Cardiovascular Pharmacology Update

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Disclosure

- I am not affiliated with nor do I have any financial ties to any pharmaceutical companies that manufacture the medications discussed in this presentation.
Outline of Topics

- New Oral Anticoagulant Drug Classes (OAC)
- Reversal of New Anticoagulants
- New Antiplatelet Agents
Oral Anticoagulant Drug Classes

- Vitamin K antagonists
  - Warfarin
- Xa Inhibitors
  - rivaroxaban and apixaban
- Direct Thrombin Inhibitors
  - Dabigatran
It’s All About The Factors

Figure 2. The coagulation cascade\(^3\)
Vitamin K Antagonists = Warfarin

- Blocks the Vitamin K Dependent Factors
  - Factor II (prothrombin), VII, IX, X

- Monitored using International Normalized Ratio (INR)
  - Goal INR 2-3 for atrial fibrillation, DVT/PE, tissue valves and mechanical aortic valve
  - Goal INR 2.5 -3.5 for mechanical mitral valves

- Dose varies by patient and influenced by:
  - Diet, low albumin, liver disease, heart failure, thyroid disorders and drug interactions (i.e. antibiotics)
Warfarin

Figure 2. The coagulation cascade

Extrinsic pathway
- Vascular cell
  - TF
  - FIXa
  - FVIII
  - FXa
  - FV

Intrinsic pathway
- Platelet
  - FXIa
  - FXI

Plasma thrombin
- Thrombin
- Fibrinogen
- Fibrin
Xa Inhibitors

- Blocks the conversion of prothrombin to thrombin
- FDA approved agents
  - Rivaroxaban (Xarelto®) approved 2011
  - Apixaban (Eliquis®) approved 2012
- No Routine Monitoring Necessary
  - However, does affect the PT/INR and aPTT
    - Can be used when deciding if need to reverse
Xa Inhibitors

Figure 2. The coagulation cascade

Extrinsic pathway
- FVII
- TF
- FVIIa
- TF
- FX
- Prothrombin

Intrinsic pathway
- FXI
- FXIa
- FIX
- FIXa
- FVIII
- Thrombin

Vascular cell

Platelet
Rivaroxaban (Xarelto®)

Approved for:
- DVT prophylaxis for post hip and knee replacement surgeries
- Therapeutic treatment of DVT and PE
- Non-valvular atrial fibrillation
## Rivaroxaban

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dose</th>
<th>Duration</th>
<th>Renal Adjustment</th>
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<tbody>
<tr>
<td>TKR/THR surgery prophylaxis</td>
<td>10mg daily with or without food</td>
<td>Recommended by ACCP</td>
<td>Contraindicated if CrCl &lt;30mL/min</td>
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<td>- Minimum of 12-14 days hip and 10-12 days knee and up to 35 days for both</td>
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<tr>
<td>Active DVT/PE</td>
<td>15mg twice daily x 21 days then 20mg once daily</td>
<td>ACCP recommends at least 3 months</td>
<td>Contraindicated if CrCl &lt;30mL/min</td>
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<td>Non-valvular atrial fibrillation</td>
<td>20mg once daily with evening meal</td>
<td>Indefinitely</td>
<td>Reduce to 15mg daily if CrCl 15-50mL/min. Contraindicated if CrCl &lt;15mL/min</td>
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</tbody>
</table>

- Doses >10mg/day need to be given with food for adequate absorption
- During twice daily regimen important to get both doses
Rivaroxaban

- **Absorption**
  - Rapid
  - Dependent on GI tract
    - Can be given via nasogastric or gastric feeding tubes
    - Do not give if tube ends distal to stomach

- **Metabolism**
  - Liver
    - Potential for drug interactions

- **Elimination**
  - half life – 5-9 hours (up to 13 hours in the elderly)
  - Primarily by kidneys
Rivaroxaban (cont.)

