LEARNING OBJECTIVES

- Describe risk factors for bleeding for patients receiving anticoagulants or anti-platelets.
- Describe different bleeding risks among patients receiving warfarin, direct oral anticoagulants, and anti-platelets.
- Identify a management strategy for a patient with AFIB at a high risk of bleeding.

ATRIAL FIBRILLATION

- 33.5 million men and women estimated worldwide
- Average annual stroke rate is 1.5% in randomized control trials
  - Differs in real world
- Oral anticoagulation (OAC) can prevent the majority of ischemic strokes in AF
BENEFIT AND USE OF OAC

- Net clinical benefit almost universal
- Exception – patients at very low stroke risk
- Underuse or premature termination of OAC is common
- Bleeding events, severe and nuisance can occur with OAC
  - Lead to perceived “high bleed risk”
- Stroke risk often exceeds the bleed risk on OAC

European Heart Journal 2016;37:2893-2962

ASSESSING THE RISK

STROKE RISK ASSESSMENT

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score</th>
<th>Adjusted Stroke Risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHADS2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congestive failure</td>
<td>1</td>
<td>1.0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
<td>1.0</td>
</tr>
<tr>
<td>Age ≥75</td>
<td>1</td>
<td>2.0</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
<td>3.0</td>
</tr>
<tr>
<td>Prior stroke, transient ischaemic attack</td>
<td>1</td>
<td>5.0</td>
</tr>
<tr>
<td>Age ≥65</td>
<td>1</td>
<td>12.5</td>
</tr>
<tr>
<td>Female</td>
<td>1</td>
<td>1.9</td>
</tr>
</tbody>
</table>

European Heart Journal 2016;37:2893-2962
Circulation. 2014;130:e199-e267
WHAT MAKES A PATIENT HIGH RISK FOR BLEED?

- Hypertension (especially when systolic blood pressure is >140 mmHg)
- Labile INR or INR results that are not within the therapeutic range
- Recent cerebrovascular accident (CVA or TIA)
- Prior stroke
- Heart failure
- Heparin-induced thrombocytopenia
- Reduced platelet count or function
- Older age (≥75 years)
- History of major bleeding
- Older age
- Hemorrhagic stroke
- High-risk platelet function
- Atrial fibrillation
- Reduced platelet count or function

WHAT FACTORS ARE ASSOCIATED WITH BLEED RISK?

- Overlapping factors for bleed and stroke
  - HTN
  - Age
  - Prior stroke
- Leads to many high stroke risk patients being high bleed risk

HOW CAN I ASSESS THESE FACTORS?

- Multiple tools available to assess
  - Developed in differing populations
- Bleed risk scoring tools
  - HAS-BLED
  - HEMORRHAGES
  - ATRIA
  - ORBIT
  - ABC
HAS-BLED

- Population
  - Euro Heart Survey on AF in 3,456 patients with atrial fibrillation followed for 12 months

- Interpretation:
  - Low (0)
  - Intermediate (1–2)
  - High (3)

- Components:
  - 1 point for each
  - Hypertension
  - Abnormal renal function
  - Abnormal liver function
  - Stroke
  - Bleeding history or predisposition
  - Labile INR
  - Age > 65
  - Drug/alcohol use concomitantly

HEMORRHAGES

- Population:
  - National Registry of Atrial Fibrillation (NRAF)
  - 3791 hospitalized Medicare patients with atrial fibrillation
  - Discharged on warfarin and followed for 36 months

- Interpretation:
  - Low (0–1)
  - Intermediate (2–3)
  - High (≥ 4)

- Components:
  - 1 point for each of the following
  - Hepatic disease/Renal disease
  - Alcohol abuse
  - Malignancy
  - Hypertension (uncontrolled)
  - Anemia
  - Genetic lesions
  - Excessive fall risk
  - Isolated
  - 2 points for
    - Previous hemorrhage

ATRIA BLEEDING RISK SCORE

- Population:
  - Developed in 9,186 atrial fibrillation patients enrolled in a large integrated healthcare system
  - Followed for 6 years

- Interpretation:
  - Low (0–3)
  - Intermediate (4)
  - High (5–10)

- Components:
  - Aneurysm (3 points)
  - Severe renal disease (3 points)
  - Age ≥ 75 yrs (2 points)
  - Prior bleed (2 points)
  - Hypertension (1 point)
HOW GOOD ARE THESE TOOLS?

