Challenges and Strategies in Anticoagulation Management

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The purpose of this educational session will be to update consultant and staff long-term care pharmacists on recent recommendations from the 9th Edition American College of Chest Physicians (ACCP) Guidelines for Antithrombotic Therapy and Prevention of Thrombosis. This most recent edition of the CHEST guidelines is a burgeoning document with over 600 recommendations, many of which are new and controversial, spread across 24 separate articles. The goal of this presentation is to highlight those recommendations which are most relevant to long-term pharmacy practice with a discussion of the practical utility of the guidelines and barriers to implementation.
Educational Objectives

1) Identify key recommendations from the guidelines pertaining to dosing and monitoring of oral anticoagulants, including drug interactions, especially with antibiotics.

2) Discuss controversies surrounding some of the new recommendations and supportive evidence and rationale.

3) Summarize specific recommendations for anticoagulant therapy in the treatment of atrial fibrillation, venous thromboembolism (VTE), and prevention of ischemic stroke.

4) Identify barriers to the implementation of the guidelines and practical applicability of the recommendations.

5) Discuss the three newest anticoagulant drugs, *dabigatran*, *rivaroxiban* and *apixaban*, using the STEPS approach and patient cases to evaluate their role in geriatric patients.
Emergency Hospitalizations for Adverse Drug Events in Older Americans


Emergency Hospitalizations for Adverse Drug Events in Older Americans


Which drugs, or classes or drugs, did the investigators identify that were most frequently implicated (67%) in emergency hospitalizations of older adults?

Emergency Hospitalizations for Adverse Drug Events in Older Americans


Which drugs?
1)_____________________________________________
2)_____________________________________________
3)_____________________________________________
4)_____________________________________________

JCAHO 2012 Ambulatory Healthcare National Patient Safety Goals:

NPSG.03.05.01 - Reduce the likelihood of patient harm associated with the use of anticoagulant therapy.
Data from the PINNACLE Registry

• The Practice INNovation And CLinical Excellence (PINNACLE) Registry is the largest cardiovascular outpatient database in the U.S., and is part of the America College of Cardiology National Cardiovascular Data Registry (NCDR).*

• PINNACLE currently has 4.7 million patient records representing valid patient encounters from hundreds of outpatient practices nationwide.

• Of those patients, over 250,000 have atrial fibrillation.

• A new platform has recently been introduced: PINNACLE-AF


* Bristol-Myers Squibb and Pfizer Inc. are founding sponsors of the PINNACLE Registry
Data from PINNACLE-AF – August 2012

• It is documented in the PINNACLE Registry, as well as in the peer-reviewed atrial fibrillation literature, that nearly half of all A. fib patients at moderate to high risk of CVA are NOT anticoagulated according to current scientific guidelines.

• Recent unpublished analysis from PINNACLE-AF on approximately 121,000 unique A. fib patients from 2011 shows an overall anticoagulation rate just below 50%.

• Of all anticoagulated A. fib patients in this analysis, 87.4% were receiving warfarin and 12.6% were prescribed newer anticoagulants (e.g. dabigatran, rivaroxaban).

The Human Circulatory System

• An average human adult has five to six quarts of blood, which consists of:

- **Erythrocytes** (Red Blood Cells)
- **Neutrophils** (White Blood Cells)
- **Thrombocytes** (Platelets)
Introduction to the Coagulation Process

- Pathophysiology of thromboembolic disease:
  
  Hypercoagulateability / Thrombophilia
  
  The composition of the blood

  Virchow’s Triad

  Endothelial Injury / Dysfunction
  Quality of the blood vessel wall

  Hemodynamic Changes
  Nature of blood flow (static, turbulent)
Hypercoagability / Thrombophilia

- Genetic deficiencies
- Autoimmune Disorders
- Estrogen/Progesterone therapy
- Smoking
- Malignancy
- Sepsis
- Pregnancy

Endothelial Injury/Dysfunction

- Trauma / surgery
- Venepuncture
- Valvular disease
- Indwelling catheters
- Atherosclerosis

Hemodynamic Changes

- Atrial fibrillation
- LV dysfunction / HF
- Immobility / paralysis
- Venous obstruction
- Venous Insufficiency
Introduction to the Coagulation Process

- Coagulation begins almost instantly after an injury to a blood vessel(s) has damaged the endothelial lining of the vessel.
- Exposure of circulating blood to tissue factor initiates changes to blood platelets and the plasma protein fibrinogen, a clotting factor.
- Platelets immediately form a plug at the site of injury; this is called **primary hemostasis**.
- **Secondary hemostasis** occurs simultaneously: Proteins in the blood plasma, called *coagulation factors* or *clotting factors*, respond in a complex cascade to form fibrin strands, which strengthen the platelet plug.
Introduction to the Coagulation Process

- The classic coagulation cascade has two separate pathways which lead to fibrin formation:
  - **Intrinsic pathway**
    - AKA contact activation pathway
  - **Extrinsic pathway**
    - AKA tissue factor pathway
Safe Anticoagulant Use in Geriatric Patients

- The elderly are inherently predisposed to adverse effects from anticoagulants due to a variety of factors:
  - Age-related decline in cardiac, renal and hepatic function
  - Decreased production of RBCs, ↓ circulating blood volume, ↓ clotting factor synthesis
  - Polypharmacy, multiple patient co-morbidities, inherent complexity of anticoagulant pharmacotherapy
<table>
<thead>
<tr>
<th>CHADS&lt;sub&gt;2&lt;/sub&gt; Risk Criteria</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>C  Congestive Heart Failure</td>
<td>1</td>
</tr>
<tr>
<td>H  Hypertension (consistently &gt; 140/90 mmHg and/or treated with medication)</td>
<td>1</td>
</tr>
<tr>
<td>A  Age ≥ 75 years</td>
<td>1</td>
</tr>
<tr>
<td>D  Diabetes Mellitus</td>
<td>1</td>
</tr>
<tr>
<td>S&lt;sub&gt;2&lt;/sub&gt; Prior stroke or Transient Ischemic Attack (TIA)</td>
<td>2</td>
</tr>
</tbody>
</table>

Annual stroke risk based on CHADS<sub>2</sub> score assuming no low-dose Aspirin use

<table>
<thead>
<tr>
<th>CHADS&lt;sub&gt;2&lt;/sub&gt; Score</th>
<th>Stroke Risk</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.9%</td>
<td>1.2-3.0</td>
</tr>
<tr>
<td>1</td>
<td>2.8%</td>
<td>2.0-3.8</td>
</tr>
<tr>
<td>2</td>
<td>4.0%</td>
<td>3.1-5.1</td>
</tr>
<tr>
<td>3</td>
<td>5.9%</td>
<td>4.6-7.3</td>
</tr>
<tr>
<td>4</td>
<td>8.5%</td>
<td>6.3-11.1</td>
</tr>
<tr>
<td>5</td>
<td>12.5%</td>
<td>8.2-17.5</td>
</tr>
<tr>
<td>6</td>
<td>18.2%</td>
<td>10.5-27.4</td>
</tr>
</tbody>
</table>

Annual Incidence of Venous Thromboembolism By Age and Gender
A “Medicines Management Pathway” for Safe Anticoagulant Use in Geriatric Patients. Adapted from: J Pharm Pract Res 2004;34:293-6
Introduction to the 9th Ed. CHEST Guidelines

Guidelines exist, as their name suggests, to serve as a guide, **not** to tell clinicians exactly what to do. The responsible clinician’s judgement, along with all the complexity and intricacies of the patient-provider relationship, remains paramount.

