Thrombophilia Management with DOAC’s

Thomas L. Ortel, M.D., Ph.D.
Duke University Medical Center
1 December 2016
Pre-test Question 1

• A 21 year old man sustains a broken leg and pelvis in an automobile accident. Two days after a revision surgery on his femur, he becomes hypoxic and tachypneic, and is found to have a large right-sided PE. He is started on rivaroxaban. His mother notes that she sustained a post-partum DVT after a younger sibling’s birth.
Your poll will show here

1. Install the app from pollev.com/app
2. Make sure you are in Slide Show mode

Still not working? Get help at pollev.com/app/help
or
Open poll in your web browser
Pre-test Question 2

- A 68 year old man sustains an extensive DVT and bilateral PE ~4 weeks after robotic prostatectomy for stage pT2c pNx pMx prostate cancer. He is started on rivaroxaban and a hypercoagulable workup is performed, revealing only an anti-β₂glycoprotein I IgA antibody of 43 units.

- Repeat testing 3 months later revealed the anti-β₂glycoprotein I IgA antibody was decreasing but still slightly elevated, at 24 units.

- Repeat testing after an additional 3 months revealed the anti-β₂glycoprotein I IgA antibody to be >120 units.
Your poll will show here

1. Install the app from pollev.com/app
2. Make sure you are in Slide Show mode

Still not working? Get help at pollev.com/app/help

or

Open poll in your web browser
Pre-test Question 3

• A 74 year old woman presents with bilateral segmental PE. She was intermittently using a vaginal estrogen cream but seldom more frequently than once a week.

• She is started on apixaban, which she has been taking for three months.

• A hypercoagulable workup was sent prior to stopping the apixaban. This revealed normal anticardiolipin and anti-beta-2-glycoprotein I IgG antibody levels, but the IgM antibody levels were >150 U.
Your poll will show here

1. Install the app from pollev.com/app
2. Make sure you are in Slide Show mode

Still not working? Get help at pollev.com/app/help
or
Open poll in your web browser
Direct Oral Anticoagulants and Initial Treatment of VTE

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Regimen*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>Anti-factor Xa</td>
<td>10 mg twice daily for 7 days, then 5 mg twice daily</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Anti-factor IIa</td>
<td>5-10 days of parenteral anticoagulation, then 150 mg twice daily</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Anti-factor Xa</td>
<td>5-10 days of parenteral anticoagulation, then 60 mg once daily; decrease to 30 mg once daily if weight ≤60 kg or if on selected P-gp inhibitors</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Anti-factor Xa</td>
<td>15 mg twice daily for 21 days, then 20 mg once daily</td>
</tr>
</tbody>
</table>

* Assuming normal renal function and no other contraindications to anticoagulation
First Recurrent VTE or VTE-Related Death

## Major Bleeds

<table>
<thead>
<tr>
<th>Study</th>
<th>DOAC (n/N)</th>
<th>VKA (n/N)</th>
<th>Risk ratio (95% CI)</th>
<th>RR (95% CI)</th>
<th>P</th>
<th>ARR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMPLIFY</td>
<td>15/2676 (0.6%)</td>
<td>49/2689 (1.8%)</td>
<td>0.31 (0.17-0.55)</td>
<td>0.0001</td>
<td>-1.26% (-1.84% to -0.68%)</td>
<td></td>
</tr>
<tr>
<td>EINSTEIN-DVT</td>
<td>14/1718 (0.8%)</td>
<td>20/1711 (1.2%)</td>
<td>0.70 (0.35-1.38)</td>
<td>0.30</td>
<td>-0.35% (-1.02% to 0.31%)</td>
<td></td>
</tr>
<tr>
<td>EINSTEIN-PE</td>
<td>26/2412 (1.1%)</td>
<td>52/2405 (2.2%)</td>
<td>0.50 (0.31-0.80)</td>
<td>0.004</td>
<td>-1.08% (-1.80% to -0.37%)</td>
<td></td>
</tr>
<tr>
<td>Hokusai-VTE</td>
<td>56/4118 (1.4%)</td>
<td>66/4122 (1.6%)</td>
<td>0.85 (0.60-1.21)</td>
<td>0.37</td>
<td>-0.24% (-0.76% to 0.28%)</td>
<td></td>
</tr>
<tr>
<td>RE-COVER</td>
<td>22/1273 (1.7%)</td>
<td>29/1266 (2.3%)</td>
<td>0.75 (0.44-1.31)</td>
<td>0.31</td>
<td>-0.56% (-1.65% to 0.53%)</td>
<td></td>
</tr>
<tr>
<td>RE-COVER II</td>
<td>15/1280 (1.2%)</td>
<td>22/1288 (1.7%)</td>
<td>0.69 (0.36-1.32)</td>
<td>0.26</td>
<td>-0.54% (-1.46% to 0.38%)</td>
<td></td>
</tr>
<tr>
<td>Combined (random)</td>
<td>148/13477 (1.1%)</td>
<td>238/13481 (1.8%)</td>
<td>0.61 (0.45-0.83)</td>
<td>0.002</td>
<td>-0.68% (-1.07% to -0.30%)</td>
<td></td>
</tr>
</tbody>
</table>

