Anticoagulation – Focus on Direct Oral Anticoagulants

Tzu-Fei Wang, MD
Assistant Professor
Department of Internal Medicine
Division of Hematology
The Ohio State University Wexner Medical Center

Objectives

- Overview of the direct oral anticoagulants (DOACs) as treatment for venous thromboembolism
- Summary of pivotal trials of DOACs
- Monitoring DOACs
- Peri-op management
- Thrombophilia workup on DOACs
- Reversal of DOACs
- Patient selection for DOACs

"New" and old anticoagulants

<table>
<thead>
<tr>
<th>Features</th>
<th>Warfarin</th>
<th>DOACs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Slow</td>
<td>Rapid</td>
</tr>
<tr>
<td>Dosing</td>
<td>Variable</td>
<td>Fixed</td>
</tr>
<tr>
<td>Food/drug interactions</td>
<td>Many</td>
<td>Few</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Half-life</td>
<td>Long</td>
<td>Short</td>
</tr>
<tr>
<td>Antidote</td>
<td>Yes</td>
<td>No - except for dabigatran</td>
</tr>
</tbody>
</table>

Direct oral anticoagulants (DOACs)

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of action</td>
<td>direct thrombin inhibitor</td>
<td>direct factor Xa inhibitor</td>
<td>direct factor Xa inhibitor</td>
<td>direct factor Xa inhibitor</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>6.7 %</td>
<td>&gt;80 %</td>
<td>~66 %</td>
<td>62%</td>
</tr>
<tr>
<td>Prodrug</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>T max</td>
<td>2 hrs</td>
<td>3 hrs</td>
<td>3-4 hrs</td>
<td>1.5 hrs</td>
</tr>
<tr>
<td>Half life</td>
<td>7.17 hrs</td>
<td>8-13 hrs</td>
<td>8-13 hrs</td>
<td>10-14 hrs</td>
</tr>
<tr>
<td>Dosing</td>
<td>bid</td>
<td>Once daily</td>
<td>bid</td>
<td>Once daily</td>
</tr>
<tr>
<td>Protein Binding</td>
<td>35 %</td>
<td>90 %</td>
<td>90 %</td>
<td>40-59%</td>
</tr>
<tr>
<td>Metabolism</td>
<td>80-85% renal (activated by liver)</td>
<td>67% renal</td>
<td>25% renal</td>
<td>33% renal</td>
</tr>
<tr>
<td>Drug interaction</td>
<td>p-glycoprotein</td>
<td>CYP 3A4</td>
<td>p-glycoprotein</td>
<td>CYP 3A4</td>
</tr>
<tr>
<td></td>
<td>inducer/inhibitor</td>
<td>p-glycoprotein</td>
<td>p-glycoprotein</td>
<td>p-glycoprotein</td>
</tr>
</tbody>
</table>

RE-COVER I/II Study Schema

- Double-blinded, randomized controlled, non-inferiority study
- Primary efficacy: 6 month accumulative risk of recurrent VTE or related death
- Primary safety: Major bleeding

Confirmed symptomatic DVT/PE (N=2539)
PE 21%
Cancer 4-5%

N=1265

Initial parental therapy for 72 hr
LMWH->Warfarin + placebo

6 month

Dabigatran 150 mg bid + placebo

End of treatment and 30 day follow up

N=1274


Primary Efficacy Outcome – RECOVER Study

- 6 month accumulative risk of recurrent VTE or related death
  Warfarin vs Dabigatran: 2.1% vs 2.4%
  HR 1.10, 95% CI 0.65-1.84, p<0.001 for non-inferiority criteria
- INR in range: 60%

Primary Safety Outcome – RECOVER Study

- **Major bleeding:**
  - Warfarin vs Dabigatran: 1.9% vs 1.6%
  - HR 0.82, 95% CI 0.45-1.48, p=0.38
- **All bleeding:** 21.9% vs 16.1%
  - HR 0.71, 95% CI 0.59-0.85, p<0.001
- **Patients with an adverse event leading to discontinuation of the study drug:**
  - 6.8% vs 9.0%
    - HR 1.33; 95% CI 1.01 to 1.76; P=0.05
  - Mainly dyspepsia: 0.6% vs 2.9%, P<0.001


