Newer Anticoagulants/ Antiplatelets and Patient Teaching

Sarah Rittscher, PharmD, RP
January 2015
Disclosure

• I do not have a relevant financial interest or other relationship with a commercial provider of pharmaceutical agents, medical devices, or other related products.
Objectives

• Review pharmacology
  • Anticoagulants
    • Dabigatran (Pradaxa®)
    • Rivaroxaban (Xarelto®)
    • Apixaban (Eliquis®)
    • Edoxaban (Savaysa®)
    • Enoxaparin (Lovenox®)
  • Antiplatelets
    • Clopidogrel (Plavix®)
    • Ticagrelor (Brilinta®)
    • Prasugrel (Effient®)
• State indications, dose, frequency, and adverse effects of above listed medications
• Identify advantages of these medications when compared to older therapies
• Apply “teach back” adults learning methods to teaching medication information to patients (Shari Stonacek)
Anti-platelet vs Anticoagulants

Differentiating Thrombosis Treatments

Controlling Platelets

- Vorapaxar is an antiplatelet agent
- Oral Antiplatelets (e.g., Aspirin, Plavix, Vorapaxar)
- Target the platelet and not the coagulation cascade

Focus: Ischemic heart disease

Controlling Coagulation

- Anticoagulants (Coumadin, Heparins, Factor Xa inhibitors e.g., Betrixaban, Direct Thrombin Inhibitors)
- Target the coagulation cascade, including thrombin, but not platelets
- Betrixaban is an anticoagulant agent

Focus: Stroke prevention in Atrial Fibrillation
Coagulation Cascade

- Stable Fibrin Clot
- Activated Platelet
- GPIIb/IIIa
- Prothrombinase Complex
  - Xa-Va-Ca^{2+}-Phospholipid
- Fibrinogen
- Thrombin (IIa)
- Prothrombin
- Direct Thrombin Inhibitors
  - Dabigatran
  - Ximelagatran
- Direct Anti-Xa Inhibitors
  - Apixaban
  - Darexaban
  - Edoxaban
  - Rivaroxaban

- IXa
- IX
- VII
- TF-FVIIa
- γ-Carboxylation Inhibition
  - (II-VII-IX-X)
  - Vitamin K antagonists

- Plaque Disruption
- Tissue-Factor Bearing Cell

circresearch.com (accessed December 2015)
How does a blood clot form?

• Platelets form a plug
  • Receptors on the platelets react to different chemicals in the body and become activated when damage to the blood vessel occurs
  • These activated platelets release more chemicals to activate and attract additional platelets to the site of damage
• The clot becomes larger
  • Factors in the blood work together via the coagulation cascade to create a fibrin strand to make the clot stronger
• The clotting process ends when other proteins are released to prevent the clot from spreading further than is necessary
• As the body heals, the blood clot is slowly broken and the platelets and fibrin is absorbed back into the body

Causes of blood clots

- Damage to skin or blood vessels
- Blood flow disruptions
  - The pooling of blood in certain diseases causes platelets to come into contact with each other and stick together
    - Atrial fibrillation – heart is not moving blood properly
    - Deep Vein Thrombosis – valves in extremities or prone position can predispose
- Hypercoagulable states
  - Factor V Leiden
  - Deficiencies of natural proteins preventing clotting (antithrombin, protein C and S)
  - Cancer
  - Recent trauma or surgery
  - Central venous catheter placement
  - Pregnancy
  - Obesity
  - Supplemental estrogen use (including oral contraceptives)

my.clevelandclinic.org/services/heart/disorders/hypercoagstate
Anticoagulants

- Anticoagulants target clotting factors. These clotting factors are made in the liver using Vitamin K.
- Warfarin and heparin compete with Vitamin K preventing the circulation of certain clotting factors (II, VII, IX, and X).
- Anticoagulants are considered more aggressive than antiplatelets.
- Indicated most commonly for following types of patients:
  - High risk of stroke
  - Atrial Fibrillation with CHA$_2$DS$_2$-VASc score of 1 or higher
  - Patients with a DVT/PE or history of DVT/PE
  - Patients with certain types of valve replacements
- Anticoagulants do not dissolve the clot, they prevent the clot from growing and prevent further clots from forming while the body’s natural clot dissolving ability gradually removes the clot.
- Another drug class called thrombolytics are responsible for dissolving clots if necessary.

[Accessed December 2015]

[www.strokeassociation.org/STROKEORG/LifeAfterStroke/HealthyLivingAfterStroke/ManagingMedicines/Anti-Clotting-Agents-Explained](http://www.strokeassociation.org/STROKEORG/LifeAfterStroke/HealthyLivingAfterStroke/ManagingMedicines/Anti-Clotting-Agents-Explained)  Anti-Clotting Agents Explained
Anticoagulants

- There are several different types/forms of anticoagulants available
  - Injectable
    - Heparin*
    - Enoxaparin (Lovenox®)
    - Dalteparin (Fragmin®)*
  - Oral
    - Warfarin (Coumadin®)*
    - Apixaban (Eliquis®)
    - Rivaroxaban (Xarelto®)
    - Edoxaban (Savaysa®)
    - Dabigatran (Pradaxa®)

*Not in today’s presentation
Clotting Cascade

Intrinsic Pathway (surface contact)

Extrinsic Pathway (tissue factor)

XIIa

Xla

IXa

VIIa

Heparin / LMWH (AT-III dependent)

Hirudin/Hirulog (direct antithrombin)

Xa

Thrombin (IIa)

aPTT

PT

Thrombin-Fibrin Clot
Injectable Anticoagulants

- Enoxaparin (Lovenox®)
  - Approved for:
    - DVT Prophylaxis
    - DVT Treatment
    - ST-elevation MI
    - Unstable angina or non-ST-elevation MI
  - Prophylactic Dose
    - 30 mg Subcutaneous (SubQ) BID
    - 40 mg SubQ Daily
  - Treatment Dose
    - 1 mg/kg SubQ BID
    - 1.5 mg/kg SubQ Daily
  - Monitoring
    - Platelets: baseline and every 2-3 days from day 4 to 14
    - Anti-Xa: monitored in severe renal impairment, obesity, pregnancy
      - Once daily dosing: > 1 anti-Xa units/mL with manufacturer recommending a range of 1-2 anti-Xa units/mL
      - Twice daily dosing: 0.6 – 1 anti-Xa units/mL

