Anticoagulation Strategies: Are New Oral Anticoagulants Ready for Prime Time?

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Disclosures

• I will be speaking on the off-label use of dabigatran for treatment of DVT/PE
• I will be speaking on the off-label use of apixaban for treatment of DVT/PE
• I will be speaking on the off-label use of the new oral anticoagulants for DVT/PE prophylaxis
D. V. Tea is a 52 yr old man newly diagnosed with DVT / PE after trip from New Zealand. He had colon cancer with colectomy 5 years ago. He has GERD and creatinine clearance about 40. He was started on enoxaparin and warfarin.
I hate shots and Enoxaparin costs as much as my monthly mortgage. What choices do I have for anticoagulation. My sister is on a new anticoagulant for afib – can I take the new pill?
ANTICOAGULATION - BALANCE THE RISK

• Evidence-based guidelines outline what works for a population, take years to develop, need tweaking with age and accumulation of new data
• Doctors use guidelines to determine what works best for the patient, but guidelines lag behind current needs
• Treatment decisions require knowledge of evidence, patient specific risk assessment and patient understanding and acceptance
THE “IDEAL” ANTICOAGULANT

• Oral, once daily fixed dose
• Rapid onset and offset of action
• Predictable pharmacokinetics (PK), and pharmacodynamics (PD)
• Low propensity for food and drug interactions
• No side effects or organ toxicities
• Wide therapeutic window
• No need for monitoring
• Rapidly reversible if bleeding
# ANTICOAGULANTS—Approved US

<table>
<thead>
<tr>
<th>DRUG</th>
<th>PARENTERAL</th>
<th>ORAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin K antagonist (Inhibits II, VII, IX, X, &amp; PC, PS)</td>
<td>Warfarin – All indications</td>
<td>Warfarin – All indications (grandfathered)</td>
</tr>
<tr>
<td>Indirect inhibitors of IIa and/or Xa (require ATIII)</td>
<td>Heparin – All indications</td>
<td>NONE</td>
</tr>
<tr>
<td></td>
<td>anti-IIa = anti-Xa (grandfathered)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LMWHs – varies by drug</td>
<td></td>
</tr>
<tr>
<td></td>
<td>anti-Xa &gt; anti-IIa activity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fondaparinux – anti-Xa only</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1. Prevent DVT/PE TKA/THA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Treatment DVT/PE</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Acute coronary syndrome</td>
<td></td>
</tr>
</tbody>
</table>
## ANTICOAGULANTS—Approved US

<table>
<thead>
<tr>
<th>DRUG</th>
<th>PARENTERAL</th>
<th>ORAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct inhibitors Xa</td>
<td>NONE</td>
<td><em>RIVAROXABAN</em> — 1. Prevent DVT/PE - TKA/THA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Prevent stroke nonvalve afib</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Treatment of DVT/PE</td>
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<tr>
<td>Direct inhibitors IIa</td>
<td>Argatroban</td>
<td><em>APIXABAN</em> — Prevent stroke nonvalve afib</td>
</tr>
<tr>
<td></td>
<td>Bivalirudin (Lepirudin – discontinued)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>DABIGATRAN</em> — Prevent stroke nonvalvular afib</td>
</tr>
<tr>
<td></td>
<td>Apixaban (anti-Xa)</td>
<td>Rivaroxaban (anti-Xa)</td>
</tr>
<tr>
<td>----------------------</td>
<td>--------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td><strong>T ½</strong></td>
<td>10-14 hours</td>
<td>5-9 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(9-13 hr elderly)</td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td>~27%</td>
<td>~66 %</td>
</tr>
<tr>
<td><strong>Reversible</strong></td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td><strong>Monitor</strong></td>
<td>anti-Xa?</td>
<td>anti-Xa?</td>
</tr>
<tr>
<td><strong>Peak effect</strong></td>
<td>3-4 hours</td>
<td>2-4 hours</td>
</tr>
<tr>
<td><strong>Absorbed</strong></td>
<td>Colon</td>
<td>Stomach</td>
</tr>
</tbody>
</table>
Dabigatran (Pradaxa)–Oral Antithrombin
Dabigatran Mechanism of Action

Dabigatran etexilate

DABIGATRAN

Inhibits

THROMBIN (free)

Inhibits

THROMBIN

CLQT

MICROSOMAL CARBOXYLESTERASES
(plasma & liver)

3-7% Bioavailable with acid

80% eliminated
INDICATION

Dabigatran is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.
Absorption issues