- S.A.M.
Introduction to the 9th Ed. CHEST Guidelines

- Previous antithrombotic guidelines were released in 2008
  - Distinct differences exist between the older guidelines and the newest iteration.

- This most recent edition of the CHEST guidelines is a burgeoning document with over 600 recommendations, many of which are new and controversial, spread across 24 separate articles.
<table>
<thead>
<tr>
<th>Grade of Recommendation</th>
<th>Benefit vs. Risk/Burden</th>
<th>Strength of Supporting Evidence</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong recommendation, high-quality evidence (1A)</td>
<td>Benefits clearly outweigh risk and burdens or vice versa.</td>
<td>Consistent evidence - RCTs with no important limitations, or exceptionally strong evidence from observational studies.</td>
<td>* Recommendation can apply to most patients in most circumstances.</td>
</tr>
<tr>
<td>Strong recommendation, moderate quality evidence (1B)</td>
<td>Benefits clearly outweigh risk and burdens or vice versa.</td>
<td>Evidence from RCTs with important limitations. Very strong evidence from observational studies.</td>
<td>* Recommendation can apply to most patients in most circumstances.</td>
</tr>
<tr>
<td>Strong recommendation, low or very-low-quality evidence (1C)</td>
<td>Benefits clearly outweigh risk and burdens or vice versa.</td>
<td>Evidence for at least one critical outcome from observational studies, case series, or RCTs with serious flaws or indirect evidence.</td>
<td>* Recommendation can apply to most patients in most circumstances.</td>
</tr>
<tr>
<td>Weak recommendation, high-quality evidence (2A)</td>
<td>Benefits closely balanced with risks and burden.</td>
<td>Consistent evidence - RCTs with no important limitations, or exceptionally strong evidence from observational studies.</td>
<td>* The best action may differ depending on circumstances or patient or societal values.</td>
</tr>
<tr>
<td>Weak recommendation, moderate quality evidence (2B)</td>
<td>Benefits closely balanced with risks and burden.</td>
<td>Evidence from RCTs with important limitations. Very strong evidence from observational studies.</td>
<td>* The best action may differ depending on circumstances or patient or societal values.</td>
</tr>
<tr>
<td>Weak recommendation, low or very-low-quality evidence (2C)</td>
<td>Uncertainty in the estimates of benefits, risks, and burden.</td>
<td>Evidence for at least one critical outcome from observational studies, case series, or RCTs with serious flaws or indirect evidence.</td>
<td>* Other alternatives may be equally reasonable.</td>
</tr>
</tbody>
</table>

**Implications**

- **RCT** = Randomized Controlled Trials
- *** = Additional discussion**
• **Lifetime Anticoagulation**

• First episode of thrombosis in a patient with:
  - Cancer
  - Cardiolipin antibodies
  - Lupus anticoagulant
  - Homozygous Factor V Leiden
  - Permanent antithrombin deficiency
  - Permanent protein C or S deficiency
  - Combined thrombophilia

Chest 2012, 141:7S-47S
## Treatment of DVT

- Proximal DVT provoked by surgery: 3 months
- Proximal DVT provoked nonsurgical: 3 months
- Distal DVT **IF** treated: 3 months
- Unprovoked Proximal DVT: 3 months
  - Low risk of bleed: 6-12 months
  - High risk of bleed: 3 months
  - Extended use assess risk/benefit
- Related to cancer: Indefinite use
- INR still 2 to 3
- Warfarin still drug of choice
- Second line is LMWH, then new agents
- If patient has cancer, use LMWH over warfarin, new agents
- Weak recommendation of old agents over new agents-need data

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Chest 2012,141:7S-47S
• **Treatment of proximal DVT**

  - LMWH or *fondaparinux* instead of IV or SC UFH
  - Recommend once daily LMWH dose over twice daily (Grade 2C).*
    
    * "This recommendation only applies when the approved once-daily regimen uses the same daily dose as the twice-daily regimen (ie, the once daily injection contains double the dose of each twice-daily injection). It also places value on avoiding an extra injection per day."

  - Treatment at home over hospital if home conditions adequate
  - For those contraindicated, use IVC filter. If bleeding risk resolves, then use anticoagulant treatment course
  - Bridge at least 5 days and/or until INR therapeutic
**Treatment of Pulmonary Embolism**

- PE provoked by surgery 3 months
- PE provoked nonsurgical 3 months
- Unprovoked PE 3 months
  - Low risk of bleed 3 months
  - High risk of bleed 3 months
  - Extending use - assess risk/benefit 3 months
- First VTE as PE 6-12 months
- First VTE as PE, high bleeding risk 3 months
- Repeat PE 6-12 months
- Related to cancer Extended use no matter bleeding risk
- INR still 2 to 3
- *Warfarin* still drug of choice
- Second line is LMWH, then new agents
- If patient has cancer, use LMWH over warfarin, new agents
- Weak recommendation of old agents over new agents-need data
Treatment of Pulmonary Embolism

- LMWH or fondaparinux instead of I.V. or subcut UFH
- Recommend once daily LMWH dose over twice daily administration (Grade 2C).*

* "This recommendation only applies when the approved once-daily regimen uses the same daily dose as the twice-daily regimen (ie, the once daily injection contains double the dose of each twice-daily injection). It also places value on avoiding an extra injection per day."

- Early discharge is encouraged
- For those contraindicated, use IVC filter. If bleeding risk resolves, then use anticoagulant treatment course
Antithrombotic Therapy and Prevention of Thrombosis, 9th Ed: ACCP Evidence-Based Clinical Practice Guidelines

- Initiation Overlap for Heparin and VKA

For patients with acute VTE, we suggest that VKA therapy be started on day 1 or 2 of low-molecular-weight heparin (LMWH) or low-dose unfractionated heparin (UFH) therapy rather than waiting for several days to start (Grade 2C).