- **Drug interactions**
  - Decrease rivaroxaban metabolism (increased effect)
    - Itraconazole*, ketoconazole*, clarithromycin*, ritonavir*, conivaptan, amiodarone, dronedarone, grapefruit juice
      - * = Try to avoid in patients on these medications
  - Increase rivaroxaban metabolism (decreased effect)
    - Carbamazepine, phenytoin, rifampin, St. John's Wart
Rivaroxaban

- Adverse effects
  - **Bleeding**
    - Rocket AF trial showed an increased risk of bleeding vs. warfarin
      - GI bleed (3.6% vs. 2.6%), Major bleeding (2% vs. 1.24%), Minor bleeding (1.75% vs. 1.39%)
  - Peripheral Edema
  - CNS: dizziness, headache, fatigue
  - GI: diarrhea, constipation, abdominal pain, nausea
  - Neuromuscular/skeletal pain
Rivaroxaban

- **Black Box Warning!!**
  - Increased risk of thrombotic events in patients with atrial fibrillation if discontinued prematurely without an alternative anticoagulant on board.
    - Need to consider bridging therapy if holding for >1 day before surgery
  - Epidural and spinal hematomas can develop if on rivaroxaban and getting neuroaxial anesthesia or spinal puncture
    - Can lead to long term or permanent paralysis
Rivaroxaban

- **Converting from warfarin**
  - Stop warfarin and start rivaroxaban when INR < 3

- **Converting to warfarin**
  - Affects INR so need to bridge with warfarin and parenteral anticoagulant (LMWH or heparin)
  - Stop rivaroxaban and start bridging therapy at the next scheduled dose

- **Converting from non-warfarin anticoagulant**
  - D/C other agent and start rivaroxaban at the next scheduled dose

- **Converting to non-warfarin anticoagulant**
  - D/C rivaroxaban and start other agent at the next scheduled dose
Rivaroxaban

Surgical considerations

- Discontinue rivaroxaban at least 24 hours before surgery
  - Consider bridging therapy if stopping for extended period of time before surgery
- If epidural is needed for surgery:
  - Wait at least 6 hours after epidural catheter is removed before starting rivaroxaban
  - Wait at least 18 hours from last dose of rivaroxaban before removing epidural catheter
Apixaban (Eliquis®)

- Approved only for non-valvular atrial fibrillation
- Dosing – 5mg twice daily
  - Reduce to 2.5mg twice daily if:
    - The patient has 2 or more of the following:
      - Weight ≤ 60kg
      - Scr ≥ 1.5 mg/dL
      - Age ≥ 80
    - The patient is taking certain medications that inhibit metabolism
      - Ketoconazole, itraconazole, ritonavir, clarithromycin
Apixaban

- **Unlabeled use for DVT or PE**
  - 10mg twice daily x 7 days then 5mg twice daily for 6 months
  - Extended therapy: After 6 months reduce to 2.5mg twice daily

- **Unlabeled use for DVT prophylaxis for knee and hip replacement surgery**
  - 2.5mg twice daily
    - Start 12-24 hours post op
    - Duration: 32-38 days for hip replacement
    - Duration: 10-14 days for knee replacement
Apixaban

- **Absorption**
  - Prolonged
  - Absorbed through GI tract, small bowel and ascending colon
    - May be crushed and given through any GI tube

- **Metabolism**
  - Liver
    - Potential for drug interactions

- **Elimination**
  - Half life = 6 hours (increases to 12hrs with repeat dosing)
  - Primarily by Kidneys
Apixaban

- **Drug interactions**
  - **Decrease apixaban metabolism (increased effect)**
    - Itraconazole*, ketoconazole*, clarithromycin*, ritonavir*, conivaptan, amiodarone, dronedarone, grapefruit juice
    - * = decrease dose to 2.5mg BID
  - **Increase apixaban metabolism (decreased effect)**
    - Carbamazepine, phenytoin, rifampin, St. Johns Wart
  - **Avoid other anticoagulants unless medically necessary**
Apixaban

