New Oral Anticoagulants and Other Updates

Tracy Minichiello, M.D.
Associate Professor of Medicine
Chief, SF VA Anticoagulation & Thrombosis Service

Case

65 yo man with HTN & CHF is found on routine exam to be in AFIB. His meds include ASA, metoprolol, statin and ACE. He has normal renal function. What regimen will you suggest for stroke prevention?

1. ASA alone
2. ASA plus clopidigrel
3. Warfarin
4. Dabigatran
5. Rivaroxaban

New Oral Anticoagulants

Warfarin
- Need for frequent monitoring
- Myriad of drug interactions
- Interaction with alcohol
- Requirement for dietary stasis
- Fluctuating INR is the norm

New Agents
- No lab testing required
- Few drug interactions
- Activity independent of vitamin k – no food drug interactions
- More predictable dose effect

New Oral Anticoagulants

Ansell, J. Hematology

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New Oral Anticoagulants

<table>
<thead>
<tr>
<th>Approval status</th>
<th>Dabigatran (Pradaxa)</th>
<th>Rivaroxaban (Xarelto)</th>
<th>Apixaban (Eliquis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonvalvular AFIB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonvalvular AFIB/DVT prevention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>June 2012?</td>
<td></td>
<td></td>
<td></td>
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</table>

MOA

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran (Pradaxa)</th>
<th>Rivaroxaban (Xarelto)</th>
<th>Apixaban (n/a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>antiXa</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>antiXa</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Renal metabolism

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran (Pradaxa)</th>
<th>Rivaroxaban (Xarelto)</th>
<th>Apixaban (n/a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>80%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-60%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

New Oral Antithrombotics

<table>
<thead>
<tr>
<th>Action</th>
<th>Dabigatran (Pradaxa)</th>
<th>Rivaroxaban (Xarelto)</th>
<th>Apixaban (n/a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1/2 hours</td>
<td>12-17</td>
<td>5-9</td>
<td>8-15</td>
</tr>
<tr>
<td>CYP3A4*</td>
<td>--</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>pGP</td>
<td>Yes</td>
<td>Yes</td>
<td>--</td>
</tr>
<tr>
<td>Antidote</td>
<td>None</td>
<td>None</td>
<td>none</td>
</tr>
<tr>
<td>monitoring</td>
<td>ECT, TT, PTT</td>
<td>PT</td>
<td>Anti Xa</td>
</tr>
</tbody>
</table>

RE-LY- DABIGATRAN v WARFARIN FOR STROKE PREVENTION IN AFIB

Connolly SJ et al. NEJM 2009

RE-LY Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>DABI 150% per yr</th>
<th>WARF % per yr</th>
<th>RR (95% CI)</th>
<th>NNT or NNH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke/SEE (1° Endpt)</td>
<td>1.11</td>
<td>1.69</td>
<td>0.66* (0.53-0.82)</td>
<td>NNT=172</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>3.11</td>
<td>3.36</td>
<td>0.93 (0.81-1.07)</td>
<td>N/A</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>1.51</td>
<td>1.02</td>
<td>1.5* (1.19-1.89)</td>
<td>NNH=204</td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>0.3</td>
<td>0.74</td>
<td>0.4* (0.27-0.6)</td>
<td>NNT=227</td>
</tr>
<tr>
<td>Myocardial infarction (MI)</td>
<td>0.81</td>
<td>0.64</td>
<td>1.27 (0.94-1.71)</td>
<td>N/A</td>
</tr>
</tbody>
</table>
ANALYSIS OF REPLY TRIAL-TTR

Wallentin, L Lancet 2010

TTR <57%

TTR 57-65%

TTR 65-72%

TTR >72%

Dabigatran : Drug Interactions

- A substrate of p-glycoprotein
- Inducers may decrease dabigatran levels (rifampin), St Johns wort AVOID
- Inhibitors could theoretically increase dabigatran (amio, dronedarone, ketoconazole, quinidine) USE CAUTION

Dronedarone / Ketoconazole & CrCl 30-50: 75 mg twice daily

Rising Concerns....

