Cardiovascular Pharmacology Series: Anticoagulants

Video 1: Clotting Basics

Zachary R. Noel, PharmD, BCCP
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Road Map

Video 1: Clotting Basics

Video 2: Parenteral Anticoagulants
- Heparin and Low Molecular Weight Heparin

Video 3: Parenteral Anticoagulants
- Indirect Xa Inhibitor and Direct Thrombin Inhibitors

Video 4: Oral Anticoagulation
- Vitamin K Antagonist

Video 5: Oral Anticoagulation
- Direct Oral Anticoagulants
Learning Objectives

At the conclusion of this video, the second year PharmD student will be able to:

- Define *zymogen* and explain the role of zymogens in the clotting cascade
- Identify clotting factors and natural anticoagulants that are targets of anticoagulant drug therapy
- Distinguish the difference between anticoagulants that possess *direct* and *indirect* activity
- State the most common adverse effect of anticoagulants
Mechanisms of Hemostasis

• Primary Hemostasis
  – Platelet adhesion, activation, and aggregation to form a platelet plug (see Dr. Watson’s lectures)

• Secondary Hemostasis
  – Activation of clotting factors that culminates in the conversion of soluble fibrinogen to insoluble fibrin, forming a stable clot
Key Concepts

- **Zymogens**
  - Inactive substance that is converted to an active enzyme by another enzyme

- Physiologic coagulant vs anticoagulant

- Drug targets
Balancing Risk…

- Bleeding
- Thrombosis
Balancing Risk…

- Bleeding
- Thrombosis
  - Endothelial injury
  - Blood stasis
  - Hypercoagulability
Balancing Risk...

- Bleeding
- Thrombosis
  - Endothelial injury
  - Blood stasis
- Anticoagulants
- Hypercoagulability
Balancing Risk…

- Bleeding
- Thrombosis

Factors:
- Endothelial injury
- Blood stasis
- Hypercoagulability

Anticoagulants
### Table 1: Anticoagulants You Need to Know

<table>
<thead>
<tr>
<th>Generic (Brand)</th>
<th>Drug Class</th>
<th>Video</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unfractionated heparin</td>
<td>Heparin</td>
<td>2</td>
</tr>
<tr>
<td>Enoxaparin (Lovenox®)</td>
<td>Low molecular weight heparin (LMWH)</td>
<td>2</td>
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<td>Fondaparinux (Arixtra®)</td>
<td>Indirect Xa inhibitor</td>
<td>3</td>
</tr>
<tr>
<td>Argatroban</td>
<td>Direct thrombin inhibitor (DTI)</td>
<td>3</td>
</tr>
<tr>
<td>Bivalirudin (Angiomax®)</td>
<td>Direct thrombin inhibitor (DTI)</td>
<td>3</td>
</tr>
<tr>
<td>Warfarin (Coumadin®)</td>
<td>Vitamin K antagonist (VKA)</td>
<td>4</td>
</tr>
<tr>
<td>Apixaban (Eliquis®)</td>
<td>Direct Xa inhibitor</td>
<td>5</td>
</tr>
<tr>
<td>Rivaroxaban (Xarelto®)</td>
<td>Direct Xa inhibitor</td>
<td>5</td>
</tr>
<tr>
<td>Dabigatran (Pradaxa®)</td>
<td>Direct thrombin inhibitor</td>
<td>5</td>
</tr>
<tr>
<td>Edoxaban (Savaysa®)</td>
<td>Direct Xa inhibitor</td>
<td>5</td>
</tr>
</tbody>
</table>
# Table 2: Reversal Agents You Need to Know

<table>
<thead>
<tr>
<th>Generic (Brand)</th>
<th>Reversal Agent for…</th>
<th>Video</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protamine</td>
<td>Heparin</td>
<td>2</td>
</tr>
<tr>
<td>Phytonadione (Mephyton®)</td>
<td>Warfarin</td>
<td>4</td>
</tr>
<tr>
<td>4-Factor Prothrombin Complex (KCentra®)</td>
<td>Warfarin</td>
<td>4</td>
</tr>
<tr>
<td>Idarucizumab (Praxbind®)</td>
<td>Dabigatran</td>
<td>5</td>
</tr>
<tr>
<td>Coagulation Factor Xa (recombinant), Inactivated - zghzo (Andexxa®)</td>
<td>Apixaban, rivaroxaban</td>
<td>5</td>
</tr>
</tbody>
</table>
General Comments

• Do I need to know brand/generic names?
  – Exam questions on pharmacology will not require you to know brand and
generic names; however, please clarify with your therapeutics instructor(s)
on whether you need to know brand and generic names for their content.

