Venous Thromboembolism: Long Term Anticoagulation

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Disclosures

• No financial relationships with products discussed
• Off-label use of drug therapy always discussed
Objectives

• Review clinical practice guidelines relevant to venous thromboembolism (VTE)
• Compare the clinical trial evidence supporting novel oral anticoagulants (NOACs) for VTE
• Recommend a long term oral anticoagulant therapy given a patient scenario
• Recommend a duration of long term anticoagulant therapy for VTE given a patient scenario
Patient Case #1

JF is a 62 year old man from OSH for possible surgical embolectomy for PE due to large clot burden.

JF presented with severe SOB and chest pain
PMH significant for prior DVT/PE and remote history of ICH
Patient Case #1

Which of the following would be the best initial anticoagulant therapy for JF?

A. Dabigatran 150 mg PO BID
B. Enoxaparin 1 mg/kg Q12H
C. Apixaban 5 mg BID
D. Heparin 1000 units/hr + warfarin 5 mg qHS
“The Guidelines”

ANTITHROMBOTIC THERAPY AND PREVENTION OF THROMBOSIS, 9TH ED: ACCP GUIDELINES

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

• A brief history of anticoagulation
• Last published in 2012
• Final revision accepted August 2011

CHEST 2012; 141(2)(Suppl):e419S–e494S
The Guidelines – Which Drug?

• Little data available at the time regarding NOACs
• Long term safety data cited as a concern

3.3.1. In patients with DVT of the leg and no cancer, we suggest VKA therapy over LMWH for long-term therapy (Grade 2C). For patients with DVT and no cancer who are not treated with VKA therapy, we suggest LMWH over dabigatran or rivaroxaban for long-term therapy (Grade 2C).

6.6. In patients with PE and no cancer, we suggest VKA therapy over LMWH for long-term therapy (Grade 2C). For patients with PE and no cancer who are not treated with VKA therapy, we suggest LMWH over dabigatran or rivaroxaban for long-term therapy (Grade 2C).

CHEST 2012; 141(2)(Suppl):e419S–e494S
3.0. In patients with acute VTE who are treated with anticoagulant therapy, we recommend long-term therapy (see section 3.1 for recommended duration of therapy) over stopping anticoagulant therapy after about 1 week of initial therapy (Grade 1B).

3.1.1. In patients with a proximal DVT of the leg provoked by surgery, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (Grade 1B), (ii) treatment of a longer time-limited period (eg, 6 or 12 months) (Grade 1B), or (iii) extended therapy (Grade 1B regardless of bleeding risk).

3.1.2. In patients with a proximal DVT of the leg provoked by a nonsurgical transient risk factor, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (Grade 1B), (ii) treatment of a longer time-limited period (eg, 6 or 12 months) (Grade 1B), and (iii) extended therapy if there is a high bleeding risk (Grade 1B). We suggest treatment with anticoagulation for 3 months over extended therapy if there is a low or moderate bleeding risk (Grade 2B).

3.1.3. In patients with an isolated distal DVT of the leg provoked by surgery or by a nonsurgical transient risk factor (see remark), we suggest treatment with anticoagulation for 3 months over treatment of a shorter period (Grade 2C) and recommend treatment with anticoagulation for 3 months over treatment of a longer time-limited period (eg, 6 or 12 months) (Grade 1B) or extended therapy (Grade 1B regardless of bleeding risk).
Good Old Warfarin

- Slow onset (3-5 days)
- Numerous drug interactions
- Dietary concerns
- Unpredictable dosing
- Frequent monitoring
- Issues with bridging
- Complicated patient counseling

www.coumadin.com
Warfarin Pharmacogenetics

- Polymorphisms in metabolism (2C9) and/or site of action (VKOR)
- FDA modified package insert in 2007 to include genetic testing
- Short term benefit w. limited evidence supporting efficacy
Dabigatran (Pradaxa®)

• Oral, fixed dose direct thrombin inhibitor
  – 150 mg twice a day
  – Avoid use if CrCl <30 ml/min
  – Predictable pharmacokinetics
• Limited drug interactions, no dietary concerns
• No monitoring required
• Capsule must be swallowed whole
Dabigatran vs Warfarin in VTE
RE-COVER Trial