- Peak level occurs 1-2 hrs post dose.
- PRADAXA may be administered with or without food.
- The oral bioavailability of dabigatran **INCREASES** by 75% when the pellets are taken without the capsule shell.
- PRADAXA capsules SHOULD NOT BE BROKEN, CHEWED, OR OPENED BEFORE ADMINISTRATION.
- Capsules exposed to air only good for about 3 MONTHs,
Elimination issues

- Renal clearance is 80%.
- The half-life of dabigatran in healthy subjects is 14 to 17 hours, > 24 hrs CrCl < 30 mL/min.
- FDA approved 75mg twice daily for creatinine clearance 15-30mL/min BASE ON ESTIMATE not clinical trial. Recommend avoid in elderly with CrCl < 30.
- Drugs to avoid (P-gp inducers) – rifampin
- Drugs that DO NOT EFFECT DOSE (P-gp inhibitors)
  - Ketoconazole
  - Verapamil
  - Amiodarone
  - Quinidine
  - Clarithromycin
- Results cannot be extrapolated to other P-gp inhibitors
At therapeutic dose, dabigatran prolongs aPTT, ECT (ecarin clot time), and TT (thrombin time).

- ONLY ECT SHOWS LINEAR EFFECT.
- Dilute TT may be helpful to assess effect of drug
- May be used to “trend” or determine “some/none”
- More specific assays in development but not ready for prime time.

TAKE HOME MESSAGE
Do NOT check PT or PTT – Will Confuse not Help.
PRADAXA has higher GI adverse events vs warfarin
21% of patients in trials stopped drug due to GI effects
GI effects include abdominal / epigastric pain/discomfort, GERD, esophagitis, erosive gastritis, gastric hemorrhage, hemorrhagic gastritis, hemorrhagic erosive gastritis, and GI ulcer all reported
Likely due to tartartic acid in capsule to aid absorption not endogenous stomach acid

GASTROINTESTINAL ADVERSE REACTIONS

TAKE HOME
PPI/antacid may or may not help, doubling dose increases cost
Bleeding events (per 100 pt-years) 18,113 pts with atrial fibrillation

<table>
<thead>
<tr>
<th></th>
<th>Pradaxa</th>
<th>Warfarin</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized patients</td>
<td>6076</td>
<td>6022</td>
<td></td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>38 (0.3)</td>
<td>90 (0.8)</td>
<td>0.41</td>
</tr>
<tr>
<td>Life-threatening</td>
<td>179 (1.5)</td>
<td>218 (1.9)</td>
<td>0.80</td>
</tr>
<tr>
<td>Major bleeds</td>
<td>399 (3.3)</td>
<td>421 (3.6)</td>
<td>0.93</td>
</tr>
<tr>
<td>Any bleed</td>
<td>1993 (16.6)</td>
<td>2166 (18.4)</td>
<td>0.91</td>
</tr>
</tbody>
</table>

Post-marketing suggests greater bleeding incidence vs under-reporting of warfarin bleeding
AFIB – FDA approval of 150 mg bid dose, n = 18,111
- Re-LY: 150mg or 110mg bid vs warfarin. Event prevention - 150 mg superior p< 0.001; bleeding non-inferior to warfarin (3.1 vs 3.3%)

Acute DVT/PE Treatment – NOT FDA approved – n = 2564
- RE-COVER: 150 mg bid vs warfarin. VTE - warfarin 2.1 vs dabigatran 2.4%, p< 0.001 for non-inferiority; bleeding- warfarin 1.9 vs 1.6% dabigatran, non-inferior

Postop THA – NOT FDA approved
- RE-NOVATE I & II – 150 or 220 mg daily vs Enoxaparin 40 mg daily. Events – 150 mg 8.6%, 220mg 6%, enox 6.7% - non-inferior; bleeding, non-inferior

Postop TKA – NOT FDA approved
- RE-MODEL (non-inferior p<.003) & RE-MOBILIZE (inferior p=.02; bleeding non-inferior)
RE-COVER: Acute, symptomatic proximal DVT or PE (N = 2546)

- Dabigatran etexilate 150 mg twice daily vs. warfarin INR 2.0 to 3.0

- 6 months Dabigatran is as effective as warfarin for prevention of recurrent VTE - Absolute difference 0.4%, 95% CI 0.8-1.5 p<0.001
  - Dabigatran etexilate 150 mg twice daily (2.4%)
  - Dose adjusted warfarin (2.1%)