• Do I need to know dosing?
  – Any dosing information included in tables is purely informational and you will
not be tested on it for the pharmacology questions of the exam; however,
please clarify with your therapeutics instructor(s) on whether you need to
know dosing for their content.

• Am I responsible for any drugs that are not in Table 1 or 2?
  – Additional medications may be discussed for completeness, but you will
only be tested on the drugs covered in Table 1 and 2.
General Comments

• Do I need to know monitoring information?
  – In order to compare/contrast anticoagulants, a baseline understanding of which drugs require routine therapeutic monitoring is needed (e.g., heparin requires routine therapeutic monitoring, but enoxaparin does not). Details on relevant laboratory tests will be included for completeness, but your understanding of these various labs and application of them is at the discretion of your therapeutics instructor.

• How should I contact you for questions related to content on this material?
  – The discussion board is the preferred location for communicating content-related questions throughout the course.
Exit Slip

Please complete the “exit slip” in Blackboard before advancing to the next video.
Cardiovascular Pharmacology Series: Anticoagulants

Video 2: Parenteral Anticoagulants – Heparin and Low Molecular Weight Heparin

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Learning Objectives

For the medications (or medication classes) covered, an AST 5 student should be able to:

– Explain the mechanism(s) of action
– List the clinical effects (both beneficial and adverse) attributed to the mechanism of action
– Describe key pharmacokinetic properties, including absorption, distribution, metabolism, and elimination
– Describe features that distinguish specific medications or groups of medications within each class
– List characteristics that confer advantages and disadvantages to one class of medications over another
Clotting Cascade

Vessel Injury

XII → XIIa

XI → XIa

IX → IXa

VII → VIIa

X → Xa

II → IIa

Antithrombin III

Heparin
Enoxaparin

Physiologic inhibition
Physiologic activation
Drug inhibits
Drug activates

Intrinsic Pathway (damaged surface)

Extrinsic Pathway (trauma)

Common Pathway

Fibrinogen
Fibrin → Fibrin Clot
Unfractionated Heparin (UFH)

- Heparin is a naturally occurring polysaccharide that potentiates antithrombin III activity
  - Porcine and bovine mucosa are the key sources of unfractionated heparin worldwide
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Unfractionated Heparin

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  - Porcine and bovine mucosa are the key sources of unfractionated heparin worldwide

- “Unfractionated” refers to varying molecular weight
  - Ranges from 3,000 – 30,000 Daltons (mean 15,000)
  - Recurring pentasaccharide sequence is responsible for its anticoagulant effects
    - Only 1/3 of heparin molecules contain this unique pentasaccharide
  - The molecular weight of unfractionated heparin has important pharmacodynamic and pharmacokinetic implications
Unfractionated Heparin: MOA

- Heparin potentiates antithrombin III
- Antithrombin III-heparin complex inhibits thrombin (FIIa) and FXa in a 1:1 ratio
  - 10-100 times more potent than antithrombin III alone
- The interaction between the antithrombin III-heparin complex and thrombin relies on larger heparin molecules (> ~6000 Daltons)
- The interaction between the antithrombin III-heparin complex and FXa is independent of molecular size
Unfractionated Heparin
Unfractionated Heparin

AT III w/o heparin

AT III w/ heparin

IIa
### Relationship Between Molecular Weight and Anticoagulant Activity (FYI Only)

