Novel (new) Oral Anticoagulants (NOAC’s)

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Learning Objectives
1. Utilize a systematic process of care, including initiation and assessment of therapy and dosing adjustments, to optimize effectiveness and minimize adverse effects of patients taking warfarin.
2. Consider new agents in patients with atrial fibrillation and at least one other risk factor for stroke that do not require frequent laboratory monitoring and are as effective as warfarin for prevention of stroke or systemic embolism and have comparable risks of major bleeding.
3. Develop collaborative care plans with patient education to counsel patients on safe and effective self-administration of anticoagulants, emphasizing self-monitoring to prevent complications.
4. Establish or revise existing practice-level protocols for anticoagulation management, based on current evidence-based recommendations and guidelines, including having clearly defined staff roles and responsibilities.

The NOAC: Who are the players?
- dabigatran (Pradaxa)
- rivaroxaban (Xarelto)
- apixaban (Eliquis)
- edoxaban - not yet FDA-approved

The NOAC: How do they work?
- dabigatran: direct thrombin inhibitor
- rivaroxaban: Factor Xa inhibitor
- apixaban: Factor Xa inhibitor

NOAC’s: Approved for….
- Atrial fibrillation
- VTE (DVT/PE)
- Joint replacement (VTE prophylaxis)
The NOAC's
Pros
No monitoring needed
Cost
Long term experience
Cons
No approved reversal agent

How do these compare with warfarin?
- Afib?
- VTE (DVT/PE)?

Atrial fibrillation and anticoagulation:
Question #1: Which statement below is false?
A. Cardioembolic strokes due to aAfib (without anticoagulation) have greater morbidity and mortality than thrombotic strokes
B. Older patients are at a greater risks for sustaining a cardioembolic stroke (than a younger patient) with untreated Afib
C. The annual risk of developing a cardioembolic CVA in patients with Afib that remain off anticoagulation is 4.5%/yr.
D. Placing patients with Afib on anticoagulation results in an absolute risk reduction of CVA of 66%

Atrial Fibrillation and Stroke

- The older the patient with atrial fibrillation, the higher the risk of cardioembolic stroke.
- Strokes due to Afib have higher mortality and morbidity.
- Warfarin decreases absolute annual risk from 4.5% --> 1.4% (NNT=30).

Atrial Fibrillation: Warfarin Harms/Benefits
- Decreases CVA by 4.5% -> 1.4%
  (ARR: 3% NNT = 30, RRR 64%)
  vs. ASA 22%
- Rate of ICH 0.1 - 0.6%
  - Increased with advanced age, HTN
- Major bleeding rates: 1.2%/yr

Atrial fibrillation: Who is at risk for embolism (CVA)?

- Moderate-risk factors
  - Age > 75 yrs
  - HTN
  - CHF
  - LV ejection fraction < 35%
  - DM
- High-risk factors
  - Previous CVA,TIA,embohdism
  - Mitral stenosis
  - Prosthetic heart valve

Atrial fibrillation: Who should get anticoagulation?

- Do you like using a Scoring System?
  - CHADS2
  - CHA2DS2_Vasc
- Which one?
Atrial Fibrillation: Who Gets Warfarin? Would the CHADS\textsuperscript{2} Score Help?

- C HF
- HTN
- Age > 75 yrs
- DM
- Prior Stroke or TIA

CHADS\textsuperscript{2} Risk Criteria Score
- CHF
- HTN
- Age > 75 yrs
- DM
- Prior Stroke or TIA

<table>
<thead>
<tr>
<th>CHADS\textsuperscript{2} Score</th>
<th>Risk Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Low-risk (ASA)</td>
</tr>
<tr>
<td>1</td>
<td>Moderate (ASA or warfarin)</td>
</tr>
<tr>
<td>2+</td>
<td>High-risk (warfarin)</td>
</tr>
</tbody>
</table>

Pts. (N=1733)

