Update on Anticoagulation Agents and Reversals

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Update on anticoagulation agents and reversals

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Abbreviations

- Acute Coronary Syndrome (ACS)
- Activated prothrombin complex concentrate (aPCC)
- Body mass index (BMI)
- Coronary artery disease (CAD)
- Deep vein thrombosis (DVT)
- Direct oral anticoagulants (DOAC)
- Gastrointestinal (GI)
- Hip fracture surgery (HFS)
- Intracranial hemorrhage (ICH)
- Low molecular weight heparin (LMWH)

- Myocardial infarction (MI)
- Non-valvular atrial fibrillation (NVAF)
- Peripheral artery disease (PAD)
- Prothrombin complex concentrate (PCC)
- Pulmonary embolism (PE)
- Total hip arthroplasty (THA)
- Total knee arthroplasty (TKA)
- Unfractionated heparin (UFH)
- Venous thromboembolism (VTE)
- Vitamin K antagonist (VKA)
Objectives

1. Review direct oral anticoagulants (DOACs)
2. Discuss the place in therapy for DOACs
3. Describe agents available for the reversal of bleeding associated with the use of DOACs
4. Define the pharmacist’s role in the selection/monitoring of anticoagulation and reversal agents
# Anticoagulation Agents

<table>
<thead>
<tr>
<th>Traditional</th>
<th>Novel</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vitamin K Antagonist (VKA)</strong></td>
<td><strong>Direct Thrombin Inhibitors</strong></td>
</tr>
<tr>
<td>Warfarin (Coumadin®)</td>
<td>Dabigatran (Pradaxa®)</td>
</tr>
<tr>
<td><strong>Unfractionated Heparin (UFH) &amp; Heparinoids</strong></td>
<td></td>
</tr>
<tr>
<td>Heparin</td>
<td>Argatroban</td>
</tr>
<tr>
<td>Dalteparin (Fragmin®)</td>
<td>Bivalirudin (Angiomax®)</td>
</tr>
<tr>
<td><strong>Direct Factor Xa Inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>Fondaparinux (Arixtra®)</td>
<td>Rivaroxaban (Xarelto®)</td>
</tr>
<tr>
<td><strong>Low Molecular Weight Heparin (LMWH)</strong></td>
<td></td>
</tr>
<tr>
<td>Enoxaparin (Lovenox®)</td>
<td>Apixaban (Eliquis®)</td>
</tr>
<tr>
<td><strong>Betrixaban (Bevyxxa®)</strong></td>
<td></td>
</tr>
</tbody>
</table>
Anticoagulation Cascade

- **Warfarin**
  - Inhibits vitamin K and factors VII, IX, X, IIa
- **Dabigatran**
  - Inhibits factor IIa
- **Rivaroxaban, apixaban, edoxaban and betrixaban**
  - Inhibit factor Xa

## Direct Oral Anticoagulants (DOACs)

<table>
<thead>
<tr>
<th>Site of action</th>
<th>dabigatran</th>
<th>rivaroxaban</th>
<th>apixaban</th>
<th>edoxaban</th>
<th>betrixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication</strong></td>
<td>Factor IIa (Thrombin)</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
</tr>
<tr>
<td>Prevention (hip or knee) and treatment of VTE</td>
<td>Prevention (hip or knee) and treatment of VTE</td>
<td>Prevention (hip or knee) and treatment of VTE</td>
<td>Treatment of VTE</td>
<td>Prevention of VTE</td>
<td></td>
</tr>
<tr>
<td>NVAF</td>
<td>NVAF</td>
<td>NVAF</td>
<td>NVAF</td>
<td>NVAF</td>
<td></td>
</tr>
<tr>
<td>CAD or PAD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Half-life (hours)</strong></td>
<td>12-17</td>
<td>5-9 (elderly 11-12)</td>
<td>9-14</td>
<td>10-14</td>
<td>19-27</td>
</tr>
<tr>
<td><strong>Frequency</strong></td>
<td>Once daily</td>
<td>Once daily</td>
<td>Twice daily</td>
<td>Once daily</td>
<td>Once daily</td>
</tr>
<tr>
<td><strong>Renal excretion</strong></td>
<td>80 %</td>
<td>33 %</td>
<td>25 %</td>
<td>35-50 %</td>
<td>18 %</td>
</tr>
</tbody>
</table>