<table>
<thead>
<tr>
<th>Heparin Oligosaccharides</th>
<th>Molecular Weight (d)</th>
<th>Anti-IIa Activity</th>
<th>Anti-Xa Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>2400</td>
<td>1</td>
<td>&gt;10</td>
</tr>
<tr>
<td>12</td>
<td>3600</td>
<td>1</td>
<td>5-10</td>
</tr>
<tr>
<td>16</td>
<td>4800</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>18</td>
<td>5400</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>24</td>
<td>7200</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Unfractionated Heparin: Pharmacokinetics

• Absorption
  – Not orally absorbed due to larger molecular weight and polyanionic charge; erratic subcutaneous absorption (but considered acceptable route of administration)

• Distribution
  – 0.03 L/kg

• Metabolism
  – Binds to heparin-binding proteins, endothelial cells, and macrophages (saturable process)
  – Half-life 1-2 hours
    • Variable depending on dose, renal or liver impairment, age, and molecular weight of the heparin molecule

• Excretion
  – Low doses: negligible renal clearance
  – High doses: renally cleared
Unfractionated Heparin: Half-Life

https://doi.org/10.1161/01.CIR.103.24.2994
Unfractionated Heparin: Adverse Effects

• Heparin-induced thrombocytopenia
  – Antibody-mediated adverse reaction that results in thrombocytopenia and a paradoxical *increase* in the risk of thrombosis
  – Occurs in 1-2% of patients
Heparin Reversal - Protamine

- Protamine is strongly alkalotic and positively charged
  - Neutralizes heparin (which is acidic and negatively charged)
- Incomplete reversal of LMWH
Unfractionated Heparin: Pros and Cons

**Pro**
- Primarily non-renal elimination
- Rapid onset when administered IV
- Easily reversed (protamine)

**Con**
- Significant heterogeneity
  - Varying molecular weight
  - Only 1/3 of molecules active
  - Variable clearance
- Limited to IV and SQ routes of administration
- Requires routine therapeutic monitoring
- Heparin-induced thrombocytopenia
# Parenteral Anticoagulants

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*Cellular metabolism is saturable. Renal elimination occurs at high doses.*
Low Molecular Weight Heparins (LMWH)

• Designed to be a more pharmacokinetically favorable parenteral anticoagulant compared to unfractionated heparin
  – Depolymerization process produces more consistent MW

• Mean molecular weight ~5000 d
LMWH: MOA

- Potentiates antithrombin III (ATIII)
- Due to the smaller MW, fewer LMWH-ATIII complexes are capable of inhibiting FIIa
  - Most of the anticoagulant effects come from FXa inhibition
## Comparing LMWH Preparations

<table>
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<th>LMWH</th>
<th>Mean Molecular Weight</th>
<th>Anti-IIa Activity</th>
<th>Anti-Xa Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dalteparin</td>
<td>6000</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Tinzaparin</td>
<td>4500</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>4200</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>
LMWH (Enoxaparin): Pharmacokinetics

- **Absorption**
  - Poor oral bioavailability; readily absorbed subcutaneously

- **Distribution**
  - 4.3 L

- **Metabolism**
  - Desulfation and depolymerization in the liver
  - Half-life ~7 hours (duration of action ~12 hours)

- **Excretion**
  - Primarily renally eliminated
LMWH: Adverse Effects

- Heparin-induced thrombocytopenia
  - <1%
LMWH: Pros and Cons

**Pros**
- Consistent pharmacokinetics
- No routine therapeutic monitoring required
- Relatively long half-life (conducive for bid administration)

**Cons**
- Renal elimination (requires renal dose adjustment)
- Heparin-induced thrombocytopenia (albeit lower than with unfractionated heparin)
- Not readily reversible
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Exit Slip

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Cardiovascular Pharmacology Series: Anticoagulants

Video 3: Parenteral Anticoagulants – Fondaparinux and Direct Thrombin Inhibitors

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  *Vitamin K Antagonist*

Video 5: Oral Anticoagulation
  *Direct Oral Anticoagulants*
Vessel Injury

- XII
- XIIa

**Intrinsic Pathway (damaged surface)**

- XI
- Xla

**Extrinsic Pathway (trauma)**

- Tissue Factor

**Common Pathway**

- IX
- IXa
- VIIa
- VII
- X

- Xla
- Xa
- X

- Va, Ca++
- Antithrombin III → Fondaparinux
- Argatroban Bivalirudin

- Fibrinogen
- Fibrin → Fibrin Clot
Fondaparinux: MOA

- Synthetic pentasaccharide with a molecular weight of 1728 d
- Potentiates antithrombin III and selectively inhibits FXa
  - Does not inhibit FIIa or platelets
  - Activates antithrombin III by ~300-fold
Fondaparinux: Pharmacokinetics

