NOAC
NON VITAMIN K ORAL ANTICOAGULANTS

Kert D. Sabbath, MD FACP
Smilow Cancer Hospital
Waterbury, CT
Disclosures
None
Educational Objectives

• Review physiology of coagulation
• Review NOACs- Non-Vitamin K Anticoagulants
• Risks/benefits of NOACs
• Indications and Contraindications of NOACs
• Special situations-procedures, treatment interruptions
Why do we want to anticoagulate a patient?

• Correct coagulation imbalances that have resulted in pathological clotting
• Prevent thrombosis in high risk situations
• Reset a patients “hemostat”
Coagulation Review

• Coordinated cascade of enzymatically activated proteins and cofactors
• Function to stop bleeding and protect blood volume.
• Pathologic or excess clotting requires physicians to manipulate and “retune” the system
Intrinsic pathway

- XII
- XIIa
- XI
- Xla
- IX
- IXa
- X

Extrinsic pathway

- Tissue Injury
- Tissue factor
- VII - TF
- VII

- warfarin
- Xa inhibitors
- heparin
- Anti III
- IIa inhibitors

Prothrombin (II)

- Thrombin (IIa)

Fibrinogen

- Fibrin
- Xllla

Fibrin Clot

- Fibrin degradation products

Plasminogen

- Plasmin

- tPA
Timeline of Anticoagulants

- 1910s: Heparin
- 1950s: Warfarin
- 1980-90s: LMWH
- 2001: Fondaparinux
- 2010: Dabigatran
- 2011: Rivaroxaban
- 2012: Apixaban
Heparin and Heparinoids

- Rapidly acting anticoagulants
- Dramatically increase activity of Antithrombin III by 1000X.
- Activated ATIII inhibits activated IIa (thrombin) and Xa
- Heparinoids- Fondiparinox, Enoxaparin......
  - More selective sites of action
  - Less Heparin induced thrombocytopenia and thrombosis
Heparin

Advantages
• Rapid onset/washout
• Can be monitored
• Useful despite significant renal impairment

Disadvantages
• Parenteral
• Thrombocytopenia
• Heparinoids are relatively contraindicated with significant renal insufficiency (eGFR <30 cc/min)
Heparins/Heparinoids

Heparin: mode of action

Indirect effect on thrombin via AT. Acts like a catalyst in an enzymatic reaction.

Diagram:
- Heparin
- AT
- Thrombin
- Pentasaccharide sequence

1 and 2 represent different stages or components in the interaction.
Sites of Action

Tissue factor

X

IX

VIIIa

IXa

Factor Xa

Direct oral agents
- Apixaban
- Rivaroxaban

Indirect parenteral agents
- Fondaparinux
- UFH
- LMWH

Thrombin

Fibrinogen

Fibrin
Vit K dependent factors as targets for anti-coagulation

• Multiple factors require Vit K for activity
  – Procoagulant -II, VII, IX, X
  – Anticoagulants-Protein S, Protein C

• Warfarin is prototype and remains the most commonly used drug
Physiology of Warfarin

Vitamin K-depandan coagulation factors: II, VII, IX, X

Precursor → Biologically active

Carboxylase

Oxidative deactivation

Vitamin K (reduced) → Vitamin K (epoxide)

VKORC1

CYP2C9

S-warfarin

Warfarin

CYP1A2 CYP3A4

R-warfarin
Challenges of Vit K antagonists

• Primarily oral
• Depends of dietary and enteral bacterial production of Vit K
• Require adequate hepatic factor synthesis
• Multiple sites of potential pathway disruption
• Numerous pharmaceutical interactions that both increase and decrease activity
• Frequent monitoring
• No proven algorithms for dosing
Warfarin

• Highly effective-Yes
• Oral-Yes, Parenteral Alternatives-No
• Schedule-Daily but frequent dose changes
• Easy to monitor-No
• Drug/food interactions-Extensive
• Risk of bleeding-Variable
• Easy to reverse-Somewhat-Vit K/FFP
Ideal Anticoagulant