Chest 2012,141:7S-47S
• **Loading Dose for Initiation of Vitamin K Antagonist (VKA) Therapy**

For patients sufficiently healthy to be treated as outpatients, we suggest initiating VKA therapy with warfarin 10 mg daily for the first 2 days followed by dosing based on international normalized ratio (INR) measurements rather than starting with the estimated maintenance dose (Grade 2C).

Chest 2012,141:7S-47S
Monitoring Frequency for VKAs

For patients taking VKA therapy with consistently stable INRs, we suggest an INR testing frequency of up to 12 weeks rather than every 4 weeks (Grade 2B).
Antithrombotic Therapy and Prevention of Thrombosis, 9th Ed: ACCP Evidence-Based Clinical Practice Guidelines

• *Initiation Dose Selection and Pharmacogenetic Testing*

For patients initiating VKA therapy, we recommend against the routine use of pharmacogenetic testing for guiding doses of VKA (Grade 1B).
For patients with nonvalvular AF including those with paroxysmal AF, with recommendations in favor of oral anticoagulation (intermediate to high risk; CHADS\(_2\) score = 1 or 2) and excluding those patients with mitral stenosis, stable CAD, bare-metal or drug-eluting stents, or patients with ACS, we suggest *dabigatran* 150 mg twice daily rather than adjusted-dose VKA therapy (target INR range, 2.0-3.0) (Grade 2B).
Pharmacological Treatment of Thromboembolic Disease: Vitamin K Antagonists
Anticoagulant Development Timeline

1955
The research of Karl P. Link with the Wisconsin Alumni Research Foundation leads to the development of warfarin sodium, first used as a rodenticide.

1960s
First studies demonstrate that anticoagulant therapy reduces death and recurrent VTE in patients with pulmonary embolism.

1970s
The Kimray-Greenfield filter is introduced.
Low Molecular Weight Heparin (LMWH) is discovered.

1980s
The International Normalized Ratio (INR) is introduced into clinical practice.

1990s
LMWH is found to be as effective as UFH in treatment of DVT and PE. Outpatient treatment with LMWH is shown to be safe and effective.

2004
Ximelagatran rejected by the FDA.

2010
Dabigatran approved for stroke prevention in patients with non-valvular atrial fibrillation.

2011
Rivaroxaban approved for prophylaxis of DVT and prevention of stroke in patients with non-valvular A. fib.

2012
FDA has requested additional safety data before approval of Apixaban.
Vitamin K antagonists (VKAs)

- Until recently, vitamin K antagonists have been the only oral anticoagulant drugs available for the primary and secondary prevention of arterial and venous thromboembolic disease.

- VKAs have demonstrated consistently high successful treatment rates in various patient settings, have been utilized by millions of patients throughout the world, and have been historically regarded as a gold-standard oral treatment for thromboembolic disease.
Warfarin - Mechanism of Action

- Warfarin inhibits the Vitamin-K dependent synthesis of the biologically active forms of the following clotting factors:
  - II (i.e. prothrombin)
  - VII
  - IX
  - X

- Warfarin also inhibits the naturally occurring anticoagulants, *Protein C* and *Protein S*. 
Warfarin acts as an anticoagulant by blocking the ability of Vitamin K to hepatically carboxylate the Vitamin K dependent clotting factors, thereby reducing their coagulant activity.

Biologically active substances in the coagulation cascade inhibited by *warfarin*:

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Function</th>
<th>Half-Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein C</td>
<td>Anti-coagulant</td>
<td>≤ 6 hours</td>
</tr>
<tr>
<td>Protein S</td>
<td>Anti-coagulant</td>
<td>~ 40 hours</td>
</tr>
<tr>
<td>Factor II</td>
<td>Pro-coagulant</td>
<td>65-110 hours</td>
</tr>
<tr>
<td>Factor VII</td>
<td>Pro-coagulant</td>
<td>4-7 hours</td>
</tr>
<tr>
<td>Factor IX</td>
<td>Pro-coagulant</td>
<td>18-30 hours</td>
</tr>
<tr>
<td>Factor X</td>
<td>Pro-coagulant</td>
<td>24-50 hours</td>
</tr>
</tbody>
</table>
Warfarin - Mechanism of Action

- The time to warfarin steady-state concentration and full therapeutic effects are determined by the rate of elimination of previously synthesized clotting factors corresponding to their individual half-lives; therefore the full anticoagulant effect of warfarin can be delayed for several days.

- When warfarin is first initiated (especially in the setting of an active thrombus), it may create a transient pro-coagulant/anti-coagulant imbalance due to a rapid decline in Factor VII and Protein C, which are both vitamin K dependent.
Clotting Factors

- Factor II: $t_{1/2} = 65$ to $110$ hours
- Factor VII: $t_{1/2} = 4$ to $7$ hours
- Factor IX: $t_{1/2} = 18$ to $30$ hours
- Factor X: $t_{1/2} = 24$ to $50$ hours
- Protein C: $t_{1/2} = \leq 6$ hours
- Protein S: $t_{1/2} = \sim 40$ hours
Time-curve relationship showing changes in clotting factor concentration and activity % upon initiation of *warfarin* and corresponding INR values:

![Graph showing changes in clotting factors](image)

Warfarin STEPS

- SAFETY
- TOLERABILITY
- EFFICACY
- PRICE
- SIMPLICITY
Warfarin STEPS

• SAFETY
  ▫ Stratified bleeding risks
  ▫ Significant drug-drug, drug-food, and drug-alcohol interactions (> 200 interactions per mfg.)
  ▫ Classified as Pregnancy Category X medication
    • Safe in breastfeeding
  ▫ Rare adverse reactions
    • Purple Toes Syndrome
    • Warfarin Skin Necrosis
Warfarin STEPS

- SAFETY - Drug Interactions
  - Potentiation of anticoagulant effects –

**HIGHLY PROBABLE INTERACTION:** Anti-infectives

- Ciprofloxacin
- TMP-SMX
- Erythromycin
- Fluconazole
- Isoniazid
- Metronidazole
- Miconazole (oral gel and vaginal suppository)
- Voriconazole

Warfarin STEPS

HIGHLY PROBABLE INTERACTION (Potentiation):
- Cardiovascular
  - Amiodarone
  - Clofibrate
  - Diltiazem
  - Fenofibrate
  - Propafenone
  - Propranolol

HIGHLY PROBABLE INTERACTION (Potentiation):
- Analgesics, Anti-inflammatories, Immunologics:
  - Phenylbutazone
  - Piroxicam