Stop The Bleeding: FDA Probes Pradaxa Deaths

505 reports over 20% hem CVA age 80

More Concerns.....
MI/ACS with Dabigatran

<table>
<thead>
<tr>
<th>Study</th>
<th>Dabigatran No.</th>
<th>ACS &amp; Stat</th>
<th>Control No.</th>
<th>ACS &amp; Stat</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-BIDASSAO 2007</td>
<td>13</td>
<td>2206</td>
<td>0</td>
<td>1130</td>
<td>0.71 (0.63-0.80)</td>
</tr>
<tr>
<td>RE-MOSS 2007</td>
<td>18</td>
<td>1572</td>
<td>4</td>
<td>608</td>
<td>1.26 (0.95-1.69)</td>
</tr>
<tr>
<td>PETAL 2007</td>
<td>2</td>
<td>443</td>
<td>0</td>
<td>78</td>
<td>0.79 (0.44-1.43)</td>
</tr>
<tr>
<td>RE-CYCLE 2008</td>
<td>175</td>
<td>1196</td>
<td>63</td>
<td>3958</td>
<td>1.39 (1.04-1.88)</td>
</tr>
<tr>
<td>RE-DARWIN 2008</td>
<td>4</td>
<td>1209</td>
<td>2</td>
<td>1294</td>
<td>1.20 (0.93-1.54)</td>
</tr>
<tr>
<td>RE-CONFIRM 2011</td>
<td>52</td>
<td>1458</td>
<td>4</td>
<td>313</td>
<td>1.70 (0.86-3.39)</td>
</tr>
<tr>
<td>RE-MOBILE 8.2011</td>
<td>1</td>
<td>1009</td>
<td>1</td>
<td>1002</td>
<td>0.90 (0.58-1.38)</td>
</tr>
</tbody>
</table>

RR ↑ 33% AR ↑ 0.27%


ROCKET AF- Rivaroxaban v Warfarin in AFIB

-20mg QD
-Non Inferior to warfarin
-Major bleeding same
-↑ risk fatal & intracranial bleed

• ↑ risk GI bleed
• CHADS2 score- 3-3.5
• TTR 55%
• No effect of TTR on efficacy
• ↑ CVA when back to warfarin


Patient Selection-Cautions

Dabigatran
- History of GI bleeding-unclear source
- Age > 80
- Concomitant therapy with P-gp inhibitors
- At risk for renal function deterioration

Rivaroxaban
- History of GI bleeding-unclear source
- Concomitant therapy with P-gp inhibitors/CYP3A4 inhibitors
- At risk for renal function deterioration

Case

You decide to start your patient with new AFIB on dabigatran or rivaroxaban because he will be unable to get INR draws regularly due to his work/travel schedule.
**Starting Dabigatran/Rivaroxaban**

- Baseline labs-CBC, Cr, PTT/PT, LFTS
- Patient education-med guide
- Monitoring
  - Adherence
  - Adverse effects-GI
  - Bleeding/Stroke
  - +/-Labs

**Dabigatran : Prescribing Info**

- Indicated for stroke prevention in non-valvular AFIB
- 150 mg po twice daily; 75 mg po twice daily if CrCl 15-30 ml/min or on dronaderone and CrCL< 50 ml/min.
- Not recommended if CrCl< 15ml/min
- Capsule cannot be broken or chewed

**Dabigatran : Baseline labs**

- CBC
- Cr
- PTT/PT
- LFTS

**Patient education-med guide**

**Monitoring**

- Adherence
- Adverse effects-GI
- Bleeding/Stroke
- +/-Labs

**Follow up**

- 2 weeks
- 1 month
- 3 months
- continue monthly check in

**Rivaroxaban-Prescribing Info**

- Dose 20 mg q.h.s @ meal if CrCl> 50 ml/min
- Dose 15 mg q.h.s @ meal if CrCl 15-50ml/min
  - (beware CYP 3a4-dilt, amio verapamil, dronaderone)
- When Δ from warfarin start rivaroxaban when INR is 3.0
- When Δ from rivaroxaban to warfarin consider stopping rivaroxaban, starting parenteral agent and warfarin together