<table>
<thead>
<tr>
<th>CVA Rate (%/yr) (95%CI)</th>
<th>CHAD\textsuperscript{2} Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.9 (1.2 - 3.6)</td>
<td>0</td>
</tr>
<tr>
<td>2.8 (2.0 - 3.6)</td>
<td>1</td>
</tr>
<tr>
<td>4.0 (3.1 - 5.1)</td>
<td>1</td>
</tr>
<tr>
<td>5.9 (4.5 - 7.3)</td>
<td>1</td>
</tr>
<tr>
<td>6.5 (6.3 - 11.1)</td>
<td>1</td>
</tr>
<tr>
<td>12.5 (8.2 - 17.5)</td>
<td>1</td>
</tr>
<tr>
<td>18.2 (10.6 - 27.4)</td>
<td>1</td>
</tr>
</tbody>
</table>

NNT 417

CHADS\textsuperscript{2} vs. CHA\textsubscript{2}DS\textsubscript{2}-VASc?

- C HF
- HTN
- Age > 75 yrs
- DM
- Prior Stroke or TIA
- Vascular disease
- Age 65-74 yrs
- Female sex

CHADS\textsuperscript{2} Score
- Low risk = 0 points
- Intermediate = 1 pt

<table>
<thead>
<tr>
<th>CHADS\textsuperscript{2} Score</th>
<th>Risk Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Low risk = 0 points</td>
</tr>
<tr>
<td>1</td>
<td>Intermediate = 1 pt</td>
</tr>
</tbody>
</table>

N= 73,538 pts with AFib, not on warfarin

March 28, 2014

NEW!!! AHA/ACC Guideline for the management of patients with Atrial Fibrillation

"In patients with nonvalvular AF, the CHA2DS2-VASc score is recommended for assessment of stroke risk. (Level of Evidence: B)"

2014 AHA/ACC guideline on atrial fibrillation

- Nonvalvular AF and a CHA2DS2-VASc, Score = 0, it is reasonable to omit antithrombotic therapy (Class IIA, Level of Evidence: B)
- Nonvalvular AF and a CHA2DS2-VASc, Score = 1, no antithrombotic therapy or treatment with an oral anticoagulant or aspirin may be considered (Class IIb, Level of Evidence: C)
- Nonvalvular AF and a CHA2DS2-VASc, Score of ≥ 2 or prior CVA/TIA oral anticoagulants are recommended (Class I, Level of evidence A)

Atrial Fibrillation: Warfarin Harms/Benefits

- Decreases CVA by 4.5% - 1.4% (ARR: 3% NNT = 30, RRR 64%) vs. ASA 22%
- Rate of ICH 0.1 - 0.6%
- Increased with advanced age, HTN
- Major bleeding rates: 1.2%/yr
Two new scoring systems: HAS-BLED and ATRIA


Who needs to avoid anticoagulation??

HAS-BLED: Results

<table>
<thead>
<tr>
<th>Score</th>
<th># of bleeds</th>
<th># of bleeds</th>
<th>Bleeds per 100 pt yrs</th>
<th>Derivation Cohort</th>
<th>Validation Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1517</td>
<td>9</td>
<td>0.59</td>
<td>798</td>
<td>9</td>
</tr>
<tr>
<td>1</td>
<td>1589</td>
<td>24</td>
<td>1.51</td>
<td>1296</td>
<td>13</td>
</tr>
<tr>
<td>2</td>
<td>219</td>
<td>7</td>
<td>3.20</td>
<td>744</td>
<td>14</td>
</tr>
<tr>
<td>3</td>
<td>41</td>
<td>8</td>
<td>19.51</td>
<td>187</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>14</td>
<td>3</td>
<td>21.43</td>
<td>46</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>0</td>
<td>12.50</td>
<td>8</td>
<td>1</td>
</tr>
</tbody>
</table>

*Major bleeds* defined as:
1) bleeding requiring hospitalization
2) require transfusion
3) drop in Hgb > 2 g/L
4) Hemorrhagic CVA