# Warfarin STEPS

Highly Probable Interaction (Potentiation):
- **CNS Drugs**
  - Alcohol (if concomitant liver disease)
  - *Citalopram*
  - *Entacapone*
  - *Sertraline*

Highly Probable Interaction (Potentiation):
- **GI Drugs and Food**
  - *Cimetidine*
  - *Fish Oil*
  - *Mango*
  - *Omeprazole*

**Warfarin STEPS**

- SAFETY - Drug Interactions
  - **Inhibition** of anticoagulant effects –

**HIGHLY PROBABLE INTERACTION:** Anti-infectives

- *Griseofulvin*
- *Nafcillin*
- *Ribavirin*
- *Rifampin*

Inhibition of warfarin’s anticoagulant effects

Warfarin STEPS

HIGHLY PROBABLE INTERACTION (Inhibition):
- Cardiovascular
  - Cholestyramine
- GI Drugs and Food
  - High Vitamin K content foods/enteral feeds
  - Avocado (large amounts)

HIGHLY PROBABLE INTERACTION (Inhibition):
- Analgesics, Anti-inflammatories, Immunologics:
  - Mesalamine
- CNS Drugs
  - Barbiturates
  - Carbamazepine

Warfarin Skin Necrosis

• Caused by extensive thrombosis of the venules and capillaries within the subcutaneous fat
  ▫ Formation of *microemboli*

• 1 in every 5,000 patients?
  ▫ Women affected 6:1

• Has been associated with loading doses
Anatomical Sites typically affected in Warfarin-Induced Skin Necrosis:

Microcirculation-rich areas:
In Women:
• Breasts
• Buttocks
• Thighs
In Men:
• Penile skin may be affected

• Less common sites: face, trunk, extremities
Warfarin STEPS

• TOLERABILITY
  ▫ Bleeding is the major adverse effect of warfarin.
  ▫ Hemorrhage may occur at virtually any site. Risk is dependent on multiple variables, including the intensity of anticoagulation and patient susceptibility.
  ▫ Cardiovascular: Vasculitis
  ▫ Central nervous system: Signs/symptoms of bleeding (eg, dizziness, fatigue, fever, headache, lethargy, malaise, pain)
  ▫ Dermatologic: Alopecia, bullous eruptions, dermatitis, rash, pruritus, urticaria
  ▫ Gastrointestinal: Abdominal pain, diarrhea, flatulence, gastrointestinal bleeding, nausea, taste disturbance, vomiting
**Warfarin STEPS**

- **TOLERABILITY**
  - Genitourinary: Hematuria
  - Hematologic: Anemia, retroperitoneal hematoma, unrecognized bleeding sites (e.g., colon cancer) may be uncovered by anticoagulation
  - Hepatic: Hepatitis (including cholestatic hepatitis), transaminases increased
  - Neuromuscular & skeletal: Osteoporosis (potential association with long-term use), paralysis, paresthesia, weakness
  - Respiratory: Respiratory tract bleeding, tracheobronchial calcification
Warfarin STEPS

- EFFICACY

- Warfarin remains the “gold-standard” therapy in the treatment of VTE

- Newer therapies have demonstrated “non-inferiority” but not superiority.
Warfarin STEPS

• Product and strength availability:

In the case of Coumadin® and various generic warfarin products, the manufacturers have attempted to keep the colors consistent with the strength of the pills. The goal is to allow the patient to identify the color-coded dose and prevent mix-ups or errors.

Two commercial products in the USA:
Coumadin® manufactured by Bristol-Myers Squibb
Jantoven® manufactured by Upsher-Smith ($18 for #30)

Warfarin STEPS

- Patient Counseling Information:
  - Use a soft-bristle toothbrush
  - Floss with waxed floss rather than unwaxed floss
  - Shave with an electric razor rather than a blade
  - Take care when using sharp objects, such as knives and scissors
  - Avoid activities that have a risk of falling or injury (e.g., contact sports)
Warfarin STEPS

• SIMPLICITY:
  ▫ NOT simple!
  ▫ Various dosing nomograms & algorithms
  ▫ The most important underlying principle of warfarin therapy is that there is no true “one dose for all.”
    • Frequent adjustments in dosage should be expected
  ▫ INR monitoring
Warfarin Pharmacokinetics

- 99% protein bound
- half-life = ~40 hrs (20-60 hrs)
- Maximum pharmacological effects can occur up to 48 hours after a dose
- Hepatically metabolized
  - Issues affecting hepatic clearance
  - presence of liver disease
    - decrease clotting factor synthesis, unable to metabolize warfarin
  - hepatic congestion
  - hypermetabolic states
    - thyrotoxicosis
    - pyrexia
# Sample Warfarin Dosing Schedule

<table>
<thead>
<tr>
<th>Mon</th>
<th>Tue</th>
<th>Wed</th>
<th>Thu</th>
<th>Fri</th>
<th>Sat</th>
<th>Sun</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.5</td>
<td>5</td>
<td>5</td>
<td>2.5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.5</td>
<td>5</td>
<td>2.5</td>
<td>5</td>
<td>2.5</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total Weekly Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>35 mg</td>
</tr>
<tr>
<td>30 mg</td>
</tr>
<tr>
<td>27.5 mg</td>
</tr>
</tbody>
</table>

INR Monitoring

• The result (in seconds) for a prothrombin time performed on a normal individual will vary according to the type of analytical system employed.

• This is due to the variations between different batches of manufacturer's tissue factor used in the reagent to perform the test.

• The International Normalized Ratio (INR) was devised to standardize the results. Each manufacturer assigns an ISI value (International Sensitivity Index) for any tissue factor they manufacture.

