“New Anticoagulants for the Treatment of Thromboembolism”

With a little subplot on superficial thrombophlebitis

Mark Crowther
Disclosures

- Advisory Boards in last 24 months
  - Pfizer, Alexion, Bayer, CSL Behring, Leo Pharma and others
- Slide preparation/educational materials
  - Pfizer, Octapharma, CSL Behring, Bayer
- Research funding
  - Leo Pharma, BI, Pfizer
- DSMB
  - Bayer, Daiichi-Sankyo
- Speakers Bureau
  - Bayer, Leo Pharma
- Endowed chair
  - Leo Pharma Chair in Thromboembolism at McMaster University
> To gain insight and knowledge of the new novel oral anticoagulants
> Understand the differences between efficacy and safety
> > When to use which new oral anticoagulant (patient type) and when to avoid their use
New agents

- More expensive than warfarin
- Cause more GI bleeding than warfarin
- Are more likely to be impacted by non-compliance than warfarin
- Have significant drug-drug interactions
- Are confusing
- Are no more effective than well controlled warfarin
- **SHOULD NOT BE USED IN PATIENTS WITH PROSTHETIC HEART VALVES**
New agents

• Are far easier to use than warfarin
• Reduce rates of intracerebral hemorrhage
• When used in the correct patient, at the correct dose, are associated with lower stroke rates
• Are probably preferred by patients
• Greatly simplify acute treatment of VTE
The ‘ideal’ anticoagulant

- Oral
- Rapid onset and offset of action
- Predictable PK and PD
- Low propensity for food and drug interactions
- Fixed doses
- Wide therapeutic window
- Reversible
- Monitoring not needed, but possible
Xa inhibitors

Bind to and inactivate factor Xa which is at the confluence of coagulation
• Rivaroxaban is the only novel agent approved for VTE treatment in Canada
Rivaroxaban (Xarelto)

- High bioavailability and rapid onset of action
- Half-life of up to 9 hours at steady state in healthy young subjects, and up to 12 hours in subjects aged >75 years
- Plasma concentrations and pharmacodynamic effects correlate closely
- Pharmacodynamic effects last for 24 hours after a single dose
- Low propensity for drug–drug interactions
- Fixed doses for all patients in phase III
- **Higher doses should be taken with food**

OMG… do I need to worry about drug interactions?

<table>
<thead>
<tr>
<th>Inhibitors of CYP 3A4 and P-gp</th>
<th>Ketoconazole and other “azole” drugs, lopinavir/ritonavir, clarithromycin, conivaptan, grapefruit</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP 3A4 and P-gp inducers</td>
<td>Rifampin, St. John's wort, phenytoin, carbamazepine, phenobarbitone</td>
</tr>
<tr>
<td>Enhanced hemorrhagic risk due to coincident anticoagulant effect</td>
<td>NSAIDs, antiplatelet agents, other oral anticoagulants, heparins and related compounds</td>
</tr>
</tbody>
</table>
Clinical use
Prevention of venous disease

• The best way to treat a VTE is to prevent it...
• Rivaroxaban has become the agent of choice for VTE prevention after orthopedic surgery in many jurisdictions
  – Probably better, cheaper, easier to use and preferred by hospitals compared with LMWH
If they are useful for orthopedic prophylaxis…

• Where else can we use them?
  – Medical prophylaxis?
  – Acute coronary syndromes?
Medical prophylaxis

- Magellan study

- The primary efficacy end point is a composite of asymptomatic proximal DVT detected by bilateral ultrasound, symptomatic DVT, non-fatal PE and VTE-related death

- The safety end points are major bleeding and clinically relevant non major bleeding
In the Prevention of VTE in Acutely ill Patients, Rivaroxaban Compares Favorably with Enoxaparin but Does Not Show a Consistent Net Clinical Benefit

- In the short-term (10 ± 4 days) evaluation, rivaroxaban achieved non-inferiority compared to enoxaparin [2.7% vs. 2.7%, p=0.0025] in the per-protocol population.

- Evaluated in the extended period (35 ± 4 days), rivaroxaban was superior to short-term enoxaparin (10 ± 4 days) followed by placebo, in the modified intent-to-treat (MITT) population [4.4% vs. 5.7%, respectively, RR 0.77, p=0.0211].


Rivaroxaban for thromboprophylaxis in acutely ill medical patients.

DVT treatment...