- Highly effective
- Oral vs. parenteral
- Rapid onset
- Schedule that optimizes compliance-daily vs. multiple daily doses
- Easy to monitor-rarely if ever needed
- Minimal drug or food interactions
- Low risk of bleeding
- Easy to reverse
NOACs
Non Vit K Oral Anti-Coagulants

• Developed in an attempt to create the “ideal” anti-coagulant
• Target the one of the two major regulatory sites of coagulation cascade-
  – IIa (thrombin)
  – Xa
• As a class
  – Minimal monitoring
  – Fewer (not zero) drug-drug interactions
  – Lower risk of bleeding-potentially
IIa Inhibitors
Mechanism of Action
Direct Xa Inhibitors

• Rivaroxiban-Xarelto
• Eliquis-Apixiban
NOAC Indications

- Postoperative VTE prophylaxis
- Atrial fibrillation
- Venous ThromboEmbolus-VTE
NOAC Indications

- Postoperative VTE prophylaxis
- Atrial fibrillation
- Venous Thromboembolism-VTE
VTE Prophylaxis
Who is at risk?

- General surgical patients 10%-40%
- Orthopedic surgical patients 40%-60%
- Medical patients-critically ill
VTE Prophylaxis
Clinical Trials

- RECORD TRIALS
- Hip and knee replacement
- Rivaroxaban 10 mg daily Started postop versus enoxaparin started preop
- Slight increase bleeding with rivaroxaban
- Good alternative to subcutaneous medication
## VTE Prophylaxis: Apixaban
### ADOPT Trial: Results

<table>
<thead>
<tr>
<th>Outcome</th>
<th>APIX (N=2211)</th>
<th>ENOX (N=2284)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total VTE/VTE-related death during treatment period</td>
<td>2.71%</td>
<td>3.06%</td>
<td>0.87 (0.62 - 1.23)</td>
</tr>
<tr>
<td>Secondary Outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite total VTE/VTE-related death at the end of parenteral treatment period</td>
<td>1.73%</td>
<td>1.61%</td>
<td>1.06 (0.69 – 1.63)</td>
</tr>
<tr>
<td>Major bleeding during treatment period</td>
<td>0.47% (N=3184)</td>
<td>0.19% (N=3217)</td>
<td>2.58 (1.02 – 7.24)</td>
</tr>
<tr>
<td>Major bleeding during post-parenteral treatment period</td>
<td>0.44% (N=3181)</td>
<td>0.19% (N=3210)</td>
<td>2.35 (0.92 – 6.65)</td>
</tr>
</tbody>
</table>

APIX=apixaban; ENOX=enoxaparin; DVT=deep vein thrombosis; RR=relative risk; CI=confidence interval; VTE=venous thromboembolism

Atrial fibrillation: Epidemiology

- Affects about 1% of population - about 350,000 Canadians\textsuperscript{1,2}
- Most common cardiac arrhythmia requiring medical care\textsuperscript{1}
- Lifetime risk 1 in 4 for age $\geq$ 40 years\textsuperscript{3}
- Prevalence increases with age; hence increasing due to increasingly elderly population\textsuperscript{2}
Stroke risk in AF

- 4-5 fold increase in stroke risk in AF; 1 in 6 strokes occurs in AF patients\(^1,2\)
- Stroke risk in AF increases from 1.5% at age 50-59 to 23.5% at age 80-89\(^1\)
- About 40% of AF patients in primary care may be at high risk of stroke\(^3\)
Warfarin is highly effective for the prevention of stroke in patients with atrial fibrillation

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Relative Risk Reduction (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted-dose warfarin compared with placebo or control</td>
<td></td>
</tr>
<tr>
<td>AFASAK I, 1989 (2); 1990 (3)</td>
<td></td>
</tr>
<tr>
<td>SPAF I, 1991 (5)</td>
<td></td>
</tr>
<tr>
<td>BAATAF, 1990 (4)</td>
<td></td>
</tr>
<tr>
<td>CAFA, 1991 (6)</td>
<td></td>
</tr>
<tr>
<td>SPINAF, 1992 (7)</td>
<td></td>
</tr>
<tr>
<td>EAFT, 1993 (8)</td>
<td></td>
</tr>
<tr>
<td>All trials (n = 6)</td>
<td></td>
</tr>
</tbody>
</table>