Bleeding:

- Risk of major bleeding was similar (HR 0.82, 95% CI 0.45 to 1.48)
- Dabigatran etexilate 150 mg twice daily (1.6% major, 16.1% any)
- Warfarin (60% TTR) (1.9% major, 21.9% any)
Average age is 55 – is this applicable
Only treated 6 months, longer term excluded
Median weight 85kg, (38-175kg dabigatran) (39-161kg warfarin) so little info on weight extremes
All patients received parenteral anticoagulation first; therefore, not studied as initial treatment
95% white race
90% had CrCl >50
No report on treatment of bleeding patients

TAKE HOME
Caution using for DVT/PE – too many unknowns
SPECIAL CONSIDERATIONS

- NOT reversible – use local hemostatic measures.
- ALL clot based coag labs may be abnormal – LAC, fibrinogen, Protein C/S, ATIII
- DO NOT BREAK CAPSULE - NO G/J tube
- Packed in acid to absorb better, will reducing stomach acid help with GERD??
- Post marketing suggests more bleeding
  - Age? More susceptible to GI bleeding??
  - Renal? Is it appropriate at CrCl < 30 mL / min
  - Comorbidities?
  - Cracking capsule?
Rivaroxaban (Xarelto): Oral Factor Xa Inhibitor
RIVAROXABAN INDICATIONS

• Prevent DVT and PE with knee or hip arthroplasty (Jul 2011)
• Prevent stroke and systemic emboli in nonvalvular atrial fibrillation (Oct 2011)
• Treatment of DVT/PE (Nov 2012)
• Reduction in the risk of recurrence of DVT and of PE – continued after 6-12 mon
Overview of Characteristics

- Rapid onset of action 1 hr, peak 2-4 hrs
- Half life 5-9 hrs at steady state, longer in elderly
- Elimination: Renal(66%)
- Dose 20 mg/d CrCl > 50, 15mg/d CrCl 30-50, NOT recommended CrCl < 30 and contraindicated CrCl < 15
- FOOD IMPROVES absorption (66vs76%) for 20mg
- Absorbed in stomach, should not be given by J-tube
- Bioavailability high – 80-100% for 10mg dose, 70-80 for 20 mg dose
- No dosage adjustment with mild liver impairment but not recommend for moderate / severe liver impairment
MONITORING

- May be monitored with anti-Xa level BUT therapeutic range not established, cannot use heparin ranges
- PT and PTT prolong but not reliable for dose adjustment
- Therapeutic range or goal for PT PTT not published.

TAKE HOME MESSAGE
May be easier to monitor in kidney patients/weight extremes/ bleeding situation
XARELTO DRUG INTERACTIONS

- Drugs DECREASE effect (P-gp & CYP3A4 inducers)
  - Carbamazepine
  - Phenytoin
  - Rifampin
  - St John’s wort

- Drugs that INCREASE effect (CYP3A4/P-gp inhibitors)
  - May still use – Clarithromycin/erythromycin
  - Avoid - Ketoconazole/itraconazole, Ritonavir lopinavir/ritonavir indinavir/ritonavir, conivaptan
  - IF CONCURRENT RENAL – limit diltiazem, erythromycin/azithromycin, verapmil, quinidine, ranolazine, dronedarone, amiodarone, and felodipine
RIVAROXABAN CLINICAL TRIALS

➢ A-fib – ROCKET AF, FDA approved
  ✓ 20 mg daily (15 mg CrCl < 30-49) vs warfarin
  ✓ Events: warfarin 2.4% vs rivaroxaban 2.1%, p< 0.001
  ✓ Bleeding: warfarin 14.5%/y vs rivaroxaban 14.9%, p=.44

➢ THA/TKA – RECORD 1 & 2 & 3 & 4, FDA approved
  ✓ 1-3 10 mg daily vs enoxaparin 40 mg qd; 4 enox 30 mg bid
  ✓ Events: P< 0.001 for superiority of rivaroxaban in all
  ✓ Bleeding: < 1% in all, p<.18, not significant, p< .77

➢ Medical prophylaxis – NOT FDA approved
  ✓ 10 mg vs 40 mg enox; event p=.0025 non-inf; bleeding
    MORE bleeding with rivaroxaban p < .001
RIVAROXABAN VTE TREATMENT TRIALS

➢ Treatment of acute DVT (EINSTEIN DVT study)
  ✓ 15mg bid X 3wk, 20 mg daily vs enox-warfarin INR 2-3
  ✓ Events: p<.001 for non inferiority of rivaroxaban
  ✓ Bleeding: 8.1% for both, p=.77