Injectable Anticoagulants

• Enoxaparin (Lovenox®)
  • Use in Pregnancy
    • Pregnancy Category B – enoxaparin does not cross the placenta and is not expected to result in fetal exposure to the drug which corresponds with human data from a retrospective cohort study
    • 1 mg/kg/dose every 12 hours, discontinue ≥24 hours prior to induction or c-section, continue anticoagulation therapy for ≥6 weeks postpartum (minimum duration of therapy: 3 months)
  • Use in Obese Patients
    • Prophylactic doses may be increased by 30% in some patients (BMI ≥ 40 kg/m2)
    • Weight based dosing is appropriate and dose capping is not recommended, use of twice daily dosing preferred
    • Anti-Xa levels are increased to appropriate levels when enoxaparin is dosed on actual weight in obese patients weighing up to 144 kg
      • Monitoring of anti-Xa 4 hours after the dose is recommended

Injectable Anticoagulants

- **Enoxaparin (Lovenox®)**
  - Commonly used to “bridge” with warfarin therapy

- **Epidurals**
  - Boxed warning that spinal or epidural hematomas, including subsequent long-term or permanent paralysis, may occur with recent or anticipated neuraxial anesthesia or spinal puncture in patients anticoagulated with LMWH or heparinoids. Optimal timing between neuraxial procedures and enoxaparin is not known. Delay placement or removal of catheter for at least 12 hours after administration of low-dose enoxaparin and at least 24 hours after high-dose enoxaparin and consider doubling these times in patients with creatinine clearance <30 mL/min. Upon removal of catheter, consider withholding enoxaparin for at least 4 hours.

- **Adverse Effects**
  - Hemorrhage
  - Local Reactions

- **Reversal Agent**
  - Can use protamine but considered a partial reversal agent

Oral Anticoagulants
Oral Anticoagulants

- Direct Factor Xa Inhibitors
  - Apixaban (Eliquis®)
  - Edoxaban (Savaysa®)
  - Rivaroxaban (Xarelto®)
- Direct Thrombin Inhibitors
  - Dabigatran (Pradaxa®)
## Oral Anticoagulants (Factor Xa Inhibitors)

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Nonvalvular Atrial Fibrillation</th>
<th>DVT/PE Treatment</th>
<th>DVT/PE Prophylaxis</th>
<th>Postop DVT/PE thromboprophylaxis</th>
<th>DDIs</th>
<th>Additional Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban (Eliquis&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>*5 mg BID</td>
<td>10 mg BID for 7 days, then 5 mg BID</td>
<td>2.5 mg BID after 6 months of tx</td>
<td>2.5 mg BID</td>
<td>CYP3A4 and P-glycoprotein inhibitors</td>
<td>*If patient has any 2 of the following: Age ≥80 years, body weight ≤60 kg, or Scr ≥1.5 mg/dL, reduce dose to 2.5 mg BID</td>
</tr>
<tr>
<td>Renal Adjustment</td>
<td>*see note, ESRD requiring hemodialysis: 5 mg BID, reduce to 2.5 mg BID if another parameter is met</td>
<td>No Reduction (patients w/Scr of 2.5 or CrCl &lt;25 mL/min excluded)</td>
<td>No Reduction</td>
<td>No Reduction</td>
<td>Apixaban affects INR, so if converting to apixaban cannot rely upon INR initially</td>
<td></td>
</tr>
<tr>
<td>Hepatic Impairment</td>
<td>Not recommended in severe impairment</td>
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</tr>
<tr>
<td>Conversion from inj. AC</td>
<td>Discontinue other non-warfarin anticoagulant and begin taking apixaban at the usual time of the next scheduled dose of the other non-warfarin anticoagulant</td>
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</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban (Xarelto&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>20 mg QD w/PM meal</td>
<td>15 mg BID w/food for 21 days, followed by 20 mg QD</td>
<td>20 mg QD after 6 month</td>
<td>10 mg QD</td>
<td>CYP3A4 and P-glycoprotein inhibitors</td>
<td>Not affected by extremes of body weight (≥50 kg or &gt;120 kg)</td>
</tr>
<tr>
<td>Renal Adjustment</td>
<td>CrCl: 15-50: 15 mg QD w/PM</td>
<td>CrCl &lt;50: Avoid Use</td>
<td>CrCl &lt;50: Avoid Use</td>
<td>CrCl &lt;50: Avoid Use</td>
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</tr>
<tr>
<td>Hepatic Impairment</td>
<td>Not recommended in moderate to severe hepatic impairment</td>
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<tr>
<td>Conversion from inj. AC</td>
<td>Initiate rivaroxaban at time of continuous infusion discontinuation. For non-continuous, initiate ≤2 hours prior to next regularly scheduled evening dose</td>
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</tbody>
</table>

**AC** = anticoagulant  
**LMWH** = low molecular weight heparin

Lexicomp (accessed January 2016)
Oral Anticoagulants

• Direct Thrombin Inhibitors
  • Dabigatran (Pradaxa®)
    • DVT and pulmonary embolism (treatment and prevention)
      • 150 mg PO twice daily
      • After 5-10 days of parenteral anticoagulation
    • Renal Impairment
      • Patients with CrCl 30-50 and on p-glycoprotein, see below
      • Patients with CrCl less than 30 were excluded from trials
    • Hepatic Impairment – no dosage adjustment
  • Nonvalvular atrial fibrillation
    • 150 mg PO twice daily
    • Renal Impairment
      • Use with caution in patients with mild renal impairment (CrCl 50-80 mL/min)
      • No dosage adjustment for CrCl 30-50 mL/min unless on p-glycoprotein, see below
      • CrCl 15-30 reduce dose to 75 mg BID unless on p-glycoprotein, see below
    • Hepatic Impairment – no dosage adjustment
  • Drug-Drug Interactions:
    • Avoid use with p-glycoprotein inducer (rifampin) and inhibitors (amiodarone, clarithromycin, dronedarone, quinidine, verapamil) for DVT and pulmonary embolism
    • For nonvalvular atrial fibrillation
      • Dronedarone or ketoconazole with CrCl 30-50 mL/min: Reduce dose to 75mg twice daily
      • Avoid with any p-glycoprotein inducer (rifampin)
      • With CrCl <30 mL/min avoid use with any p-glycoprotein inhibitor (amiodarone, clarithromycin, dronedarone, quinidine, verapamil)

Lexicomp. Dabigatran. (accessed December 2015)
Oral Anticoagulants

• Dabigatran (Pradaxa®)
  • GI symptoms (dyspepsia, gastritis-like symptoms): 25-35%
  • Hemorrhage (11-19%)
    • Major hemorrhage ≤6%
    • Life-threatening hemorrhage: 2%
  • Wound secretion (5%)
  • Dyspepsia (8%)
  • Hematuria (1%)
  • Anemia (1-4%)
• Highest excess anticoagulation with dabigatran was seen in older adults
• Vascular outcomes dependent on quality of adjusted-dose warfarin treatment