NVAF-non-valvular atrial fibrillation; VTE-venous thromboembolism; CAD-coronary artery disease; PAD-peripheral artery disease

## DOACs Compared to Warfarin

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>As effective as warfarin</td>
<td>Expensive</td>
</tr>
<tr>
<td>Lower overall risk of major bleeding</td>
<td>Increased gastrointestinal bleeding</td>
</tr>
<tr>
<td>Less intracranial hemorrhage (ICH)</td>
<td>Shorter half-lives</td>
</tr>
<tr>
<td>No monitoring required</td>
<td>Limited ability to assess effectiveness</td>
</tr>
<tr>
<td>No diet restrictions</td>
<td>Limited data in end-stage renal/hepatic impairment</td>
</tr>
<tr>
<td>Less drug interactions</td>
<td>Costly antidote</td>
</tr>
</tbody>
</table>

Lawrence, LK. Direct oral anticoagulants and parenteral direct thrombin inhibitors, UpToDate, Waltham, MA, 2018.
ICH with DOACs

- Incidence varies between 0.6% to 1%

- VTE treatment
  - 52% reduction in ICH compared with warfarin
  - Van Der Hulle, et al (2014)
    - Meta-analysis of 5 trials (n=24,555)
    - Non-fatal ICH
      - DOACs 0.09% vs. warfarin 0.25%

ICH with DOACs

- AF
  - Lower risk of ICH for the treatment of stroke prevention

<table>
<thead>
<tr>
<th>DOAC vs. warfarin</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban</td>
<td>0.80 vs. 1.2</td>
</tr>
<tr>
<td>Apixaban</td>
<td>0.33 vs. 0.80</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>0.39 vs. 0.85</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>0.10 vs. 0.39</td>
</tr>
</tbody>
</table>

GI Bleeding with DOACs

- DOACs associated with 25–30% increased risk when compared to warfarin
  - Apixaban has shown to have a favorable profile
  - Rivaroxaban associated with highest risk among DOACs

<table>
<thead>
<tr>
<th>Apixaban vs. dabigatran</th>
<th>Apixaban vs. rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.38 vs. 2.73 %/year</td>
<td>1.34 vs. 3.54 %/year</td>
</tr>
<tr>
<td>P &lt; 0.001</td>
<td>P &lt; 0.001</td>
</tr>
</tbody>
</table>

GI Bleeding with DOACs

- Rate of GI bleeding increases with age among patients using DOACs
  - Higher risk in patients 65 years or older

- Co-therapy with proton pump inhibitors (PPI) or H2 antagonists has shown to reduce the incidence of GI bleed

PLACE IN THERAPY
Indications

1. Prophylaxis of Venous Thromboembolism (VTE)

2. Treatment of VTE

3. Non-valvular Atrial Fibrillation (AF)

4. Acute Coronary Syndrome (ACS)
VTE Prophylaxis in Medical Patients

- CHEST Guidelines (2012)
  - Recommended agents for at risk patients
    - LMWH, UFH, fondaparinux, intermittent pneumatic compression and/or graduated compression stockings
    - Limited guidance on DOACs

- Betrixaban (Bevyxxa®) is the only FDA approved DOAC for medical VTE prophylaxis

VTE Prophylaxis in Medical Patients

- American Society Hematology (ASH) recommendation (2018)
  - **LMWH** over DOACs
  - Alternatives
    - Unfractionated heparin
    - Fondaparinux
  - Inpatient only treatment recommended, rather than inpatient plus extended duration outpatient

VTE Prophylaxis in Surgical Orthopedic Patients

- Total hip arthroplasty (THA) or total knee arthroplasty (TKA)
  - LMWH
  - Fondaparinux
  - Warfarin
  - Aspirin
  - Heparin
  - Rivaroxaban
  - Dabigatran
  - Apixaban

Treatment duration—Minimum 10 to 14 days

VTE Prophylaxis in Surgical Orthopedic Patients

- Hip fracture surgery (HFS)
  - **LMWH**
  - Heparin
  - Fondaparinux
  - Warfarin
  - Aspirin