Rivaroxaban

Author: Brenton CC BY-SA 4.0

EINSTEIN DVT/PE Study Schema

- **Open label, randomized controlled, non-inferiority study**
- **Primary efficacy:** symptomatic and recurrent VTE
- **Primary safety:** Major and clinically relevant non-major bleeding

**Confirmed symptomatic DVT/PE**
- (N=5395)

**Designated PE study**
- Cancer 4-6%

**Rivaroxaban 15 mg bid x 21 days then 20 mg daily**

**End of treatment and 30 day follow up**

**Pre-defined treatment period at 3, 6, 12 month**

**Enoxaparin + warfarin**

**N=4832**

**N=3449**

Primary Efficacy Outcome - Einstein study (combined DVT and PE studies)

2.3% vs 2.1 %,
HR 0.89, 0.66-1.19, p<0.001

Prins MH et al. Thrombosis Journal 2013;11:21
Primary Safety Outcome - Einstein study (combined DVT and PE studies)

Prins MH et al. Thrombosis Journal 2013;11:21

Primary safety: 10% vs 9.4%, HR 0.93, 0.81-1.06, p=0.27

MB: 1.7% vs 1.0%, HR 0.54, 0.37-0.79, p=0.002

AMPLIFY Study

- Open label, randomized controlled, non-inferiority study
- Primary efficacy: Recurrent VTE or related death
- Primary safety: Major bleeding

N=2704

Confirmed symptomatic DVT/PE (N=5395)

PE 25%
Cancer 2.5-2.8%

R

Enoxaparin + warfarin

End of treatment and 30 day follow up

6 month

Apixaban 10mg bid x 7d, then 5 bid

N=2691

Primary Efficacy Outcome – AMPLIFY Study

- Recurrent VTE or related death:
  Warfarin vs Apixaban: 2.7% vs 2.3%
  HR 0.84, 95% CI 0.60-1.18, p<0.001 for non-inferiority
- INR in range: 61%

Primary Safety Outcome – AMPLIPY Study

- Major bleeding:
  Warfarin vs Apixaban: 1.8% vs 0.6%
  HR 0.31, 95% CI 0.17-0.55, p<0.001


Edoxaban

Author: Vaccinationist

Hokusai Study Schema

- Double-blinded, randomized controlled, non-inferiority study
- Primary efficacy: symptomatic recurrent VTE
- Primary safety: Major and clinically relevant non-major bleeding

Confirmed symptomatic DVT/PE (N=8292)

PE 40%
Cancer 10%

Initial parental therapy for 5 days

LMWH→Warfarin + placebo

Edoxaban 60 mg daily + placebo

End of treatment and 30 day follow up

Primary Efficacy Outcome – Hokusai Study

- Symptomatic recurrent VTE:
  Warfarin vs Edoxaban: 3.5% vs 3.2%
  HR 0.89, 95% CI 0.70-1.13, p<0.001 for non-inferior
- INR in range: 63.5%

Primary Safety Outcome – Hokusai Study

- Major and clinically relevant non-major bleeding
  Warfarin vs Edoxaban: 10.3% vs 8.5%
  HR 0.81, 95% CI 0.71-0.94, p=0.004
- Major Bleeding: 1.4% vs 1.6%, p=0.35


Summary of use of DOAC for VTE

<table>
<thead>
<tr>
<th>Drug</th>
<th>Recurrent Thrombosis</th>
<th>Major Bleeding</th>
<th>Major and CRNMB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>Equal</td>
<td>Equal</td>
<td>Reduced</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Equal</td>
<td>Reduced</td>
<td>Equal</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Equal</td>
<td>Reduced</td>
<td>Reduced</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Equal</td>
<td>Equal</td>
<td>Reduced</td>
</tr>
</tbody>
</table>

Effectiveness of novel oral anticoagulants as compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism: a systematic review and meta-analysis