- Favors Warfarin
- Favors Placebo or Control
## Trials Comparing NOACs vs. Warfarin

<table>
<thead>
<tr>
<th></th>
<th>RE-LY</th>
<th>ROCKET AF</th>
<th>ARISTOTLE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sample size</strong></td>
<td>18,113</td>
<td>14,264</td>
<td>18,201</td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td>Non-valvular A fib</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CHADS ≥ 1</td>
<td>Non-valvular A fib</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CHADS ≥ 2</td>
<td>Non-valvular A fib</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CHADS ≥ 1</td>
</tr>
<tr>
<td><strong>NOACs</strong></td>
<td>Dabigatran 110 mg or</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>150 mg BID</td>
<td>Rivaroxaban 20 mg OD</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Apixaban 5 mg BID</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>Open RCT with two</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>doses of double-blind</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>dabigatran</td>
<td>Double-blind</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Double-blind</td>
</tr>
</tbody>
</table>
Dabigatran vs Warfarin in atrial fibrillation risk of stroke

Figure 1. Cumulative Hazard Rates for the Primary Outcome of Stroke or Systemic Embolism, According to Treatment Group.
Dabigatran vs Warfarin in atrial fibrillation risk of bleed

<table>
<thead>
<tr>
<th>Event</th>
<th>Dabigatran, 110 mg</th>
<th>Dabigatran, 150 mg</th>
<th>Warfarin</th>
<th>Dabigatran, 110 mg, vs. Warfarin</th>
<th>P Value</th>
<th>Dabigatran, 150 mg, vs. Warfarin</th>
<th>P Value</th>
<th>Dabigatran, 150 mg vs. 110 mg</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td>322</td>
<td>2.71</td>
<td>375</td>
<td>3.11</td>
<td>0.80</td>
<td>0.93</td>
<td>0.31</td>
<td>1.16</td>
<td>0.052</td>
</tr>
<tr>
<td>Life threatening</td>
<td>145</td>
<td>1.22</td>
<td>175</td>
<td>1.45</td>
<td>0.68</td>
<td>0.81</td>
<td>0.04</td>
<td>1.19</td>
<td>0.11</td>
</tr>
<tr>
<td>Non-life threatening</td>
<td>198</td>
<td>1.66</td>
<td>226</td>
<td>1.88</td>
<td>0.94</td>
<td>1.07</td>
<td>0.47</td>
<td>1.14</td>
<td>0.17</td>
</tr>
<tr>
<td>Gastrointestinal†</td>
<td>133</td>
<td>1.12</td>
<td>182</td>
<td>1.51</td>
<td>1.10</td>
<td>1.50</td>
<td>&lt;0.001</td>
<td>1.36</td>
<td>0.007</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>1566</td>
<td>13.16</td>
<td>1787</td>
<td>14.84</td>
<td>0.79</td>
<td>0.91</td>
<td>0.005</td>
<td>1.16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Major or minor bleeding</td>
<td>1740</td>
<td>14.62</td>
<td>1977</td>
<td>16.42</td>
<td>0.78</td>
<td>0.91</td>
<td>0.002</td>
<td>1.16</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>27</td>
<td>0.23</td>
<td>36</td>
<td>0.30</td>
<td>0.31</td>
<td>0.40</td>
<td>&lt;0.001</td>
<td>1.32</td>
<td>0.28</td>
</tr>
<tr>
<td>Extracranial bleeding</td>
<td>299</td>
<td>2.51</td>
<td>342</td>
<td>2.84</td>
<td>0.94</td>
<td>1.07</td>
<td>0.38</td>
<td>1.14</td>
<td>0.11</td>
</tr>
<tr>
<td>Net clinical benefit outcome‡</td>
<td>844</td>
<td>7.09</td>
<td>832</td>
<td>6.91</td>
<td>901</td>
<td>7.64</td>
<td>0.92</td>
<td>0.91</td>
<td>0.98</td>
</tr>
</tbody>
</table>

* Data are shown for all patients who had at least one event. All analyses were based on the time to the first event. Hemorrhagic stroke was a subcategory of stroke in the efficacy analysis.
Warfarin the underdog!

