**Objectives**

- Compare current FDA-approved oral anticoagulants
- Understand practical issues that arise with novel oral anticoagulants
- Consider future outlook of this class of medications

**Timeline: FDA approval of NOACs**

<table>
<thead>
<tr>
<th>Year</th>
<th>Generic</th>
<th>Brand</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>Dabigatran</td>
<td>Pradaxa</td>
<td>NVAF</td>
</tr>
<tr>
<td>2011</td>
<td>Rivaroxaban</td>
<td>Xarelto</td>
<td>NVAF</td>
</tr>
<tr>
<td>2012</td>
<td>Apixaban</td>
<td>Eliquis</td>
<td>NVAF, DVT/PE</td>
</tr>
<tr>
<td>2014</td>
<td>Dabigatran</td>
<td>Pradaxa</td>
<td>DVT/PE</td>
</tr>
<tr>
<td>2015</td>
<td>Apixaban</td>
<td>Eliquis</td>
<td>DVT/PE</td>
</tr>
<tr>
<td></td>
<td>Edoxaban</td>
<td>Savaysa</td>
<td>NVAF, DVT/PE</td>
</tr>
</tbody>
</table>

**FDA-approved oral anticoagulants**

- **Edoxaban**
  - Route: Oral once daily
  - Bioavailability: 62%
  - Tmax: 1-2 h
  - Renal excretion: 50%
  - Plasma protein binding: 55%

**Stroke risk reductions: afib RCTs**

**Primary Safety Endpoint: Major Bleed**

<table>
<thead>
<tr>
<th>Trial (afib)</th>
<th>Novel Agent (%/y)</th>
<th>Warfarin (%/y)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P (superiority)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY</td>
<td>Dabigatran 150 mg BID</td>
<td>3.11</td>
<td>3.36</td>
<td>0.93 (0.81–1.07)</td>
</tr>
<tr>
<td>ROCKET-AF</td>
<td>Rivaroxaban 20 mg QD</td>
<td>3.60</td>
<td>3.45</td>
<td>1.04 (0.90–1.20)</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>Apixaban 5 mg BID</td>
<td>2.13</td>
<td>3.09</td>
<td>0.69 (0.60–0.80)</td>
</tr>
<tr>
<td>ENGAGE AF-TIMI 48</td>
<td>Edoxaban 60 mg QD</td>
<td>2.75</td>
<td>3.43</td>
<td>0.80 (0.71–0.91)</td>
</tr>
</tbody>
</table>

**Secondary Safety Endpoint: ICH**

<table>
<thead>
<tr>
<th>Trial (afib)</th>
<th>Novel Agent (%/y)</th>
<th>Warfarin (%/y)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P (superiority)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY</td>
<td>Dabigatran 150 mg BID</td>
<td>0.10</td>
<td>0.38</td>
<td>0.26 (0.14–0.49)</td>
</tr>
<tr>
<td>ROCKET-AF</td>
<td>Rivaroxaban 20 mg QD</td>
<td>0.8</td>
<td>1.2</td>
<td>0.67 (0.47–0.93)</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>Apixaban 5 mg BID</td>
<td>0.33</td>
<td>0.80</td>
<td>0.42 (0.30–0.58)</td>
</tr>
<tr>
<td>ENGAGE AF-TIMI 48</td>
<td>Edoxaban 60mg QD</td>
<td>0.85</td>
<td>0.39</td>
<td>0.47 (0.34–0.63)</td>
</tr>
</tbody>
</table>

**Secondary Safety Endpoint: GIB**

<table>
<thead>
<tr>
<th>Trial (afib)</th>
<th>Novel Agent (%/y)</th>
<th>Warfarin (%/y)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P (superiority)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY</td>
<td>Dabigatran 150 mg BID</td>
<td>1.56</td>
<td>1.67</td>
<td>1.55 (1.19–1.89)</td>
</tr>
<tr>
<td>ROCKET-AF</td>
<td>Rivaroxaban 20 mg QD</td>
<td>1.04 (0.90–1.20)</td>
<td>0.58</td>
<td></td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>Apixaban 5 mg BID</td>
<td>0.76</td>
<td>0.86</td>
<td>0.89 (0.70–1.15)</td>
</tr>
<tr>
<td>ENGAGE AF-TIMI 48</td>
<td>Edoxaban 60 mg QD</td>
<td>1.51</td>
<td>1.23</td>
<td>1.23 (1.02–1.50)</td>
</tr>
</tbody>
</table>