- DOACs not recommended

Treatment duration—Minimum 10 to 14 days

Aspirin Role in VTE Prophylaxis in Surgical Patients

  - Retrospective review of post-op medication claims of patients who received aspirin, warfarin or enoxaparin within 6 months of THA and TKA
  - DVT rates
    - Aspirin 2.20%, warfarin 4.74%, enoxaparin 3.73%

  - Compared rivaroxaban 10 mg PO daily for 5 days followed by aspirin 81 mg PO daily versus rivaroxaban
  - VTE occurrence
    - Aspirin/rivaroxaban 0.64% vs. 0.70% rivaroxaban alone (p<0.001)

VTE Prophylaxis in General Surgical Patients

- **CHEST Guidelines (2012)**
  - General and abdominal-pelvic surgery
    - Low risk of VTE
      - Mechanical over pharmacological prophylaxis
    - Moderate and high risk of VTE in patients with low risk of bleeding
      - Unfractionated heparin
      - LMWH
    - High risk of VTE and high risk of bleeding
      - Mechanical prophylaxis

DOACs not recommended

## VTE Prophylaxis Dosing

<table>
<thead>
<tr>
<th>Name</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heparin</strong></td>
<td>5000 units subQ Q12h (low risk) Q8h (high risk)</td>
</tr>
<tr>
<td><strong>Enoxaparin</strong></td>
<td>40 mg subQ Q24h 30 mg Q24h (renal impairment)</td>
</tr>
<tr>
<td><strong>Dabigatran</strong></td>
<td>220 mg PO daily (hip surgery only)</td>
</tr>
<tr>
<td><strong>Rivaroxaban</strong></td>
<td>10 mg PO daily (hip or knee surgery only)</td>
</tr>
<tr>
<td><strong>Apixaban</strong></td>
<td>2.5 mg PO twice daily (hip or knee surgery only)</td>
</tr>
<tr>
<td><strong>Betrixaban</strong></td>
<td>160 mg PO on day 1 then 80 mg PO daily</td>
</tr>
</tbody>
</table>
VTE TREATMENT
VTE Treatment

- Initial treatment (first 5 days of therapy)
  - Unfractioned heparin
  - LMWH
  - Fondaparinux
  - Rivaroxaban
  - Apixaban

- Maintenance
  - DOACs preferred over warfarin (except betrixaban)

Can be given without initial parenteral anticoagulation (in hemodynamically stable pts without extensive clot burden)

## VTE Treatment

<table>
<thead>
<tr>
<th>Type</th>
<th>Duration of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal provoked VTE</td>
<td>3 months</td>
</tr>
<tr>
<td>Isolated distal DVT</td>
<td>3 months</td>
</tr>
<tr>
<td>Unprovoked VTE</td>
<td>3 months</td>
</tr>
<tr>
<td>First unprovoked VTE</td>
<td>• Extended treatment</td>
</tr>
<tr>
<td></td>
<td>(low-moderate risk of bleeding)</td>
</tr>
<tr>
<td></td>
<td>• 3 months</td>
</tr>
<tr>
<td></td>
<td>(high bleeding risk)</td>
</tr>
<tr>
<td>Second unprovoked VTE</td>
<td>3 months</td>
</tr>
<tr>
<td>Cancer</td>
<td>3 months</td>
</tr>
<tr>
<td></td>
<td>Independent of risk of bleeding</td>
</tr>
</tbody>
</table>

*Extended treatment – no stop date*
VTE Extended Treatment with Aspirin

CHEST Guidelines (2016)

- Recommend aspirin to prevent recurrence of VTE
  - Dose: 100 mg once daily (low dose)
  - Criteria:
    - Unprovoked proximal DVT/PE
    - No contraindication to aspirin use
    - Stopped oral anticoagulation or completed anticoagulation treatment
    - Low risk of bleeding

VTE Treatment in Special Population

CHEST Guidelines (2016)

- Cancer
  - LMWH recommended over warfarin or DOACs (long term therapy)

- Pregnancy
  - LMWH recommended
  - Duration of therapy: 3 to 6 months
  - Not recommended:
    - DOACs (insufficient safety information)
    - Warfarin
    - Fondaparinux

VTE Treatment Dosing
(Initial)

- Enoxaparin 1mg/kg subQ Q12h
  (reduce to Q24h in renal impairment)
  - Alternative: 1.5 mg/kg subQ Q24h