<table>
<thead>
<tr>
<th>Outcome Study</th>
<th>Recurrent Thrombosis</th>
<th>Major Bleeding</th>
<th>Major and CRNMB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinolytic</td>
<td>2.0%</td>
<td>2.2%</td>
<td></td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>2.0%</td>
<td>2.2%</td>
<td></td>
</tr>
<tr>
<td>Heparin</td>
<td>2.0%</td>
<td>2.2%</td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>2.0%</td>
<td>2.2%</td>
<td></td>
</tr>
</tbody>
</table>

N=24,455

Safety of novel oral anticoagulants as compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism: a systematic review and meta-analysis

<table>
<thead>
<tr>
<th>Outcome Study</th>
<th>Recurrent Thrombosis</th>
<th>Major Bleeding</th>
<th>Major and CRNMB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinolytic</td>
<td>1.1%</td>
<td>1.7%</td>
<td>NNT=149</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>1.1%</td>
<td>1.7%</td>
<td>NNT=263</td>
</tr>
<tr>
<td>Heparin</td>
<td>1.1%</td>
<td>1.7%</td>
<td>NNT=56</td>
</tr>
<tr>
<td>Warfarin</td>
<td>1.1%</td>
<td>1.7%</td>
<td>NNT=714</td>
</tr>
</tbody>
</table>

2016 ACCP guideline

- For VTE and no cancer, as long-term anticoagulant therapy, we suggest dabigatran, rivaroxaban, apixaban, or edoxaban over vitamin K antagonist (VKA) therapy (Grade 2B).
- For VTE and cancer, we suggest LMWH over VKA (Grade 2B), dabigatran, rivaroxaban, apixaban, or edoxaban.
- For VTE treated with anticoagulants, we recommend against an inferior vena cava filter (Grade 1B).

FDA activity

<table>
<thead>
<tr>
<th>FDA activity</th>
<th>Dabigatran Pradaxa®</th>
<th>Rivaroxaban Xarelto®</th>
<th>Apixaban Eliquis®</th>
<th>Edoxaban Savaysa®</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE treatment</td>
<td>FDA approved 4/7/2014</td>
<td>FDA approved 11/2/2012</td>
<td>FDA approved 8/22/2014</td>
<td>FDA approved 1/8/2015</td>
</tr>
<tr>
<td>VTE secondary prevention</td>
<td>FDA approved 11/23/2015</td>
<td>FDA approved 11/2/2012</td>
<td>FDA approved 8/22/2014</td>
<td>No FDA activity</td>
</tr>
<tr>
<td>VTE prevention (ortho surgery)</td>
<td>FDA approved 11/24/2015</td>
<td>FDA approved 7/1/2011</td>
<td>FDA approved 3/14/2014</td>
<td>No FDA activity</td>
</tr>
</tbody>
</table>

Dosages

<table>
<thead>
<tr>
<th>Dosages</th>
<th>Dabigatran Pradaxa®</th>
<th>Rivaroxaban Xarelto®</th>
<th>Apixaban Eliquis®</th>
<th>Edoxaban Savaysa®</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE treatment</td>
<td>150 mg bid (CrCl &gt;30 mL/min) after 5-10 days of parenteral</td>
<td>10 mg bid ± 2 days then 5 mg bid (CrCl &gt;25 and/or Cr &gt;2.5)</td>
<td>60 mg daily</td>
<td>60 mg daily</td>
</tr>
<tr>
<td>VTE secondary prevention</td>
<td>150 mg bid</td>
<td>20 mg daily</td>
<td>2.5 mg bid</td>
<td>N/A</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>150 mg bid (CrCl &gt;30)</td>
<td>15 mg daily (CrCl 15-30)</td>
<td>2.5 mg bid</td>
<td>30 mg daily (if CrCl &gt;95 mL/min)</td>
</tr>
<tr>
<td>Orthopedic VTE prevention</td>
<td>11 mg on first day, then 220 mg daily</td>
<td>15 mg daily</td>
<td>2.5 mg bid</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Dose adjustment in renal dysfunction – more details