**VTE: Safety vs. Efficacy**


**Warfarin (Coumadin): Indications**

- Atrial fibrillation (AF)
- DVT & PE (treatment and secondary prevention)
- Artificial valve
- Medical management post-MI

---

**Updates to CHEST guidelines (January 2016)**

“Non-vitamin K antagonist oral anticoagulants (NOACs) are suggested over warfarin for initial and long-term treatment of VTE in patients without cancer. Since publication of the 9th edition, new studies show that NOACs are as effective as VKA therapy with reduced risk of bleeding and increased convenience for patients and health-care providers.”
**Warfarin (Coumadin)**

**Strengths**
- Monitoring / Customized Goals
- Cost
- Reversal
- Most indications/ clinical experience

**Weaknesses**
- Monitoring
- Genetic variability
- DDIs
- Drug-food interactions

---

**Case Study 1: Valvular afib**

<table>
<thead>
<tr>
<th>Admit Dx</th>
<th>Acute CVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age/Gender</td>
<td>77 y/o M</td>
</tr>
<tr>
<td>Weight</td>
<td>64 kg</td>
</tr>
<tr>
<td>PMH</td>
<td>Afib, Bioprosthetic MVR</td>
</tr>
<tr>
<td>Home meds</td>
<td>Eliquis 5mg BID</td>
</tr>
</tbody>
</table>

---

**Artificial valves**

- Warfarin is only anticoagulant approved in setting of prosthetic heart valve
- RE-LY (Pradaxa):
  - phase 2 study
  - included aortic and mitral valve replacement; used higher than currently approved doses
  - Terminated early due to problems with patients post-op:
    - More stroke
    - Increased pericardial bleeding
  - Result: contraindication for all NOACs

---

**Artificial Valve**

- 51 y/o F with h/o mechanical AVR (no AF)
  - warfarin → dabigatran (150 mg, twice daily)
  - normal renal function
  - 2mo later:
    - Progressive exertional dypnea
    - TEE: multiple clots on prosthetic AV

---

**Artificial Valves**

<table>
<thead>
<tr>
<th>Valve type</th>
<th>Goal INR range</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial (mechanical)</td>
<td>2-3</td>
<td>Lifelong</td>
</tr>
<tr>
<td>Mitral (bioprosthetic)</td>
<td>2-3</td>
<td>3 months post-op, then ASA</td>
</tr>
<tr>
<td>Mitral (mechanical)</td>
<td>2.5-3.5</td>
<td>Lifelong</td>
</tr>
</tbody>
</table>

---

**Artificial Valve**

- 59 y/o F with h/o mechanical MVR (no AF)
  - warfarin → dabigatran (150 mg, twice daily)
  - compliant to therapy
  - normal renal function
  - 3 months later: large thrombus on mitral valve

---

**Artificial Valves: Warfarin**

- CHEST 2012; 141(2)(Suppl):7S–47S

---

**Case Study 2: Mechanical MVR**

- 59 y/o F with h/o mechanical MVR (no AF)
  - warfarin → dabigatran (150 mg, twice daily)
  - compliant to therapy
  - normal renal function
  - 3 months later: large thrombus on mitral valve

---

**Artificial Valves**

- CHEST 2012; 141(2)(Suppl):7S–47S

---

**Artificial Valve**

- 59 y/o F with h/o mechanical MVR (no AF)
  - warfarin → dabigatran (150 mg, twice daily)
  - compliant to therapy
  - normal renal function
  - 3 months later: large thrombus on mitral valve

---

**Artificial Valves**

- CHEST 2012; 141(2)(Suppl):7S–47S
Case Study 2: Labile INR

<table>
<thead>
<tr>
<th>Indication</th>
<th>PAF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age/Gender</td>
<td>87 y/o F</td>
</tr>
<tr>
<td>Weight</td>
<td>88 kg</td>
</tr>
<tr>
<td>Scr</td>
<td>1.4 - 2.1 (CrCl 21-32)</td>
</tr>
<tr>
<td>Additional info</td>
<td>Admit INR: &gt;17.54; Labile, requiring weekly monitoring</td>
</tr>
</tbody>
</table>