**Case**

Which is a good candidate for dabigatran

1. 66 yo w/ AFIB, ESRD, poorly controlled INR admitted with TIA
2. 66 you with AFIB & MVR
3. 83 yo 50 kg woman with CRI (Cr Cl 35 ml/min) with new AFIB
4. none of the above
ARISTOTLE: Apixaban versus Warfarin in Patients with Atrial Fibrillation


Granger CB, N Engl J Med

September 15, 2011

ARISTOTLE: APIXABAN V WARFARIN in AFIB

5mg BID

20% prior CVA↓

stroke 21%

major bleed 13%

death 11%


AVERROES-Apixaban v ASA in AFIB

Connolly SJ et al. NEJM 2011

New Comers v Warfarin- Stroke

DABIGATRAN RIVAROXABAN APIXABAN

↓ stroke X → X

↓ INTRACRANIAL BLEED X X X

↓ MORTALITY X X X

BLEEDING ↑ GI bleeding ↑ GI bleeding ↓ any cause

DRUG INTERACTIONS Least-pGP pGp & CYP3A4 CYP 3A4

NUISANCE Side effects 10-20% dyspepsia

DOSING BID QD BID

METABOLISM 80% RENAL 60% RENAL 25% RENAL
**QUIZ**

Anticoagulation should be considered for spontaneous superficial thrombophlebitis of the lower extremity

1. true
2. false

**NEW CHEST GUIDELINES**

“In patients with superficial vein thrombosis of the lower limb of at least 5cm we suggest use of prophylactic doses of LMWH/fonda for 45 days” (2B)

**QUIZ**

A 60 year old man with hyperlipidemia & hypertension on atenolol, a statin and ASA develops a PE and is started on anticoagulation. You:

1. stop his aspirin now that he is on warfarin due to concerns of increased risk of bleeding
2. continue ASA for primary prophylaxis

**NEW CHEST GUIDELINES**

“For patients taking warfarin we suggest AVOIDING concomitant antiplatelet therapy except where benefit is likely to be greater than harm: valves, ACS, stents, CABG” (2C)
NEW CHEST GUIDELINES

- AFIB CHADS2=0 no therapy (2B); CHADS ≥1 anticoagulant (1B); if unsuitable for AC use asa+clopidigrel rather than asa (1B)

- "For patients with AF we suggest dabigatran 150 mg BID rather than warfarin" (2B)

CASE

A 55 yo man with no PMHx was diagnosed with PE 3 months ago, treated with LMWH→warfarin. He has had no bleeding complications thus far. His work up for cancer is unrevealing.

How long would you recommend he stay on anticoagulation?

1. 3 months
2. 6 months
3. 12 months
4. indefinitely
**Risk of VTE Recurrence After Cessation of VTE**

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>1st yr</th>
<th>Next 5 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distal DVT</td>
<td>3% (6%)</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>Distal DVT (minor-transient)</td>
<td>5-6%</td>
<td>15%</td>
</tr>
<tr>
<td>Distal DVT (unprovoked)</td>
<td>At least 10%</td>
<td>30%</td>
</tr>
<tr>
<td>Recurrent</td>
<td>&gt; 10%</td>
<td>&gt; 30%</td>
</tr>
</tbody>
</table>

Kearon, Blood 2005

**Guidelines for Duration of Anticoagulation for VTE**

<table>
<thead>
<tr>
<th>Indication</th>
<th>8th ACCP guidelines 2012</th>
<th>AHA 2010</th>
<th>ASH recommendations 2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>First episode of VTE secondary to a transient risk factor</td>
<td>3 months (Grade 1B)</td>
<td>3 months (Class I Level A)</td>
<td>3 months</td>
</tr>
<tr>
<td>First episode of idiopathic (unprovoked) VTE</td>
<td>At least 3 months, prefer long-term treatment if risk/benefit ratio ok (Grade 2B).</td>
<td>At least 6 months, consider indefinite (Class I Level A)</td>
<td>6 months</td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td>Long term (Grade 1B)</td>
<td>Indefinite Class I Level A,</td>
<td>Long term if APLS, AT deficiency or recurrence</td>
</tr>
</tbody>
</table>