Types of Bleeding Complications

<table>
<thead>
<tr>
<th>Type</th>
<th>Pooled DOAC (n/N)</th>
<th>Pooled VKA (n/N)</th>
<th>Risk ratio (95% CI)</th>
<th>RR (95% CI)</th>
<th>P</th>
<th>ARR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial bleeding</td>
<td>15/13477 (0.1%)</td>
<td>43/13841 (0.3%)</td>
<td>0.37 (0.21-0.68)</td>
<td>0.001</td>
<td></td>
<td>-0.17% (-0.30% to -0.03%)</td>
</tr>
<tr>
<td>Fatal bleeding</td>
<td>7/13477 (0.1%)</td>
<td>22/13481 (0.2%)</td>
<td>0.36 (0.15-0.84)</td>
<td>0.02</td>
<td></td>
<td>-0.08% (-0.16% to -0.01%)</td>
</tr>
<tr>
<td>Major GI bleeding</td>
<td>63/13477 (0.5%)</td>
<td>76/13481 (0.6%)</td>
<td>0.78 (0.47-1.31)</td>
<td>0.35</td>
<td></td>
<td>-0.12% (-0.37% to 0.13%)</td>
</tr>
<tr>
<td>CRNM bleeding</td>
<td>854/13477 (6.3%)</td>
<td>1103/13481 (8.0%)</td>
<td>0.73 (0.58-0.93)</td>
<td>0.01</td>
<td></td>
<td>-1.88% (-3.24% to -0.52%)</td>
</tr>
</tbody>
</table>
## Incidence of VTE

<table>
<thead>
<tr>
<th>Study</th>
<th>Overall VTE incidence per 1,000 person/hrs, (95% CI)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cushman, 2004</td>
<td>1.61 (1.43-1.81)</td>
<td>Incidence increased with age</td>
</tr>
<tr>
<td>Naess, 2007</td>
<td>1.43 (1.33-1.54)</td>
<td>Incidence increased exponentially with age; more frequent in females</td>
</tr>
<tr>
<td>Spencer, 2009</td>
<td>1.14 (1.08-1.20)</td>
<td>Incidence increased with age; incidence higher in females</td>
</tr>
<tr>
<td>Puurunen, 2016</td>
<td>2.68 (2.38-3.01)</td>
<td>Incidence increased with age; 40% PE</td>
</tr>
</tbody>
</table>
Provoked VTE

- Transient acquired hypercoagulable states
  - Hospitalization (n=99, 52%)
  - Surgery (n=80, 42%)
  - Major trauma (n=11, 6%)

- Most patients had $\geq 2$ acquired states (n=124, 65%)

366 validated thromboses, 265 incident VTE
## DOACs in Unprovoked vs. Provoked VTE