Case Study 3: Bleed Risk

<table>
<thead>
<tr>
<th>Indication</th>
<th>AF (new onset): LE arterial embolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age/Gender</td>
<td>84 y/o F</td>
</tr>
<tr>
<td>Weight</td>
<td>69 kg</td>
</tr>
<tr>
<td>Scr</td>
<td>2-2.5 (CrCl 19-23)</td>
</tr>
<tr>
<td>Baseline INR</td>
<td>1.19</td>
</tr>
<tr>
<td>FOBT</td>
<td>Positive; multiple episodes of melena</td>
</tr>
<tr>
<td>Additional info</td>
<td>Pt requests &quot;new agent&quot; w/o monitoring</td>
</tr>
</tbody>
</table>

Dabigatran (Pradaxa)

- NVAF (2010):
  - CrCl > 30 ml/min: 150mg PO BID
  - CrCl 15-30 ml/min: 75mg PO BID
  - Do not use if CrCl < 15 ml/min
- DVT/PE treatment and secondary prevention (2014):
  - CrCl > 30 ml/min: 150mg PO BID after 5-10 days of parenteral anticoagulation
  - Do not use if CrCl < 30 ml/min

Dabigatran (Pradaxa)

**Strengths**
- Less ICH vs. warfarin
- No monitoring
- Reversal

**Weaknesses**
- Higher GIB vs. warfarin
- Dyspepsia
- No monitoring
- Significant renal elimination
- Parenteral therapy requirements (VTE)
- Cost
- BID dosing
- Increased risk of MI?
Reversal: Idarucizumab

- Reversal for DTIs
- Phase 3 trial, published Aug 2015

Rivaroxaban (Xarelto)

- NVAF (2011):
  - CrCl > 50 ml/min: 20mg PO daily with evening meal
  - CrCl 30-50 ml/min: 15mg PO daily with evening meal
  - Do not use if CrCl < 15 ml/min
- DVT/PE treatment and secondary prevention (2012):
  - CrCl > 30 ml/min:
    - 15mg PO Bid with food x 21 days
    - Then 20mg PO daily with food
  - Do not use if CrCl < 30 ml/min
- Prophylaxis of DVT following hip/knee replacement
  - 10mg once daily with or without food
  - Do not use if CrCl < 30 ml/min

Data in obese population

- EINSTEIN-PE: 15% of patients weighed >100 kg
- Bariatric Surgery Case Study:
  - Switched from warfarin to Xarelto post-op, due to unstable INR.
  - Plasma concentrations measured for 1st and 2nd dose.
  - Peak levels within acceptable range for therapy.
- Kinetic Study:
  - Prophylactic dosing of Xarelto
  - Cmax and AUC unaffected in patients >120 kg

Case Study 4: Cost

<table>
<thead>
<tr>
<th>Admit Dx</th>
<th>Acute CVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age/Gender</td>
<td>66 y/o M</td>
</tr>
<tr>
<td>Weight</td>
<td>105 kg</td>
</tr>
<tr>
<td>PMH</td>
<td>Afib; CVA one month prior</td>
</tr>
<tr>
<td>Home med</td>
<td>Xarelto 20mg QPM</td>
</tr>
<tr>
<td>Insurance</td>
<td>Medicare Advantage</td>
</tr>
</tbody>
</table>

Apixaban (Eliquis)

- NVAF (2012):
  - 5mg PO BID for all patients, including ESRD on HD, except 2.5mg PO BID if ≥ 2 of the following:
    - Age ≥ 80
    - Weight ≤ 60 kg
    - Scr ≥ 1.5 mg/dL
- DVT/PE treatment and secondary prevention (2014):
  - 10mg PO BID x 7 days
  - Then 5mg PO BID x 6 months
  - Then 2.5mg PO BID thereafter if necessary
- Prophylaxis of DVT following hip/knee replacement
  - 2.5mg BID