- Fondaparinux 5 – 10 mg subQ daily
  - Dependent on weight

- Heparin infusion
  - 80 units/kg IV bolus then 18 units/kg/h infusion
VTE Treatment Dosing

- Rivaroxaban 15 mg PO Q12h for 21 days followed by 20 mg PO daily

- Apixaban 10 mg PO Q12h for 7 days followed by 5 mg PO Q12h

- Dabigatran 150 mg PO Q12h*

- Edoxaban 60 mg PO Q24h (>60 kg)*
  30 mg PO Q24h (≤60 kg)*

*At least 5 days of initial therapy with parenteral anticoagulation
STROKE PREVENTION IN ATRIAL FIBRILLATION
Stroke Prevention in AF

- DOACs shown to be at least as safe and effective as warfarin for the prevention of stroke and systemic embolism
- Reduced events by 19% compared to warfarin (p<0.0001)

Safety

<table>
<thead>
<tr>
<th>Major Bleeds</th>
<th>Reduced by 14% (p=0.06)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial hemorrhage</td>
<td>Reduced by 52% (p&lt;0.0001)</td>
</tr>
<tr>
<td>GI Bleeds</td>
<td>Increased (p=0.04)</td>
</tr>
</tbody>
</table>

Assessment Tools in AF

- **CHADS\textsuperscript{2} → CHA\textsubscript{2}DS\textsubscript{2}—VASc**
  - Used to determine stroke risk

- **HAS—BLED score**
  - Developed originally for warfarin
  - Predicts serious bleeding
    - Only score predictive of intracranial bleeding

Both scores complement each other

Stroke Risk Assessment Tool

**CHA$_2$DS$_2$–VASc**
- Congestive Heart Failure
- Hypertension
- Age $\geq 75$ years*
- Diabetes
- Stroke*
- Vascular disease
- Age ($> 65$ years)
- Sex (Female)

*Two (2) points assigned to these parameters

<table>
<thead>
<tr>
<th>Score</th>
<th>Risk</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 male 1 female</td>
<td>Low</td>
<td>None</td>
</tr>
<tr>
<td>$\geq 1$ male $\geq 2$ female</td>
<td>Moderate</td>
<td>No therapy or DOAC or warfarin</td>
</tr>
<tr>
<td>$\geq 2$</td>
<td>Moderate or High</td>
<td>DOAC or warfarin</td>
</tr>
</tbody>
</table>

Bleeding Risk Assessment Tool

- **HAS—BLED** used to address modifiable bleeding risk factors
- Performed at every patient contact

<table>
<thead>
<tr>
<th>HAS-BLED</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>1 point</td>
</tr>
<tr>
<td>Abnormal renal/liver function</td>
<td>1 point each</td>
</tr>
<tr>
<td>Stroke</td>
<td>1 point</td>
</tr>
<tr>
<td>Bleeding tendency (i.e. gastric ulcer disease)</td>
<td>1 point</td>
</tr>
<tr>
<td>Labile INR</td>
<td>1 point</td>
</tr>
<tr>
<td>Age</td>
<td>1 point</td>
</tr>
<tr>
<td>Drugs (i.e NSAIDs or aspirin)</td>
<td>1 point</td>
</tr>
</tbody>
</table>

Score >3 (high risk): warrant more frequent monitoring

AF Treatment

CHEST Guidelines (2018)

- Treatment of choice
  - DOACs over warfarin (strong recommendation)
- Prior unprovoked bleeding, warfarin-associated bleeding or high risk of bleeding (weak recommendation)
  - Apixaban
  - Edoxaban
  - Dabigatran

AF Treatment in Mechanical Heart Valves

- DOACs not recommended—limited studies

- RE-ALIGN trial (n=252)
  - Studied dabigatran vs. warfarin
    - Stroke occurrence: 5% vs. 0%
    - Bleeding: 27% vs. 12% (p<0.01)
    - Study terminated prematurely due to safety concerns