Lexicomp. Dabigatran. (accessed in December 2015)
ISMP Smetzer 2015
Adam SS, Comparative Effectiveness of Warfarin and Newer Oral Anticoagulants for the Long-term Prevention and Treatment of Arterial and Venous Thromboembolism. April 2012. pg 43
Oral Anticoagulants

- Dabigatran (Pradaxa®)
  - Reversal Agent
    - Idarucizumab (Praxbind®)
      - Humanized monoclonal antibody that binds to dabigatran and its metabolites with higher affinity than the binding affinity of dabigatran to thrombin, neutralizing the anticoagulant effect
      - Administered IV as two consecutive infusions of 2.5 grams each
      - Line must be flushed with 0.9% sodium chloride solution prior to infusion
      - No other infusion should be administered in parallel via the same intravenous access
      - If reappearance of clinically relevant bleeding together with elevated coagulation parameters is observed after administration of 5 g idarucizumab, may consider additional 5 g dose
## Significant Drug Interactions

<table>
<thead>
<tr>
<th>Type of Interaction</th>
<th>Outcome</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacokinetic</td>
<td>Increase of at least 50% in anticoagulant plasma concentrations</td>
<td>Amiodarone&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Clarithromycin&lt;sup&gt;a b&lt;/sup&gt;</td>
<td>Itraconazole&lt;sup&gt;a b&lt;/sup&gt;</td>
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<tr>
<td></td>
<td></td>
<td>-Dronedarone&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-Itraconazole&lt;sup&gt;a b&lt;/sup&gt;</td>
<td>-Ketoconazole&lt;sup&gt;a b&lt;/sup&gt;</td>
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<td></td>
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<td>-Ketoconazole&lt;sup&gt;a b&lt;/sup&gt;</td>
<td>-Ketoconazole&lt;sup&gt;a b&lt;/sup&gt;</td>
<td>-Posaconazole&lt;sup&gt;a b&lt;/sup&gt;</td>
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<td></td>
<td></td>
<td>Quinidine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-Posaconazole&lt;sup&gt;a b&lt;/sup&gt;</td>
<td>-Ritonavir&lt;sup&gt;a b&lt;/sup&gt;</td>
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<td></td>
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<td>Ticagrelor&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-Ritonavir&lt;sup&gt;a b&lt;/sup&gt;</td>
<td>-Voriconazole&lt;sup&gt;a b&lt;/sup&gt;</td>
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<td></td>
<td></td>
<td>Verapamil&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-Voriconazole&lt;sup&gt;a b&lt;/sup&gt;</td>
<td>-Carbamazepine&lt;sup&gt;d&lt;/sup&gt;</td>
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<tr>
<td>Pharmacokinetic</td>
<td>Decrease of at least 50% in anticoagulant plasma concentrations</td>
<td>-Carbamazepine&lt;sup&gt;d&lt;/sup&gt;</td>
<td>-Carbamazepine&lt;sup&gt;d&lt;/sup&gt;</td>
<td>-Carbamazepine&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>Rifampin&lt;sup&gt;c d&lt;/sup&gt;</td>
<td>-Phenobarbital&lt;sup&gt;d&lt;/sup&gt;</td>
<td>-Phenobarbital&lt;sup&gt;d&lt;/sup&gt;</td>
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<tr>
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<td>-St. John’s wort&lt;sup&gt;c d&lt;/sup&gt;</td>
<td>-Phenytoin&lt;sup&gt;d&lt;/sup&gt;</td>
<td>-Phenytoin&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>Rifampin&lt;sup&gt;c d&lt;/sup&gt;</td>
<td>-Rifampin&lt;sup&gt;c d&lt;/sup&gt;</td>
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<td>-St. John’s wort&lt;sup&gt;c d&lt;/sup&gt;</td>
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<tr>
<td>Pharmacodynamic</td>
<td>Increased risk of bleeding</td>
<td>ASA</td>
<td>ASA</td>
<td>ASA</td>
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<td>NSAIDs</td>
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<td>Platelet aggregation inhibitors&lt;sup&gt;g&lt;/sup&gt;</td>
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<td>-Anticoagulants&lt;sup&gt;f&lt;/sup&gt;</td>
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<td></td>
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<td>-Thrombolytics&lt;sup&gt;g&lt;/sup&gt;</td>
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<td>-Thrombolytics&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Massicotte A. Can Pharm J. 2014 Jan 147 (1) 25-32
Significant Drug Interactions

ASA – Aspirin
NSAIDs – Nonsteroidal anti-inflammatory drugs
*Concomitant use is contraindicated or not recommended

\( ^{a} \)P-glycoprotein (P-gp) inhibition
\( ^{b} \)CYP450 3A4 inhibition
\( ^{c} \)P-gp induction
\( ^{d} \)CYP 450 3A4 induction
\( ^{e} \)Platelet aggregation inhibitors include abciximab, clopidogrel, dipyridamole, eptifibatide, prasugrel, ticagrelor, ticlodipine and tirofiban
\( ^{f} \)Anticoagulants include argatroban, bivalirudin, danaparoid, heparin, lepirudin, LMWHs, warfarin
\( ^{g} \)Thrombolytics include alteplase, reteplase, and tenecteplase

Massicotte A. Can Pharm J. 2014 Jan 147 (1) 25-32
Comparing NOACs with Warfarin

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Summary Risk Ratios (95% CI)</th>
<th>Tests for Heterogeneity</th>
<th>Summary Risk Ratios (95% CI)</th>
<th>Test for differences between drug classes</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>0.88 (0.82 to 0.95)</td>
<td>Q = 1.05, I² = 0% p &lt; 0.90</td>
<td>DTI: 0.90 (0.79 to 1.01)</td>
<td>p = 0.77</td>
</tr>
<tr>
<td>Discontinued due to adverse effects</td>
<td>1.23 (0.94 to 1.61)</td>
<td>Q = 57.96, I² = 93% p &lt; 0.001</td>
<td>DTI: 1.61 (1.14 to 2.27)</td>
<td>p = 0.03</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0.86 (0.71 to 1.04)</td>
<td>Q = 16.08, I² = 75% p = 0.003</td>
<td>DTI: 0.93 (0.82 to 1.06)</td>
<td>p = 0.49</td>
</tr>
<tr>
<td>Fatal bleeding</td>
<td>0.59 (0.46 to 0.77)</td>
<td>Q = 1.57, I² = 0% p = 0.81</td>
<td>DTI: 0.72 (0.45 to 1.16)</td>
<td>p = 0.35</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>1.30 (1.01 to 1.68)</td>
<td>Q = 12.04, I² = 75% p = 0.007</td>
<td>DTI: 1.50 (1.24 to 1.80)</td>
<td>p = 0.05</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1.02 (0.76 to 1.39)</td>
<td>Q = 9.37, I² = 57% p = 0.05</td>
<td>DTI: 1.35 (0.99 to 1.85)</td>
<td>p = 0.03</td>
</tr>
<tr>
<td>Liver dysfunction</td>
<td>0.82 (0.61 to 1.11)</td>
<td>Q = 14.48, I² = 72% p = 0.006</td>
<td>DTI: 0.88 (0.72 to 1.09)</td>
<td>p = 0.65</td>
</tr>
</tbody>
</table>