- Validation studies performed in subgroups of clinical trials, outpatients with atrial fibrillation, prospective cohorts, and administrative databases of hospitalized patient
- No single risk score consistently superior to others in predicting hemorrhage
- HAS-BLED is better at discriminating risk than the HEMORRHAGES or ATRIA scoring systems
- All scores had C indexes <0.70 in the receiver operating curves.
- Indicating only modest performance and poor predictive accuracy.


ASSESS YOUR ASSESSMENT

- Carefully evaluate the risk factors that attribute to the high risk score
  - Are they modifiable?
    - If so, intervene!
  - Are they non-modifiable?
    - Weigh the risks of stroke vs bleed associated with the factors

MODIFIABLE RISK FACTORS

- Uncontrolled hypertension
  - Increases the risk of ICH
  - Treat according to current HTN guidelines
- Labile INR
  - If high TTR cannot be maintained (>70%)
  - Consider use of DOACs
- Alcohol use
- Medication predisposing to bleeding
  - Triple therapy
  - Minimize time on triple therapy
  - Use lowest dose and combination with lowest bleed risk
A NOTE ON FALLS AND DEMENTIA

- Associated with increased mortality in AF patients
- But without evidence of increased ICH
- Withhold anticoagulation in certain situations
- Severe uncontrolled falls
  - Epilepsy or advanced multisystem atrophy with backwards falls
  - Dementia where compliance and adherence cannot be ensured

ASSESSMENT KEY POINTS

- Use a tool
  - HAS-BLED most widely utilized
  - Keep in mind the accuracy of the score
- When evaluating the performance of a risk score
  - Consider if the ability to categorize a patient at high or low risk for an outcome would change the decision to anticoagulate or not

EVALUATING TREATMENT OPTIONS
AVAILABLE ANTITHROMBOTIC TREATMENTS

- No treatment
- Aspirin
- Aspirin + Clopidogrel
- Warfarin
- Apixaban
- Dabigatran
- Edoxaban
- Rivaroxaban

ANTIPLATELET THERAPY

- Limited evidence
- VKA therapy is superior to ASA or ASA + clopidogrel in stroke prevention
- Annual stroke risk: 5.6% vs 3.9%
- Antiplatelet treatment increases bleeding risk
- Similar rates bleeding rates to OAC
- Best suited for
  - Patients at low stroke risk
  - Need for stroke prevention in patients who cannot take DOAC, adequately monitor a VKA, or have significant drug-drug interactions with all other options

WARFARIN THERAPY

- Adjusted dose warfarin compared with placebo or control
  - ARASAR I: 1996, 1999
  - SAFIR, 1996
  - CARIS, 1996
  - DOAT, 1999
  - All trials (n=12)
  - Relative Risk Reduction (95% CI)

- Adjusted dose warfarin compared with placebo or control
  - ARASAR I: 1996, 1999
  - SAFIR, 1996
  - CARIS, 1996
  - DOAT, 1999
  - All trials (n=12)
  - Relative Risk Reduction (95% CI)
### OAC Pharmacokinetics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Metabolism</th>
<th>Absolute Bioavailability</th>
<th>Tmax (hours)</th>
<th>Protein Binding (%)</th>
<th>Half-life (hours)</th>
<th>Renal Clearance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>No</td>
<td>100%</td>
<td>4</td>
<td>99%</td>
<td>20 to 60</td>
<td>&lt; 1% (1% removed by HD)</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>No</td>
<td>62%</td>
<td>1 to 2</td>
<td>40% to 59%</td>
<td>8 to 10</td>
<td>50% (9% removed by HD)</td>
</tr>
<tr>
<td>Apixaban</td>
<td>No</td>
<td>50%</td>
<td>3 to 4</td>
<td>87%</td>
<td>~12</td>
<td>27% (7% removed by HD)</td>
</tr>
<tr>
<td>Rivaroxoban</td>
<td>No</td>
<td>10% to 20%</td>
<td>2 to 4</td>
<td>92% to 95%</td>
<td>5 to 9</td>
<td>36% (&lt; 1% removed by HD)</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Yes</td>
<td>3% to 7%</td>
<td>1</td>
<td>35%</td>
<td>12 to 17</td>
<td>80% (50 - 60% removed by HD)</td>
</tr>
</tbody>
</table>