• The ISI value indicates how a particular batch of tissue factor compares to an international reference tissue factor. The ISI is usually between 1.0 and 2.0

• The INR is the ratio of a patient's prothrombin time to a normal (control) sample, raised to the power of the ISI value for the analytical system used.

\[
INR = \left( \frac{\text{Prothrombin Time (Patient)}}{\text{Prothrombin Time (Mean Normal)}} \right)^{\text{ISI}}
\]
Errors made in calculating the INR

- Error Example 1: \[
\frac{\text{PT (patient)}^\text{ISI}}{\text{PT (Mean Normal)}}
\]

- Error Example 2: Patient PT / Mean Normal PT

- Error Example 3: \[
\left(\frac{\text{PT (patient)}}{\text{PT (Mean Normal)}}\right)^\text{ISI} \times \text{ISI}
\]

## INR Monitoring

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Normal Reference Range*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prothrombin Time (PT)</td>
<td>10 - 13 seconds</td>
</tr>
<tr>
<td>Activated Partial Thromboplastin Time (aPTT)</td>
<td>25 - 35 seconds</td>
</tr>
<tr>
<td>International Normalized Ratio (INR)</td>
<td>0.8 – 1.2</td>
</tr>
</tbody>
</table>

*Note: Normal value ranges may vary slightly among different laboratories

\[
\text{INR} = \left( \frac{\text{Prothrombin Time (Patient)}}{\text{Prothrombin Time (Mean Normal)}} \right)^{\text{ISI}}
\]
Formula: $PTR^{ISI} = INR$

Example:
$1.3^{2.3} = 1.83$
$1.5^{2.3} = 2.54$
How Different Thromboplastins Influence the PT Ratio and INR

![Diagram of blood from a single patient with thromboplastin reagents and corresponding PT and INR values.](image)

<table>
<thead>
<tr>
<th>Thromboplastin reagent</th>
<th>Patient’s PT (Seconds)</th>
<th>Mean Normal (Seconds)</th>
<th>PTR</th>
<th>ISI</th>
<th>INR</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>16</td>
<td>12</td>
<td>1.3</td>
<td>3.2</td>
<td>2.6</td>
</tr>
<tr>
<td>B</td>
<td>18</td>
<td>12</td>
<td>1.5</td>
<td>2.4</td>
<td>2.6</td>
</tr>
<tr>
<td>C</td>
<td>21</td>
<td>13</td>
<td>1.6</td>
<td>2.0</td>
<td>2.6</td>
</tr>
<tr>
<td>D</td>
<td>24</td>
<td>11</td>
<td>2.2</td>
<td>1.2</td>
<td>2.6</td>
</tr>
<tr>
<td>E</td>
<td>38</td>
<td>14.5</td>
<td>2.6</td>
<td>1.0</td>
<td>2.6</td>
</tr>
</tbody>
</table>

INR Monitoring (Limitations)

• Although the INR ranks among the most commonly performed laboratory tests*, its biological basis and limitations are often poorly understood.

*It is estimated over 40 million PT/INR assays are performed in the U.S. annually.

• While use of the INR has resulted in better agreement between labs, in reality, INR results from the same specimen performed on different analyzers with different thromboplatin reagents still are not the same.


## Warfarin Reversal

<table>
<thead>
<tr>
<th>INR range</th>
<th>Vitamin K dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 4.5, no bleeding</td>
<td>no vitamin K</td>
</tr>
<tr>
<td>4.5 to 10, no bleeding</td>
<td>no vitamin K</td>
</tr>
<tr>
<td>&gt; 10 and no bleeding</td>
<td>hold dose, 3 to 5 mg oral, should see effect in 24-48 hrs</td>
</tr>
<tr>
<td>Bleeding or &gt; 10</td>
<td>10 mg slow I.V. infusion + FFP, check INR in 6 hours, may repeat every 12 hours</td>
</tr>
<tr>
<td>Life-threatening bleed</td>
<td>replace with 4 factor prothrombin complex + 10 mg vitamin K I.V.</td>
</tr>
</tbody>
</table>

Adapted from: Chest 2012,141:7S-47S
Pharmacological Treatment of Thromboembolic Disease: Direct Thrombin Inhibitors & Factor Xa Inhibitors
Direct Thrombin Inhibitors

• *Dabigatran Etexilate* (Pradaxa®)
  
  ▫ Selective, reversible, direct thrombin inhibitor
  
  ▫ Administered as a pro-drug since *dabigatran* itself is a very polar, lipophobic molecule that is not absorbed from the GI tract.
  
  ▫ Approved by the FDA, October 19th 2010
  
  ▫ Indication: Reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.
**Intrinsic activation**
- Surface contact
  - Factor XII
  - Factor XI
  - Factor VIII
  - Factor IXa
  - Factor X

**Extrinsic activation**
- Vessel injury
  - Factor VII

- Prothrombin
- Factor Xa

- Thrombin

- Fibrinogen → Fibrin

**Inhibitors**
- Rivaroxaban
- Dabigatran etexilate
Dabigatran STEPS

• SAFETY
  - Risk of bleeding increases with other drugs that increase the risk of hemorrhage (i.e., aspirin, NSAIDs, UFH, LMWH)

  - Monitor Hemoglobin/Hematocrit

  - Higher risk of gastrointestinal bleeds vs. warfarin
    - (Absolute Risk Increase 0.49% per year; 1 out of every 200 patients treated with dabigatran as compared to treatment with warfarin)
Dabigatran STEPS

- SAFETY
  - More minor bleeding with warfarin
    - Absolute Risk Increase 1.6%, 1 out of every 63 patients treated with warfarin vs. dabigatran
  - More intracranial bleeding with warfarin
    - Absolute risk increase 0.44%, 1 out of every 227 patients treated with warfarin vs. dabigatran
Dabigatran STEPS

• SAFETY
  ▫ **Bleeding**
    ▫ No direct antidote is available
    ▫ Dabigatran is dialyzable in the event of a catastrophic bleed
    ▫ No difference in effect on liver function between *dabigatran* and placebo in both the RELY and RECOVER trials
Dabigatran STEPS

• SAFETY
  ▫ Drug interactions
    • Inducers: rifampin reduce the Css of dabigatran by 66%
    • Inhibitors increase Cpss of dabigatran:
      • ketaconazole (150% increase)
      • amiodarone (50% increase)
      • These studies were done “in vitro”
      • No effect of verapamil or amiodarone in the RE-LY trial
      • No effect with clarithromycin
      • No effect with H2 blockers, PPI’s, atorvastatin, digoxin
Dabigatran STEPS

• TOLERABILITY

  ▫ Dyspepsia (1 out of every 18 patients treated are affected)

  ▫ Dabigatran is an acidic molecule
    • nausea
    • upper abdominal pain (1 out of every 67 patients treated)
    • Diarrhea
Dabigatran STEPS

- **EFFICACY**
- Dabigatran versus warfarin in patients with atrial fibrillation
- 2 year trial, n = 18,113
- **Drugs:** Dabigatran 110 mg or 150 mg twice daily vs dose-adjusted warfarin (target INR 2-3)
- **Patients:** mean age = 71, 64% men, mean CHADS$_2$ score was 2.1 (moderate risk of stroke, 32% high risk), BP 130/77, prior stroke or TIA 20%, HTN 78%, 40% on ASA (allowed by study)