ATRIA: 13,559 pts in Kaiser system

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
<th>Derivation</th>
<th>Validation</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Anemia: Hgb &lt;13 male, &lt;12 female...</td>
<td>0.72</td>
<td>0.83</td>
</tr>
<tr>
<td>3</td>
<td>GFR &lt; 30</td>
<td>0.72</td>
<td>0.83</td>
</tr>
<tr>
<td>3</td>
<td>Age &gt; 75 yrs</td>
<td>0.72</td>
<td>0.83</td>
</tr>
<tr>
<td>2</td>
<td>Any prior hemorrhage Dx</td>
<td>0.72</td>
<td>0.83</td>
</tr>
<tr>
<td>1</td>
<td>HTN</td>
<td>0.72</td>
<td>0.83</td>
</tr>
</tbody>
</table>

Atrial fibrillation: Lets do a case....

- 87 y/o female, newly recognized Afib
  - No associated symptoms (palpitations, CP, syncope/lightheadedness)
  - PMHx: HTN, mild CHF, hypercholesterolemia
  - Meds: HCTZ, Coreg, atorvastatin, baby ASA
  - Past surgery: GB, TAH/BSO, Hip fracture
  - ROS: has fallen 3 times in past 6 months
  - PE: In office BP: 150/82, P=60, RR=20

Would you start anticoagulation?

Atrial fibrillation: Lets do a case....

- 87 y/o female, newly recognized Afib
  - No associated symptoms (palpitations, CP, syncope/lightheadedness)
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  - ROS: has fallen 3 times in past 6 months
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CHADS2-Vasc = 5/10 (high risk for CVA) HAS-BLED = 1 points (low risk for bleed)
Atrial fibrillation: Lets do a case....

- 87 y/o female, newly recognized Afib
  - No associated symptoms (palpitations, CP, syncope/lightheadedness)
  - PMHx: HTN, mild CHF, hypercholesterolemia
  - Meds: HCTZ, Coreg, atorvastatin, baby ASA
  - Past surgery: GB, TAH/BSO, Hip fracture
  - ROS: has fallen 3 times in past 6 months

PE: In office BP: 150/82, P=60, RR=20

But I Am Fearful of My Elderly Patient Falling (ie, Subdural)

- Using an analytic model ...
- A patient over age 65 with Afib must sustain 295 falls in one year for the risk of subdural to outweigh benefit of stroke prevention


Note 1: Pts on warfarin, spontaneous ICH more common than subdural
Note 2: Model uses assumptions - are they correct?

Incidence of ICH in patients with Afib who are prone to fall

- Methods: Retrospective study, pts 80+ yrs of age
  1,245 “high risk” for falls vs. 18,261 “controls”

<table>
<thead>
<tr>
<th></th>
<th>High risk</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Results: ICH per 100pt/ys</td>
<td>2.8</td>
<td>1.1</td>
</tr>
</tbody>
</table>

However... a 25% RRR in death, stroke and hemorrhage (including ICH) in high risk group persists


You are going to start anticoagulation... but, which one????

- Warfarin
  - Cons: Frequent monitoring, Drug interactions, Dietary restrictions

You are going to start anticoagulation... but, which one????

- Warfarin
- Clopidogrel (Plavix)?


- Methods: 250 pts, with stable INR x 6 months, randomized:
  - q 4 week
  - q 12 week

- Results:
  - Time in therapeutic range 74% 71%
What About Clopidogrel + ASA vs Warfarin?
Don't Go There!!!

• Methods: 6,706 pts with Afib, randomized double blind:

• Results:  
<table>
<thead>
<tr>
<th></th>
<th>ASA + Clopidogrel</th>
<th>Warfarin</th>
</tr>
</thead>
</table>
  Rate of CVA (%/yr) | 2.39% | 1.4% |
  CVA/embolus/MI, vascular death | 5.6% | 3.9% |
  Hemorrhage | 15.4% | 13.2% |
  Total mortality | No difference |

Trial stopped early because of superiority of warfarin!!

You are going to start anticoagulation… but, which one????

• Warfarin
• clopidogrel (Plavix)
• dabigatran (Pradaxa)
• rivaroxaban (Xarelto)
• apixaban (Eliquis)

Dabigatran: Is it really 35% better??????