**Residual Vein Thrombosis & VTE Recurrence**

- No RVO 1%
- RVO-AC 19%
- RVO-AC 27%


**Management Trial Using D-dimer Results to Determine Duration of Anticoagulation**

- Table 2: Main Outcomes (Intention-to-Treat Analysis)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Normal D-dimer Level (N=180)</th>
<th>Abnormal D-dimer Level without Anticoagulation (N=274)</th>
<th>Abnormal D-dimer Level with Anticoagulation (N=274)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of recurrent venous thromboembolism</td>
<td>No. of events/person-py</td>
<td>No. of events/person-py</td>
<td>No. of events/person-py</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>19</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Deep vein thrombosis with pulmonary embolism</td>
<td>3</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Isolated pulmonary embolization</td>
<td>2</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Major bleeding episode</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

D-Dimer to Predict Recurrent VTE - Meta Analysis & Systematic Review

- Systematic Review
  - D-dimer + 8.9%
  - D-dimer – 3.5%

Vienna Prediction Model for Recurrent VTE

Clinical Decision Rule

- Clinical predictors
  - Leg red or swollen or hyperpigment 5-7 mos after event
  - D-dimer >250 ug/L on AC
  - BMI >30kg/m2
  - Age > 65
- Female patients with 0-1 risk factor had recurrence risk of 1.6%: ≥2 = 14%

Clinical presentation predicts likelihood and type of recurrence

- Distal (calf vein thrombosis)
  - Low risk of recurrence/PE
- Proximal- nearly 5 fold increased recurrence risk over distal
- PE vs. DVT
  - Patients presenting with PE are 3x more likely to suffer recurrent PE than those presenting with DVT


Eichinger, Circulation 2010

Rodgers et al CMAJ August 2008

Baglin T etJ Thromb Haemost. 2010
**Impact of Thrombophilia on Recurrence Risk**

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Recurrence of VTE per Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>total</td>
<td>2.6%</td>
</tr>
<tr>
<td>1 thrombophilia defect</td>
<td>2.5%</td>
</tr>
<tr>
<td>Initial VTE provoked</td>
<td>1.8%</td>
</tr>
<tr>
<td>Initial VTE unprovoked</td>
<td>3.3%</td>
</tr>
<tr>
<td>Unprovoked with thrombophilia</td>
<td>3.4%</td>
</tr>
<tr>
<td>Unprovoked without thrombophilia</td>
<td>3.2%</td>
</tr>
</tbody>
</table>

- Christiansen JAMA 2005
- Shulman Amer J Med 1998

**Impact of Acute Thrombosis & Anticoagulation on Thrombophilia Testing**

<table>
<thead>
<tr>
<th>Test</th>
<th>Acute VTE</th>
<th>Heparin</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticardiolipin antibodies</td>
<td>May be elevated</td>
<td>no effect</td>
<td>no effect</td>
</tr>
<tr>
<td>Lupus anticoagulant</td>
<td>May be prolonged</td>
<td>prolonged</td>
<td>prolonged</td>
</tr>
<tr>
<td>Protein C, S</td>
<td>decreased</td>
<td>No effect</td>
<td>decreased</td>
</tr>
<tr>
<td>Antithrombin level</td>
<td>decreased</td>
<td>decreased</td>
<td>increased</td>
</tr>
<tr>
<td>Factor VIII level</td>
<td>increased</td>
<td>no effect</td>
<td>no effect</td>
</tr>
</tbody>
</table>

**Individual Bleeding Risk on Anticoagulation**

- Age > 75
- Previous GI bleed with no reversible cause
- Previous bleed on warfarin
- Renal/hepatic failure
- Antiplatelet therapy
- Cancer

- Case fatality rate VTE
  - Case fatality rate of recurrent VTE highest in 1st 3-6 months - 11%
  - Case fatality rate of recurrent VTE decreases after 3-6 months to 3.6%

- Carrier Ann Intern Med 2010

**Duration of Anticoagulation Unprovoked VTE**

- If DVT Get u/s and measure d-dimer. If d-dimer up continue AC