*Only four studies reported this outcome.
Abbreviations: CI = confidence interval; NA = not applicable

Adam SS, Comparative Effectiveness of Warfarin and Newer Oral Anticoagulants for the Long-term Prevention and Treatment of Arterial and Venous Thromboembolism. April 2012. pg 36
Increased Risk for Hemorrhage

- Demographics
  - Age (>75 y/o)
  - Low Body Mass (<50 kg)
- Comorbidities
  - Renal Insufficiency
  - Liver Disease
  - Prior hemorrhage
  - Stroke Hx
  - Peptic Ulcer Disease
- Concomitant Medications
  - Intensity of anticoagulation
  - P2Y12 inhibitor (clopidogrel, prasugrel, ticagrelor)
  - Aspirin
  - Others

Ageno. Chest 2012; 141: e44s-e88s
Summary of Evidence

• Chronic Atrial Fibrillation
  • NOACs associated with lower rate of all-cause mortality compared with warfarin
  • NOACs associated with a fewer hemorrhagic strokes
  • VTE-related mortality and ischemic stroke not significantly lower with NOACs

• Venous Thromboembolism
  • NOACs no worse than adjusted-dose warfarin for major clinical outcomes (all-cause mortality, VTE-related mortality, recurrent DVT/PE, major bleeding, discontinuation due to adverse effects)

• Mechanical Heart Valves
  • Insufficient evidence to make recommendations

• Adverse Effects
  • On earlier slide
  • Advantages to these medications is purported to be the lack of monitoring labwork, dietary restrictions, reduced drug-drug interactions

Adam SS, Comparative Effectiveness of Warfarin and Newer Oral Anticoagulants for the Long-term Prevention and Treatment of Arterial and Venous Thromboembolism. April 2012. pg 43-5
Reversal Agents

- Xa Inhibitors
  - No direct antidote
    - In development (andexanet alfa)
  - Prothrombin Complex Concentrates
    - The use of 4 factor PCC in healthy subjects has been shown to reverse the anticoagulant effect
  - Recombiant Factor VII
  - Plasma

- Protamine and Vitamin K are not expected to affect the anticoagulant activity of rivaroxaban
Anti-platelet vs Anticoagulants

Differentiating Thrombosis Treatments

Controlling Platelets

- **Vorapaxar** is an antiplatelet agent
- Oral Antiplatelets (e.g., Aspirin, Plavix, Vorapaxar)
- Target the platelet and not the coagulation cascade

Focus: Ischemic heart disease

Controlling Coagulation

- **Anticoagulants** (Coumadin, Heparins, Factor Xa inhibitors e.g., Betrixaban, Direct Thrombin Inhibitors)
- Target the coagulation cascade, including thrombin, but not platelets

Focus: Stroke prevention in Atrial Fibrillation

*MERCK Be well*
Anti-platelets Mechanism of Action

Circresearch.com  (accessed December 2015)
Stent Thrombosis

- Premature interruption of therapy may result in stent thrombosis with subsequent fatal and nonfatal MI
- Recent data indicate greater than 12 months may be considered in patients with drug-eluting stent (DES) placement
  - Continued therapy for 30 month compared to 12 months significantly reduced the risk of stent thrombosis and major adverse cardiovascular/cerebrovascular events but was associated with a higher risk of bleeding

Mauri 2014
Definitions

• Major bleed vs Life-threatening bleed
  • Major bleed (next slide)

• Life-threatening bleed
  • Intracranial bleeding
  • Bleeding requiring inotropes
  • Surgical interventions
  • ≥4 transfusions
  • Fatal bleeds
### Definitions of major bleeding

<table>
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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Intracranial bleed</td>
<td>Intracranial bleed</td>
<td>Intracranial bleed</td>
<td>Intracranial or intraocular</td>
<td>Intracranial, intraocular, or retroperitoneal</td>
<td>Intracranial or intraocular</td>
</tr>
<tr>
<td>Hgb ↓ &gt;5 g/dL or Hct ↓ &gt;15 percent</td>
<td>Hgb ↓ &gt;5 g/dL or Hct ↓ &gt;15 percent</td>
<td>Hgb ↓ ≥3 g/dL with overt bleeding</td>
<td>Any Hgb ↓ ≥4 g/dL</td>
<td>Hgb ↓ ≥3 g/dL with overt bleeding</td>
<td>Any Hgb ↓ ≥4 g/dL</td>
</tr>
<tr>
<td>Any transfusion</td>
<td>Any transfusion</td>
<td>Access site bleeding requiring intervention</td>
<td>Hematoma ≥5 cm Reoperation for bleeding</td>
<td>Access site bleeding requiring intervention</td>
<td>Hematoma ≥5 cm Reoperation for bleeding</td>
</tr>
</tbody>
</table>

TIMI and GUSTO were trials of fibrinolytic therapy for acute myocardial infarction. The remaining studies examined adjunctive pharmacology during percutaneous coronary intervention.

PBRC: packed red blood cell.

* ISAR-REACT, ISAR-SWEET, ISAR-SMART, ISAR-REACT 2.
Antiplatelet Medications

- Thromboxane Inhibitors
  - Aspirin
    - MOA – Irreversibly inhibits cyclooxygenase-1 and 2 enzymes, via acetylation, which results in decreased formation of prostaglandin precursors; irreversibly inhibits formation of prostaglandin derivative, thromboxane A2, via acetylation of platelet cyclooxygenase, thus inhibiting platelet aggregation; has antipyretic, analgesic, and anti-inflammatory properties

- ADP Receptor Antagonists
  - Clopidogrel (Plavix®)
  - Prasugrel (Effient®)
  - Ticagrelor (Brilinta®)
Antiplatelet Medications - MOA

