events in trauma</td>
</tr>
</tbody>
</table>

1. The bleeding outcomes were assessed in patients who received at least one dose of a study drug and were free from the time of their last dose of study drug to the first day of bleeding, defined as any bleeding event occurring after the first day of the study drug. The bleeding outcomes were assessed in patients who received at least one dose of study drug and were free from their last dose of study drug to the first day of the study drug. The bleeding outcomes were assessed in patients who received at least one dose of study drug and were free from their last dose of study drug to the first day of the study drug.

ARISTOTLE Trial - Conclusions

- In patients with atrial fibrillation, apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality.

Target-Specific Oral Anticoagulants

- Anticoagulation with each of these newer oral anticoagulants ( dabigatran, rivaroxaban, and apixaban) led to similar or lower rates both of ischemic stroke and major bleeding compared to adjusted dose warfarin (INR of 2.0 to 3.0) in patients with nonvalvular atrial fibrillation (AF) in large randomized trials.
Target-Specific Oral Anticoagulants

- These newer oral anticoagulants (compared to warfarin) are associated with the following:
  - A significant reduction of stroke/systemic embolism (odds ratio [OR] 0.85, 95% confidence interval [CI] 0.74-0.99; absolute risk reduction, 0.7 percent) and major bleeding (OR 0.86, 95% CI 0.75-0.99; absolute risk reduction 0.8 percent).
  - A significant and marked reduction in hemorrhagic stroke (RR 0.48, 95% CI 0.36-0.62) and a significant reduction in all-cause mortality (relative risk [RR] 0.88, 95% CI 0.82-0.96).
  - In these meta-analyses, there was a trend toward reduced major bleeding with newer oral anticoagulants (relative risk 0.86, 95% CI 0.72-1.02 and 0.80, 95% CI 0.63-1.01).

Bleeding Concerns

- Assessment of bleeding/hemodynamics
- Appropriate monitoring (ICU, etc)
- Discontinue anticoagulants
- Establish airway, large-bore IV access
- Optimize pH, electrolyte status
- Determine site of bleeding (intracranial, retroperitoneal, GI, etc.)
- Transfusions if required, including:
  - Red blood cells for severe anemia or ongoing blood loss
  - Platelets for thrombocytopenia and/or severe platelet dysfunction
  - Plasma for trauma-associated coagulopathy

HAS BLED Score

<table>
<thead>
<tr>
<th>Condition</th>
<th>Points</th>
<th>HAS-BLED Score</th>
<th>Bleeds per 100 patient-years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>1</td>
<td>0</td>
<td>1.13</td>
</tr>
<tr>
<td>Abnormal renal or liver function</td>
<td>1</td>
<td>1</td>
<td>1.02</td>
</tr>
<tr>
<td>Stroke</td>
<td>2</td>
<td>2</td>
<td>1.88</td>
</tr>
<tr>
<td>Bleeding</td>
<td>1</td>
<td>3</td>
<td>3.74</td>
</tr>
<tr>
<td>Labile INRs</td>
<td>1</td>
<td>4</td>
<td>8.70</td>
</tr>
<tr>
<td>Elderly (&gt; 65 years)</td>
<td>1</td>
<td>5</td>
<td>12.5</td>
</tr>
<tr>
<td>Drugs or alcohol (1 point each)</td>
<td>1 or 2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Reversal of Anticoagulation

- Idarucizumab (Praxbind) was FDA approved in October 2015
- It is a monoclonal antibody that can quickly reverse the effects of Pradaxa
- Andexanet alfa is currently being investigated as a reversal agent for the factor Xa inhibitors
- Activated prothrombin complex concentrate (aPCC) such as factor eight inhibitor bypassing agent (FEIBA)
- Remember, shorter half life than warfarin

Peri-operative Management

- Estimate thromboembolic risk:
  - A higher thromboembolic risk increases the importance of minimizing the interval without anticoagulation.
  - Estimate thromboembolic risk for patients with atrial fibrillation based on age and comorbidities.
  - If thromboembolic risk is transiently increased (eg, recent stroke), try to delay surgery until the risk returns to baseline, if possible.
- Estimate bleeding risk:
  - A higher bleeding risk confers a greater need for perioperative hemostasis, and hence a longer period of anticoagulant interruption.
  - Bleeding risk is dominated by the type and urgency of surgery.
  - Procedures with a low bleeding risk (dental extractions, minor skin surgery) often can be performed without interruption of anticoagulation.
- Determine the timing of anticoagulant interruption

Peri-operative Management

- RE-LY Trial: One-fourth of the patients required an invasive procedure or surgery during a two-year period.
- Of the 4591 patients who underwent elective procedures or surgery, the perioperative thromboembolic risk was 1.2 percent, based on a composite endpoint of stroke, cardiovascular death, and pulmonary embolus.
- There were no differences according to the anticoagulant used (ie, warfarin or dabigatran) or the dabigatran dose.
- However, urgent surgery was associated with a higher risk of ischemic stroke or systemic embolism than elective surgery.
Peri-operative Management

- Neuraxial (i.e., spinal or epidural) anesthesia should not be used in anticoagulated individuals, due to the risk of potentially catastrophic bleeding into the epidural space.
- The increased risk of bleeding applies both at the time of catheter placement and the time of removal.

**Non-Valvular Afib**

- Many, but not all, of the major clinical trials of antithrombotic therapy and subsequent meta-analyses have excluded patients with any type of prosthetic heart valves
- Mitral stenosis
- Decompensated valvular heart disease who were likely to require valve replacement in the near future.
- Based on these studies, the newer anticoagulants should not be prescribed for these patients.
References