Anticoagulants in Atrial Fibrillation
Starting and Stopping Them Safely

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Atrial Fibrillation Anticoagulation

Overview

- Learning objectives
- Introduction
- Basic concepts
- Treatment strategy & options
- Summary
Atrial Fibrillation Anticoagulation

Learning objectives

1. List the major considerations to be addressed in the management of atrial fibrillation.
2. Determine which patients with atrial fibrillation are appropriate candidates for anticoagulation.
3. Compare and contrast the various oral anticoagulants currently available for stroke prevention in atrial fibrillation.
4. Describe the adjustments in dosage or choice of oral anticoagulant that may be necessary due changes in patients’ renal or hepatic function.

Learning objectives (cont.)

5. Explain the safest way to stop and restart the various oral anticoagulants for procedures that carry considerable bleeding risk.
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Introduction

Atrial fibrillation (AF) prevalence

- 2.5 million persons in the United States are currently afflicted with AF
- Increases with age
  - 0.1% of adults younger than 55 years
  - > 9% of adults 80 years or older

Introduction (cont.)

Atrial fibrillation (AF) incidence

- Increases with age:
  - < 0.1 % per year in people < 40 years old
  - > 1.5 % per year in women > 80 years old
  - > 2 % per year in men > 80 years old
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Introduction (cont.)

Definitions of AF

- Paroxysmal
- Persistent
- Permanent
- Nonvalvular
- Lone

Cornerstones of AF Management

- Rate Control
- Rhythm Control
- Antithrombotic Therapy

Therapeutic Goals

- Control of symptoms
- Control of symptoms
- Prevention of thromboembolism
- Treatment or prevention of tachycardia-induced cardiomyopathy
- Reduction in hospitalizations
- Minimization of bleeding risk
- Reduction in Hospitalizations
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Basic Concepts

- Antithrombotic therapy
  - Rationale
    - CVA risk
      - AF = 5 x age-matched controls
      - AF = A. flutter
      - Paroxysmal = Persistent = Permanent

Basic Concepts (cont.)

- Antithrombotic drugs
  - Interfere with thrombus formation
  - Include:
    - Antiplatelet drugs
      - Interfere with platelet plug formation
    - Anticoagulant drugs
      - Interfere with fibrin formation
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Basic Concepts (cont.)

- Thrombus composition varies with the site of thrombus formation
  - Thrombi that form in arteries (high flow conditions)
    - Platelets predominate
    - Relatively little fibrin
    - “White thrombi”
  - Thrombi that form in veins (slow flow conditions)
    - Rich in fibrin and trapped red blood cells
    - Relatively few platelets
    - “Red thrombi”

Strategy for Antithrombotic Selection

<table>
<thead>
<tr>
<th>PATHOGENESIS</th>
<th>Arterial Platelets and fibrin (PI and/or A/C)</th>
<th>Acute cor. syndr. PCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chambers/Venous</td>
<td>A. fib. Very low LVEF DVT Pulm. embolism</td>
<td></td>
</tr>
<tr>
<td>Fibrin (A/C)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostheses</td>
<td>Fibrin more than platelets</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(A/C &gt; PI)</td>
<td></td>
</tr>
</tbody>
</table>
Antithrombotic therapy (cont.)

Antithrombotic strategy must be individualized based on risk stratification.

For nonvalvular AF, the CHADS\textsubscript{2} scoring system and, more recently, the CHA\textsubscript{2}DS\textsubscript{2}–VASc scoring system is a useful method for estimating stroke risk in AF patients.

Antithrombotic strategy must be individualized based on risk stratification (cont.).