- **Adverse effects**
  - **Bleeding**
    - Statistically significant less major bleeding than warfarin (2%/year vs. 3%/year) found in ARISTOTLE trial
  - **GI** - Nausea
  - **Hepatic** - increase in liver enzymes
  - **Dermatologic** - bruising
Apixaban

- **Black Box Warning!!**
  - Increased risk of thrombotic events in patients with atrial fibrillation if discontinued prematurely without an alternative anticoagulant on board.
    - Consider bridging therapy if holding for extended period before surgery
Apixaban

- **Surgical Considerations**
  - Discontinue 24 hours before surgeries with a low risk of bleeding
  - Discontinue 48 hours before surgeries with a moderate to high risk of bleeding
Apixaban

- Converting from warfarin
  - d/c warfarin and start apixaban when INR <2

- Converting to warfarin
  - Falsely elevates INR
  - D/C apixaban and start warfarin and parenteral anticoagulant and next scheduled dose

- Converting from non-warfarin anticoagulants
  - D/C other agent and begin apixaban at next scheduled dose

- Converting to non-warfarin anticoagulants
  - D/C apixaban and begin other anticoagulant at next scheduled dose
Direct Thrombin Inhibitors

- Blocks the conversion of fibrinogen to fibrin
- FDA approved agents
  - Dabigatran (Pradaxa®) approved 2010
- No Routine Monitoring Necessary
  - However, does affect the aPTT and INR
    - aPTT can be used when deciding if need to reverse
Direct Thrombin Inhibitors

Figure 2. The coagulation cascade

Extrinsic pathway
- FVII
- TF
- FVIIa

Intrinsic pathway
- FXIa
- FIXI

Vascular cell
- TF
- FVII
- FVIIa
- TF

Platelet
- FXIa
- FIXI

Prothrombin

Fibrinogen

Fibrin

FXa

FX

FV

FIXa

FIX

TFa

Thrombin

FXa

Prothrombin
Dabigatran

- Approved for **non-valvular** atrial fibrillation
  - Recommended over warfarin in 2012 CHEST guidelines

- December 2012 FDA announces that dabigatran should **NOT** be used in patients with mechanical heart valves
  - Based on a clinical trial in Europe (RE-ALIGN)
    - Trial was stopped early due to a statistically significant increase in heart attacks, stroke, and blood clots vs. warfarin
Dabigatran

- **Dosing - 150mg twice daily**
  - Reduce to 75mg twice daily if:
    - CrCl is 15-30mL/min
    - Consider reducing if pt is taking certain medications (i.e. ketoconazole, dronedarone) and CrCL is 30-50mL/min
    - Avoid in this patient population if CrCl is <30mL/min
Dabigatran

- **Absorption**
  - Rapid, but low bioavailability (3-7%)
    - Pellets taken without capsule increase absorption by 75%
      - Do **NOT** break, chew or open before administration
      - Do not give via feeding tubes

- **Metabolism**
  - Liver, but not by Cytochrome P450 enzymes
    - Less drug interactions

- **Elimination**
  - Half life 12-17 hours (increases to 27 hours if CrCl is 15-30mL/min)
  - Primarily by Kidneys
Dabigatran

Drug interactions

- Increase dabigatran levels
  - Amiodarone, dronedarone, ketoconazole
    - Reduce dose if CrCl 30-50mL/min
  - Quinidine and verapamil
    - Give dabigatran 2 hours before other medication

- Decrease dabigatran levels
  - Rifampin, St. John’s wart

- Avoid other anticoagulants unless medically necessary
Dabigatran

- **Adverse Effects**
  - **Bleeding**
    - Major bleed risk similar to warfarin (3.3% vs. 3.6%)
    - Higher rate of GI bleeds than warfarin (6.1% vs. 4% for any GI bleed and 1.6% vs. 1.1% major GI bleed)
    - RE-LY trial notes a trend for increased bleeding risk in the elderly (≥75), especially in patients with low body weight
  - **GI** – dyspepsia, GERD, esophagitis, ulcer
    - Incidence of GI adverse reactions was higher than warfarin (35% vs. 24%)
  - **Hepatic** – increase in liver enzymes (AST)
  - **Rare (<1%)**
    - Angioedema, thrombocytopenia, anaphylaxis
Dabigatran