- Treatment of choice: LMWH or UFH until stable on warfarin

### AF Treatment in Elderly

Age increases risk of intracranial hemorrhage (ICH) and mechanical falls

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Findings</th>
</tr>
</thead>
</table>
| Sardar, et al. (2014)  | • Meta-analysis of pts ≥75 yo  
                         • Compared DOACs (rivaroxaban, apixaban and dabigatran) vs. warfarin | DOACs:                                       |
|                        |                                                                         | • No excess bleeding  
                         • Equal or greater efficacy                  |
| Chao, et al. (2018)    | • Cohort study in the very elderly (≥90 yo)  
                         • Evaluated the risk of ICH and stroke in patients in 2 groups (DOACs vs. warfarin) | Risk of ICH:  
                         • DOACs 0.42% vs. warfarin 1.63%; p<0.044) |

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AF Treatment in Elderly

- **Risk of falls**
  - Individual risk assessment prior to starting DOACs
  - A patient would have to fall 295 times per year for the risk from falls to outweigh the benefits of anticoagulation

- **Conclusion**
  - DOACs rarely considered a contraindication

**Fear the clot, not the bleed**

AF Treatment in End-Stage Renal Disease (ESRD)

- **Dias, et al. (2016)**
  - Rivaroxaban (15 mg PO daily)
    - Single-dose study resulted in similar exposure to patients studied who had CrCl 15 to 49 mL/minute

- **Siontis, et al. (2018)**
  - Apixaban (5 mg PO twice daily)
    - Lower risk of stroke, major bleeding and death vs. VKA

- Limited studies available – use with caution

AF Treatment in Special Population

CHEST Guidelines (2018)

- Pregnancy
  - Treatment of choice: LMWH Q12h
  - Avoid use of DOACs

- Breast feeding
  - Use LMWH, unfractionated heparin, or warfarin
  - DOACs not recommended
AF Treatment in Obese Patients

- International Society of Hemostasis and Thrombosis (2016) Guidelines
  - Patients with BMI >40 kg/m² or >120 kg
    - Limited clinical data available
    - Warfarin preferred agent
    - DOACs not recommended
      - No FDA approved dosage recommendation

**Treatment Based on Patient Characteristics**

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Therapeutic options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent stroke/SE/TIA</td>
<td>dabigatran</td>
</tr>
<tr>
<td>Moderate-severe renal impairment*</td>
<td>apixaban, dabigatran, edoxaban, rivaroxaban</td>
</tr>
<tr>
<td>High risk of GI bleeding</td>
<td>apixaban, dabigatran</td>
</tr>
<tr>
<td>Major GI symptoms or dyspepsia</td>
<td>apixaban, rivaroxaban, edoxaban</td>
</tr>
<tr>
<td>High risk of bleeding**</td>
<td>apixaban, dabigatran, edoxaban</td>
</tr>
<tr>
<td>Low pill burden</td>
<td>edoxaban, rivaroxaban, warfarin</td>
</tr>
</tbody>
</table>

TIA - transient ischemic attack; GI - gastrointestinal  
*CrCl 15-49 mL/min  
**Defined as a HAS-BLED of ≥3 points
## AF Treatment Dosing

<table>
<thead>
<tr>
<th>Name</th>
<th>Dose</th>
<th>Renal impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>1 mg/kg subQ Q12h</td>
<td>1 mg/kg subQ Q24h</td>
</tr>
<tr>
<td><strong>Chronic treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>Dose to INR goal of 2-3</td>
<td>No dose adjustment</td>
</tr>
<tr>
<td>Aspirin</td>
<td>75–100 mg PO daily</td>
<td>No dose adjustment</td>
</tr>
<tr>
<td><strong>Acute and chronic treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td>5 mg PO Q12h</td>
<td>2.5 mg PO Q12h</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>20 mg PO daily</td>
<td>15 mg PO daily</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>150 mg PO Q12h</td>
<td>75 mg PO Q12h</td>
</tr>
</tbody>
</table>
ACUTE CORONARY SYNDROME
Acute Coronary Syndrome

ATLAS ACS 2–TIMI 51 Trial

- Compared placebo vs. rivaroxaban 2.5 mg PO Q12 h vs. rivaroxaban 5 mg PO Q12 h

Conclusion

- Reduced death from cardiovascular causes, MI, or stroke (rivaroxaban 8.9 vs. placebo 10.7%; p<0.008)
- Rivaroxaban 2.5 mg PO twice daily may be considered in patients with low risk of bleeding not requiring chronic anticoagulation for other indications

PERIOPERATIVE MANAGEMENT
To Bridge or Not to Bridge?