Strengths

- Less ICH vs. warfarin
- No monitoring
- No parenteral therapy requirements (VTE)
- Once daily dosing
- Data in obese population

Weaknesses

- Cost
- Significant renal elimination
- Reliance on food for absorption
- No reversal

**Apixaban (Eliquis)**

**Strengths**
- Best bleeding profile
- Superior efficacy
- No monitoring
- Minimal renal elimination
- Labeled for HD population
- No parenteral therapy requirements

**Weaknesses**
- Cost
- BID dosing
- No reversal

---

**Case Study 5: No monitoring!**

**Indication**
- Acute PE

**Age/Gender**
- 40 y/o F

**Weight**
- 100 kg

**SCr**
- ESRD on HD

**Additional info**
- Refuses any treatment requiring monitoring

---

**Apixaban: ESRD on HD**

- Population was not included in clinical efficacy or safety studies
- Approved based on single dose PK/PD data in patients with ESRD on HD
- Use standard dosing

---

**Edoxaban (Savaysa)**

**Strengths**
- Less major bleeding
- Less ICH vs. warfarin
- No monitoring
- Once daily dosing
- Co-pay card

**Weaknesses**
- Significant renal elimination
- Warning for use in normal renal function
- Parenteral therapy requirements (VTE)
- More GIB vs. warfarin
- No reversal

---

**ENGAGE AF–TIMI 48:**

**Primary Endpoint (Stroke/SEE)**

<table>
<thead>
<tr>
<th>Population</th>
<th>Warfarin</th>
<th>Edox 60 mg</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 95 (Indicated Population)</td>
<td>211 (5485)</td>
<td>142 (5417)</td>
<td>0.68 (0.55, 0.84)</td>
</tr>
<tr>
<td>≤ 50 b</td>
<td>Warfarin 50 (1356)</td>
<td>Edox 60 mg 45 (1372)</td>
<td>0.90 (0.60, 1.34)</td>
</tr>
<tr>
<td>&gt; 50 to ≤ 80</td>
<td>Warfarin 135 (3053)</td>
<td>Edox 60 mg 71 (3020)</td>
<td>0.53 (0.40, 0.70)</td>
</tr>
<tr>
<td>&gt; 80 to ≤ 95</td>
<td>Warfarin 26 (1076)</td>
<td>Edox 60 mg 26 (1025)</td>
<td>1.05 (0.61, 1.82)</td>
</tr>
<tr>
<td>&gt; 95</td>
<td>Warfarin 21 (1527)</td>
<td>Edox 60 mg 40 (1595)</td>
<td>1.87 (1.10, 3.17)</td>
</tr>
</tbody>
</table>

---

**WARNING (A) REDUCED EFFICACY IN NONVALVULAR ATRIAL FIBRILLATION PATIENTS WITH CREATININE CLEARANCE (CRI) > 95 ML/MIN**

---

**Example for Edoxaban (Savaysa)**

- NVAF (2015):
  - CrCl > 95 ml/min: Do not use
  - CrCl 50-95 ml/min: 60 mg once daily
  - CrCl 15-50 ml/min: 30 mg once daily
  - CrCl < 15 ml/min: Do not use

  - CrCl > 50ml/min: 60 mg once daily ***after 5-10 days of parenteral anticoagulation***
  - CrCl 15-50 ml/min or weight ≤ 60 kg: 30 mg once daily
  - CrCl < 15 ml/min: Do not use

---

### Case Study 6: Non-responder

**Indication:** Acute PE  
**Age/Gender:** 32 y/o F  
**Weight:** 230 kg  
**SCr:** 0.6 (CrCl > 95)  
**Additional Info:** Dose escalation to 10mg with no response

---

### Objectives
- Compare current FDA-approved oral anticoagulants  
- Understand practical issues with these agents:  
  - Drug-drug interactions (DDIs)  
  - Appropriate hold times  
- Consider future outlook