- Is **NOT** rat poison
  - Rats have evolved (and so should you...)

- Advantages of warfarin
  - Active by the oral route
  - Once daily dosing
  - Can be monitored
    - Surgeries
    - Bleeding episodes
    - Recurrent events
    - Adherence
  - Rapidly-acting antidote available
  - Low cost
A Cardiologist's Perspective:
On The Evolving Treatment Paradigm for SPAF

- Compared with warfarin, each of the 3 new agents:
  - Are at least as effective in preventing stroke/systemic embolism
  - Are associated with less intracranial bleeding
  - Are associated with similar or less major bleeding
  - Offer greater ease of use

- Many patients will benefit from the advantages offered by these drugs that ideally should be started by primary care or emergency department physicians rather than cardiologists
VTE Treatment
CONCLUSIONS

For the treatment of acute venous thromboembolism, a fixed dose of dabigatran is as effective as warfarin, has a safety profile that is similar to that of warfarin, and does not require laboratory monitoring. (ClinicalTrials.gov number, NCT00291330.)
Risk of Recurrent VTE

Figure 1. Cumulative Risk of Recurrent Venous Thromboembolism or Related Death during 6 Months of Treatment among Patients Randomly Assigned to Dabigatran or Warfarin.
Risk of Major and any Bleeding

![Graph showing the cumulative risk of major and any bleeding over months since first intake of study drug.](image)

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Dabigatran and major bleeding</th>
<th>Warfarin and any bleeding</th>
<th>Dabigatran and any bleeding</th>
<th>Warfarin and major bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1273</td>
<td>1266</td>
<td>1273</td>
<td>1266</td>
</tr>
<tr>
<td></td>
<td>1194</td>
<td>1178</td>
<td>1117</td>
<td>1064</td>
</tr>
<tr>
<td></td>
<td>1153</td>
<td>1146</td>
<td>1055</td>
<td>993</td>
</tr>
<tr>
<td></td>
<td>1124</td>
<td>1128</td>
<td>1002</td>
<td>950</td>
</tr>
<tr>
<td></td>
<td>1105</td>
<td>1110</td>
<td>971</td>
<td>909</td>
</tr>
<tr>
<td></td>
<td>1080</td>
<td>1093</td>
<td>931</td>
<td>870</td>
</tr>
<tr>
<td></td>
<td>884</td>
<td>859</td>
<td>747</td>
<td>692</td>
</tr>
</tbody>
</table>

**Figure 2.** Cumulative Risks of a First Event of Major Bleeding and of Any Bleeding among Patients Randomly Assigned to Dabigatran or Warfarin.

The hazard ratio with dabigatran for major bleeding at 6 months was 0.82 (95% CI, 0.45 to 1.48; P=0.38), and the hazard ratio with dabigatran for any bleeding at 6 months was 0.71 (95% CI, 0.59 to 0.85; P<0.001).
EINSTEIN Studies
Warfarin vs. Rivaroxaban

• Acute DVT or PE
• Enoxaparin followed by warfarin vs. rivaroxaban 15 mg BID for 3 wk then 20 mg daily.
• Rivaroxaban was noninferior. Major and non-major bleeding not significantly different.
• Extended study-rivaroxaban had 82% decrease for current rate with 0.7% major bleeding and 5.4% nonmajor bleeding over 190 days
• no need for bridging
Challenges and Complications of NOAC Medications
Comparison of new anticoagulants

- No head-to-head comparative studies comparing new anticoagulants with each other
- Different study designs and patient populations; hence indirect comparisons are difficult
## Indirect comparison/meta-analysis of new anticoagulants

<table>
<thead>
<tr>
<th>Author</th>
<th>Findings</th>
</tr>
</thead>
</table>
| Lip¹     | - No significant differences between new anticoagulants for preventing stroke and systemic embolism  
           - Less major bleeding with apixaban than dabigatran 150 mg BID and rivaroxaban, but not significantly different from dabigatran 110 mg BID |
| Adam²    | Higher MI risk with direct thrombin inhibitors than with factor Xa inhibitors |
| Miller³  | - New anticoagulants decreased risk for stroke, systemic embolism, all-cause mortality, and vascular mortality  
           - Also lower risk for intracranial bleeding  
           - Inconclusive data on risks for major bleeding and GI bleeding |