Methods: 18,113 pts with Afib, randomized to:
  dabigatran         dabigatran      warfarin  
  110mg BID         150mg BID      

• Results
  – CVA/embolism | 1.53% | 1.11%* | 1.69% |
  – Major bleeding/yr | 2.71% | 3.11% | 3.36% |
  – Mortality rate/yr | 3.75% | 3.64% | 4.13% |

ARR = 0.58% \( \text{NNT} = 172 \)

Cost: Pradexa = $343 per month, $4116 per year

Price accessed @ CVS, accessed 11/10/13.

What about rivaroxaban (Xarelto)?

ROCKET-AF: *NEJM* 2011; 365: 883-91
Methods: 14,264 pts with Afib, randomized to: followed approx 2 yrs
  rivaroxaban | warfarin
  20mg qd | 5mg BID |

• Results
  – CVA/embolism | 2.1% | 2.4% |
  – Major/minor bleeding/yr | 5.6% | 5.4% |

No difference

Cost: Xarelto = $329 per month, $3948 per year

Price accessed @ CVS, accessed 11/10/13.

What about apixaban (Eliquis)?

Methods: 18,201 pts with Afib, randomized to: followed for 1.8 yrs
  apixaban | warfarin
  5mg BID | 5mg BID |

• Results
  – CVA/embolism | 1.27% | 1.60% |
  – Major bleeding/yr | 2.13% | 3.09% |
  – Mortality rate | 3.52% | 3.94% |

ARR = 0.33% \( \text{NNT} = 303 \)

Cost: Eliquis = $316 per month, $3792 per year

Price accessed @ CVS, accessed 11/10/13.
### The NOAC's

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>No monitoring needed</td>
<td>No approved reversal agent</td>
</tr>
<tr>
<td>Slightly better outcomes (?)</td>
<td>Cost</td>
</tr>
<tr>
<td></td>
<td>Long term experience</td>
</tr>
</tbody>
</table>

**How do these compare with warfarin?**
- Afib ?
- VTE (DVT/PE) ?

**Remember: efficacy vs. effectiveness**

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### You are going to start anticoagulation...

but, which one???

- **Warfarin**
- **Ticlopidine (Plavix)**
- **Dabigatran (Pradaxa)**
- **Rivaroxaban (Xarelto)**
- **Apixaban (Eliquis)**

**Cons:**
- Frequent monitoring
- Drug interactions
- Dietary restrictions

- ? Increase MI's?

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### Update: May 13, 2014

- FDA review announces *no increase risk of MI associated with dabigatran*
  - 134,000 Medicare pts (age 65+) with Afib

  - Controversy: includes observational studies, not just randomized trials.

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### What happened to dabigatran 110mg dose?

- Not FDA approved
- The lower dose has similar efficacy, decreased bleeding

<table>
<thead>
<tr>
<th>Dabigatran</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>110mg BID</td>
<td>150mg BID</td>
</tr>
<tr>
<td>warfarin</td>
<td></td>
</tr>
<tr>
<td>AMI/ACS</td>
<td></td>
</tr>
<tr>
<td>237/20,000</td>
<td>83/10,514</td>
</tr>
<tr>
<td>(1.19%)</td>
<td>(0.79%)</td>
</tr>
</tbody>
</table>

**Results:**
- CVA/embolism
  - Dabigatran: 1.32% vs 1.39%
  - Control: 1.97% vs 1.95%

**Major bleeding/yr**
- Dabigatran: 2.71% vs 2.73%
- Control: 3.01% vs 3.16%

- Company knew single-dose strategy was risky because there are 5-fold variations in plasma levels in 80% of pts
  - Especially in elderly pts
  - Company was reluctant to share this with regulators fearing increased monitoring and disadvantage with competitors.
Dabigatran: watch the dosing

- Ingested as pro-drug
- No food interaction
- PPI's decrease absorption 20-30%
- Renal excretion:
  - change dose in renal impairment
  - CrCl 30-50 mL/min: + P-gp inhibitor: Decrease dose to 75 mg PO BID
  - CrCl 15-30 mL/min: Decrease dose to 75 mg PO BID
  - CrCl 15-30 mL/min + P-gp inhibitor: Avoid concurrent use
  - CrCl <15 mL/min or dialysis:
    - No data available; not recommended

Dabigatran: Nuances

- Unstable if not store in original bottle (desiccant in lid) or blister pack
- Must be used within 60 days (if maintained in original bottle or blister packs)
- No pill boxes

Can you monitor dabigatran effect?