- **Black Box Warning!!**
  - Increased risk of thrombotic events if discontinued. Consider another anticoagulant if stopped for a reason other than pathological bleeding
    - Consider bridging therapy if holding for extended period before surgery
Dabigatran

- Surgical considerations
  - Discontinue 1-2 days before surgery if CrCl is $\geq 50\text{mL/min}$
  - Discontinue 3-5 days before surgery if CrCl is $<50\text{mL/min}$
  - Consider longer times for patients undergoing spinal puncture or if an epidural is to be used
Dabigatran

- Converting from warfarin
  - D/C warfarin and start dabigatran when INR <2

- Converting to warfarin
  - CrCl is ≥ 50mL/min = 3 days of overlap
  - CrCl is 30-50mL/min = 2 days of overlap
  - CrCl is 15-30mL/min = 1 day of overlap

  Note: dabigatran can increase INR and will be more accurate 2 days after last dabigatran dose

- Converting from non-warfarin anticoagulants
  - Start dabigatran 0-2 hours before the next dose

- Converting to non-warfarin anticoagulant
  - Wait 12 hours if CrCl ≥ 30mL/min or 24 hours if CrCl <30mL/min
Things to Consider

- **Cost**
  - Warfarin
    - 5mg tabs #30 ~ $25
  - Rivaroxaban
    - 15mg #30 ~ $275
    - 20mg # 30 ~ $310
  - Apixaban
    - 5mg # 60 ~ $300
  - Dabigatran
    - 75mg #60 ~ $300
    - 150mg #60 ~ $300

*cash price per www.goodrx.com*
More things to consider

- Monitoring
  - Warfarin = lots of monitoring
    - INR lab costs ~ $20
  - Xa Inhibitors = no monitoring necessary
  - Thrombin inhibitors = no monitoring necessary

- Emergent need to reverse the effects
  - Warfarin has a known antidote
  - New anticoagulants have no official antidote

- Warfarin is the currently the only approved oral anticoagulant for valve replacement surgery
Anticoagulant Reversal

- **Warfarin**
  - Vitamin K given PO, SQ, or IV
    - IV push has been associated with anaphylaxis
      - Need to dilute and give slowly over 1 hour
  - Fresh Frozen Plasma (FFP)

- **Xa Inhibitors and Direct Thrombin Inhibitors**
  - No proven antidote at this point
  - Studies and case reports suggest successful reversal with prothrombin complex concentrates (PCC)
Prothrombin Complex Concentrate

- Contains the vitamin K-dependent coagulation factors II, VII, IX, and X
- Kcentra – first 4 factor PCC approved by FDA (April 2013)
  - Approved for vitamin K antagonist reversal
- Profilnine – contains factors II, IX, X (FDA approved in 2010 for Factor IX deficiency)
  - Also has low levels of factor VII not considered therapeutic
Kcentra

- **Dosing**
  - Based on Factor IX content
    - 25 units/kg (INR 2-4), 35 units/kg (INR 4-6) and 50 units/kg if INR > 6
      - Not to exceed 5000 units of factor IX
  - Shown to reduce INR to ≤ 1.3 within 30 minutes
  - Contains a small amount of heparin
    - Do not give in patients with heparin induced thrombocytopenia
      - Use Factor IX (Profilnine®) and Factor VIIa in this patient population
Kcentra

- **Black Box Warning**
  - Both fatal and nonfatal arterial and venous thromboembolic events have been reported.
    - Reserve use for life or brain threatening bleeding

- **Cost = Expensive**
  - 5000 unit dose is around $8000
Oral Antiplatelet Agents

- Blocks a receptor (P2Y$_{12}$) on platelets making them unable to interact with other platelets
  - This makes the platelet “slippery”

- Primarily used during Acute Coronary Syndrome and to prevent stent thrombosis and/or restenosis
  - Used for both drug eluting stents and bare metal stents
Antiplatelet Agents for ACS

