# Anticoagulants and their Reversal in the Setting of Acute Major BLEEDING or Need for URGENT SURGERY

Allison R. Lauver, PharmD, BCPS, BCCCP

CME Procedures

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# Objectives

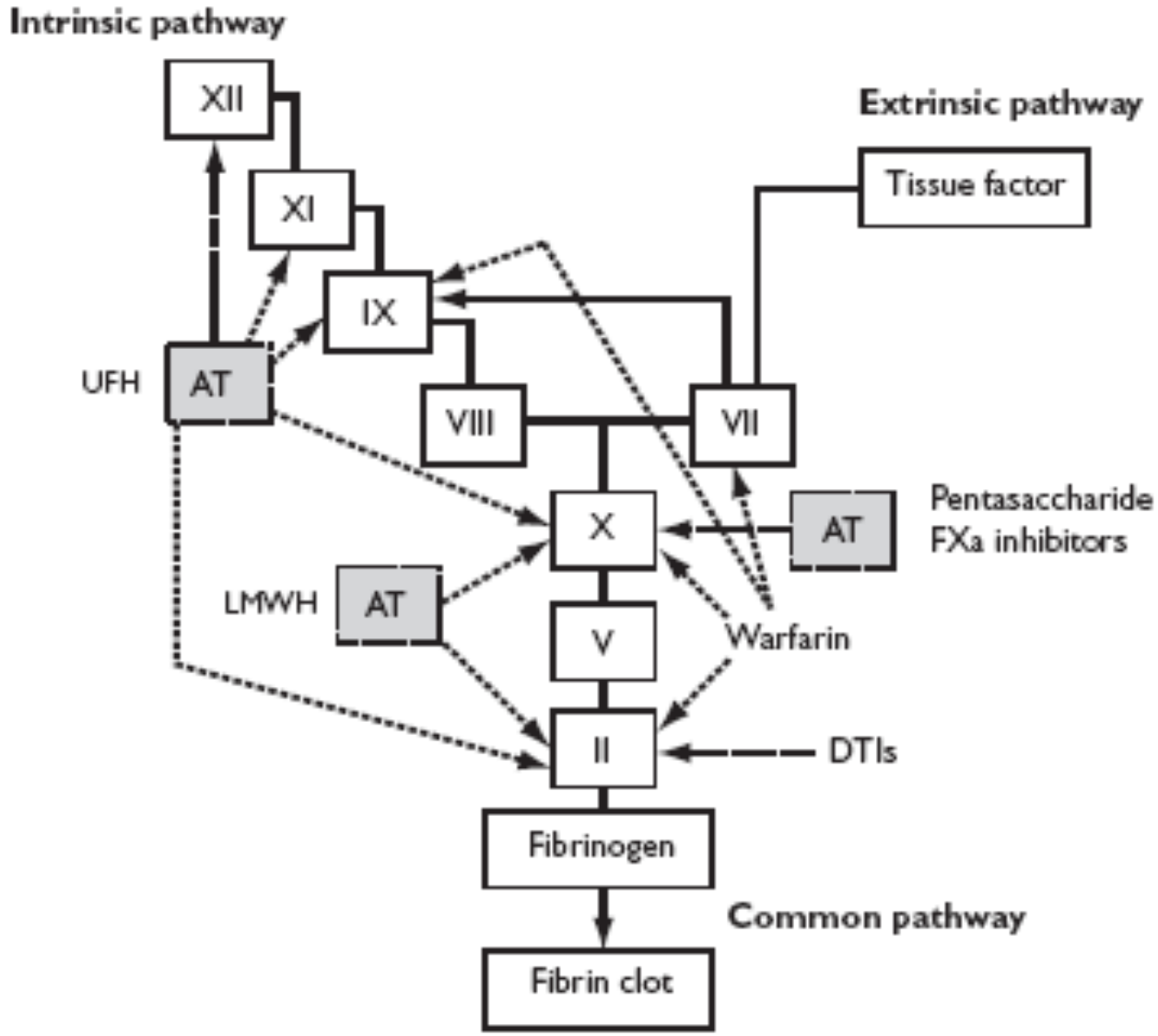
Discuss the intrinsic, extrinsic and common pathways of the coagulation cascade

List the various parenteral and oral anticoagulants and demonstrate how they affect the coagulation cascade based on their various mechanisms of action

List the various parenteral and oral antithrombotic reversal agents and demonstrate how they affect the coagulation cascade based on their various mechanisms of action

Evaluate the most recent literature on Factor Xa Reversal

# The Coagulation Cascade



# Anticoagulants for today's lecture

Unfractionated Heparin (UFH)

Low Molecular Weight Heparin

Warfarin

Direct-Acting Oral Anticoagulants (DOACs)

- Factor Xa Inhibitors
- Direct Thrombin Inhibitors


# Unfractionated Heparin (UFH)

# Unfractionated Heparin

Prepared from porcine or bovine gastrointestinal mucosa of bovine lung

Molecular weight (MW) of 3,000 to 30,000 daltons (mean 15,000)