➢ Treatment of acute PE (EINSTEIN PE Study)
  ✓ 15mg bid X 3wk, 20 mg daily vs enox-warfarin INR 2-3
  ✓ Events: p<.003 for non inferiority of rivaroxaban
  ✓ Bleeding: 11.4% warfarin vs 10.3% warfarin p=.23

➢ Continued treatment DVT / PE (EINSTEIN-EXT)
  ✓ 20 mg daily for additional 6-12 months AFTER initial treat
  ✓ Events: 7.1% placebo vs 1.3% riva; Bleeding 0.7% p=.11
## Non-Bleeding Adverse Events

<table>
<thead>
<tr>
<th>System/Organ– Adverse Reaction</th>
<th>Xarelto (N= 4487)</th>
<th>Enoxaparin (N=4524)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injury, procedural complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Wound secretion</td>
<td>125 (2.8%)</td>
<td>89 (2.0%)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Pain in extremity</td>
<td>74 (1.7%)</td>
<td>55 (1.2%)</td>
</tr>
<tr>
<td>- Muscle spasm</td>
<td>52 (1.2%)</td>
<td>32 (0.7%)</td>
</tr>
<tr>
<td>Nervous system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Syncope</td>
<td>55 (1.2%)</td>
<td>32 (0.7%)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Pruritis</td>
<td>96 (2.1%)</td>
<td>79 (1.8%)</td>
</tr>
<tr>
<td>- Blister</td>
<td>63 (1.4%)</td>
<td>40 (0.9%)</td>
</tr>
</tbody>
</table>
Use 10 mg dose for short term prophylaxis ie, travel, short-term immobility (OFF LABEL)
First line for DVT and increasingly PE if kidney good
Most common reason patients stop Xarelto
  ✓ Headaches
  ✓ Muscle aches and pains
  ✓ One neurologic diplopia, fatigue, better off drug
Bleeding – menorrhagia maybe more common?
Anti-Xa levels helpful to trend anticoagulant effect, ie present/gone, falling/rising
Haven’t used with CrCl < 35ish
APIXABAN (Eliquis): Oral Factor Xa Inhibitor
APIXABAN INDICATIONS

Prevent stroke and systemic emboli in non-valvular atrial fibrillation
Overview of Apixaban Characteristics

- Bioavailability approximately 50% - not effected by food
- Maximum concentrations 3-4 hours after oral intake
- Prolonged absorption and short clearance half-life result in apparent half-life ~12 hr = twice a day dose
- Dual modes of elimination: feces and renal (27%), recent FDA approval for use in renal insufficient updated package insert on the way
- Absorbed distal small bowel/colon – feeding tube OK
- Avoid in moderate-severe liver dysfunction
May be monitored with anti-Xa level BUT therapeutic range not published

PT and PTT prolong but highly variable

PT PTT should not be used to monitor

TAKE HOME MESSAGE

May be able to monitor ONLY with anti-Xa assay
APIXABAN DRUG INTERACTIONS

- **Drugs DECREASE effect (P-gp & CYP3A4 inducers)**
  - Carbamazepine
  - Phenytoin
  - Rifampin
  - St John’s wort

- **Drugs that INCREASE effect (CYP3A4/P-gp inhibitors)**
  - Decrease dose to 2.5 mg twice daily
  - Drugs include: Ketoconazole/itraconazole, Ritonavir/lopinavir/ritonavir indinavir/ritonavir, clarithromycin
  - IF already on 2.5mg dose, avoid co-administration with above drugs
The recommended dose of ELIQUIS is 2.5 mg twice daily in patients with any 2 of the following characteristics:

- age ≥80 years
- body weight ≤60 kg
- serum creatinine ≥1.5 mg/dL

TAKE HOME MESSAGE
May be better for renal impaired
APIXABAN CLINICAL TRIALS

- A-fib – AVERROES and ARISTOTLE, FDA approved
  - AVERROES - 5 mg bid vs aspirin – terminated apixaban better
  - ARISTOTLE – 5 mg bid vs warfarin.
    - EVENT: apixaban non-inferiority p < 0.001, superiority p = 0.01
    - Bleeding: apixaban 2.1% vs warfarin 3.1%, p< 0.001