- **Absorption**
  - Poor oral absorption; rapidly absorbed subcutaneously

- **Distribution**
  - ~10L

- **Metabolism**
  - Minimal
  - Half-life 17-21 hours

- **Excretion**
  - Eliminated unchanged (as active drug) in the urine
Fondaparinux: Adverse Effects

- No incidence of heparin-induced thrombocytopenia
# Fondaparinux: Pros and Cons

**Pros**
- Longer half-life conducive for once daily administration
- No incidence of heparin-induced thrombocytopenia
- Consistent pharmacokinetics

**Cons**
- Extensively renally eliminated (renal dose adjustment)
- More expensive than UFH and LMWH
- Not easily reversible
## Parenteral Anticoagulants

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Direct Thrombin Inhibitors (DTI)

• Originally derived from hirudin, a peptide found in the saliva of medicinal leeches

• *Directly* inhibits thrombin
DTI: Mechanism of Action

![Diagram of DTI mechanism involving Thrombin, Exosite 2, Active enzyme site, Ila Thrombin, Exosite 1, Exosite 1 fibrin binding site, Exosite 2 heparin binding site.](image)
Bivalirudin: MOA and Pharmacokinetics

• Synthetic, 20-amino acid, bivalent analogue of hirudin

• Reversibly inhibits thrombin
  – Inhibits thrombin-mediated platelet activation at high doses

• Metabolism
  – Primarily proteolysis
  – Half-life ~25 minutes

• Elimination
  – ~20% renally eliminated
Argatroban: MOA and Pharmacokinetics

• Small molecule that reversibly inhibits thrombin

• Metabolism
  – Primarily metabolized in the liver to less potent metabolites
  – Half-life ~45 minutes

• Excretion
  – Primarily in the feces
  – Minimal renal elimination
DTIs: Pros and Cons

**Pros**
- Alternative to UFH or LMWH in heparin-induced thrombocytopenia
- Predictable pharmacokinetics (in normal renal/liver function)

**Cons**
- Short half-life (IV only)
- Cost
- Routine therapeutic monitoring required
- Interference with common coagulation assays
- Dose adjustment in liver dysfunction (argatroban)
- Dose adjustment in renal dysfunction (bivalirudin)
# Parenteral Anticoagulants

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</tr>
<tr>
<td>Argatroban</td>
<td>Direct thrombin inhibitor (DTI)</td>
<td>IV</td>
<td>Yes (aPTT)</td>
<td>Liver</td>
<td>Feces</td>
</tr>
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<td>Bivalirudin (Angiomax®)</td>
<td>Direct thrombin inhibitor (DTI)</td>
<td>IV</td>
<td>Yes (aPTT)</td>
<td>Proteolysis</td>
<td>Renal</td>
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Video 4: Oral Anticoagulants – Vitamin K Antagonist

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Direct Oral Anticoagulants
Warfarin

- Originally developed as a rodenticide (AKA “rat poison”) in the 1940’s
  - Wisconsin Alumni Research Foundation coumARIN
- Approved for medicinal use in 1954
- Inhibits *synthesis* of vitamin K dependent clotting factors
- Racemic mixture of R- and S-warfarin
  - S-warfarin is 5-fold more potent than R-warfarin
Vitamin K Cycle

- Reduced Vitamin K
- Vit K epoxide reductase (VCOR1)*
- Oxidized Vitamin K
- γ-glutamyl carboxylase