---

### Case Study 7: DDIs

<table>
<thead>
<tr>
<th>Indication</th>
<th>Acute DVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age/Gender</td>
<td>33 y/o M</td>
</tr>
<tr>
<td>Weight</td>
<td>60 kg</td>
</tr>
<tr>
<td>SCr</td>
<td>ESRD on HD</td>
</tr>
<tr>
<td>HAART regimen</td>
<td>Atazanavir, Ritonavir, Dolutegravir, Abacavir</td>
</tr>
<tr>
<td>Other DDIs</td>
<td>Fluconazole</td>
</tr>
<tr>
<td>Insurance</td>
<td>Medicaid</td>
</tr>
</tbody>
</table>

---

### Drug-Drug Interactions

**Rivaroxaban & Apixaban:** Dual CYP3A4 and p-gp  
**Dabigatran & Edoxaban:** p-gp  

- **Strong inhibitors:** ketoconazole, itraconazole, (fluconazole), ritonavir, indinavir, clarithromycin, (erythromycin), conivaptan  
- **Strong inducers:** rifampin, carbamazepine, phenytoin, St. John’s wort

---

### Case Study 8: Hold Times

<table>
<thead>
<tr>
<th>Indication</th>
<th>Acute DVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age/Gender</td>
<td>67 y/o M</td>
</tr>
<tr>
<td>Weight</td>
<td>74 kg</td>
</tr>
<tr>
<td>Home regimen</td>
<td>Xarelto 20mg daily</td>
</tr>
<tr>
<td>PMH</td>
<td>DVT/PE; Off Xarelto x 5 days for upper endoscopy/colonoscopy</td>
</tr>
<tr>
<td>Admit Dx</td>
<td>Acute RLE DVT requiring thrombectomy</td>
</tr>
</tbody>
</table>

---

### Boxed Warning on all NOACs
- Increased risk of thrombosis if prematurely stopped without adequate bridge therapy  
- Events occurred during end-of-trial transition back to warfarin  
  - only 1.8% of patients received bridge therapy

---

BJH 2011;155(2):137-149  
J Thromb Thrombolysis 2013 Nov;36(4):533-5 (Xarelto- s/p bariatric surgery)  
Swiss Med Wkly. 2014 Jan 22;144:w13906  
Peri-operative Management: Appropriate Hold Times

<table>
<thead>
<tr>
<th>Drug</th>
<th>Standard</th>
<th>Special Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>5 – 7 days</td>
<td></td>
</tr>
<tr>
<td>Dabigatran</td>
<td>1 – 2 days</td>
<td>3 – 5 days if CrCl &lt; 50 ml/min</td>
</tr>
<tr>
<td>Resume therapy post-op, as soon as adequate hemostasis has been established</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>24 hours</td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td>48 hours</td>
<td>24 hours if low bleeding risk</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>24 hours</td>
<td></td>
</tr>
</tbody>
</table>

Objectives
- Compare current FDA-approved oral anticoagulants
- Understand practical issues with these agents
- Consider future outlook

Artificial valves: Phase 2 Trials
- DAWA (Dabigatran):
  - Bioprosthetic MVR and/or AVR
  - ≥ 3 months post-op
  - Dosing at 110 mg BID
  - Brazil
- CATHAR (Rivaroxaban)
  - Mechanical AVR
  - Switzerland

Oncology population
- Currently LMWH is the standard of care:
  - 52% lower risk of recurrence compared to VKA
  - Difficulty maintaining therapeutic INR
- CALLISTO: Rivaroxaban
  - Registry of >4000 patients
  - Secondary prevention of VTE in active cancer
- Phase 2 trial: Apixaban
  - Primary prevention of VTE in active cancer
  - Developing risk stratification tool

Pipeline: Betrixaban
- Oral Xa inhibitor, once daily dosing
- Phase 2 trials:
  - Half life: 20 h
  - Least renal elimination (5-7%)
  - Least hepatic metabolism
  - Lowest peak-to-trough concentration ratio
- Phase 3 trial: APEX
  - Extended VTE prophylaxis inpatient and post-discharge in acute medically ill population (35-42 days)
  - Control: Lovenox 40mg SC daily (6-14 days)

Pipeline: Andexanet alfa
- Reversal for Xa inhibitors
- Phase 3 trials ongoing:
  - Annexa-A (Apixaban)
  - Annexa-R (Rivaroxaban)
Objectives
- Compare current FDA-approved oral anticoagulants
- Understand practical issues with these agents
- Consider future outlook