Risk of bleeding

Risk of thrombosis
### Perioperative Bleeding Risk Assessment

<table>
<thead>
<tr>
<th>Minimal risk</th>
<th>Low risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endoscopy without surgery</td>
<td>Dental procedures</td>
<td>Major surgery (duration &gt;45 min)</td>
</tr>
<tr>
<td>Central venous catheter removal</td>
<td>Hand/foot/shoulder surgery</td>
<td>Cardiac surgeries (coronary artery bypass)</td>
</tr>
<tr>
<td>Abscess incision</td>
<td>Cardiac procedures (i.e. implantable devices and catheter ablation)</td>
<td>Dental procedures (i.e. multiple teeth extraction)</td>
</tr>
<tr>
<td>Glaucoma or cataract intervention</td>
<td>Cholecystectomy</td>
<td>Major orthopedic surgeries (i.e. joint arthroplasty)</td>
</tr>
</tbody>
</table>

## Perioperative Bleeding Risk Assessment

<table>
<thead>
<tr>
<th>Calculated CrCl (mL/min)</th>
<th>Timing of Last Dose Before Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low Risk of Bleeding</td>
</tr>
<tr>
<td><strong>Dabigatran</strong></td>
<td></td>
</tr>
<tr>
<td>&gt; 50</td>
<td>Minimum 24 hours</td>
</tr>
<tr>
<td>31-50</td>
<td>2 days</td>
</tr>
<tr>
<td>&lt; 30</td>
<td>4 days</td>
</tr>
<tr>
<td><strong>Rivaroxaban, apixaban, edoxaban</strong></td>
<td></td>
</tr>
<tr>
<td>&gt; 50</td>
<td>1 day</td>
</tr>
<tr>
<td>31-50</td>
<td>1-2 days</td>
</tr>
<tr>
<td>&lt; 30</td>
<td>2 days</td>
</tr>
</tbody>
</table>
When to Restart DOACs?

- Delay until adequate hemostasis

<table>
<thead>
<tr>
<th>Procedural Bleed Risk</th>
<th>DOAC Resumption time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal</td>
<td>May not require interruption of DOAC therapy</td>
</tr>
<tr>
<td>Low</td>
<td>24 hours post-operative</td>
</tr>
<tr>
<td>High</td>
<td>48-72 hours post-operative</td>
</tr>
</tbody>
</table>

RISK OF BLEEDING
Critical sites

- Intraocular
- GI tract
- Retroperitoneal
- Brain

BLEEDING MANAGEMENT AND REVERSAL AGENTS
General Measures of Bleeding

- **Assessment:**
  - Determine the urgency of event
  - Assess the risk of bleeding and thrombosis
  - Obtain accurate medication history

- **Discontinue/hold anticoagulation**
  - Provide supportive measures

- **Pharmacological intervention**
  - Specific reversal agents

- **Replace blood losses**

Garcia DA, Management of bleeding in patients receiving DOACs, UpToDate, Waltham, MA, 2018.
# Reversal Agents

<table>
<thead>
<tr>
<th>Name</th>
<th>Reversal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin</td>
<td>Protamine sulfate</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>Protamine sulfate</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>No specific reversal&lt;br&gt;Fresh Frozen Plasma (FFP); PCC (Kcentra®);&lt;br&gt;Recombinant Factor VIIa</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Vitamin K (Mephyton®)—PO or IV&lt;br&gt;FFP; PCC (Kcentra®); Recombinant Factor VIIa</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Idarucizumab (Praxbind®)&lt;br&gt;aPCC (FEIBA®)&lt;br&gt;Activated charcoal (within 2 h of ingestion)&lt;br&gt;Antifibrinolytic (i.e. tranexamic acid)</td>
</tr>
<tr>
<td>Apixaban, Rivaroxaban</td>
<td>PCC (Kcentra®)&lt;br&gt;Andexanet alfa (Andexxa®)&lt;br&gt;Activated charcoal (within 2 h of ingestion)&lt;br&gt;Antifibrinolytic (i.e. tranexamic acid)</td>
</tr>
</tbody>
</table>
Management of ICH