These scoring systems, along with the HAS-BLED bleeding risk scoring system, may be used to guide antithrombotic therapy.
**Atrial Fibrillation Anticoagulation**

**CHADS<sub>2</sub> Risk Stratification Scheme**

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>C Congestive heart failure</td>
<td>1</td>
</tr>
<tr>
<td>H Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>A Age ≥75 years</td>
<td>1</td>
</tr>
<tr>
<td>D Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>S&lt;sub&gt;2&lt;/sub&gt; History of stroke or transient ischemic attack</td>
<td>2</td>
</tr>
</tbody>
</table>


**Atrial Fibrillation Anticoagulation**

**CHADS<sub>2</sub> Risk Stratification Scheme (cont.)**

<table>
<thead>
<tr>
<th>Score</th>
<th>Recommended therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Aspirin (81 to 325 mg daily)</td>
</tr>
</tbody>
</table>
| 1     | Aspirin (81 to 325 mg daily)  
or Warfarin (INR 2.0 – 3.0) |
| 2 - 6 | Warfarin (INR 2.0 – 3.0) |

### Atrial Fibrillation Anticoagulation

#### CHA₂DS₂–VASc Risk Stratification Scheme

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>H</td>
<td>Hypertension</td>
</tr>
<tr>
<td>A₂</td>
<td>Age ≥75 years</td>
</tr>
<tr>
<td>D</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>S₂</td>
<td>History of stroke or transient ischemic attack</td>
</tr>
<tr>
<td>V</td>
<td>Vascular disease</td>
</tr>
<tr>
<td>A</td>
<td>Age 65 - 74 years</td>
</tr>
<tr>
<td>Sc</td>
<td>Sex category (female gender)</td>
</tr>
</tbody>
</table>


#### Atrial Fibrillation Anticoagulation

#### CHA₂DS₂–VASc Risk Stratification Scheme (cont.)

<table>
<thead>
<tr>
<th>Score</th>
<th>Recommended therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>“It is reasonable to omit antithrombotic therapy.”</td>
</tr>
<tr>
<td>1</td>
<td>**** “No antithrombotic therapy, treatment with oral anticoagulant, or aspirin may be considered.”</td>
</tr>
<tr>
<td>≥ 2</td>
<td>“Oral anticoagulants recommended.”</td>
</tr>
</tbody>
</table>

**CHA₂DS₂–VASc Score of “1”**

- Females with a CHA₂DS₂–VASc Score of “1” are probably truly low-risk for stroke (and may not require anticoagulation for nonvalvular AF), whereas males with a CHA₂DS₂–VASc Score of “1” are probably at higher risk for stroke (and thus probably should be anticoagulated).

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**Treatment Strategy / Options (cont.)**

- **Antithrombotic therapy (cont.)**
  - **Additional recommendations:**
    - For lone AF (<60 y/o and no heart disease), ASA or no antithrombotic therapy is acceptable.
    - Regardless of CHA₂DS₂–VASc score, anticoagulation is recommended for patients with AF and:
      - Hypertrophic cardiomyopathy
      - Mitral stenosis
      - Mechanical and bioprosthetic valve prostheses
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HAS-BLED Risk Stratification Scheme

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Score</th>
<th>Risk Factor Specifics</th>
</tr>
</thead>
<tbody>
<tr>
<td>H  Hypertension</td>
<td>1</td>
<td><strong>Uncontrolled</strong> hypertension (systolic BP &gt; 160 mmHg)</td>
</tr>
<tr>
<td>A  Abnormal renal and liver function (1 point each)</td>
<td>1 or 2</td>
<td>Abn. renal function (dialysis, transplant, Cr &gt; 2.6 mg/dL)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Abn. liver function (cirrhosis, bilirubin &gt; 2 x NL, AST/ALT/AP &gt; 3 x NL)</td>
</tr>
<tr>
<td>S  Stroke</td>
<td>1</td>
<td>Stroke history</td>
</tr>
<tr>
<td>B  Bleeding predisposition</td>
<td>1</td>
<td>Prior major bleeding or predisposition to bleeding</td>
</tr>
<tr>
<td>L  Labile INR's</td>
<td>1</td>
<td>Unstable/high INR’s, time in therapeutic range &lt; 60%</td>
</tr>
<tr>
<td>E  Elderly (Age &gt; 65)</td>
<td>1</td>
<td>Elderly (Age &gt; 65)</td>
</tr>
<tr>
<td>D  Drugs and/or alcohol usage</td>
<td>1 or 2</td>
<td>Drugs (medication usage predisposing to bleeding (antiplatelet agents, NSAID’s)) and/or alcohol usage (&gt; 8 drinks/week)</td>
</tr>
</tbody>
</table>

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HAS-BLED Risk Stratification Scheme (cont.)