## RE-LY Results

<table>
<thead>
<tr>
<th>% Event per year</th>
<th>Dabigatran 110 mg</th>
<th>Dabigatran 150 mg</th>
<th>Warfarin</th>
<th>Dabigatran 110 mg vs warfarin</th>
<th>Dabigatran 150 mg vs warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke of Embolism</td>
<td>1.53%</td>
<td>1.11%</td>
<td>1.69%</td>
<td>NS, but noninferior</td>
<td>noninferior, ARR 0.58%, NNT 172</td>
</tr>
<tr>
<td>All stroke</td>
<td>1.44%</td>
<td>1.01%</td>
<td>1.57%</td>
<td>NS</td>
<td>noninferior, ARR 0.56%, NNT 178</td>
</tr>
<tr>
<td>MI</td>
<td>0.72%</td>
<td>0.74%</td>
<td>0.53%</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>PE</td>
<td>0.12%</td>
<td>0.15%</td>
<td>0.09%</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>19.4%</td>
<td>20.2%</td>
<td>20.8%</td>
<td>ARR 1.4%, NNT 71</td>
<td>NS</td>
</tr>
<tr>
<td>Death from CV causes</td>
<td>2.43%</td>
<td>2.28%</td>
<td>2.69%</td>
<td>NS</td>
<td>ARR 0.41%, NNT 244</td>
</tr>
<tr>
<td>All death</td>
<td>3.75%</td>
<td>3.64%</td>
<td>4.13%</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>
Dabigatran STEPS

• **EFFICACY**
  • Dabigatran versus warfarin in the treatment in acute venous thromboembolism
  • 6 months, n = 2539
  • Double-dummy design – all patients got a study drug with placebo and INR’s (real and sham)
  • **Drugs:** Dabigatran 150 mg twice daily vs. dose-adjusted warfarin (INR 2-3) for 6 months
  • **Patients:** mean age = 55, 42% female, 95% white, 83 kg, BMI = 28, normal renal function, most patients were bridged with LMWH
  • **Index events:** DVT 69%, 21% PE, both 9.5%, neither 0.2%

# RE-COVER Results

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Dabigatran</th>
<th>Warfarin</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE or death</td>
<td>2.4%</td>
<td>2.1%</td>
<td>NS</td>
</tr>
<tr>
<td>VTE or death + 30 day follow-up</td>
<td>2.7%</td>
<td>2.5%</td>
<td>NS</td>
</tr>
<tr>
<td>DVT</td>
<td>1.3%</td>
<td>1.4%</td>
<td>NS</td>
</tr>
<tr>
<td>PE</td>
<td>1.0%</td>
<td>0.6%</td>
<td>NS</td>
</tr>
<tr>
<td>VTE death</td>
<td>0.1%</td>
<td>0.2%</td>
<td>NS</td>
</tr>
<tr>
<td>All death</td>
<td>1.6%</td>
<td>1.7%</td>
<td>NS</td>
</tr>
</tbody>
</table>

Dabigatran STEPS

- **PRICE**
  - #60, 150mg capsules = $230.00  
    www.drugstore.com
  - #30, 75mg capsules = $116.00  
    www.drugstore.com
  - Discard stock bottles 4 months after opening
**Transitioning from other anticoagulants**

<table>
<thead>
<tr>
<th>Converting from warfarin</th>
<th>D/C warfarin and start dabigatran once INR &lt; 2.0</th>
</tr>
</thead>
</table>
| **Converting to warfarin** | CrCL >50 mL/min: start warfarin 3 days before stopping dabigatran  
CrCL 31–50 mL/min: start warfarin 2 days before stopping dabigatran  
CrCL 15–30 mL/min: start warfarin 1 day before stopping dabigatran  
CrCL <15 mL/min: no recommendations can be made |
| **Converting to parenteral anticoagulation** | Wait 12 hours if CrCl ≥30 mL/min or 24 hours if CrCL < 30mL/min after the last dose of dabigatran before starting parenteral anticoagulation |
| **Converting from parenteral anticoagulation** | Start dabigatran 0 to 2 hours before the time that the next dose of parenteral drug was to be given or at the time of D/C of a continuously administered parenteral drug (e.g. UFH) |
| **Surgical/invasive interventions** | D/C dabigatran 1 to 2 days (CrCL >50 mL/min) or 3 to 5 days (CrCL <50 mL/min) before an invasive procedure; longer times should be considered for patients undergoing major surgery or those receiving spinal puncture/epidural catheter |
Dabigatran Check-List for Dispensing LTC Pharmacists

✓ Check renal function (DO NOT use if patient is on dialysis)
  Dose = 150mg BID for CrCL ≥ 30mL/min.
  Dose = 75mg BID for CrCL < 30mL/min.

✓ Verify a recent serum creatinine is available
  • At least within 30 days of dispense date

✓ CALCULATE the patient’s estimated CrCL
  • Just do it!
The Cockcroft & Gault Equation

Creatinine Clearance (CrCL) = \frac{(140 - \text{age}) \times \text{IBW}}{72 \times \text{stable creatinine}}

Substitute “85” for female patients

(Ideal Body Weight) \text{IBW} \ ♂ = 50 + (2.3)\text{(inches > 5 feet)}
(Ideal Body Weight) \text{IBW} \ ♀ = 45 + (2.3)\text{(inches > 5 feet)}
Limitations of MDRD Equation

- Developed in patients with average GFR of 40 mL/min/1.73 m²
- Not proven in pediatrics or patients > 70 yoa
- ONLY valid for use in *caucasians* and *african americans*
- Nutritional status
- Medication interference
- Based on serum creatinine
The Non-Linear Relationship of Serum Creatinine to CrCL:


Lab Abnormalities of Renal Failure typically start, e.g. elevated phosphorus, mild anemia
Dabigatran Check-List for Dispensing LTC Pharmacists

✔ Verify INR < 2
  – If INR available (or warfarin within 5 days)

✔ Discontinue all other anticoagulants; no need for “bridge therapy”
  – SC heparin or LMWH for DVT prophylaxis
    • Start *dabigatran* immediately after D/C
  – Heparin drip
    • Start *dabigatran* immediately after D/C
  – LMWH weight-based dosing i.e. VTE treatment-doses
    Start *dabigatran* when next scheduled dose due (usually 12 hours after last dose, but may be 24 hours if poor renal function)
Dabigatran Check-List for Consultant LTC Pharmacists

✓ On-going monitoring of renal function while patient is receiving dabigatran
  ▪ Would not be unreasonable to check a SrCr every 4 months; esp. for patients > 70 yoa

✓ Vigilant monitoring of any drugs that can affect renal function
  ▪ ACE-Is/ARBs/Aliskiren
  ▪ NSAIDs
  ▪ Certain CCBs (esp. if patient has diabetic nephropathy)
Dabigatran STEPS