<table>
<thead>
<tr>
<th>Drug</th>
<th>Unprovoked</th>
<th>Provoked</th>
<th>Cancer</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>4845 (90%)</td>
<td>544 (10%)</td>
<td>143 (2.7%)</td>
<td>Agnelli, 2013</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Not provided</td>
<td>Not provided</td>
<td>121 (4.7%)</td>
<td>Schulman, 2009</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>5410 (66%)</td>
<td>2272 (28%)</td>
<td>771 (9.4%)</td>
<td>Buller, 2013</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>2138 (62%)</td>
<td>1470 (43%)</td>
<td>207 (6%)</td>
<td>Bauersachs, 2012</td>
</tr>
</tbody>
</table>
Anticoagulation for VTE: ACCP Guidelines

• In patients with DVT of the leg or PE and no cancer, as long-term (first 3 months) anticoagulant therapy, we suggest dabigatran, rivaroxaban, apixaban, or edoxaban over vitamin K antagonist (VKA) therapy (all Grade 2B).

• For patients with DVT of the leg or PE and no cancer who are not treated with dabigatran, rivaroxaban, apixaban, or edoxaban, we suggest VKA therapy over low-molecular weight heparin (LMWH) (Grade 2C).

Treatment Duration for Provoked VTE: ACCP Guidelines

• In patients with a proximal DVT of the leg or PE 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, 12, or 24 months) (Grade 1B), or (iii) extended therapy (no scheduled stop date) (Grade 1B).

Treatment Duration for Provoked VTE: ACCP Guidelines

• In patients with a proximal DVT of the leg or PE provoked by a nonsurgical transient risk factor, we recommend treatment with anticoagulation for 3 months over (i) treatment of a shorter period (Grade 1B) and (ii) treatment of a longer time-limited period (eg, 6, 12, or 24 months) (Grade 1B).

• We suggest treatment with anticoagulation for 3 months over extended therapy if there is a low or moderate bleeding risk (Grade 2B), and recommend treatment for 3 months over extended therapy if there is a high risk of bleeding (Grade 1B).
Anticoagulation for Provoked VTE: ASH Choosing Wisely

• Do not test for thrombophilia in adult patients with VTE occurring in the setting of major transient risk factors (surgery, trauma, or prolonged immobility).


• Do not treat with an anticoagulant for more than 3 months in a patient with a first VTE occurring in the setting of a major transient risk factor.

Question 4

• In a patient with a provoked VTE, who has a family history of *unprovoked* VTE, which of the following would you recommend:

  A. No hypercoagulable workup
  B. Partial hypercoagulable workup (focus on the inherited thrombophilias)
  C. Partial hypercoagulable workup (focus on testing for antiphospholipid syndrome)
  D. Complete hypercoagulable workup
Issues to consider before testing...

Know what you are going to do with the data before ordering the test

- Will it change your choice of therapy?
- Will it change your duration of therapy?
- Will it change what you recommend after the patient has stopped therapy (if you stop)?
- Will it change what you would recommend to the patient’s family members?

- Referring the patient to someone else to explain the results should not be an option...
Thrombophilia and Provoked VTE

• There are no data that a patient who has a provoked VTE related to a transient risk factor, and who has an underlying hypercoagulable state, should change anticoagulant therapy, or should stay on anticoagulant therapy for a longer duration of time.

• But...are all transient risk factors the same?
Risk of Recurrent VTE

- Group C: Unprovoked VTE
- Group D: Provoked VTE, non-surgical (e.g., immobilization, OCP use)
- Group A: Provoked VTE, surgery in the preceding 6 weeks

Bleeding with Anticoagulant Therapy

Unprovoked VTE

- Study sample included the Framingham Heart Study Original, Offspring, Third Generation, and Omni cohorts (N=9754)
- Study period was 1995-2014
- Cancer-related VTE was associated with high mortality

Treatment Duration for Unprovoked VTE: ACCP Guidelines

• In patients with an unprovoked DVT of the leg (isolated distal or proximal) or PE, we recommend treatment with anticoagulation ... for 3 months over treatment of a longer time-limited period (eg, 6, 12, or 24 months) (Grade 1B).

• In patients with a first unprovoked proximal DVT of the leg or PE and who have a (i) low or moderate bleeding risk, we suggest extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy (Grade 2B), and (ii) high bleeding risk, we recommend 3 months of anticoagulant therapy over extended therapy (no scheduled stop date) (Grade 1B).