- Currently...No
- Hemoclot Thrombin Inhibitor assay
  - A dilute Thrombin time (TT) with internal dabigatran calibrators.
  - Correlates closely and linearly with dabigatran levels.
  - Company tested and noted "This rapid, standardized and calibrated assay should provide accurate and consistent results"

You are going to start anticoagulation... but, which one???

- Warfarin
  - Cons:
    - Frequent monitoring
    - Drug interactions
    - Dietary restrictions
  - Pros:
    - Decrease MIs
    - Renal dosing
    - Bleeding risks?
- Rivaroxaban (Xarelto)
- Apixaban (Eliquis)

Rivaroxaban: Nuances

- Onset within 4 hours
- Factor Xa does not return to normal for 24 hours
- 80 - 100% absorption/bioavailability, take with food
- 33% renal excretion, 66% metabolic degradation
- Drug interactions: Inhibitors of CYP3A4 and P-gp (e.g., ketoconazole, itraconazole, ritonavir, or clarithromycin)

Apixaban: Nuances

- Onset within 3-3.5 hours
- 1/2 life 8-15 hours (BID dosing)
- 27% renal excretion, 73% metabolic degradation
- Drug interactions: Inhibitors of CYP3A4 and P-gp (e.g., ketoconazole, itraconazole, ritonavir, or clarithromycin)
You are going to start anticoagulation… but, which one????

- Warfarin
- *clopidogrel* (Plavix)
- dabigatran (Pradaxa)
- rivaroxaban (Xarelto)
- apixaban (Eliquis)

Cons:
- Frequent monitoring
- Drug interactions
- Dietary restrictions
- Increase MI's
- Renal dosing
- Bleeding risks?
- Renal dosing

Atrial fibrillation: Is there an easy way to decide?

- 87 y/o female, newly recognized Afib
  - No associated symptoms (palpitations, CP, syncope/lightheadedness)
  - PMHx: HTN, mild CHF, hypercholesterolemia
  - Meds: HCTZ, Coreg, atorvastatin, baby ASA
  - Past surgery: GB, TAH/BSO, Hip fracture
  - ROS: has fallen 3 times in past 6 months
- PE: In office BP: 150/82, P=60, RR=20

www.Afib.ca
The NOAC's

Pros
- No monitoring needed
- Slightly better outcomes (?)

Cons
- No approved reversal agent*
- Cost
- Long term experience

Remember: efficacy vs. effectiveness

Question #2: 65 y/o with Afib on warfarin with acute ICH.
The ACCP recommends:

A. Start FFP and Vitamin K 10mg IV
B. Start FFP and Vitamin K 10mg IM
C. Start Activated Factor VII + Vitamin K 10mg IV
D. Start a Prothrombin Complex Concentrate (PCC) + Vitamin K 10mg IV

FFP and Vitamin K

**FFP** - normalize INR 13-48 hours
- Need ABO testing
- 30-60 minutes to thaw
- 15ml/kg - approx 1L (4units) for 70kg
  - May need 30ml/kg
**Vit K** - normalize INR 12-24 hours
- 10mg IV (over 30min) - 3/100,000 anaphylaxis

rFVIIa

**Only indication in US is use in hemophilia**
- 97% of use is off-label
Will reverse INR in 10minutes
- INR is sensitive to factors VII and X, not II or IX
- **So clinical impact is unknown**
  - Study healthy adults given warfarin, then rVIIa ===> Normalized INR, but persistent bleeding punch biopsy
  - Dose - unknown with Short-half life