• Important Patient Counseling Information:

1) Do NOT skip doses (rapid decline in pharmacologic effect and loss of therapeutic benefit)

2) May be taken with or without food

3) Do NOT open capsules, swallow whole

* If a geriatric patient has swallowing difficulty, then that patient IS NOT a suitable candidate for dabigatran treatment

4) Counsel on signs/symptoms of bleeding (as with other anticoagulants)

5) High rate of GI side effects
Factor Xa Inhibitors

- *Rivaroxaban* (Xarelto®)
  - (S)-enantiomer
  - Blocks the active site of factor Xa
- Oral anticoagulant
- Indication(s)
  - Indicated for the prophylaxis of DVT in patients undergoing knee or hip surgery replacement
  - Non-valvular A. fib to prevent stroke and systemic embolism
Rivaroxaban STEPS

• SAFETY
  ▫ Box warning for epidural or spinal hematomas in those receiving neural anesthesia
  ▫ Avoid CYP3A4 inducers
    • Carbamazepine, rifampin, phenytoin, St. John’s Wort
    • Lowers efficacy, increase dose to 20 mg
  ▫ Avoid CYP3A4 inhibitors
    • Ketoconazole, protease inhibitors, clarithromycin, erythromycin
    • Increase bleeding
  ▫ Bleeding
    • Bleeding leading to drug discontinuation 3.7% (mean of 3 trials) vs Enoxaparin (~6% in each group)
Rivaroxaban STEPS

- **TOLERABILITY**
  - Secretion from wound 2.8%
  - Syncope 1.2% vs 0.7% with LMWH, NNH 200
  - LFT elevation was greater with LMWH than rivaroxaban
Rivaroxaban STEPS

**EFFICACY**

**RECORD 1 and 2 trials**

- **RCT’s Rivaroxaban 10 mg vs Enoxaparin 40 mg daily**
  - **RECORD 1 (HIP)**
    - VTE prevention 1.1% (Riv) vs 3.7% (LMWH), NNT 38
    - Proximal DVT, Nonfatal PE, VTE-related death, ARR 1.7%, NNT 59
    - Symptomatic VTE, p = NS
  - **RECORD 2 (HIP)**
    - VTE prevention 2% (Riv) vs 8.4% (LMWH), NNT 16
    - Proximal DVT, Nonfatal PE, VTE-related death, ARR 4.1%, NNT 25
    - Symptomatic VTE, p = NS
Rivaroxaban STEPS

• **EFFICACY**
  ▫ RECORD 3 Trial (Knee)
    • VTE prevention 9.7% (Riva) vs 18.8% (LMWH), NNT = 11
    • Proximal DVT, Nonfatal PE, VTE-related death, ARR 1.6%, NNT 63
    • Symptomatic VTE, p = NS
Rivaroxaban STEPS

- EFFICACY
  - ROCKET-AF Trial (Afib)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rivaroxaban</th>
<th>Warfarin</th>
<th>p-Value</th>
<th>p-value for noninferiority</th>
<th>ARR</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or Systemic Embolism Treated population</td>
<td>1.7%</td>
<td>2.2%</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>0.5%</td>
<td>200</td>
</tr>
<tr>
<td>Stroke or Systemic Embolism Intention-to-treat population</td>
<td>2.1%</td>
<td>2.4%</td>
<td>NS</td>
<td>&lt;.001 (.12 for superiority)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major and nonmajor Bleeding – Safety outcome</td>
<td>14.9%</td>
<td>14.5%</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite of stroke, systemic embolism, or death from CV causes</td>
<td>3.1%</td>
<td>3.6%</td>
<td>.03</td>
<td>N/A</td>
<td>0.5%</td>
<td>200</td>
</tr>
<tr>
<td>Composite of stroke, systemic embolism, or death from CV causes + MI</td>
<td>6.1%</td>
<td>7.3%</td>
<td>.01</td>
<td>N/A</td>
<td>1.2%</td>
<td>83</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>3%</td>
<td>3.5%</td>
<td>NS</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bleeding Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any major bleed**</td>
<td>5.6%</td>
<td>5.4%</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial Hemorrhage</td>
<td>0.8%</td>
<td>1.2%</td>
<td>.02</td>
<td>0.4%</td>
<td>250</td>
<td></td>
</tr>
<tr>
<td>Nonmajor clinical bleeding</td>
<td>16.7%</td>
<td>16.2%</td>
<td>NS</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Rivaroxaban STEPS

- **PRICE**
  - Tablets, 10 mg (light red), 15mg (red) and 20mg (dark red) tablets
  - $245 / #30

- **SIMPLICITY**
  - Take with or without food (orthopedic thromboprophylaxis)
  - Take WITH food (evening meal) for A. fib indication
  - No need for INR monitoring
  - Can be given via feeding tube
  - Do not use with other anticoagulants at this time
  - Avoid in patients with renal dysfunction (specific dosing)
Rivaroxaban STEPS

• Dosing Guidelines:

• Postoperative thromboprophylaxis:
  **Note:** Initiate therapy after hemostasis has been established, 6-10 hours postoperatively.

• Knee replacement: 10 mg once daily; recommended total duration of therapy: 12-14 days

• Hip replacement: 10 mg once daily; total duration of therapy: 35 days
Rivaroxaban STEPS (dosing cont.)

- **Nonvalvular A. fib to prevent stroke and systemic embolism:** Oral: 20 mg once daily

- **Conversion to warfarin:** *Note:* Rivaroxaban affects INR; therefore, initial INR measurements after initiating warfarin may be unreliable.

- **U.S. labeling:** Initiate warfarin and a parenteral anticoagulant 24 hours after discontinuation of rivaroxaban (other approaches to conversion may be acceptable).
Rivaroxaban STEPS (dosing cont.)

- **Conversion from** continuous infusion UFH:
  - Initiate rivaroxaban at the time of heparin discontinuation

- **Conversion to** continuous infusion UFH:
  - Initiate continuous infusion unfractionated heparin 24 hours after discontinuation of rivaroxaban

- **Conversion from** anticoagulants (other than warfarin and UFH):
  - Discontinue current anticoagulant and initiate rivaroxaban ≤2 hours prior to the next regularly scheduled evening dose of the discontinued anticoagulant.