**European Heart Journal 2016;37:2893-2962**

### META ANALYSIS DATA: ATRIAL FIBRILLATION

**Lancet 2014;383:955-62**
WHERE IS DATA LACKING?

Indications not studied
- LV thrombus (case reports)
- Cardiomyopathy
- Acute stroke
- Secondary prevention of CV disease
- HFH

Indications with no benefit/harm:
- Post-ACS
- Mechanical heart valves

Populations not tested
- Pregnancy
- Extreme of body weight (< 45 kg or > 150 kg)

Certain subgroups
- Valvular AF
- Triple therapy
- High risk thrombophilia
- Cancer related thrombosis

Potentially interacting drugs
- Non-bleeding adverse events
- Allergy
- Rash
- Dyspepsia

PUTTING TOGETHER A PLAN
1. HISTORY AND ASSESSMENT
   - Stroke risk assessment
     - CHADS-VASc
   - Bleed risk assessment
     - HAS-BLED

2. DECISION TO ANTICOAGULATE
   - Shared decisions making
     - Patient
     - Caregiver
     - Providers
   - Provide EDUCATION
     - Patients/caregivers seem to have more awareness of bleed risk than stroke risk

3. WHAT AGENT TO CHOOSE
   - Use patient risk factors and drug specific factors to guide
     - Bleeding events
     - ICH risk lower with DOACs vs warfarin
     - GI bleed risk varies with agents
     - Ability to monitor
     - Patients with drug-drug interactions
     - Patients not well represented in clinical trials with DOACs (renal/hepatic dysfunction)
     - Affordability
     - Adherence
     - Once vs twice daily regimens
     - Longer vs shorter half life and missed doses
4. USE STRATEGIES TO MINIMIZE BLEEDING ON OAC

- Identify modifiable risk factors
- Regular follow up and monitoring (where applicable)
- Re-assess risk factors on a regular basis
- Patient education

WHAT ABOUT TRIPLE THERAPY?

- Therapy should be paused to control active bleeding
- However, absolute contraindications to long-term OAC after a bleeding episode are rare
- Nuisance bleeds → consider a change from one anticoagulant to another
- Address causes or triggers of major bleeding events can be treated and/or eliminated
  - Uncontrolled hypertension, gastrointestinal ulcers, and intracranial aneurysms
- Reinitiating of anticoagulation after a bleeding event is often clinically justified
  - Balancing the estimated risk of recurrent stroke and bleeding
  - Considering the bleeding risk of different stroke prevention therapies.
  - LAA exclusion or occlusion might be an alternative in selected patients

SO YOU DID EVERYTHING RIGHT, AND YOUR PATIENT HAD A BLEED. NOW WHAT?

- Therapy should be paused to control active bleeding
- However, absolute contraindications to long-term OAC after a bleeding episode are rare
- Nuisance bleeds → consider a change from one anticoagulant to another
- Address causes or triggers of major bleeding events can be treated and/or eliminated
  - Uncontrolled hypertension, gastrointestinal ulcers, and intracranial aneurysms
- Reinitiating of anticoagulation after a bleeding event is often clinically justified
  - Balancing the estimated risk of recurrent stroke and bleeding
  - Considering the bleeding risk of different stroke prevention therapies.
  - LAA exclusion or occlusion might be an alternative in selected patients
ANTICOAGULATION POST ICH

If re-initiating
- Choose agent with low ICH risk
- Wait 4-8 weeks after bleed to resume

CONCLUSIONS
- Use of OAC in high bleed risk is challenging
- Proper assessment of stroke and bleed risk are critical
- Warfarin and DOACs are preferred over ASA + Clopiogrel, even in high bleed risk
- DOAC may afford a reduction in bleed risk in some situations
- Regular monitoring and follow up are critical for success
- Patient education is CRITICAL!

RISKY BUSINESS:
HOW TO MANAGE ATRIAL FIBRILLATION IN PATIENTS WHO ARE AT A HIGH BLEEDING RISK

APRIL 3, 2017

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