Clinical trials vs. Real World

• Trial patients
  – Patients highly selected
  – Consistent f/u
  – Monitored compliance

• Real World
  – Generally sicker, multiple co-morbid conditions
  – More opportunity for medication interactions
  – Less monitoring of meds and labs
  – Less compliance, longer times between visits, multiple physician interactions
Table 1. Properties of warfarin and oral inhibitors of thrombin and factor Xa inhibitors approved for use in the United States

<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>Dabigatran etexilate</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>Vitamin K epoxide reductase (VKORC1) lowers levels of vitamin K-dependent coagulation factors</td>
<td>Thrombin</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
</tr>
<tr>
<td><strong>Prodrug</strong></td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Bioavailability</strong></td>
<td>&gt; 95%</td>
<td>6.5%</td>
<td>80%</td>
<td>~ 66%</td>
</tr>
<tr>
<td><strong>Tmax</strong></td>
<td>2 h</td>
<td>2.5-4 h</td>
<td>3 h</td>
<td></td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>40 h</td>
<td>12-14 h</td>
<td>7-13 h</td>
<td>8-13 h</td>
</tr>
<tr>
<td><strong>Routine coagulation monitoring</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>Once daily (INR-adjusted)</td>
<td>Fixed, BID</td>
<td>Fixed, BID</td>
<td>Fixed, BID</td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td>Hepatically metabolized</td>
<td>80% renal</td>
<td>67% renal (half is inactive drug), 33% fecal</td>
<td>25% renal, 75% fecal</td>
</tr>
<tr>
<td><strong>Potential drug interactions</strong></td>
<td>CYP 2C9, 3A4, and 1A2</td>
<td>Potent P-gp inhibitors and P-gp inducers</td>
<td>Strong dual CYP 3A4 and P-gp inhibitors/inducers</td>
<td>Strong dual CYP 3A4 and P-gp inhibitors/inducers</td>
</tr>
</tbody>
</table>

Adapted from Bauer² and Ansell.⁴

Tmax indicates time to peak plasma levels; and P-gp, P-glycoprotein.
Potential Drug Interactions

• Avoid combined P-gp and Strong CYP3A4 inhibitors: Ketoconazole, Itraconazole, tironavir, conivaptan

• Avoid Combined P-gp and strong CYP3A3 inducers: Carbamazepine, phenytoin, rifampin, St. John’s Wort

• Caution: ASA, Plavix
## Switching from warfarin to new anticoagulant

<table>
<thead>
<tr>
<th>To</th>
<th>Instructions</th>
</tr>
</thead>
<tbody>
<tr>
<td>To apixaban</td>
<td>Discontinue warfarin and start apixaban when INR is &lt; 2.0</td>
</tr>
<tr>
<td>To dabigatran</td>
<td>Start dabigatran only after warfarin has been discontinued and INR is &lt; 2.0</td>
</tr>
<tr>
<td>To rivaroxaban</td>
<td>Stop warfarin and determine INR</td>
</tr>
<tr>
<td></td>
<td>- INR ≤ 2.5: Start rivaroxaban at usual dose</td>
</tr>
<tr>
<td></td>
<td>- INR &gt; 2.5: Delay start rivaroxaban until INR is ≤ 2.5</td>
</tr>
</tbody>
</table>

# Switching from new anticoagulant to warfarin

| From apixaban | • Start warfarin and continue apixaban for ≥2 days  
|               | • After 2 days, obtain INR prior to next apixaban dose  
|               | • Continue coadministration until INR is ≥ 2.0 |
| From dabigatran | Start warfarin according to CrCl:  
|                 | • ≥50 ml/min: 3 days before discontinuing dabigatran  
|                 | • 30- <50 ml/min: 2 days before discontinuing dabigatran  
|                 | INR not reliable to assess warfarin effect till ≥2 days after discontinuation |
| From rivaroxaban | • First 2 days: give warfarin at usual starting dose; no INR testing  
|                 | • Continue rivaroxaban till INR ≥2.0; then discontinue  
|                 | • INR ≥24 hours after last dose of rivaroxaban for warfarin effect |