- LMWH
- Warfarin
- LMWH
- Dabigatran
- Rivaroxaban

Thrombus in the left common femoral vein
Oral Rivaroxaban for Symptomatic Venous Thromboembolism

The EINSTEIN Investigators*

EINSTEIN DVT

- Open-label, noninferiority study
  - rivaroxaban 15 mg BID for 3 weeks, followed by 20 mg OD compared with SC enoxaparin followed by VKA
  - 3449 patients
    - 1731 rivaroxaban & 1718 given E + VKA
    - 36 events with R [2.1%], vs. 51 events with E + VKA [3.0%]; hazard ratio, 0.68; 95% confidence interval [CI], 0.44 to 1.04; P<0.001)
- Parallel study of rivaroxaban vs placebo for extended prophylaxis
  - 602 R and 594 P patients
    - 8 events with R [1.3%] and 42 with P [7.1%]; hazard ratio, 0.18; 95% CI, 0.09 to 0.39; P<0.001)
    - 4 R nonfatal major bleeds (0.7%), vs 0


Oral rivaroxaban for symptomatic venous thromboembolism.

Equivalent to warfarin for DVT prevention without the upfront LMWH
Current status

- Rivaroxaban is licensed in Canada for DVT treatment
  - Rivaroxaban offers a very interesting alternative to traditional therapy!

- 15 mg PO BID x 3 weeks followed by 20 mg OD for duration of therapy
Pulmonary Embolism

Oral rivaroxaban for the treatment of symptomatic pulmonary embolism.


• Randomized, open-label noninferiority trial
  – 4832 patients with acute PE
  – compared rivaroxaban (15 mg BID for 3 weeks, followed by 20 mg OD) with standard therapy with enoxaparin followed by an adjusted-dose vitamin K antagonist

• Primary efficacy outcome was symptomatic recurrent venous thromboembolism

• Rivaroxaban was noninferior
  – 50 events with R (2.1%) versus 44 events E + VKA (1.8%)
  – safety outcome in 10.3% of R and 11.4% of E + VKA

• rivaroxaban alone was noninferior to standard therapy for the initial and long-term treatment of PE
• Rivaroxaban is the agent of choice for uncomplicated VTE
  – Assuming:
    • Compliance
    • Coverage
    • Willingness

• Remember: VTE is a fatal disease without appropriate treatment
Are there other choices for VTE?

• Apixaban

ORIGINAL ARTICLE
Oral Apixaban for the Treatment of Acute Venous Thromboembolism
Giancarlo Agnelli, M.D., Harry R. Buller, M.D., Ph.D., Alexander Cohen, M.D., Madelyn Curto, D.V.M., Alexander S. Gallus, M.D., Margot Johnson, M.D., Urszula Masiukiewicz, M.D., Raphael Pak, Ph.D., John Thompson, Ph.D., Gary E. Raskob, Ph.D., and Jeffrey I. Weitz, M.D. for the AMPLIFY Investigators

• Primary efficacy endpoint in 59 of 2609 patients (2.3%) in the apixaban group, as compared with 71 of 2635 (2.7%) in the conventional-therapy group (relative risk, 0.84; 95% confidence interval [CI], 0.60 to 1.18)

• Composite outcome of major bleeding and CRNB occurred in 4.3% of the patients in the apixaban group, as compared with 9.7% of those in the conventional-therapy group (relative risk, 0.44; 95% CI, 0.36 to 0.55; P<0.001)
Two very large studies demonstrate that dabigatran after an initial course of LMWH is as good as warfarin...
Am I actually comfortable…

- Treating a person with a great big DVT with a little tiny pill?
- 100% percent for sure and absolutely!
• What is it?
  – Clot confined to the superficial circulation of the arm or leg

• Why is it important?
  – Causes symptoms that are frequently very bothersome
  – Can extend to the deep venous circulation and cause PE
Evidence of importance

- prospective evaluation of 844 patients with acute SVT > 5 cm
  - 4% had symptomatic PE
  - US detected proximal DVT in 10%
  - US detected distal DVT in 13%
  - Male sex, history of VTE, cancer, and absence of varicose veins about doubled the risk of VTE during follow-up.

Treatment

- CALISTO study
  - Randomized 3000 patients with SVT > 5 cm to fondaparinux (2.5 mg/d for 45 days) or placebo
  - Placebo group: thrombotic complications occurred more often if involved the greater saphenous vein, extended to within 10 cm of saphenofemoral junction, above the knee and with prior VTE/SVT
• **Primary outcome:**
  – Death, PE, DVT, symptomatic extension to the saphenofemoral junction or symptomatic recurrence of SVT by 47

• **Safety outcome:**
  – Major bleeding
• Results:
  – primary outcome: 13/1502 vs 88/1500
  – NNT 88 to prevent one instance of pulmonary embolism or deep-vein thrombosis