- **Conversion to** other anticoagulants (other than warfarin):
  - Initiate the anticoagulant 24 hours after discontinuation of rivaroxaban
Rivaroxaban STEPS

Dosing Guidelines: Renal Impairment

- **Nonvalvular atrial fibrillation:**
  - CrCL >50 mL/minute: No dosage adjustment necessary, use standard dose = 20mg
  - CrCL 15-50 mL/minute: 15 mg once daily.
  - CrCL <15 mL/minute: Avoid use.
  - ESRD requiring hemodialysis: Avoid use.
Rivaroxaban STEPS

Dosing Guidelines: Renal Impairment

- **Postoperative thromboprophylaxis:**
  - CrCL >50 mL/minute: No dosage adjustment necessary. Dose = 10mg once daily.
  - CrCL 30-50 mL/minute: No dosage adjustment provided in manufacturer’s labeling; use with caution. Dose = 10mg once daily.
  - CrCL <30 mL/minute: Avoid use.
  - ESRD requiring hemodialysis: Avoid use.
Apixaban is coming...

- Another Direct Factor Xa Inhibitor
- Trademarked as Eliquis®
- It is being developed jointly by Pfizer and BMS.
- A trial published last year in the NEJM showed that in patients with A. fib who have failed or are not candidates for VKA therapy, apixaban vs. ASA, reduced the risk of stroke or systemic embolism from 3.7% per year with ASA to 1.6% per year with Apixaban).
- No statistical differences in mortality
Apixaban is coming...

- In another recent head-to-head study of apixaban versus warfarin, apixaban met the primary endpoint of “noninferiority” as compared to warfarin in preventing CVA and a key secondary endpoint (superior compared to warfarin in avoiding major bleeding).

- ARISTOTLE Trial Investigators
Pharmacological Measures to reverse dabigatran and rivaroxaban for severe bleeding or intracranial hemorrhage:

- Factor VIIa (Novoseven®)

- Dose: 45-90 micrograms/kg (actual body weight) rounded to the nearest 1 mg vial. Administer IVP over 3 - 5 minutes; repeat in 30 min to 2 hours if adequate hemostasis not achieved.


Pharmacological Measures to reverse dabigatran and rivaroxaban for severe bleeding or intracranial hemorrhage:

- For continued bleeding following 2 doses of Factor VIIa

- Prothrombin Complex Concentrate (PCC): Factor IX Complex (Profilnine®)

- Administer 25 - 50 units/kg IVP (2000 - 4000 units) rounded to vial size; repeat in 30 minutes in the presence of persistent bleeding or elevated aPTT / TT / ECT

Pharmacological Measures to reverse *dabigatran* and *rivaroxaban* for severe bleeding or intracranial hemorrhage:

- Alternative / Rescue Therapies:
  - *** In the case of intractable bleeding despite appropriate intervention or in place of Profilnine®: ***
  
  - **FEIBA®** 25 - 50 units/kg IVP (Max 5000 units) rounded to vial size; may repeat in 30 minutes in the presence of persistent bleeding or elevated aPTT/TT/ECT to a maximum total dose of 100 units/kg.
  
  FEIBA = Factor VIII Inhibitor Bypassing Activity

Patient Case 1:

- EW is an elderly white female and an independent living resident who receives her Rx from your LTC pharmacy.

- She is 85 years old and has a prosthetic/mechanical mitral valve with rate-controlled atrial fibrillation.

- What is the correct anticoagulant medication for this patient?
Patient Case 1:

A. Rivaroxaban (Xarelto®) 15mg daily

B. Dose-adjusted warfarin; target INR 2.5

C. Dabigatran (Pradaxa®) 75mg BID

D. Dose-adjusted warfarin; target INR 3.0
Patient Case 2: Uncontrolled Hypertension, Advanced Heart Failure and Atrial Fibrillation

JD is a 78 year old African-American man living in an SNF serviced by your LTC pharmacy. He has a history of advanced HF, CAD, dyslipidemia, severe rheumatoid arthritis and has recently developed A. fib

- NYHA Class III symptoms
- ACCF/AHA Stage C Heart Failure
- Most recent LVEF < 25%
- Current BP 150/90 mmHg
Patient Case 2: Uncontrolled Hypertension, Advanced Heart Failure and Atrial Fibrillation

• Current laboratory values:
  ▫ Serum Potassium 5.0 mEq/L
  ▫ Serum Creatinine 2.4 mg/dL
  ▫ Serum Sodium 142 mEq/L

• JD weighs 162 lbs

• Height = 5’8”

• eGFR = 32mL/minute/1.73m² via MDRD eq.
Patient Case 2: Which is the correct anticoagulant medication for JD?

A. *Dabigatran* *(Pradaxa®)* 150mg BID

B. *Rivaroxaban* *(Xarelto®)* 10mg daily

C. *Dabigatran* *(Pradaxa®)* 75mg BID

D. Dose adjusted warfarin; target INR 2-3

E. C or D
Patient Case 3: Hip fracture

- MG is a 75 year old Hispanic female who is a resident of the SNF serviced by your LTC pharmacy.

- Her medical diagnoses include mild dementia and urinary incontinence.

- She takes a once daily low-dose aspirin, multi-vitamin and amlodipine/valsartan 5mg/160mg combination.

- She recently fell and suffered a left hip fracture requiring orthopedic surgery.
Patient Case 3: Which of the following medications would be appropriate as thrombo-prophylaxis following MG’s orthopedic surgery?

A. Dabigatran (Pradaxa®) 75mg BID

B. Rivaroxaban (Xarelto®) 10mg daily

C. Dose-adjusted warfarin; target INR 2.5

D. B or C
Geriatric patients are inherently predisposed to adverse events and complications from anticoagulant drugs due to:

- Age-related decline in cardiac, renal and hepatic function
- Decreased production of RBCs, ↓ circulating blood volume, ↓ clotting factor synthesis
- Polypharmacy, multiple patient co-morbidities, inherent complexity of anticoagulant pharmacotherapy
Lessons for Long Term Care Pharmacy Practice - Re-cap & Summary:

- *Warfarin* remains the “gold-standard” treatment for thromboembolic disease in the elderly, despite its inherent complexity, multiple adverse effects, drug interactions, etc.

- Direct factor Xa inhibitors and direct thrombin inhibitors are alternative therapies for geriatric patients with sufficient and stable renal function who cannot tolerate *warfarin*.
Lessons for Long Term Care Pharmacy Practice - Re-cap & Summary:

• ALL anticoagulant therapies in the elderly require stringent monitoring and patient adherence to prescribed treatment for optimum effect.
  ▫ CrCL should be used to assess renal function in elderly patients prescribed direct factor Xa inhibitors and direct thrombin inhibitors, not eGFR.

• LTC pharmacists must possess working knowledge of the proper indications, contraindications, monitoring parameters, and reversal methods for traditional and newer anticoagulant drugs to ensure patient safety.
Questions?