- Adenosine diphosphate (ADP) P2Y12 receptor antagonists
  - **Clopidogrel**, requires in vivo biotransformation to an active thiol metabolite. The active metabolite irreversibly blocks the P2Y12 component of ADP receptors on the platelet surface, which prevent activation of the GPIIb/IIIa receptor complex, thereby reducing platelet aggregation. Platelets blocked by clopidogrel are affected for the remainder of their lifespan (7-10 days).
  - **Prasugrel**, an inhibitor of platelet activation and aggregation, is a prodrug which is metabolized to both active and inactive metabolites. The active metabolite irreversibly blocks the P2Y12 component of ADP receptors on the platelet, which prevents activation of the GPIIb/IIIa receptor complex, thereby reducing platelet activation and aggregation.
  - **Ticagrelor**, reversibly and noncompetitively binds the ADP P2Y12 receptor on the platelet surface which prevents ADP-mediated activation of the GPIIb/IIIa receptor complex thereby reducing platelet aggregation. Due to the reversible antagonism of the P2Y12 receptor, recovery of platelet function is likely to depend on serum concentrations of ticagrelor and its active metabolites.
Clopidogrel reduces event rate after coronary stenting

In the PCI CURE trial of 2658 patients who underwent a percutaneous coronary intervention (PCI), clopidogrel, administered with aspirin for six days before the intervention and continued for four weeks after, significantly reduced the 30-day and one-year incidence of cardiovascular death, myocardial infarction, or repeat revascularization compared to aspirin alone.

A: median time from randomization to PCI; B: 30 days after median time of PCI.

Antiplatelet Medications

- **Clopidogrel**
  - **Time to onset**
    - 300-600 mg loading dose – detected within 2 hours
  - **Peak effect**
    - Time to maximal inhibition of platelet aggregation – about 6 hours
    - Inhibition of platelet aggregation (IPA) ranges from 20-37% depending on adenosine diphosphate concentration
  - **Duration of action**
    - Platelet aggregation and bleeding time gradually return to baseline after around 5 days after discontinuation

*Clinical Pharmacology. Clopidogrel (accessed January 2016)*
*Lexicomp. Clopidogrel (accessed January 2016)*
Antiplatelet Medications

• **Clopidogrel**
  - Geriatric differences – effects on platelet aggregation were similar between elderly (≥75 years) and younger patients
  - Gender Differences – less inhibition of ADP-induced platelet aggregation was seen in females in a small gender comparison study
  - Ethnic Differences – Differences in CYP2C19 genes are found in approximately 30% Caucasians, 40% of Blacks, and more than 55% of East Asians
    - One study found carriers of at least 1 reduced-function CYP2C19 gene had a 32.4% reduction in plasma concentration of the active clopidogrel metabolite and a reduction
  - Poor metabolizers – Patients with poor metabolizer status have 2 loss-of-function alleles.
    - Affects 2% of Caucasians, 4% of Blacks, 14% of Chinese
    - Patients designated as poor metabolizers have a diminished antiplatelet response to clopidogrel. A higher dosage regimen 600mg loading dose followed by 150 mg PO daily can increase dosage response but clinical outcomes do not appear to be affected by this increased dose

Clinical Pharmacology. Clopidogrel (accessed January 2016)
Lexicomp. Clopidogrel (accessed January 2016)
Price 2011; Simon 2011
Antiplatelet Medications

• Clopidogrel
  • No adjustments in dose with renal impairment, however low inhibition of ADP-induced platelet aggregation was seen in patients with severe (CrCl 5-15 ml/min) and moderate (CrCl 30-60 ml/min) renal impairment after repeated clopidogrel doses of 75mg/day
  • Recommendations not available for dosing in hepatic impairment, however it appears dosage adjustments are not needed

Antiplatelet Medications

• Clopidogrel
  • Indications & Dosing
    • Arterial thromboembolism prophylaxis (myocardial infarction, stroke prophylaxis, thrombosis prophylaxis)
      • Patient with recent ischemic stroke, transient ischemic attack (TIA), or myocardial infarction, or established coronary artery disease or peripheral arterial disease
        • 75 mg PO daily for 1 year post coronary syndrome or long-term for patients with history of TIA or ischemic stroke
      • Patients with unstable angina or acute myocardial infarction, NSTEMI
        • 300 mg PO once, then 75 mg PO daily with aspirin for 12 months
      • Patients with acute myocardial infarction (STEMI)
        • With or without 300 mg PO once, then 75 mg PO daily with aspirin (LD is dependent on age), continue for 12 months
      • Patients undergoing percutaneous coronary intervention
        • 600 mg PO given as early as possible before or at the time of PCI, followed by 75 mg once for at least 12 month with aspirin 81 mg/day
  • Administration
    • May be administered with or without food

ACCF/AHA (Anderson 2013)
Antiplatlet Medications

• Clopidogrel
  • Adverse Effects
    • Bleeding at any site (3.7-5.1%)
      • Major bleeding (3.7%)
      • Life-threatening bleeding (2.2%)
      • Fatal bleeding (0.2%)
      • Risk of bleeding increases as age increases
    • Hematological effects – aplastic anemia, pancytopenia, acquired hemophilia A
    • Thrombotic thrombocytopenic purpura (TTP) has been reported
    • Diarrhea
    • N/V (less frequent than aspirin)
    • Rash
    • Hypersensitivity reactions
    • Headache
    • Dizziness
    • Vertigo

Antiplatelet Medications

• Clopidogrel
  • Drug-Drug Interactions
    • Avoid the use of omeprazole or esomeprazole if patient taking clopidogrel, both can significantly reduce the antiplatelet activity of clopidogrel when given at the same time or 12 hours apart
    • Evidence is inconsistent but recommendations state routine use of PPI not recommended for patients at lower risk of GI bleed
    • Use with other anticoagulants contribute to a additive risk for bleeding, however, they are not affecting the same targets
  • Monitor CBC and LFTs
Antiplatelet Medications

- Clopidogrel
  - Black Box Warning
    - Carriers of a reduced function CYP2C19 allele have a reduced pharmacodynamic response to clopidogrel and a higher risk of arterial thrombotic events; tests to determine the genetic differences are available.
Antiplatelet Medications

• Prasugrel
  • Time to onset
    • 60 mg loading dose - <30 minutes, median time to reach ≥20% IPA: 30 minutes
  • Peak effect
    • Time to maximal IPA – about 4 hours
    • Inhibition of IPA ranges from 78.8-84.1%
  • Duration of action
    • Platelet aggregation gradually returns to baseline values over 5-9 days following discontinuation

Antiplatelet Medications

- **Prasugrel**
  - **Geriatric**
    - recommended to avoid prasugrel in patients ≥75 years, except for high risk patients
  - **Ethnic Differences**
    - Active metabolite is 19% higher in the Asian population than in the Caucasian, African, or Hispanic populations.
  - **Low Body Weight**
    - Patients with low body weight (<60 kg) were at an increased risk of bleeding with no net clinical benefit, manufacturer recommends lowering the maintenance dose to 5mg daily
      - AUC of active metabolite is 38% lower in subjects <60kg taking 5mg than in subjects ≥60kg taking 10mg
  - **No adjustment with mild hepatic impairment, no recommendations for moderate or severe**
  - **No dosage adjustment in patients with mild renal impairment, patients with moderate to severe renal impairment are at increased risk for bleeding**