Does a thrombophilic state alter these recommendations?

- Prospective follow-up study of 474 consecutive patients (aged 18-70 years) without a known malignancy treated for a first VTE.
- Tested for elevated FVIII, FIX, FXI, or fibrinogen, deficiencies of AT, PC, or PS, and factor V Leiden and prothrombin G20210A

Are DOAC’s effective in patients with VTE and thrombophilia?
Dabigatran in VTE patients with thrombophilia

- Post-hoc analysis of data from RE-COVER, RE-COVER II, and RE-MEDY

<table>
<thead>
<tr>
<th>Thrombophilia, n (%)</th>
<th>RE-COVER/RE-COVER II</th>
<th>RE-MEDY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DE (n=2553)</td>
<td>Warfarin  (n=2554)</td>
</tr>
<tr>
<td>No</td>
<td>668 (26.2)</td>
<td>670 (26.2)</td>
</tr>
<tr>
<td>Yes</td>
<td>209 (8.2)</td>
<td>199 (7.8)</td>
</tr>
<tr>
<td>Factor V Leiden</td>
<td>102 (4.0)</td>
<td>82 (3.2)</td>
</tr>
<tr>
<td>Prothrombin mutation</td>
<td>27 (1.1)</td>
<td>28 (1.1)</td>
</tr>
<tr>
<td>Antithrombin deficiency</td>
<td>11 (0.4)</td>
<td>10 (0.4)</td>
</tr>
<tr>
<td>Protein C/S deficiencies</td>
<td>29 (1.1)</td>
<td>33 (1.3)</td>
</tr>
<tr>
<td>Antiphospholipid antibodies and/or lupus anticoagulants</td>
<td>43 (1.7)</td>
<td>43 (1.7)</td>
</tr>
<tr>
<td>Not tested</td>
<td>1676 (65.6)</td>
<td>1685 (66.0)</td>
</tr>
</tbody>
</table>

DE, dabigatran etexilate.

Dabigatran in VTE patients with thrombophilia

What about DOAC’s in APS?
Antiphospholipid Antibodies and Recurrent VTE

- 8 prospective studies (6 randomized trials, 2 cohort studies) investigated impact of aPL on risk of recurrent VTE after stopping anticoagulants.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>APLA</th>
<th>No APLA</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>Ginsberg 1995</td>
<td>2</td>
<td>11</td>
<td>6</td>
<td>34</td>
</tr>
<tr>
<td>Kearon 1999</td>
<td>4</td>
<td>6</td>
<td>12</td>
<td>71</td>
</tr>
<tr>
<td>Kearon 2004</td>
<td>1</td>
<td>17</td>
<td>6</td>
<td>124</td>
</tr>
<tr>
<td>Rodger 2008</td>
<td>56</td>
<td>384</td>
<td>31</td>
<td>235</td>
</tr>
<tr>
<td>Schulman 2006</td>
<td>38</td>
<td>116</td>
<td>194</td>
<td>694</td>
</tr>
<tr>
<td>Taliani 2009</td>
<td>3</td>
<td>6</td>
<td>76</td>
<td>291</td>
</tr>
<tr>
<td>Wahlander 2005</td>
<td>5</td>
<td>48</td>
<td>49</td>
<td>465</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>588</strong></td>
<td><strong>1914</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td><strong>109</strong></td>
<td><strong>374</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.08; Chi² = 10.96, df = 6 (P = 0.09); I² = 45%
Test for overall effect: Z = 1.92 (P = 0.06)

Dabigatran in Patients with APS

- “APS was defined as at least one positive test for lupus anticoagulant and/or for anticardiolipin antibodies combined with symptomatic, objectively verified VTE”