- “In patients with a HAS-BLED score $\geq 3$, caution and regular review are recommended, as well as efforts to correct the potentially reversible risk factors for bleeding.”

- “A high HAS-BLED score per se should not be used to exclude patients from oral anticoagulant therapy.”


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Treatment Strategy / Options (cont.)

- Antithrombotic therapy (cont.)
  - There’s an app for that!
    - ACC Guideline Clinical Apps
### CHADS₂* Score

<table>
<thead>
<tr>
<th>Factor</th>
<th>No (0)</th>
<th>Yes (1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HF/LV dysfunction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≥ 75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke/TIA/TE</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### CHA²DS₂-VASc Score

<table>
<thead>
<tr>
<th>Factor</th>
<th>No (0)</th>
<th>Yes (1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular Disease History</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 65-74</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### HAS-BLED Score

<table>
<thead>
<tr>
<th>Factor</th>
<th>No (0)</th>
<th>Yes (1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal RF²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal LF³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding³</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Interactive Tools**

**Anticoag Evaluator [AF]**

### HAS-BLED

|HAS-BLED|  
|---|---|
|Abnormal RF²| No (0) Yes (1) |
|Abnormal LF³| No (0) Yes (1) |
|Bleeding⁴| No (0) Yes (1) |
|Labile INR⁵| No (0) Yes (1) |
|Medication⁵| No (0) Yes (1) |
|Alcohol or Drug Usage History⁷| No (0) Yes (1) |

**Score (must answer all questions)**

### CHADS₂*: 1

### CHA₂DS₂-VASc: 2

### HAS-BLED: 3

**Choice of Therapy**

- RIVAROXABAN 20 mg or

**Risks/Benefits§**

Patient’s ANNUAL risk of ischemic stroke + thromboembolism: 1.2% with rivaroxaban (based on CHADS₂)

Relative risk reduction: 66%

Absolute risk reduction: 2.4%
Interactive Tools

Anticoag Evaluator [AF]

Patient's ANNUAL risk of ischemic stroke + thromboembolism with rivaroxaban (based on CHADS2)

Relative risk reduction 66%
Absolute risk reduction 2.4%
Chance of benefit per year 1 in 41

Patient's ANNUAL risk of ischemic stroke + thromboembolism with rivaroxaban (based on CHA2DS2-VASc)

Relative risk reduction 68%
Absolute risk reduction 1.9%

Chance of benefit per year 1 in 52

ANNUAL risk of major bleed (population avg) 3.8%
Chance of being harmed by rivaroxaban (per year, major bleeding, vs. no therapy) 1 in 31

Patient's ANNUAL risk of major bleed (HAS-BLED) 5.6%
Chance of being harmed by rivaroxaban (per year, major 1 in 20)
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Treatment Strategy / Options (cont.)

- Oral anticoagulants
  - Warfarin
  - Dabigatran
  - Rivaroxaban
  - Apixaban
  - Edoxaban
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Treatment Strategy / Options (cont.)

- Oral anticoagulants (cont.)
  - Warfarin
    - Inhibits formation of the reduced form of vitamin K
    - Long half-life (37 hours)
      - Delayed onset of anticoagulation: 2-7 days
    - Variability in warfarin’s anticoagulant effect
      - Dietary variations in vitamin K content
      - Many drug interactions
    - Requires monitoring of PT/INR

- Dabigatran
  - Oral direct thrombin inhibitor
    - At least as effective as warfarin (in reducing the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation), without increased bleeding risk
  - No monitoring of coagulation studies needed
  - No dietary restrictions
  - Minimal drug interactions
  - Dose reduction necessary in renal insufficiency
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Treatment Strategy / Options (cont.)