- THA/TKA – ADVANCE 1 & 2 & 3, not FDA approved
  - A1- 2.5 mg bid vs enox 30 mg bid; A2&3 - enox 40 mg daily
  - Events: A1 P< 0.06 non-inferior, A2 p < 0.001 superior, A3 p< 0.001 for superior. for A-1 for superiority of rivaroxaban in all
  - Bleeding: A1 apixaban 2.9%, enox 4.3% p=0.03; A2 apixaban 3.5%, enox 4.8% p=.09; A3 apixaban 4.8%, enox 5% p=.72
TREATMENT OF ACUTE VTE – off label

- 2 Phase III studies in DVT / PE
  - AMPLIFY-EXT published NEJM December 8, 2012
  - AMPLIFY published NEJM June 30, 2013
- For treatment of acute DVT/PE – apixaban 10 mg bid X 7 days then 5 mg BID VS LMWH / warfarin; EXT vs placebo
- Apixaban superior to warfarin bleeding risk
  - Warfarin 1.8% major bleeding
  - Apixaban 0.6% major bleeding
- Apixaban non-inferior for prevention of recurrence
- Patients with CrCl 25 mL/min enrolled, no drug
- Submitted to FDA December 2013
APIXABAN ADVERSE EVENTS

- Bleeding most common but less than or equal to comparator

- Other reported side effects
  - GI symptoms: nausea (3%), increase LFTs (<1%)
  - Reported at < 1%: syncope, rash, anaphylaxis
Prefer for patients with CrCl < 40
Prefer in higher risk bleeding patient
Use is patient intolerant to Rivaroxaban for DVT / PE treatment.
Anti-Xa levels helpful to trend anticoagulant effect, ie present/gone, falling/rising
Use for extended therapy after completion of treatment for DVT/PE at 2.5 mg bid (off label)
<table>
<thead>
<tr>
<th>The Ideal Anticoagulant</th>
<th>Eliquis</th>
<th>Pradaxa</th>
<th>Xarelto</th>
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<tbody>
<tr>
<td>Oral</td>
<td>Yes</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Rapid onset and offset of action</td>
<td>2-4 hr 24 hr</td>
<td>1-2 hr 24 hr?</td>
<td>2-4 hr 24 hr?</td>
</tr>
<tr>
<td>Predictable pharmacokinetics</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Predictable pharmacodynamics</td>
<td>Yes?</td>
<td>Yes?</td>
<td>Yes?</td>
</tr>
<tr>
<td>Low propensity of food and drug interactions</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Fixed dose</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Wide therapeutic window</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Monitoring required</td>
<td>No – available</td>
<td>No – not available</td>
<td>No – available</td>
</tr>
<tr>
<td>Easily reversible</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
</tr>
</tbody>
</table>
Direct Thrombin Inhibitors - Dabigatran

- Not reversible (similar to LMWH)
- FFP/PCC do NOT reverse but may replace clotting factors consumed with bleeding or “dilute” drug
- PCC/rFVIIa do NOT reverse but cause a “hypercoagulable state” that may clot bleeding site at risk of unwanted thrombotic event
- Antifibrinolytics do NOT reverse but may slow clot break down and slow bleeding
- Dabigatran may be dialysed but inefficient, time consuming and requires line
Direct anti-Xa Drugs

- Rivaroxaban and Abixaban are NOT reversible
- FFP/PCC/rFVIIa do NOT reverse but may have an effect on hemostasis as noted above
- Antifibrinolytics do NOT reverse but may stabilize clot at bleeding site
- Rivaroxaban and Apixaban are highly protein bound and unlikely to be dialyzable.
- Apixaban is less reliant on kidney for clearance, better choice in renal impaired.
- Apixaban shorter clinical effect.
For all 3 new drugs, hold 24 hours before minor procedures/low risk of bleeding and 48 hours for major/high risk of bleeding procedures. If kidney function marginal I add a day (except for apixaban). Holding >2-3 days risk of clot.

For rivaroxaban/apixaban may check anti-Xa level to make sure drug gone particularly for renal or high risk procedure.

Don’t use dabigatran if CrCl < 30, < 40 elderly

Age seems to slow clearance of all these drugs

Consider longterm low dose for prevention, ie 10 mg rivaroxaban/2.5 apixaban (off label)
Mr. Tea we recommend xarelto 15 mg once a day. We will start now as your INR is only 1.8 and your last dose of enox was 12 hours ago. Since you are missing your colon apixaban is not an option. Dabigatran not advisable due to your GERD. Any questions?
Tune in again for more
- Cascade of Caveats -
during the next COAG HOUR