- For apixaban use in A fib patients:
  - ESRD requiring HD: 5 mg bid, unless if age ≥80 or weight ≤60 kg, then 2.5 mg bid
  - This dosing is approved purely based on a single dose PK/PD study in 8 patients so the use needs to be cautious
  - Major guidelines recommend against use and recommend warfarin to be the anticoagulant of choice
- For edoxaban use in A fib patients, avoid use if CrCL > 95 mL/min
### Dose adjustment in hepatic dysfunction

<table>
<thead>
<tr>
<th></th>
<th>Child-Pugh Class A</th>
<th>Child-Pugh Class B</th>
<th>Child-Pugh Class C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>no dosage adjustment</td>
<td>no dosage adjustment</td>
<td>No information on package insert</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>no dosage adjustment</td>
<td>no dosage adjustment</td>
<td>Avoid use</td>
</tr>
<tr>
<td>Apixaban</td>
<td>no dosage adjustment</td>
<td>no dosage adjustment</td>
<td>Avoid use</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>no dosage adjustment</td>
<td>Avoid use</td>
<td>Avoid use</td>
</tr>
</tbody>
</table>

### Drug interaction

- Strong P-gp inhibitors that require dose adjustment
- Macrolide antibiotics: erythromycin, azithromycin, clarithromycin
- Azole antifungals: itraconazole, ketoconazole
- Protease inhibitors: ritonavir, nelfinavir, indinavir, saquinavir
- Hormone agents: tamoxifen, enzalutamide, abiraterone
- Tyrosine kinase inhibitors: imatinib, nilotinib, lapatinib, sunitinib, crijotinib, vandetanib
- verapamil, quinidine
- Immunosuppressants: cyclosporin, tacrolimus
- Reduce dose by 50% in dabigatran, apixaban, and edoxaban in patients using these medications concurrently, or avoid use (rivaroxaban)

### Use in patients with morbid obesity

- No dose adjustment specified in all DOACs
- International Society of Thrombosis and Haemostasis (ISTH) 2016 guideline:
  - Avoid use all DOACs in patients with a BMI > 40 kg/m2 or weight > 120 kg
  - If used, peak and trough levels using anti-Fx assays or mass spectrometry is recommended
  - Controversial and not evidence-based
  - Meta-analysis of phase III pivotal trials showed that overweight patients had similar bleeding and thrombotic outcomes compared to normal weight patients (but few extremely high weight patients were enrolled)

### Use in patients with cancer

- Meta-analyses of phase III studies showed DOACs to have similar efficacy and safety outcomes when compared to warfarin
- Indirect comparison to LMWH across studies also showed similar results
- However, no good quality data on direct comparison are available
- Major guidelines (NCCN, ACCP, ASCO) continue to recommend LMWH over DOACs in cancer patients
- Awaiting the results of Hokusai cancer VTE study

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K. Martin et al., JTH. 2016;14:1-6.


### Monitoring of DOACs

- **Dabigatran**
  - PT is insensitive
  - aPTT can be elevated but highly variable
  - Thrombin time is too sensitive
  - Dilute thrombin time and ecarin clotting time can be used but are not widely available
- **Xa inhibitors**
  - aPTT is insensitive
  - PT can be elevated with rivaroxaban but highly variable
  - Anti-Xa levels can be used but have to be calibrated against each particular anticoagulant, which is not widely available
  - Actual drug levels by mass spectrometry (not widely available)

### Peri-op management with NOACs

- Factors to consider:
  - Half-life of DOACs
  - Renal function (plus liver function for dabigatran)
  - Risk of bleeding according to the type of surgery
- In general, in patients with normal kidney function, stop 24 hours prior to a surgery with standard bleeding risk and 48 hours prior to a surgery with high risk of bleeding
- In patients with compromised kidney function (or liver dysfunction for dabigatran), decisions have to be individualized but generally at least double the time proposed above
- No bridging is required