### Table: Comparison of DE and Warfarin

<table>
<thead>
<tr>
<th></th>
<th>DE</th>
<th>Warfarin</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients, N</td>
<td>71</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>VTE/VTE-related deaths, n (%)</td>
<td>3 (4.2)</td>
<td>4 (5.0)</td>
<td>0.43 (0.08, 2.38)</td>
</tr>
<tr>
<td>MBEs, n (%)a</td>
<td>1/70 (1.4)</td>
<td>2/77 (2.6)</td>
<td>0.46 (0.04, 5.43)</td>
</tr>
<tr>
<td>MBEs/CRBEs, n (%)a</td>
<td>6/70 (8.6)</td>
<td>14/77 (18.2)</td>
<td>0.53 (0.20, 1.41)</td>
</tr>
<tr>
<td>Any bleeding event, n (%)a</td>
<td>14/70 (20.0)</td>
<td>31/77 (40.3)</td>
<td>0.50 (0.26, 0.95)</td>
</tr>
</tbody>
</table>

aBleeding events were counted from the start of the double-dummy, oral-only treatment period.

For rollover patients from RE-COVER/RE-COVER II to RE-MEDY without treatment switch, the combined time period is considered for VTE/VTE-related deaths and bleeding.

Non-rollover patients in RE-COVER/RE-COVER II and rollover patients from RE-COVER/RE-COVER II to RE-MEDY with treatment switch are censored at day 180 in RE-COVER/RE-COVER II for VTE/VTE-related deaths or at the end of the post-treatment period in RE-COVER/RE-COVER II for bleeding events.

RAPS

- Open-label, phase 2/3, non-inferiority trial that randomized APS patients with VTE to rivaroxaban or continued warfarin.
- 116 patients studied.
- ETP used as a surrogate outcome for recurrent VTE

“ETP for rivaroxaban did not reach the non-inferiority threshold, but as there was no increase in thrombotic risk compared with standard-intensity warfarin, this drug could be an effective and safe alternative in patients with antiphospholipid syndrome and previous venous thromboembolism.”

DOAC’s in APS: Systematic Review and Meta-analysis

- 122 published APS patients treated with DOAC’s
- 19 (16%) experienced recurrent thrombosis:
  - 17 had prior VTE
  - 8 had prior stroke or other ATE
  - 2 had prior microvascular thrombosis

- Recurrences:
  - 9 had VTE
  - 9 had stroke/ATE
  - 1 had microvascular thrombosis

- Triple positivity associated with highest risk of recurrence

What about DOAC’s in VTE and Cancer?
VTE and Cancer

- Temporary acquired risk factors included surgery (20%), trauma (12%), and marked immobility (10%).

Probability of Survival After First VTE

![Graph showing survival probability over time for different causes of VTE]

Edoxaban and Cancer-Associated VTE

- Pre-specified non-inferiority subgroup analysis of Hokusai VTE
- 771 of 8240 patients (9%) had a cancer-associated VTE
- 24% had metastatic disease, and 39% were receiving anti-neoplastic therapy
Cancer Venous Thromboembolism

• Randomized, open-label study comparing edoxaban to dalteparin in patients with VTE and cancer
• Clinicaltrials.gov #NCT02073682
Summary

• DOAC’s are effective and safe in provoked VTE due to transient risk factors
• DOAC’s are effective and safe in unprovoked VTE (with or without inherited thrombophilia)
• Additional data are necessary to prove the efficacy and safety of DOAC’s in patients with VTE and APS or cancer
A 32 year old woman with a history of SLE presents with a TIA involving transient weakness of the right arm. MRI of the brain reveals no evidence for an ischemic infarct, but several small white matter lesions are noted. Lupus anticoagulant testing is positive.

You would recommend which of the following:

A. Aspirin 81 mg daily
B. Enoxaparin 1 mg/kg twice daily
C. Enoxaparin 1 mg/kg twice daily and transition to warfarin
D. Rivaroxaban
Your poll will show here

1. Install the app from pollev.com/app
2. Make sure you are in Slide Show mode

Still not working? Get help at pollev.com/app/help
or
Open poll in your web browser
Post-test Question 6

• A 34 year old man presents with a painful, swollen leg and is found to have a DVT. No provocative factors can be identified. He is started on rivaroxaban, and you initiate a hypercoagulable workup.
Your poll will show here

1. Install the app from pollev.com/app
2. Make sure you are in Slide Show mode

Still not working? Get help at pollev.com/app/help
or
Open poll in your web browser