  - Dabigatran, rivaroxaban or apixaban induced
    - Activated PCC or other type of PCC
    - Activated charcoal if last dose within <2 hrs
  - Optimal time to resume anticoagulation
    - 4 weeks (reduces risk of ICH recurrence)
      - Exception: patients with mechanical heart valves

Management After GI Bleed

- Based on available evidence
  - Warfarin may be restarted 7 to 14 days following a GI bleed
  - DOAC resumption after a GI bleed
    - Data is limited, consider the following
      - Faster onset of action
        - Delay restarting therapy for a few more days (compared to warfarin)
      - Select DOAC with less GI bleed risk (i.e. apixaban)

Reversal of DOAC with Prothrombin Complex Concentrates (PCC)

- Plasma derived products of human clotting factors
- Preferred non-hemostatic agent for DOAC reversal
- Weight based dosing more effective than standard dosing
- Adverse effect– hypercoagulability

Kcentra (4FPCC), Profilnine (3FPCC), Feiba (aPCC) prescribing information.
## Reversal of DOAC with PCC

<table>
<thead>
<tr>
<th>Types</th>
<th>Factors</th>
<th>Dosage (units/kg)</th>
<th>Target</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 factor PCC (Kcentra®)</td>
<td>II (prothrombin), VII, IX, and X</td>
<td>50 (off label use)</td>
<td>apixaban, rivaroxaban, edoxaban, betrixaban</td>
<td>$9,695*</td>
</tr>
<tr>
<td>3 factor PCC (Profilnine®)</td>
<td>II, IX, and X (not contain factor VII)</td>
<td>50</td>
<td>apixaban, rivaroxaban, edoxaban, betrixaban</td>
<td>$3,930*</td>
</tr>
</tbody>
</table>
| activated PCC (Feiba®) | II, VIIa, IX and X | • ICH: 50  
• Life threatening bleed: 25 to 100 (off label use) | dabigatran        | $3,100 to 11,630*          |

*Assuming 70 kg patient, and recommended dose range  
*Based on hospital acquisition cost  

Kcentra (4FPCC), Profilnine (3FPCC), Feiba (aPCC) prescribing information.  
Reversal of DOAC with PCC

Low grade evidence

- **Indications**
  - Use only in life-threatening circumstances or urgent surgery/procedures

- **PCC recommended over aPCC**
  - Higher incidence of thrombosis with aPCC
When to Use PCC?

- **First line agent**
  - Apixaban, edoxaban and rivaroxaban
  - 4 factor-PCC most extensively studied

- **Second line agent**
  - Dabigatran
    - Reversal agent not available
    - Use aPCC
      - May consider PCC

Idarucizumab (Praxbind®)

- Humanized monoclonal antibody fragment (Fab)
- First line agent for reversal of dabigatran (Pradaxa®)
  - Binds irreversibly to free and thrombin-bound dabigatran
- Onset of action: reverses within 10 minutes of administration
Idarucizumab (Praxbind®)

- Supplied: 2.5 g/50 mL ($2,100 per dose*)
- Administration (within 1 hr of removal from vial)

2.5 g IV bolus over 5-10 min → Within 15 minutes → 2.5 g IV bolus over 5-10 min

Consider additional 5 g if re-elevated aPTT and/or clinically relevant bleeding

*Based on hospital acquisition cost
Praxbind (idarucizumab) prescribing information.
Idarucizumab (Praxbind®)

RE-VERSE AD study (n=503)

- Predominant sites of bleeding
  - GI (45.5%)
  - ICH (32.6%)

- Cessation of bleeding
  - Median time 2.5 h

- Conclusion
  - More than 98% of the patients achieved complete and rapid reversal of anticoagulation
  - Idarucizumab is effective for patients with uncontrolled bleeding or undergoing urgent surgery

Idarucizumab (Praxbind®)

- Adverse effects
  - Pyrexia
  - Bronchospasm
  - Hyperventilation
  - Rash and pruritis

- Monitoring Parameters
  - Coagulation parameters
    - aPTT, TT and ECT normalized
  - Signs and symptoms of re-bleeding
Andexanet alfa (Andexxa®)

- Recombinant modified human factor Xa decoy protein
  - Temporary shuts down the activity of factor Xa