### Thrombophilia workup on DOACs

- **Reliable**
  - Genetic testing (FVL, prothrombin gene mutation)
  - Anti-cardiolipin and anti-beta-2-glycoprotein I antibody
  - Protein S (free and total), protein C, anti-thrombin antigen
- **Not reliable**
  - Protein S and protein C activity
  - Anti-thrombin activity
  - APC resistance assay
  - Lupus anticoagulant (Rivaroxaban can use high risk of false positivity)

### Indirect Reversal Agents

- FFP, 3 factor PCC (prothrombin complex concentrate), 4 PCC factor, aPCC, aFVII have all been considered
- Evidence remains very poor, either based on animal model, human volunteers, or case reports on bleeding patients
- No high quality data so cannot be recommended for routine use

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**Direct Reversal Agents**

<table>
<thead>
<tr>
<th></th>
<th>IDARUCIZUMAB (Praxbind®)</th>
<th>ANDEXANET (PRT064445)</th>
<th>ARIPAZINE (PER977)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism of action</strong></td>
<td>A humanized mouse monoclonal antibody (Fab fragment) directed against dabigatran</td>
<td>A recombinant, modified factor Xa molecule that sops up the anti-Xa anticoagulant</td>
<td>A synthetic small molecule (D-arginine compound) with broad activity against various anticoagulants</td>
</tr>
<tr>
<td><strong>Drugs targeted against</strong></td>
<td>Dabigatran</td>
<td>Rivaroxaban, apixaban, edoxaban, LMWH</td>
<td>Dabigatran, rivaroxaban, apixaban, edoxaban, heparin, LMWH</td>
</tr>
<tr>
<td><strong>Status of clinical trials</strong></td>
<td>Phase III study ongoing</td>
<td>Phase II/III studies ongoing</td>
<td>Not yet been used in humans</td>
</tr>
<tr>
<td><strong>FDA activity</strong></td>
<td>FDA approved 10/16/2015</td>
<td>FDA discussion in August 2016 but not been approved</td>
<td>No activities</td>
</tr>
</tbody>
</table>

**Idarucizumab**

- A humanized monoclonal antibody fragment specific for dabigatran, with 350 fold higher affinity than that of dabigatran for thrombin
- Reverse-AD study
  - The use of Idarucizumab to reverse dabigatran in patients with 1) bleeding, 2) urgent procedure in 8 hrs
  - Dose: 5 grams of IV infusion
  - Idarucizumab completely revered the anticoagulant effects of dabigatran within minutes (based on drug concentration, dilute thrombin time, and ecarin clotting time)

**Andexanet**

- Andexanet is a recombinant engineered version of human factor Xa produced in CHO cells
- Acts as FXa decoy and binds up all FXa inhibitors with good affinity, but will not function as FXa to initiate coagulation cascade
- The ANNEXA-4 study (The Ability of Andexanet Alfa to Reverse the Anticoagulant Activity-4) study is to evaluate the efficacy and safety of andexanet for serious bleeding in patients on rivaroxban, apixaban, edoxaban, or enoxaparin
- Dose: a bolus followed by 2 hr infusion
- Use of Andexanet following in all FXa inhibitors have been shown to cause a significant decrease in anti-Xa activity by ~90%, a significant decrease in anticoagulant drug concentration, and normalization of thrombin generation.

**Things to consider prior to DOACs initiation**

- The importance of compliance
- Pros
  - No need for regular lab monitoring
  - Less interaction with diet and medications
  - Reduced risk of bleeding
- Cons
  - Lack of antidotes in anti-Xa inhibitors
  - Lack of extensive experiences
  - Lack of monitoring
  - Potential higher co-pay
  - Poor evidence in special population: cancer, morbid obesity, rare thromboses, antiphospholipid syndrome, hearin-induced thrombocytopenia, etc.

Connolly SJ et al. NEJM 2016;375:1131-1141.
http://www.slideshare.net/derosaMSKCC/k-martin
Conclusions

• DOACs is becoming the main stream of anticoagulation
• DOACs have been shown to have significantly reduced risk of bleeding and similar efficacy compared to warfarin
• Direct reversal agents are coming
• Thorough discussion or pros and cons should be done with patients prior to initiation of DOACs
• Hematology consultants can provide assistance in achieving the best care for these patients