- Randomized, double-blind, non-inferiority trial
- Parenteral anticoagulation started initially
- Warfarin vs. dabigatran
  - Warfarin goal INR 2-3 for 2 consecutive days
  - Dabigatran 150 mg BID
- Primary outcome recurrent symptomatic VTE or death
- 2,564 patients enrolled
- Parenteral anticoagulation given for median 10 days
- Therapy continued for 6 months

## RE-COVER Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Dabigatran (N=1274)</th>
<th>Warfarin (N=1265)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent VTE or death</td>
<td>30 (2.4%)</td>
<td>27 (2.1%)</td>
<td>1.10 (0.65-1.84)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>20 (1.6%)</td>
<td>24 (1.9%)</td>
<td>0.82 (0.45-1.48)</td>
</tr>
<tr>
<td>Major +relevant Non-major bleeding</td>
<td>71 (5.6%)</td>
<td>111 (8.8%)</td>
<td>0.63 (0.47–0.84)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>39 (3.1%)</td>
<td>9 (0.7%)</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>

RE-COVER Conclusions

• Dabigatran is non-inferior to warfarin for VTE
  – Not superior
• Major bleeding similar between groups
  – Fewer overall bleeding events with dabigatran
• Immediate transition to dabigatran **not** studied
• FDA approved indication includes treatment with parenteral anticoagulant for 5-10 days
GL is an 88 year old woman being started on dabigatran for DVT. Which of the following are needed to calculate a CrCl?

A. IBW, SCr and Height
B. ABW and BUN
C. Age, ABW and SCr
D. Age, race and SCr
Rivaroxaban (Xarelto)

- Oral Factor Xa inhibitor
- Take with or without food
- Substrate of CYP P450 3A4 and pGP
- Half life 5-9 hours
EINSTEIN PE & DVT

• Rivaroxaban vs. warfarin in VTE
• Rivaroxaban 15 mg BID X 21 days followed by 20 mg daily
  – Excluded from trial if CrCl <30 ml/min
• Treatment duration 3, 6 or 12 months
• Patients excluded if >48 hrs parenteral anticoagulation

## EINSTEIN DVT Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rivaroxaban (N=1731)</th>
<th>Warfarin (N=1718)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent VTE</td>
<td>36 (2.1%)</td>
<td>51 (3.0%)</td>
<td>0.68 (0.44–1.04)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p&lt;0.001 (NI)</td>
</tr>
<tr>
<td>Major bleeding + clinically relevant bleeding</td>
<td>139 (8.1%)</td>
<td>138 (8.1%)</td>
<td>0.97 (0.76–1.22)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p=0.77</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>14 (0.8)</td>
<td>20 (1.2)</td>
<td>0.65 (0.33–1.30)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p=0.21</td>
</tr>
</tbody>
</table>

## EINSTEIN PE Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rivaroxaban (N=2420)</th>
<th>Warfarin (N=2413)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent VTE</td>
<td>50 (2.1%)</td>
<td>44 (1.8%)</td>
<td>1.12 (0.75–1.68) p=0.003 (NI)</td>
</tr>
<tr>
<td>Major bleeding + clinically relevant bleeding</td>
<td>249 (10.3%)</td>
<td>274 (11.4%)</td>
<td>0.90 (0.76–1.07) p=0.23</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>26 (1.1%)</td>
<td>52 (2.2%)</td>
<td>0.49 (0.31–0.79) p=0.003</td>
</tr>
</tbody>
</table>

Apixaban (Eliquis)

- Oral Factor Xa inhibitor
- Half life approximately 12 hours
- Approximately 25% renal elimination
- Twice a day dosing
Apixaban in VTE (AMPLIFY)

- Enrolled 5,395 patients with acute VTE
  - Apixaban 10 mg BID for 7 days followed by 5 mg BID
- Excluded if:
  - CrCl <25 ml/min
  - More than two doses of daily LMWH/fonda
  - More than 36 hrs UFH infusion

## AMPLIFY Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Apixaban (N=2691)</th>
<th>Warfarin (N=2704)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent VTE or death</td>
<td>30 (2.4%)</td>
<td>71 (2.7%)</td>
<td>0.84 (0.60–1.18)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001 (NI)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>15 (0.6%)</td>
<td>49 (1.8%)</td>
<td>0.31 (0.17–0.55)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Major +relevant Non-major bleeding</td>
<td>115 (4.3%)</td>
<td>261 (9.7%)</td>
<td>0.44 (0.36–0.55)</td>
</tr>
<tr>
<td></td>
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<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Edoxaban (Savaysa)