Non-functional Zymogen†

- Functional Zymogen

Factors II, VII, IX, X, Protein C and S

- Dietary Vitamin K*

CYP1A1
CYP1A2
CYP3A4

*Contributes to interpatient variability of warfarin's effects

Warfarin

R-warfarin
S-warfarin

CYP2C9*

Adapted from Harrison's Principles of Internal Medicine, 19th Edition.
Similarity in Vitamin K and Warfarin (FYI Only)
Warfarin: Pharmacokinetics

• Absorption
  – Completely absorbed orally

• Distribution
  – 0.14 L/kg
  – 99% protein bound

• Metabolism
  – S-warfarin: CYP2C9; Half-life 29 hr
  – R-warfarin: CYP1A2 (among other CYP enzymes); Half-life 45 hr

• Excretion
  – Inactive metabolites (not active drug) eliminated in urine
**Warfarin: Onset/Duration of Action**

- Onset of action is dependent on *clotting factor half-life*
  - Full anticoagulant effect takes ~96 hours

- Offset dependent on *clotting factor regeneration/synthesis*
# Vitamin K Dependent Clotting Factors

<table>
<thead>
<tr>
<th>Factor</th>
<th>Half-Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>60 hours</td>
</tr>
<tr>
<td>VII</td>
<td>4-6 hours</td>
</tr>
<tr>
<td>IX</td>
<td>24 hours</td>
</tr>
<tr>
<td>X</td>
<td>48-72 hours</td>
</tr>
<tr>
<td>Protein C</td>
<td>8 hours</td>
</tr>
<tr>
<td>Protein S</td>
<td>30 hours</td>
</tr>
</tbody>
</table>
Warfarin: Onset/Duration of Action

Warfarin: Interpatient Variability

- Dietary vitamin K consumption
- 40% of variability attributed to *CYP2C9* and *VCOR1* genotype
- Age, body weight, interacting drugs, also contribute

<table>
<thead>
<tr>
<th>VKORC1 Genotype</th>
<th>CYP2C9 Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>*1/*1</td>
</tr>
<tr>
<td>GG</td>
<td>5-7 mg</td>
</tr>
<tr>
<td>AG</td>
<td>5-7  mg</td>
</tr>
<tr>
<td>AA</td>
<td>3-4  mg</td>
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Medical Genetics Summaries. 2012.
## Warfarin: Drug Interactions*

<table>
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<tr>
<th>Mechanism</th>
<th>Effect on Warfarin Concentration</th>
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<td>--</td>
<td>Increased or decreased anticoagulant effect</td>
</tr>
<tr>
<td>Drugs that inhibit warfarin metabolism</td>
<td>↑</td>
<td>Increased anticoagulant effect (CYP 2C9 inhibitors &gt; CYP 1A2 inhibitors)</td>
</tr>
</tbody>
</table>

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*Interactions are not intended to imply that there is a contraindication. Warfarin doses can be adjusted to attain desired clinical effect in many scenarios.
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# Warfarin: Drug Interactions*

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<td>Drugs that inhibit platelet function</td>
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<td>Platelet dysfunction increases bleeding risk (e.g., non-steroidal anti-inflammatory drugs)</td>
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†Barbiturates, carbamazepine, griseofulvin, rifampin, phenytoin
Warfarin: Adverse Effects

- Warfarin-induced skin necrosis (1 in 10,000)
  - Believed to be caused, in part, by acute protein C deficiency

Warfarin: Reversal

- Phytonadione (vitamin K)
  - Promotes liver synthesis of vitamin K dependent clotting factors
  - Delayed reversal due to time needed for the liver to synthesize clotting factors

- Four factor prothrombin complex concentrate (KCentra®)
  - Exogenous vitamin K dependent clotting factors, include protein C and S
  - Rapid reversal
Warfarin: Pros and Cons

**Pros**
- Oral
- Inexpensive
- Readily reversible

**Cons**
- Drug & dietary interactions
- Significant interpatient variability
- Routine monitoring and dose changes required
- Delayed onset/offset
# Oral Anticoagulants

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PT = prothrombin time; INR = international normalized ratio
Exit Slip

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Cardiovascular Pharmacology Series: Anticoagulants