Antiplatelet Medications

• Prasugrel
  • Indications & Dosing
    • For arterial thromboembolism prophylaxis (thrombotic cardiovascular events including stent thrombosis) in patients with acute coronary syndrome (unstable angina, NSTEMI, STEMI) who are to be managed with percutaneous coronary intervention
      • Adults < 75 years of age and weighing ≥ 60kg: 60 mg PO as loading dose, then 10 mg PO daily with aspirin therapy
      • Adults < 75 years of age and weighing < 60 kg: 60 mg PO as loading dose, then consider lowering to 5mg PO daily
      • Adults ≥ 75 years of age: use in this population is generally not recommended, except in high-risk patients with a past history of myocardial infarction or diabetes
  • No adjustments for hepatic impairment or renal impairment
  • Administration
    • May be administered with or without food
    • Do not prematurely discontinue therapy
Antiplatelet Medications

• Prasugrel
  • Adverse Effects
    • Bleeding from any site
      • Higher incidence of major bleeding not related to surgery when compared with patients treated with clopidogrel (2.4% vs 1.8%)
      • Higher incidence of life-threatening bleed when compared to patients treated with clopidogrel (1.4% vs 0.8%)
    • Cardiovascular
      • Atrial fibrillation (2.9%)
      • Bradycardia (2.9%)
      • Hypertension (7.5%)
      • Hypotension (3.9%)
      • Peripheral edema (2.7%)
    • Hypersensitivity or anaphylactoid reactions (0.36%)
    • Hematologic adverse reactions
      • Anemia (2.2%), leukopenia (2.8%), neutropenia (<0.1%), severe thrombocytopenia (0.3%)
      • Back pain (5%), cough (3.9%), diarrhea (2.3%), dizziness (4.1%), fatigue (3.7%), fever (2.7%), headache (5.5%), hypercholesterolemia and hyperlipidemia (7%), nausea (4.6%), pain in extremity (2.6%), secondary malignancy (1.6%)

Antiplatelet Medications

• Prasugrel
  • Drug-Drug Interactions
    • Potential for bleeding is increased when prasugrel and oral anticoagulants are coadministered
      • Avoid coadministration of prasugrel and warfarin when possible
      • Administer prasugrel cautiously to patients receiving chronic NSAID therapy
  • Monitor
    • CBC
Antiplatelet Medications

- Prasugrel
  - Black Box Warning
    - Prasugrel can cause significant, sometimes fatal bleeding. Contraindicated in any patients with active pathological bleeding including GI bleeding and intracranial bleeding. Administer with caution in patients who may be at risk of increased bleeding from recent trauma or surgery.

Antiplatelet Medications

- Ticagrelor (Brilinta®)
  - Time to onset
    - 180 mg loading dose within 30 minutes (similar to clopidogrel 600 mg at 8 hours)
  - Peak effect
    - Time to maximal IPA: about 2 hours
    - IPA around 88%
  - Duration of action
    - 24 hours after last maintenance dose IPA is 58%
    - Mean IPA observed with ticagrelor at 3 days post-discontinuation was comparable to that observed with clopidogrel at 5 days post discontinuation
    - Subsequently, discontinue 5 days prior to surgery
Antiplatelet Medications

• Ticagrelor
  • Geriatric differences – the AUC and Cmax of ticagrelor are somewhat increased in geriatric patients, no adjustment is required
  • Gender differences – AUC and Cmax somewhat increased, no adjustment is required
  • Ethnic differences – exposure and Cmax somewhat increased in Japanese patients compared to Caucasians, no adjustment is required
  • No adjustment with mild hepatic impairment, no recommendations for moderate or severe
  • No adjustment in renal impairment patients, but AUC and Cmax are decreased
Antiplatelet Medications

• Ticagrelor
  • Indications & Dosing
    • For arterial thromboembolism prophylaxis in patients with acute coronary syndrome (ACS) (unstable angina, acute myocardial infarction), including patients undergoing PCI
      • Loading dose of 180 mg PO once, then 90 mg PO BID in combination with aspirin during the first year after an ACS event. After 1 year, administer 60 mg PO BID
      • Do not give maintenance doses of aspirin > 100 mg/day as it reduces the effectiveness of ticagrelor.
      • Ticagrelor is superior to clopidogrel for at least the first 12 months following ACS.
      • Ticagrelor also reduces the rate of stent thrombosis in patients who have been stented for treatment of ACS
  • Administration
    • May be administered with or without food
    • If a patient misses a dose, they should take their next dose at its scheduled time
    • Can crush tablets and can be administered via NG. Be sure to flush after administration

Antiplatelet Medications

• Ticagrelor
  • Adverse Effects
    • Increases in serum creatinine of >50% (7.4%)
      • Typically did not progress with continued treatment and often decreased
      • Reversal was seen upon treatment discontinuation
    • Increases the risk of bleeding and can cause significant, even fatal bleeding
      • Minor bleeding
      • Major bleeding (4.5 vs 3.8%)
      • Fatal bleeding (0.2%)
      • Intracranial bleeding (0.3 vs 0.2%)
    • Dyspnea (13.8 vs 7.8%)
      • If patient develops worsening, prolonged, or newly reported dyspnea during therapy, exclude underlying diseases
        • If determined to be caused by ticagrelor, continue treatment without interruption, as discontinuation or interruption can increase risk of MI, stent thrombosis, or death
      • No treatment for dyspnea caused by ticagrelor
      • Most often mild to moderate in intensity and resolves with continued ticagrelor treatment

Antiplatelet Medications

• Ticagrelor
  • Adverse Effects
    • Cardiovascular
      • Hypertension (3.2 vs 3.3%)
      • Chest pain (3.1%)
      • Atrial fibrillation (4.2 vs 4.6%)
      • Bradyarrhythias
    • Headache
    • Dizziness
    • Nausea (4.3 vs 3.8%)
    • Diarrhea (3.7 vs 3.3%)
    • Fatigue (3.2%)
    • Hypersensitivity reactions have been reported
Antiplatelet Medications