- Factor Xa inhibitor
- Half-life of 10 to 14 hours
- Renal clearance 50%
- Once a day dosing
Edoxaban in VTE – Hokusai VTE

• Enrolled 8,292 patients with VTE to Edoxaban 60 mg daily or warfarin
• Dosage reduced by 50% for any of the following:
  – CrCl 30-50 ml/min
  – Weight ≤ 60 kg
• Open label enoxaparin or heparin for at least 5 days

## Hokusai VTE Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Edoxaban (n=4118)</th>
<th>Warfarin (n=4122)</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent VTE</td>
<td>130 (3.2%)</td>
<td>146 (3.5%)</td>
<td>0.89 (0.70 to 1.13)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P&lt;0.001 NI</td>
</tr>
<tr>
<td>Major or clinically relevant nonmajor bleeding</td>
<td>349 (8.5%)</td>
<td>423 (10.3%)</td>
<td>0.81 (0.71–0.94)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P=0.004</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>56 (1.4%)</td>
<td>66 (1.6%)</td>
<td>0.84 (0.59–1.21)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P=0.35</td>
</tr>
</tbody>
</table>

Edoxaban for VTE

• Non-inferior with less bleeding for VTE

• Dosing
  – Give 60 mg daily for CrCl >50
  – Reduce dose to 30 mg daily for CrCl 15-50 ml/min
  – Is good renal function a bad thing with edoxaban?
Patient Case #3

VW is a 68 year old female being treated with edoxoban 60 mg daily for a PE. No obvious cause was identified for her PE. She has done well after 3 months of therapy & presents to clinic for follow-up. Physical exam and labs are unremarkable.
Patient Case #3

Given the patient’s progress to date, which of the following would be best regarding their anticoagulation?

A. Stop anticoagulation
B. Continue edoxaban for 3 more months
C. Transition to warfarin for indefinite therapy
D. Continue current therapy indefinitely
Revisiting Duration of Therapy

• Prolonged therapy with NOACs may be an attractive option
  – More convenient than warfarin
  – Less bleeding
• Cost would be primary factor limiting use
• Duration of therapy different in many of the trials
Extended Therapy Trials

• RESONATE Trial with dabigatran
  – Non-inferior to warfarin, superior to placebo
  – Less bleeding than warfarin but more than placebo

• EINSTEIN Extension with Rivaroxaban
  – Reduced risk of recurrent VTE
  – Increase risk of bleeding

AMPLIFY EXT with Apixaban

- Apixaban 2.5 mg or 5 mg BID vs. placebo
- Reduced risk of Recurrent VTE/death
- No difference in major bleeding
  - Other bleeding endpoints varied by apixaban dose
- Primary goal for extended therapy trial would be reduced VTE with minimal increased bleeding

NOAC Checklist

- Does evidence support your indication?
- Can the patient afford the medication?
- Is your dose correct?
  - Renal function
- Peri-procedural concerns
- If you are not sure about a NOAC, just start heparin/LMWH
Patient Case #4

AW is a 92 year old retired farmer admitted to the ICU with a 3 day history of SOB. Admission labs are normal (SCr=1.2) with vital signs as follows:

HR – 112
BP – 134/92
RR – 22
O2 sat – 97%
Patient Case #4

Upon further work up, AW is found to have a pulmonary embolism. Which of the following would be the most important reason **NOT** to start AW on a NOAC?

A. Lack of reversal agent
B. Cost
C. Lack of evidence supporting use
D. Renal dysfunction
NOAC Future Directions

• More drugs in the pipeline
  – Betrixaban

• Reversal agents on the horizon
  – Idarucizumab (dabigatran)
  – Andexanet alfa (Factor Xa inhibitors)
  – Aripazine (NOACs & heparins)
Selecting Your Drug and Duration

• NOACs offer promising alternative to warfarin but with limitations

• Involve the patient in the decision
  – Is the higher cost of convenience worth it?
  – NOACs do offer some clinical advantage for VTE

• Can prolonged treatment with NOACs reduce thrombotic events without significantly increasing bleeding?