Video 5: Oral Anticoagulants – Direct Oral Anticoagulants

Zachary R. Noel, PharmD, BCCP
Virtual Office: https://umaryland.webex.com/meet/znoel
Email: znoel@rx.umaryland.edu
Road Map

Video 1: Clotting Basics

Video 2: Parenteral Anticoagulants
Heparin and Low Molecular Weight Heparin

Video 3: Parenteral Anticoagulants
Indirect Xa Inhibitor and Direct Thrombin Inhibitors

Video 4: Oral Anticoagulation
Vitamin K Antagonist

Video 5: Oral Anticoagulation
Direct Oral Anticoagulants
Vessel Injury

XII

XIIa

XI

XIa

Apixaban
Rivaroxaban
Edoxaban

Tissue Factor

VIIa

VII

Common Pathway

Intrinsic Pathway
(damaged surface)

Extrinsic Pathway
(trauma)

Physiologic inhibition
Physiologic activation
Drug inhibits
Drug activates

XIIIa

II

Va, Ca++

Dabigatran

Fibrinogen

Fibrin

Fibrin Clot
Direct Oral Anticoagulants (DOACs)*

- First marketed in 2010 (dabigatran)
- Do not require routine therapeutic monitoring
- Fewer dietary and drug interactions

*Also referred to as non-vitamin K oral anticoagulants (NOAC) or target-specific oral anticoagulants (TSOAC)
DOACs: MOA

• Direct thrombin inhibitor
  – Dabigatran etexilate

• Direct Xa inhibitor
  – Apixaban, rivaroxaban, edoxaban
## DOAC Pharmacokinetics

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<tr>
<th>Drug</th>
<th>Bioavailability</th>
<th>Liver Metabolism</th>
<th>CYP3A4 Substrate</th>
<th>P-gp Substrate</th>
<th>Renal Elimination</th>
<th>T_{1/2} (hrs)</th>
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<td>No</td>
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<td>15</td>
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<td></td>
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<td>Rivaroxaban (Xarelto®)</td>
<td>&gt;80%*</td>
<td>Yes (18%)</td>
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DOACs: Drug Interactions

- Apixaban and rivaroxaban
  - Contraindicated with drugs that are strong inhibitors or inducers of both CYP 3A4 and P-gp

- Dabigatran and edoxaban
  - Contraindicated with drugs that are strong inhibitors or inducers of P-gp
Dabigatran: Adverse Effects and Special Considerations

- Prodrug that is hydrolyzed by plasma esterases
- Associated with significant dyspepsia secondary to tartaric acid formulation (~10%)

Weitz JI, et al. Canadian Journal of Cardiology. 2018
DOAC Reversal

- Idarucizumab (Praxbind®)
  - Monoclonal antibody that directly binds to and inhibits dabigatran with an affinity 350-fold greater than thrombin

- Coagulation Factor Xa (recombinant), Inactivated - zhzo (Andexxa®)
  - Binds and sequesters apixaban and rivaroxaban*

*Effects are likely not limited to apixaban and rivaroxaban, but to date these are the only drugs Andexxa® is approved for reversal of
DOACs: Pros and Cons

**Pros**
- Oral
- No routine therapeutic monitoring required
- Rapid onset/offset
- Less bleeding and similar or improved efficacy compared to warfarin

**Cons**
- Costly
- Not well studied in special populations (e.g., very old adults, obesity, severe renal dysfunction etc.)
- Dose adjustment necessary for renal dysfunction
- Caution in liver dysfunction
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Clotting Cascade

Vessel Injury

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**Intrinsic Pathway**
*damaged surface*

XI → Xla

**Extrinsic Pathway**
*trauma*

Tissue Factor

IX → IXa

Apixaban
Rivaroxaban
Edoxaban

VIIa → VII

**Common Pathway**

X → Xla

Xla

**Drug inhibits**
- Argatroban
- Bivalirudin
- Dabigatran

**Drug activates**
- Warfarin

**Antithrombin III**

Heparin
Enoxaparin
Fondaparinux

**Physiologic inhibition**
- Physiologic activation

**Protein S**

**Protein C**

Activated Protein C

**Fibrinogen**

**Fibrin** → **Fibrin Clot**