**Up to 10-20% ==> thrombosis**
- **Black Box warning**


Prothrombin Complex Concentrate (PCC)

Pooled human plasma
Stored as a powder
- ABO testing not required
- Volume <100ml
Contains II, IX, X, varying amounts VII and Protein C and S
Rapidly reverse INR: 3-15 minutes
Prothrombin Complex Concentrate (PCC)

- Profilnine SD - 3 factor
- Feiba NH - 3 factor “activated”
- Kcentra - 4 factor

**Most studies are limited by:**
- Differing brands, doses, adjunctive therapy,
- Retrospective designs, small sample sizes,
- Lack of controls, randomization or comparisons
- Heterogeneous populations

**Dose:** 25-50 IU/kg

These organizations recommend PCC for warfarin-associated bleeding

- AHA/ASA
- European Stroke Organization
- Australasian Society of Thrombosis and Haemostasis
- Canadian Advisory Committee on Blood and Blood Products

Question #3: Which of the following PCC’s are FDA-approved for reversing life-threatening bleeding associated with warfarin?

A. Profilnine SD - 3 factor
B. Feiba NH - 3 factor “activated”
C. Kcentra - 4 factor
D. None of the above

Suggested Protocol

**In life-threatening bleeding, on warfarin**

- Vitamin K 10mg IV + Kcentra
  - INR 2-4, give 25U/kg
  - INR 4-6, give 35U/kg
  - INR> 6, give 50U/kg
- B. If hx of HIT: Profilnine 50IU/kg
- C. If blood product contraindicated...
  - Consider rFVIIA 1-2mg (off-label)

Kcentra Cost

- 70 kg: 25IU = $2363
- 70 kg: 50IU = $4725
What about bleeding associated with NOAC's?

Only anectodal, animal models and small human (healthy) volunteer studies

PCC's may be useful

Consider hemodialysis for dabigatran (not protein bound)

April 7, 2014

Dabigatran (Pradaxa) gains FDA approval for DVT/PE treatment

Dabigatran versus Warfarin in the Treatment of Acute Venous Thromboembolism. RE-COVER Study, NEJM, 2009

<table>
<thead>
<tr>
<th>Method</th>
<th>Dabigatran</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>After 9 days of parenteral anticoagulation</td>
<td>2.4%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td>1.6%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Bleeding</td>
<td>2.4%</td>
<td>2.1%</td>
</tr>
</tbody>
</table>

Question #4: Which of the following new oral anticoagulants is approved for the management of DVT/PE?

- A. dabigatran (Pradaxa)
- B. rivaroxaban (Xarelto)
- C. apixiban (Eliquis)
- D. A and B
- E. All of the above

Warning!!!!

After 5-10 days of parenteral anticoagulation

Question #4: Which of the following new oral anticoagulants is approved for the management of DVT/PE?

- A. dabigatran (Pradaxa)
- B. rivaroxaban (Xarelto)
- C. apixiban (Eliquis)
- D. A and B
- E. All of the above
**Question #4:** Which of the following new oral anticoagulants is approved for the management of DVT/PE?

- A. dabigatran (Pradaxa)
- B. rivaroxaban (Xarelto)
- C. apixiban (Eliquis)
- D. A and B
- E. All of the above

**Warning… Change in dosing!**

15mg BID x 3 weeks, then 20mg qd

**Study #1**

Rivaroxaban for Symptomatic Venous Thromboembolism
The EINSTEIN Investigators

NEJM 2010

**Methods:** open-label, non-inferiority study, followed 12 months

**Results:**
- Recurrent VTE: Enoxaparin + Warfarin (N=1718) 51 (3.0%) vs. rivaroxaban 15mg x 3wks, then 20mg qd (N=1731) 36 (2.1%), Hazard Ratio 95%CI (0.44-1.04)
- Bleeding: 8.1% vs. 8.1%

**Study #2**

Oral Rivaroxaban for the Treatment of Symptomatic Pulmonary Embolism
The EINSTEIN Investigators