### Switching from parenteral anticoagulant to new anticoagulant

<table>
<thead>
<tr>
<th>From</th>
<th>To</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>apixaban</td>
<td>To apixaban</td>
<td>Done at the next scheduled dose</td>
</tr>
<tr>
<td>dabigatran</td>
<td>To dabigatran</td>
<td>Initiate dabigatran 0-2 hours before next dose of other agent is due, or at time of discontinuation in case of continuous treatment</td>
</tr>
<tr>
<td>rivaroxaban</td>
<td>To rivaroxaban</td>
<td>Start rivaroxaban when heparin is stopped, or 0-2 hours before next scheduled injection of full-dose of LMWH or fondaparinux. If receiving prophylactic anticoagulant, start rivaroxaban ≥6 hours after the last dose</td>
</tr>
</tbody>
</table>
Switching from new anticoagulant to parenteral anticoagulant

<table>
<thead>
<tr>
<th>From</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>Done at the next scheduled dose</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>For prevention of VTE after hip- or knee-replacement surgery, wait 12 hours after last dose of dabigatran before switching</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Discontinue rivaroxaban; give first dose of parenteral anticoagulant when next rivaroxaban dose was scheduled</td>
</tr>
</tbody>
</table>
Bridging anticoagulation

- Bridging anticoagulation with LMWH is often used empirically, before and after surgery
- Debate on need for bridging anticoagulation\cite{1,2,3,4}
- Manufacturers’ recommendations for dabigatran and rivaroxaban:
  - Discontinue these drugs at least 1 day before the procedure
  - Consider longer times if major surgery, spinal puncture, or placement of a spinal or epidural catheter or port, where complete hemostasis may be required, or if moderate renal impairment

\begin{itemize}
  \item ACCP Guidelines 2012.
  \item Douketis JD. Blood 2011;117(19):5044-5049.
  \item Wysokinski WE, McBane RD. Circulation 2012;126(4):486-490.
  \item BRIDGE Study Overview.
\end{itemize}
Interruptation of dabigatran or rivaroxaban before surgery or invasive procedures

<table>
<thead>
<tr>
<th>Calculated creatinine clearance, mL/min</th>
<th>Half-life, hours</th>
<th>Timing of last dose before surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Standard risk of bleeding*</td>
</tr>
<tr>
<td>Dabigatran</td>
<td></td>
<td>24 h</td>
</tr>
<tr>
<td>&gt; 80</td>
<td>13 (11-22)</td>
<td></td>
</tr>
<tr>
<td>&gt; 50- ≤ 80</td>
<td>15 (12-34)</td>
<td></td>
</tr>
<tr>
<td>&gt; 30- ≤ 50</td>
<td>18 (13-23)</td>
<td></td>
</tr>
<tr>
<td>≤ 30</td>
<td>27 (22-35)</td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td></td>
<td>24 h</td>
</tr>
<tr>
<td>&gt; 30</td>
<td>12 (11-13)</td>
<td></td>
</tr>
<tr>
<td>&lt; 30</td>
<td>Unknown</td>
<td>2 d</td>
</tr>
</tbody>
</table>

*Examples are cardiac catheterization, ablation therapy, colonoscopy without removal of large polyps, and uncomplicated laparoscopic procedures, such as cholecystectomy.

†Examples are major cardiac surgery, insertion of pacemakers or defibrillators (resulting from the risk for pocket hematoma), neurosurgery, large hernia surgery, and major cancer/urologic/vascular surgery.