Mechanism of Action (MOA): Augments the natural anticoagulant, antithrombin III (AT)

A pentasaccharide sequence on heparin binds to AT to cause a conformational change

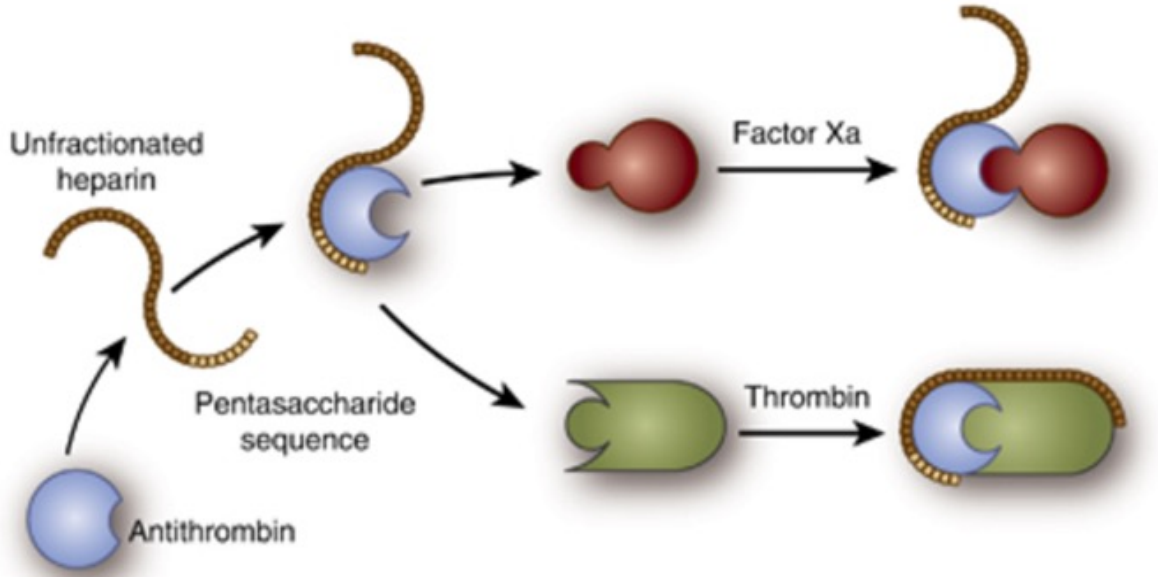
Complex inhibits thrombin (factor IIa) and factors Xa, IXa, XIa, and XIIa

*To inhibit thrombin, the heparin molecule needs to form a ternary complex by binding to AT and thrombin*

Important to note:

Does NOT "dissolve" clots

Does NOT inactivate clot-bound thrombin




# UFH Mechanism of Action

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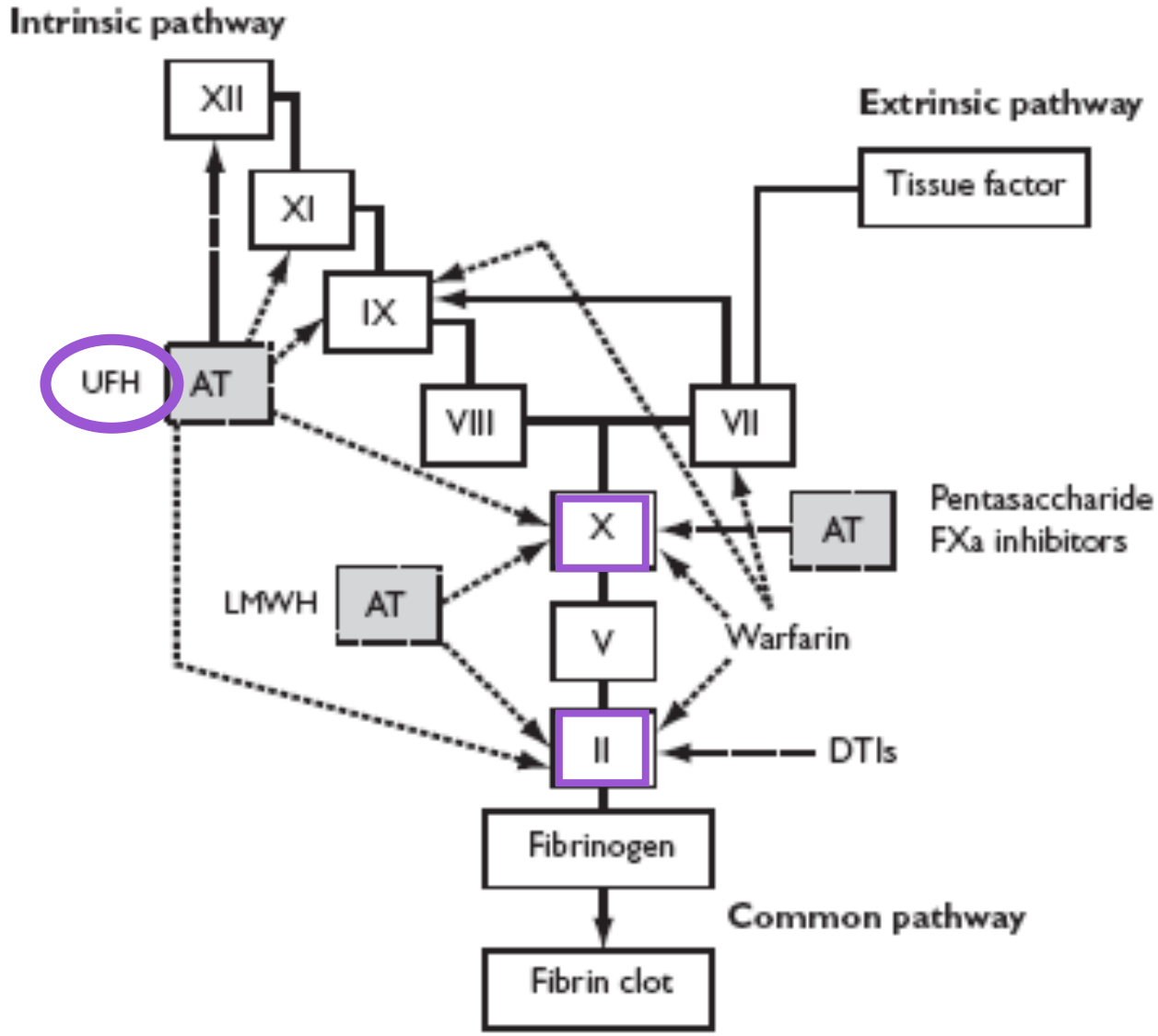
# The Coagulation Cascade