- FDA approved May 2018
  - Indications (rivaroxaban or apixaban):
    - Life threatening bleeding
Andexanet alfa (Andexxa®)

Dosing regimen

<table>
<thead>
<tr>
<th>Dose</th>
<th>Initial IV Bolus</th>
<th>Follow-up IV infusion</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low dose</td>
<td>400 mg at a rate of 30 mg/min</td>
<td>4 mg/min for up to 120 minutes</td>
<td>$25,000*</td>
</tr>
<tr>
<td>High dose</td>
<td>800 mg at a rate of 30 mg/min</td>
<td>8 mg/min for up to 120 minutes</td>
<td>$50,000*</td>
</tr>
</tbody>
</table>

The safety and efficacy of more than one dose has not been evaluated

*Cost includes bolus plus the follow-up infusion

*Based on hospital acquisition cost ($2,750 per 100 mg vial)
<table>
<thead>
<tr>
<th>FXa inhibitor</th>
<th>Last dose</th>
<th>Timing of FXa Inhibitor Last Dose Before Andexanet alfa initiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>&lt; 5 mg</td>
<td>Low dose</td>
</tr>
<tr>
<td></td>
<td>&gt; 5 mg or unknown</td>
<td>High dose</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>≤10 mg</td>
<td>Low dose</td>
</tr>
<tr>
<td></td>
<td>&gt;10 mg or unknown</td>
<td>High dose</td>
</tr>
</tbody>
</table>

Andexanet alfa (Andexxa®) prescribing information.
Andexanet alfa (Andexxa®)

- ANNEXA-4 Trial (n=67)
  - Assessed acute major bleeding within 18 h after administration of a factor Xa inhibitor
    - GI: 33 patients (49%)
    - Intracranial: 28 patients (42%)
    - Other: 6 patients (9%)
  - Clinical hemostasis
    - Reached in 53 patients (79%)
    - 12 h after the end of the infusion
  - Conclusion
    - Andexanet rapidly reversed anti-factor Xa activity

Andexanet alfa (Andexxa®)

- **Adverse effects**
  - Urinary tract infections
  - Pneumonia
  - Infusion site reactions

- **Monitoring**
  - Signs and symptoms
    - Arterial and venous thromboembolic events
    - Re-bleeding
    - Cardiac arrest
Reversal Pipeline

➢ Ciraparantag (PER977®)
  • Investigational agent specifically for direct thrombin inhibitors, factor Xa inhibitors, and heparin (including LMWH)
  • Dose: 100—300 mg (single IV dose)
  • Exception
    • Argatroban
    • Warfarin (Coumadin®)
Pharmacist’s Role in Therapy

- **Review**
  - Medication history
  - Laboratory parameters
  - Appropriate reversal agent

- **Prevent delays**
  - Establish protocol for use of reversal agents
  - Develop order sets

- Collaborate with prescribers to determine when to restart anticoagulation therapy
Pharmacist’s Role in Therapy

- **Role in transitions of care**
  - Assure appropriate therapy
  - Ensure medication access
  - Provide patient and caregiver education

- **Follow-up is critical in order for patients to know when to restart therapy**

Take Home Points

DOACs

- First line treatment for
  - Stroke prevention in AF patients
  - Patients with DVT of the leg or PE and no cancer

- Alternative agents for
  - Prophylaxis
    - Orthopedic surgical patients
    - Medical patients (hospitalized/non-hospitalized)
Take Home Points

- PCC’s are non-hemostatic reversal agents used as
  - First line for DOACs
  - Second line for dabigatran (Pradaxa®)
- Idarucizumab (Praxbind®)
  - Specific reversal agent for dabigatran (Pradaxa®)
- Andexanet alfa (Andexxa®)
  - Specific reversal agent for rivaroxaban (Xarelto®) and apixaban (Eliquis®) in life threatening bleeding
1. True or False: Andexanet alfa (Andexxa®) is approved as a reversal agent for apixaban (Eliquis®) or rivaroxaban (Xarelto®).

2. True or False: The betrixaban (Bevyxxa®) dose for atrial fibrillation is 160 mg PO twice daily.

3. True or False: Direct oral anticoagulants (DOACs) may not be used in patients with valvular atrial fibrillation.
Thank You!