- Oral anticoagulants (cont.)
  - Rivaroxaban
    - *Oral* factor Xa inhibitor
    - *Does not* bind to antithrombin III
    - Once daily dosing
    - Dose reduction necessary in renal insufficiency
Atrial Fibrillation Anticoagulation

Treatment Strategy / Options (cont.)

- Oral anticoagulants (cont.)
  - Apixaban
    - *Oral* factor Xa inhibitor
    - *Does not* bind to antithrombin III
    - Twice daily dosing
    - Dose reduction necessary in renal insufficiency
Atrial Fibrillation Anticoagulation

Treatment Strategy / Options (cont.)

- Oral anticoagulants (cont.)
  - Edoxaban
    - *Oral* factor Xa inhibitor
    - Does *not* bind to antithrombin III
    - Once daily dosing
    - Dose reduction necessary in renal insufficiency
    - Avoid use if CrCl > 95 ml/min.

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Treatment Strategy / Options (cont.)

- Temporary interruption of oral anticoagulant therapy for invasive procedures:
  - For nonvalvular atrial fibrillation, short-term interruption of oral anticoagulant therapy is safe for most low-risk invasive procedures.
  - For patients at higher thromboembolic risk who are undergoing high risk procedures, “bridging” with a parenteral anticoagulant becomes a stronger consideration.
Treatment Strategy / Options (cont.)

- Temporary interruption of oral anticoagulant therapy for invasive procedures (cont.):
  - Warfarin
    - Number of days warfarin must be withheld prior to procedure depends on that individual’s usual maintenance dose
    - Check INR prior to procedure to assure subtherapeutic level
  - Dabigatran
    - If CrCl > 50 ml/min, stop dabigatran at least 1-2 days prior to procedure
    - If CrCl < 50 ml/min, stop dabigatran at least 3-5 days prior to procedure
  - Apixaban
    - For moderate-high-bleeding risk procedures, stop apixaban at least 48 hours prior to the procedure.
    - For low bleeding-risk procedures, stop apixaban at least 24 hours prior to the procedure.
  - Rivaroxaban & edoxaban
    - Stop rivaroxaban and edoxaban at least 24 hours prior to the procedure.
Dosing considerations for oral anticoagulants in nonvalvular atrial fibrillation:

- **Warfarin**
  - Oral anticoagulant of choice for AF patients with severe renal dysfunction or end-stage renal disease
  - Caution in patients with moderate-to-severe hepatic impairment.

- **Dabigatran**
  - If CrCl > 30 ml/min, dose is 150 mg PO BID
  - If CrCl is 15-30 ml/min, dose is 75 mg PO BID
  - If CrCl < 15 ml/min, avoid use

- **Rivaroxaban**
  - If CrCl > 50 ml/min, dose is 20 mg PO daily
  - If CrCl is 15-50 ml/min, dose is 15 mg PO daily
  - If CrCl < 15 ml/min, avoid use

- **Edoxaban**
  - If CrCl is 51-95 ml/min, dose is 60 mg PO daily
  - If CrCl is 15-50 ml/min, dose is 30 mg PO daily
  - If CrCl > 95 ml/min, avoid use
Treatment Strategy / Options (cont.)

- Dosing considerations for oral anticoagulants in nonvalvular atrial fibrillation (cont.):
  - Apixaban
    - Usual dose is 5 mg PO BID, unless the patient has at least two of the following (in which case the recommended dose is 2.5 mg PO BID):
      - Age ≥ 80 years
      - Weight ≤ 60 kg
      - Serum Cr ≥ 1.5 mg/dL