## Renal impairment

Renal impairment - a risk factor for bleeding with anticoagulants

<table>
<thead>
<tr>
<th></th>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal clearance</td>
<td>25%&lt;sup&gt;1&lt;/sup&gt;</td>
<td>80%&lt;sup&gt;1&lt;/sup&gt;</td>
<td>33%&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Severe impairment</td>
<td>Not recommended for CrCl &lt; 15 ml/min&lt;sup&gt;3-5&lt;/sup&gt;</td>
<td>Contraindicated&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Not recommended for CrCl &lt; 15 ml/min&lt;sup&gt;3-5&lt;/sup&gt;</td>
</tr>
<tr>
<td>Other</td>
<td>Less affected than dabigatran, preferred in moderate impairment&lt;sup&gt;3-5&lt;/sup&gt;</td>
<td>Lower dose if age ≥ 75 with risk factors for bleeding&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Less affected than dabigatran, preferred in moderate impairment&lt;sup&gt;3-5&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Use in Renal Dysfunction

- 80%, 33% and 25% of dabigatran, rivaroxaban and apixaban are renally eliminated.
- Use Cockroft-Gault formula to measure renal function rather than eGFR.
  - Cr CL 15-30 cc/min dabigatran 75 mg BID
  - Cr Cl > 30 cc dabigatran 150 mg BID
Bleeding with new anticoagulants

- Up to ~3% of patients may develop major bleeding
- Major bleeding rates comparable/lower than with warfarin
- Factors for increased risk: ↑ age, renal impairment
- No effective antidotes known
- INR is unreliable for new anticoagulants
- No precise information with aPTT, PT; but may be qualitative indicator of drug presence

### Major Bleeding Rates in the Phase III Trials with the NOACs for VTE

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trial</th>
<th>Dose</th>
<th>N</th>
<th>Duration (mean)</th>
<th>Major bleeding (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>RE-COVER</td>
<td>150 mg BID</td>
<td>1273</td>
<td>6 m</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td>RE-COVER II</td>
<td>150 mg BID</td>
<td>1279</td>
<td>6 m</td>
<td>1.2</td>
</tr>
<tr>
<td></td>
<td>RE-MEDY</td>
<td>150 mg BID</td>
<td>1430</td>
<td>18 m</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>RE-SONATE</td>
<td>150 mg BID</td>
<td>681</td>
<td>12 m</td>
<td>0.3</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>EINSTEIN-DVT</td>
<td>15 mg BID, then 20 mg daily</td>
<td>1731</td>
<td>3 m, 6 m, 12 m</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>EINSTEIN-PE</td>
<td>15 mg BID, then 20 mg daily</td>
<td>2419</td>
<td>3 m, 6 m, 12 m</td>
<td>1.1</td>
</tr>
<tr>
<td></td>
<td>EINSTEIN-EXT</td>
<td>20 mg daily</td>
<td>602</td>
<td>6 m, 12 m</td>
<td>0.7</td>
</tr>
<tr>
<td>Apixaban</td>
<td>AMPLIFY-EXT</td>
<td>5 mg BID</td>
<td>840</td>
<td>12 m</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Management of Bleeding Complications of Anti-Xa Inhibitors

- Activated factor X inhibitors (ie, rivaroxaban, apixaban, LMWHs)
  - Activated charcoal within 2 h of drug ingestion for oral ACs
  - Prothrombin complex concentrates (PCC)
  - Recombinant activated factor VII
  - Under clinical investigation
    - PRT445
      - Universal reversal agents for factor Xa inhibitors, such as enoxaparin, and fondaparinux
      - Novel recombinant protein that is similar to the native factor Xa
    - PER997
      - Synthetic small molecule demostrated to bind to several NOACs, including dabigatran, rivaroxaban, apixaban and edoxaban

Antidotes strategy

- Dialysis removes 60% of dabagatrin over 2-3 hours.
- Rivaroxaban and apixaban highly protein bound and non-dialyzable.
NOAC Contra-indications

- Not indicated for cancer patients due to interaction with chemotherapy
- Pregnant and breast-feeding women should not be prescribed
- Don't use if thrombolytic therapy is being considered
- Caution in low weight (less than 50 kg), morbid obesity or renal dysfunction
Summary

• Highly effective drugs for anti-coagulation
  – DVT/PE prophylaxis with surgery
  – Atrial Fibrillation
  – Acute DVT/PE

• At least as effective as warfarin

• Risk of bleeding is similar or less than warfarin

• **NOT RISK FREE** and still need CLINICAL judgment
Thank You