Anticoagulation –
Focus on Direct Oral Anticoagulants

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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>6-13 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>Once daily</td>
<td></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 33% fecal</td>
<td>25% renal 75% fecal</td>
<td>33% renal</td>
</tr>
<tr>
<td>Drug interaction</td>
<td>p-glycoprotein inducer/inhibitor</td>
<td>CYP 3A4 p-glycoprotein</td>
<td>CYP 3A4 p-glycoprotein</td>
<td>p-glycoprotein</td>
</tr>
</tbody>
</table>

Dabigatran
**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

![Schema Diagram]


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**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


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Rivaroxaban

[Chemical structure of 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)
N=4832
Enoxaparin + warfarin
Pre-defined treatment period at 3, 6, 12 month
Rivaroxaban 15 mg bid x 21 days then 20 mg daily
N=3449
End of treatment and 30 day follow up

Designated PE study Cancer 4-6%

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 noninf

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

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

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

Apixaban

Author: Ed (Edgar181)
AMPLIFY Study

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

Confirmed symptomatic DVT/PE (N=5395)

PE 25%
Cancer 2.5-2.8%

N=2704

Enoxaparin + warfarin

6 month

R

End of treatment and 30 day follow up

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

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%

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**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%

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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>R R Lower limit Upper limit Weight (%)</th>
<th>R R (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent VTE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Re-Cover (abiraterone)</td>
<td>1.10 0.66 1.84 11.2</td>
<td></td>
</tr>
<tr>
<td>Edoxaban (EVT) (enoxaparin)</td>
<td>0.70 0.46 1.07 16.7</td>
<td></td>
</tr>
<tr>
<td>Edoxaban (EVT) (enoxaparin)</td>
<td>1.13 0.76 1.69 18.4</td>
<td></td>
</tr>
<tr>
<td>Amifost (apixaban)</td>
<td>0.84 0.60 1.18 25.4</td>
<td></td>
</tr>
<tr>
<td>Hoksol (edoxaban)</td>
<td>0.83 0.60 1.14 23.3</td>
<td></td>
</tr>
<tr>
<td>Subtotal (I² = 0%; P = 0.46)</td>
<td>0.88 0.74 1.05 100</td>
<td></td>
</tr>
</tbody>
</table>

| Fatal PE |                                        |             |
| Re-Cover (abiraterone) | 0.33 0.03 3.18 18.0 |             |
| Edoxaban (EVT) (enoxaparin) | 2.98 0.12 73.04 9.0 |             |
| Edoxaban (EVT) (enoxaparin) | 2.00 0.18 21.99 16.0 |             |
| Amifost (apixaban) | 0.50 0.05 5.57 16.0 |             |
| Hoksol (edoxaban) | 1.33 0.30 5.96 41.1 |             |
| Subtotal (I² = 0%; P = 0.71) | 1.02 0.39 5.96 100 |             |

| Overall mortality |                                        |             |
| Re-Cover (abiraterone) | 0.99 0.55 1.81 7.1 |             |
| Edoxaban (EVT) (enoxaparin) | 0.77 0.51 1.17 14.6 |             |
| Edoxaban (EVT) (enoxaparin) | 1.16 0.80 1.68 18.3 |             |
| Amifost (apixaban) | 0.79 0.53 1.19 15.6 |             |
| Hoksol (edoxaban) | 1.05 0.82 1.33 44.4 |             |
| Subtotal (I² = 0%; P = 0.50) | 0.97 0.83 1.14 100 |             |