• Ticagrelor
  • Interactions
    • Aspirin doses >100mg resulted in decreased effectiveness of ticagrelor
    • Avoid concomitant use of CYP3A4 inhibitors (ketoconazole), exposure can be increased
    • P-gp inhibitors (cyclosporine, lansoprazole, omeprazole) can increase the exposure to ticagrelor, increasing bleeding risk
    • Avoid concomitant use of CYP3A4 inducers (rifampin), as exposure can be decreased
    • Avoid simvastatin doses > 40mg as ticagrelor can increase levels of simvastatin
    • Coadministration of ticagrelor and amiodarone may result in increased exposure to ticagrelor which may increase bleeding risk
  • Monitor CBCs and LFTs
Antiplatelet Medications

- Ticagrelor
  - Black Box Warning
    - Avoid maintenance doses of aspirin> 100mg/day
    - Contraindicated in any patient with active pathological bleeding including peptic ulcer or intracranial bleeding
    - Do not start ticagrelor in patients planned to undergo urgent coronary artery bypass graft surgery

Clinical Pharmacology. Ticagrelor (accessed January 2016)
<table>
<thead>
<tr>
<th>Drug and Creatinine Clearance</th>
<th>Preoperative</th>
<th>Postoperative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High Bleeding Risk: Major Surgery</td>
<td>Low Bleeding Risk: Minor Surgery</td>
</tr>
<tr>
<td>Dabigatran ≥80 mL/min</td>
<td>MPM: Stop 2 days before surgery.</td>
<td>MPM: Stop 24 hours before surgery.</td>
</tr>
<tr>
<td></td>
<td>LIT: Last dose on day –3</td>
<td>LIT: Last dose on day –2</td>
</tr>
<tr>
<td>50 to &lt;80 mL/min</td>
<td>MPM: Stop 2-3 days before surgery.</td>
<td>MPM: Stop 1-2 days before surgery.</td>
</tr>
<tr>
<td></td>
<td>LIT: Last dose on day –3</td>
<td>LIT: Last dose on day –2</td>
</tr>
<tr>
<td>30 to &lt;50 mL/min</td>
<td>MPM: Stop 4 days before surgery.</td>
<td>MPM: Stop 2-3 days before surgery (at least &gt;48 hours).</td>
</tr>
<tr>
<td></td>
<td>LIT: Last dose on day –4 or day –5</td>
<td>LIT: Last dose on day –3</td>
</tr>
<tr>
<td>&lt;30 mL/min</td>
<td>MPM: Stop at least 5 days before surgery</td>
<td>MPM: NA</td>
</tr>
<tr>
<td></td>
<td>LIT: Last dose on day –6</td>
<td>LIT: Last dose on day –4</td>
</tr>
<tr>
<td>Rivaroxaban ≥30 mL/min</td>
<td>MPM: Stop 2-4 days before surgery.</td>
<td>MPM: Stop at least 24 hours before surgery.</td>
</tr>
<tr>
<td></td>
<td>LIT: Last dose on day –3</td>
<td>LIT: Last dose on day –2</td>
</tr>
<tr>
<td>&lt;30 mL/min</td>
<td>MPM: Stop at least 4 days before surgery.</td>
<td>MPM: Stop at least 24 hours before surgery.</td>
</tr>
<tr>
<td></td>
<td>LIT: Last dose on day –3</td>
<td>LIT: Last dose on day –2</td>
</tr>
<tr>
<td>Apixaban For all patients</td>
<td>MPM: Stop at least 48 hours before surgery.</td>
<td>MPM: Stop at least 24 hours before surgery.</td>
</tr>
<tr>
<td></td>
<td>LIT: Last dose on day –3</td>
<td>LIT: Last dose on day –2</td>
</tr>
<tr>
<td>&gt;50 mL/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-50 mL/min</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LIT, the medical literature4-11; MPM, manufacturer’s product monograph; NA, not available.

*As an example, if it says “Last dose on day –2,” it should be interpreted as last dose of anticoagulant given on day –2, with day 0 being the day of the surgery.

*As the new oral anticoagulants have a fast onset and offset of action, bridging anticoagulation during the perioperative period with a low-molecular-weight heparin (LMWH) may not be needed. However, in some patients in whom oral medication cannot be resumed quickly after the surgery (e.g., bowel paralysis), especially in patients at moderate to high risk of thromboembolism, bridging anticoagulation with an LMWH may be desirable. In these cases, a specialized service (e.g., thrombosis, hematology or internal medicine service) should be consulted.

*The product monograph from the manufacturer provides only this general statement.
<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Interval from last dose to placement/removal</th>
<th>Interval from placement/removal to next dose</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>4 to 5 days, verify INR &lt;1.5; no monitoring needed for single dose within 24 hours of placement</td>
<td>Continue regular neurologic evaluation until 24 hours after removal. If dosed with catheter in place, check INR daily and remove when INR &lt;1.5; if INR 1.5-3.0, remove catheter with caution; monitor neurologic status until INR stabilized; if INR &gt;3, hold/reduce warfarin dose. Use of antithrombotic medications that do not influence INR may increase risk of bleeding complications.</td>
<td></td>
</tr>
<tr>
<td>Heparin (unfractionated)</td>
<td></td>
<td></td>
<td>When heparin given for &gt;4 days, check platelets (risk of HIT) prior to insertion or removal</td>
</tr>
<tr>
<td>Therapeutic dosing (IV)</td>
<td>2 to 4 hours, check for normal aPTT</td>
<td>1 hour</td>
<td>Bloody/difficult needle placement may increase bleeding risk with subsequent IV heparin; use with caution</td>
</tr>
<tr>
<td>Prophylactic dosing (SC)</td>
<td>Delaying heparin injection until after placement may reduce risk</td>
<td>1 hour</td>
<td>No contraindication to twice daily 5000 units; safety of higher or more frequent dosage is not established</td>
</tr>
<tr>
<td>Low molecular weight heparin (LMWH)</td>
<td></td>
<td></td>
<td>Anti-Xa level is not predictive of the risk of bleeding. Do not use with antithrombin or oral anticoagulant medications as this increases risk of spinal hematoma.</td>
</tr>
<tr>
<td>Therapeutic dosing (SC) (enoxaparin 1 mg/kg every 12 hours; enoxaparin 1.5 mg/kg daily; dalteparin 100-120 U/kg every 12 hours; dalteparin 200 U/kg daily; nadroparin 86 U/kg every 12 hours; nadroplarin 171 U/kg daily; tinzaparin 175 U/kg daily)</td>
<td>&gt;24 hours</td>
<td>Do not use therapeutic dosing with catheter in place</td>
<td></td>
</tr>
<tr>
<td>Prophylactic dosing (SC) (enoxaparin 30 mg every 12 hours; enoxaparin 40 mg daily; dalteparin 2500-5000 U daily; nadroparin 2050 U daily; nadroplarin 38 U/kg daily; tinzaparin 50-75 U/kg daily; tinzaparin 3500 U daily)</td>
<td>10 to 12 hours</td>
<td>Do not use twice-daily dosing with catheter in place, due to increased risk of spinal hematoma</td>
<td></td>
</tr>
</tbody>
</table>