- **Irreversible**
  - Clopidogrel (Plavix®)
  - Prasugrel (Effient®) approved 2009

- **Reversible**
  - Ticagrelor (Brilinta®) approved 2011
Antiplatelet Agents
Prasugrel (Effient®)

- Approved for Acute Coronary Syndrome

**Loading Dose**
- 60mg one time dose

**Maintenance Dose**
- 10mg daily for patients ≥ 60kg
- Consider 5mg daily for patients <60kg

*Note: no renal adjustment necessary*

**Concomitant Therapy**
- Aspirin 75mg to 325mg daily
Prasugrel

- **Abosrpption**
  - Rapid, peak plasma concentration is 30 minutes
    - Slightly faster than clopidogrel (45 minutes)

- **Metabolism**
  - Prodrug - needs to be metabolized to an active form
  - Liver
    - Different liver enzymes than clopidogrel = no significant interaction with Prilosec or Nexium

- **Elimination**
  - Half life is 7 hours
  - Primarily by kidneys
Black Box Warning!!

- Do not give in patients with active pathological bleeding or a history of transient ischemic attacks (TIA) or stroke

- Use not recommended in patients ≥ 75 due to increased risk of fatal and intracranial bleeding
  - Can be considered if high risk (diabetes or history of MI)
Prasugrel (cont)

- **Adverse Effects**
  - **Bleeding**
    - Statistically significant higher overall incidence then clopidogrel (4.5% vs. 3.4)
  - **Cardiovascular** – a fib, bradycardia, hyper/hypotension
  - **CNS** – dizziness, fatigue, headache
  - **GI** – diarrhea, nausea
  - **Back pain**
  - **Hypercholesterolemia/lipidemia**
Ticagrelor (Brilinta)
Ticagrelor

- **Absorption**
  - Max concentration is ~ 1.5 hours (1-4)
    - slower than clopidogrel and prasugrel

- **Metabolism**
  - Liver
    - Different enzymes than clopidogrel = no significant interaction with Prilosec or Nexium
    - Similar drug interactions as the Xa inhibitors

- **Elimination**
  - Half life is ~ 7 hours
  - Liver metabolism and biliary secretion
Ticagrelor

- **Black Box Warning**
  - Associated with significant and sometimes fatal bleeding. Do not use in patients with active pathological bleeding or a history of intracranial hemorrhage.
  - Do not initiate therapy in patients planning on undergoing urgent CABG and wait at least 5 days prior to surgery.
  - Suspect bleeding in any patient who is hypotensive and has recently undergone PCI, CABG, or other surgery.
  - Reduced effectiveness with aspirin doses >100mg/day.
Ticagrelor

- **Adverse Effects**
  - **Bleeding**
    - Overall bleeding slightly higher than clopidogrel (8.7% vs. 7%)
  - **Respiratory – dyspnea, cough**
    - Dyspnea – most common reported side effect (13.8%)
  - **Cardiovascular – a. fib, CP, hyper/hypotension**
  - **CNS – dizziness, Fatigue, Headache**
  - **GI – diarrhea, nausea**
  - **Back pain**
Things to Consider

- **Cost**
  - Clopidogrel 75mg #30 ~ $150 ($15 with coupon)
  - Prasugrel 10mg #30 ~ $280
  - Ticagrelor 90mg #60 ~ $270
  *cash cost based on [www.goodrx.com](http://www.goodrx.com) prices

- **Compliance**
  - Prasugrel and clopidogrel are once daily
  - Ticagrelor twice daily (easier to miss a dose)

- **Pharmacokinetics**
  - Prasugrel has fast absorption and quick platelet inhibition
    - Potential to give as loading dose then change to clopidogrel for cost savings
      - Need to consider bleeding risk, age and weight
Questions
References


4. Xarelto [package insert]. Gurabo, PR: Janssen Pharmaceuticals Inc; August 2013


20. Effient [package insert]. Indianapolis, IN: Eli Lilly & Co; September 2011