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>R R Lower limit Upper limit Weight (%)</th>
<th>R R (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Re-Cover (abiraterone)</td>
<td>0.60 0.46 1.40 15.2</td>
<td></td>
</tr>
<tr>
<td>Edoxaban (EVT) (enoxaparin)</td>
<td>0.27 0.16 1.56 21.8</td>
<td></td>
</tr>
<tr>
<td>Edoxaban (EVT) (enoxaparin)</td>
<td>0.37 0.19 1.98 11.4</td>
<td></td>
</tr>
<tr>
<td>Amifost (apixaban)</td>
<td>0.37 0.17 1.98 11.4</td>
<td></td>
</tr>
<tr>
<td>Hoksol (edoxaban)</td>
<td>0.00 0.00 1.27 20.3</td>
<td></td>
</tr>
<tr>
<td>Subtotal (I² = 0%; P = 0.05)</td>
<td>0.41 0.38 100</td>
<td></td>
</tr>
</tbody>
</table>

| Non-major bleeding at a site of thrombus |                                        |             |
| Re-Cover (abiraterone) | 0.47 0.34 0.67 1.4 |             |
| Edoxaban (EVT) (enoxaparin) | 0.27 0.12 0.55 20.4 |             |
| Edoxaban (EVT) (enoxaparin) | 0.27 0.12 0.55 20.4 |             |
| Amifost (apixaban) | 0.00 0.00 1.27 20.3 |             |
| Hoksol (edoxaban) | 0.00 0.00 1.27 20.3 |             |
| Subtotal (I² = 0%; P = 0.05) | 0.63 0.58 156 |             |

| Clinically relevant non-major bleeding |                                        |             |
| Re-Cover (abiraterone) | 0.42 0.32 0.52 17.1 |             |
| Edoxaban (EVT) (enoxaparin) | 0.37 0.20 0.63 17.1 |             |
| Edoxaban (EVT) (enoxaparin) | 0.37 0.20 0.63 17.1 |             |
| Amifost (apixaban) | 0.00 0.00 1.27 20.3 |             |
| Hoksol (edoxaban) | 0.00 0.00 1.27 20.3 |             |
| Subtotal (I² = 0%; P = 0.05) | 0.63 0.58 156 |             |

NNT=149

NNT=263

NNT=56

NNT=714

NNT=1111
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).

<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></th>
<th>Dabigatran Pradaxa®</th>
<th>Rivaroxaban Xarelto®</th>
<th>Apixaban Eliquis®</th>
<th>Edoxaban Savaysa®</th>
</tr>
</thead>
</table>
| **VTE treatment**    | 150 mg bid (CrCl >30 mL/min) after 5-10 days of parenteral | 15 mg bid x 21 days then 20 mg daily (CrCl >30) | 10 mg bid x 7 days then 5 mg bid (CrCl >25 and/or Cr <2.5) | 60 mg daily  
• 30 mg daily (if CrCl 15–50, body weight is ≤60 kg, or strong p-GP inhibitors) after 5-10 days of parenteral |
| **VTE secondary prevention** | 150 mg bid | 20 mg daily | 2.5 mg bid | N/A |
| **Atrial fibrillation** | 150 mg bid (CrCl >30)  
• 75 mg bid (CrCl 15–30) | 20 mg daily (CrCl >50)  
• 15 mg daily (CrCl 15–50) | 5 mg bid  
• 2.5 mg bid (if ≥2 factors: age ≥80, weight ≤60 kg, Cr ≥1.5 mg/dL) | 60 mg daily  
• 30 mg daily (if CrCl 15–50, body weight is ≤60 kg, or strong p-GP inhibitors) |
| **Orthopedic VTE prevention** | 110 mg on first day, then 220 mg daily | 10 mg daily | 2.5 mg bid | N/A |

### 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, crioritinib, 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 qualify 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

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)

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**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 qualify data so cannot be recommended for routine use

# Direct Reversal Agents

<table>
<thead>
<tr>
<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>
</tr>
<tr>
<td><strong>Drugs targeted against</strong></td>
<td>Dabigatran</td>
<td>Rivaroxaban, apixaban, edoxaban, 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>
</tr>
<tr>
<td><strong>FDA activity</strong></td>
<td>FDA approved 10/16/2015</td>
<td>FDA discussion in August 2016 but has not been approved</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 reveres 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 actor 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 rivaroxaban, 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