• Major bleeding:
  – 1 patient in each group
<table>
<thead>
<tr>
<th>Event</th>
<th>Normal SCS (10)</th>
<th>shingles vaccination (917 S)</th>
<th>Difference</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite outcome†</td>
<td>13 (0.9)</td>
<td>88 (5.9)</td>
<td>−5.0 (-6.3 to −3.7)</td>
<td>0.15 (0.08 to 0.26)</td>
</tr>
<tr>
<td>Death‡</td>
<td>2 (0.1)</td>
<td>1 (0.1)</td>
<td>0.1 (−0.2 to 0.3)</td>
<td>1.99 (0.18 to 21.87)</td>
</tr>
<tr>
<td>Pulmonary embolism§</td>
<td>0</td>
<td>5 (0.3)</td>
<td>−0.3 (−0.6 to 0.0)</td>
<td>Not calculated</td>
</tr>
<tr>
<td>Deep-vein thrombosis¶</td>
<td>3 (0.2)</td>
<td>18 (1.2)</td>
<td>−1.0 (−1.6 to −0.4)</td>
<td>0.17 (0.05 to 0.56)</td>
</tr>
<tr>
<td>Extension of superficial-vein thrombosis to the saphenofemoral junction</td>
<td>4 (0.3)</td>
<td>51 (3.4)</td>
<td>−3.1 (−4.1 to −2.2)</td>
<td>0.08 (0.03 to 0.22)</td>
</tr>
<tr>
<td>Recurrence of superficial-vein thrombosis</td>
<td>5 (0.3)</td>
<td>24 (1.6)</td>
<td>−1.3 (−2.0 to −0.6)</td>
<td>0.21 (0.08 to 0.54)</td>
</tr>
<tr>
<td>Deep-vein thrombosis or pulmonary embolism</td>
<td>3 (0.2)</td>
<td>20 (1.3)</td>
<td>−1.1 (−1.8 to −0.5)</td>
<td>0.15 (0.05 to 0.50)</td>
</tr>
</tbody>
</table>
ACCP recommendation

- In patients with SVT of the lower limb of at least 5 cm in length, we suggest the use of a prophylactic dose of fondaparinux or LMWH for 45 days over no anticoagulation (Grade 2B).

- In patients with SVT who are treated with anticoagulation, we suggest fondaparinux 2.5 mg daily over a prophylactic dose of LMWH (Grade 2C).
Does this really mean…

- Five cm in length
- Identify high risk characteristics
- Do we really have to use fondaparinux?

Take home:
- Consider anticoagulation for patients with large SVT’s
Time for a reflection...
Problems with these agents...

- Renal failure
  - Dabigatran does, and rivaroxaban may, bioaccumulate in patients with renal failure

- Bleeding & Reversal
  - Bleeding will occur and will not be reversible

- Compliance
  - There is no effective way of assessing compliance

- Cost
  - Although reasonably priced, more expensive than warfarin

- GI Bleeding
  - probably increased GI bleeding

- Bridging strategies not clear, particularly in patients with impaired renal function
• Bleeding & Reversal

**NO reversal agent – don’t give FFP**

– Adhere to principals of bleeding management
– Work with thrombosis, IR, GI or surgery
– **Consider** PCC
– For life-threatening bleeding with dabigatran
  • Consider hemodialysis
• Compliance is the major limitation of these agents
  – Education and follow-up
  – INR, APTT and ? Drug levels
  – Two missed doses = no anticoagulant effect in some patients
Emergency surgery

- There is no way to reverse the drug
  - Consider delaying surgery
  - Consider PCC and/or rfVIIa
  - Avoid spinals

**If Xa is normal then the Xa inhibitor is NOT present**
• Bridging strategies
  – Elective
    • Probably hold pre-operatively for 24 to 48 hours with normal renal function
      – Longer with impaired function
    • Don’t restart immediately after surgery due to “immediate therapeutic re-anticoagulation”
      – Delay restart and consider lower initial dose
Should we use these drugs?

- In the right patient
  - Absolutely yes
  - For sure:
    - Ortho prophylaxis
    - VTE treatment
  - Likely
    - Atrial fibrillation

- NOT in the wrong patient
  - Renal failure
  - Well controlled warfarin
  - Valves
  - Non-compliance
  - Patients who desire pregnancy
Key messages...

- Rivaroxaban is the preferred agent for treatment of acute VTE
  - Right patient
    - Compliance
  - Right dose
    - 15 mg PO BID x 21 days then 20 mg OD for duration of therapy
  - With food
How long...

• What we know
  – Secondary
    • three months
  – In setting of ongoing risk factor
    • Indefinite
  – Ideopathic
    • Probably longer treatment in males and in some women
Questions…