Rosenquist R. Neuraxial (spinal, epidural) anesthesia in the patient receiving anticoagulant or antiplatelet medication. Dec 2015 (accessed January 2016)
Epidurals and Anticoagulants/Antiplatelets

<table>
<thead>
<tr>
<th>Factor Xa inhibitors</th>
<th>22 to 26 hours</th>
<th>4 to 6 hours</th>
<th>(European guidelines) Antithrombotic effect monitored with PT, aPTT, Heptest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban</td>
<td>22 to 26 hours</td>
<td>4 to 6 hours</td>
<td>AHA recommends 3 to 5 days after last dose; wait 24 hours to redose</td>
</tr>
<tr>
<td>Apixaban</td>
<td>26 to 30 hours</td>
<td>4 to 6 hours</td>
<td></td>
</tr>
<tr>
<td>Thrombin inhibitors</td>
<td>Avoid neuraxial techniques</td>
<td></td>
<td>aPTT or thrombin time</td>
</tr>
<tr>
<td>Dabigatran</td>
<td></td>
<td></td>
<td>AHA recommends 5 days after last dose (7 days for renal failure); wait 4 hours to redose</td>
</tr>
<tr>
<td>Argatroban</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hirudin derivatives (desirudin, bivalirudin)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiplatelet medication</td>
<td></td>
<td></td>
<td>Bleeding time does not predict hemostatic problems</td>
</tr>
<tr>
<td>P2Y12 receptor blockers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>7 days</td>
<td>After catheter removal</td>
<td>European guidelines</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>7 to 10 days</td>
<td>6 hours after catheter removal</td>
<td>European guidelines</td>
</tr>
<tr>
<td>Ticlodipine</td>
<td>14 days</td>
<td>After catheter removal</td>
<td>European guidelines</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>5 days</td>
<td>6 hours after catheter removal</td>
<td>European guidelines</td>
</tr>
</tbody>
</table>

Rosenquist R. Neuraxial (spinal, epidural) anesthesia in the patient receiving anticoagulant or antiplatelet medication. Dec 2015 (accessed January 2016)
# Table for CHAD and CHadsvasc

<table>
<thead>
<tr>
<th>Definition and scores for CHADS$_2$ and CHA$_2$DS$_2$-VASc</th>
<th>Stroke risk stratification with the CHADS$_2$ and CHA$_2$DS$_2$-VASc scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHADS$_2$ acronym</td>
<td>Score</td>
</tr>
<tr>
<td>Congestive HF</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥75 years</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Stroke/TIA/TE</td>
<td>2</td>
</tr>
<tr>
<td>Maximum score</td>
<td>6</td>
</tr>
<tr>
<td>CHA$_2$DS$_2$-VASc acronym</td>
<td>Score</td>
</tr>
<tr>
<td>Congestive HF</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥75 years</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Stroke/TIA/TE</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disease (prior MI, PAD, or aortic plaque)</td>
<td>1</td>
</tr>
<tr>
<td>Age 65 to 74 years</td>
<td>1</td>
</tr>
<tr>
<td>Sex category (ie, female sex)</td>
<td>1</td>
</tr>
<tr>
<td>Maximum score</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AF: atrial fibrillation; CHADS$_2$: Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Prior Stroke or
<table>
<thead>
<tr>
<th>Oral Drug</th>
<th>Generic</th>
<th>Brand</th>
<th>Reversal Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vit K Antagonist</td>
<td>Warfarin</td>
<td>Coumadin</td>
<td>PCC - 4 factor + Vitamin K 10mg IV</td>
</tr>
<tr>
<td>Factor Xa Inhibitor</td>
<td>Rivaroxaban</td>
<td>Xarelto</td>
<td>PCC - 4 factor</td>
</tr>
<tr>
<td></td>
<td>Apixaban</td>
<td>Eliquis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Edoxaban</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DTI</td>
<td>Dabigatran</td>
<td>Pradaxa</td>
<td>PCC - 4 factor</td>
</tr>
<tr>
<td>UFH</td>
<td>Heparin</td>
<td>N/A</td>
<td>Immediately after IV bolus: 1mg protamine per 100 units heparin</td>
</tr>
<tr>
<td>LMWH</td>
<td>Enoxaparin</td>
<td>Lovenox</td>
<td>$\leq8$hrs since dose: 1mg of protamine per 1mg of enoxaparin</td>
</tr>
<tr>
<td></td>
<td>Dalteparin</td>
<td>Fragmin</td>
<td>$\leq8$hrs since dose: 1mg of protamine per 100 anti-Xa units</td>
</tr>
<tr>
<td>Factor Xa Inhibitor</td>
<td>Fondaparinux</td>
<td>Arixtra</td>
<td>PCC - 4 Factor</td>
</tr>
<tr>
<td>Agent</td>
<td>Cost</td>
<td>Available</td>
<td>Volume</td>
</tr>
<tr>
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<td>-----------</td>
<td>--------</td>
</tr>
<tr>
<td>FFP</td>
<td>$</td>
<td>+</td>
<td>Lg</td>
</tr>
<tr>
<td>Kcentra</td>
<td>$$</td>
<td>-</td>
<td>Sm</td>
</tr>
<tr>
<td>FEIBA</td>
<td>$$$</td>
<td>-</td>
<td>Sm</td>
</tr>
<tr>
<td>Profilnine</td>
<td>$</td>
<td>-</td>
<td>Sm</td>
</tr>
<tr>
<td>NovoSeven</td>
<td>$$</td>
<td>-</td>
<td>Sm</td>
</tr>
</tbody>
</table>

NovoSeven. LexiComp. Hudson, OH. 2013.
Anticoagulants, Antiplatelets, Fibrinolytics

- **Anticoagulants**
  - Apixaban
  - Argatroban
  - Bivalirudin
  - Dabigatran etexilate
  - Dalteparin
  - Danaparoid
  - Edoxaban
  - Enoxaparin
  - Fondaparinux
  - Heparin
  - Rivaroxaban
  - Warfarin

- **Antiplatelets**
  - Aspirin
  - Cilostazol
  - Clopidogrel
  - Dipyridamole
  - Prasugrel
  - Ticagrelor

- **Thrombolytics**
  - Alteplase
  - Reteplase
  - Tenecteplase

- **Antiplatelet agent Iib/IIIa Inhibitor**
  - Abciximab
  - Eptifibatide
  - Tirofiban

Lexicomp. (accessed 2016)