NEJM 2012

**Methods:** open-label, non-inferiority study, followed 12 months

**Results:**
- Recurrent PE: Enoxaparin + Warfarin (N=2413) 44 (1.8%) vs. rivaroxaban 15mg x 3wks, then 20mg qd (N=2419) 50 (2.1%), Hazard Ratio 95%CI (0.75-1.68)
- Bleeding: 11.4% vs. 10.3%

**Rivaroxaban for VTE: who should not receive it?**

- Exclusion criteria:
  - Vena cava filters
  - CrCl < 30
  - Clinically significant liver dz, AST > 3X normal
  - Pregnancy
  - Potent CYP3A4 inhibitors (HIV drugs, rifampin, carbamazepine, etc.)

**Cancer patients??????**
LMWH vs. vitamin K antagonists for cancer associated VTE
• Methods: systematic literature review
• Results: 9 randomized studies, N= 1,908 patients
• Meta-analysis of 7 trials
  - Recurrent VTE: \( \text{RRR 0.47; (95\% CI 0.32 - 0.71)} \)
  - Mortality: No difference
  - Bleeding: No difference

With a NOAC (rivaroxaban), can you now treat PE as an outpatient?
• 2 randomized trials have suggested safety of outpatient therapy for PE
• 30-50% of PE are considered "low risk"/candidates for outpatient therapy

Outpatient Management of PE
• Methods: Open-label non-inferiority trial
  –19 ED’s (international)
  –Patients with acute, symptomatic PE
  • Low risk of death (PESI class I and II)
  –Enoxaparin + oral anticoagulation
• Measured outcomes:
  • Recurrent PE within 90 days
  • Major bleeding
  • Mortality
  Aujesky: Lancet 2011

PE Severity Index
• Age in years
• Male: 10
• Cancer: 30
• CHF: 10
• COPD: 10
• Pulse \( \geq 110 \): 20
• SBP < 100: 30*
• RR \( \geq 30 \): 20
• T < 36 C: 20
• Altered mental status: 60
• O2 sat < 90%: 20*

30-day mortality rates
• Class I - < 65 points 0 - 1.6%
• Class II - 65-85 1.7 - 3.5%
• Class III - 86-105 3.2 - 7.1%
• Class IV - 106-125 4.0 - 11.4%
• Class V - > 125 10.0 - 24.5%

Add up the points
Severity Class I: < 65 points
Severity Class II: 66 - 85 points

Aujesky: Lancet 2011
Outpatient Management of PE

• Results
  – 171 outpatients, 168 inpatients
  – OP vs. IP
    • Recurrent PE: 1 (0.6%) vs. 0
      – ****Upper 95% CI 2.7%
    • Major bleeding @ 90 ds: 3 (1.8%) vs. 0
      – ****Upper 95% CI 4.5%
    • Death: 1 (0.6%) in both groups
    • Mean LOS: 0.5 vs. 3.9 days

Aujesky: Lancet 2011

Inpatient vs. Outpatient PE care

• How many patients would qualify?
  470/1543 (30%)

Inpatient vs. Outpatient PE care

• Excluded from trial:
  – O2 sat < 90%, pO2 < 60
  – BP sys < 90
  – Chest pain requiring opioids
  – Active bleeding
  – Psychosis/dementia
  – Platelets < 75,000
  – CrCl < 30 mL
  – Weight > 150 kg
  – HIT or allergy to heparins
  – INR > 2.0
  – Barriers to follow up (e.g., Substance abuse)/imprisonment
  – Pregnancy
  – CVA < 10 days or GI bleed < 14 days

+ PESI Score

Conclusions

• Anticoagulation is underutilized and beneficial in patients with Afib.
• The NOAC’s may provide some advantages and disadvantages compared to warfarin
• Be aware of the various dosing issues involving the NOAC’s (one size does not fit all).
• If you are going to prescribe a NOAC, you must make certain your patient can afford it and be compliant.

Thank you for your time and consideration!!!

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