# Clinical Uses

Prevention and treatment of venous thromboembolism (VTE➔DVT/PE)

Treatment of acute coronary syndromes (ACS)

Atrial fibrillation

*Ischemic strokes secondary to atrial fibrillation*

Anticoagulation of pregnant women

Perioperative anticoagulation for extracorporeal circulation and hemodialysis

Arterial and cardiac surgeries

“Bridge” therapy

*Mechanical heart valves*

Antibiotic lock adjunctive therapy

*For catheter salvage*

Frostbite

*Adjunct to thrombolytic therapy*

# Pharmacokinetics (PK) and Administration

PK

Highly charged, very large acidic molecule → poorly absorbed from GI tract

Highly protein bound

Half-life is dose-dependent

*30 – 90 minutes*

ROUTES OF ADMINISTRATION

Can give intravenously (IV)

*Onset is immediate*

Can give subcutaneously (SQ)

*Onset of effect usually ~20 – 30 minutes*

*Dosed every 8 – 12 hours for VTE prophylaxis*

Do **NOT** give IM

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# Therapeutic Monitoring of UFH


Activated Partial Thromboplastin Time (aPTT)

- *IV Heparin usually monitored to maintain the ratio of aPTT within a defined range of ~1.2 – 2x normal values*
  - Will vary between institutions depending on reagent used
- *Check aPTT 6 hours after IV dose initiation or any dose change and at least every 24 hours once in target range*

Anti-Xa Assays

- Due to some variability in responses with aPTTs some institutions have moved to using anti-Xa levels for heparin monitoring
  - *Low dose infusion target: 0.3 – 0.5 unit/mL*
  - *High dose infusion target: 0.5 – 0.8 unit/mL*

# Therapeutic Monitoring of UFH

Activated Coagulation Time (ACT)

More sensitive test for heparin monitoring when heparin concentrations ≥1 unit/mL

Mainstay of heparin anticoagulation monitoring in perioperative management for cardiac procedures/cardiopulmonary bypass, cardiac catheterization and extracorporeal membrane oxygenation (ECMO)

Baseline levels: ~100 – 150 seconds

May be influenced by hypothermia, thrombocytopenia, presence of contact activation inhibitors (aprotinin), and preexisting coagulation deficiencies

Cardiac surgery

*Draw baseline ACT before heparin administration, 3 – 5 minutes after administration and every 30 minutes thereafter*

*Target ACT >350 seconds; some sites prefer >400 seconds*

# UFH Adverse Effects

- Bleeding
  - Consider avoiding in patients at high risk
  - Overall risk 2-10%
- Osteoporosis (long-term after 4-6 months)
  - Suppresses osteoblast formation and activates osteoclasts that promote bone loss
- Heparin-associated thrombocytopenia (HAT)
  - Non-immune type (less severe)
    - *Do not need to stop heparin*
    - *Incidence: 5-30% of patients*
    - *Platelet count rarely falls below 100,000*

# UFH Adverse Effects - HIT

Heparin Induced Thrombocytopenia (HIT)

Occurs in about 1 to 3% of heparin treated patients

Immune-mediated allergic reaction

*Heparin + platelet factor 4 + IgG antibodies complexes*

*Complexes bind to platelets → platelet activation → thrombin generation*

Diagnosis – calculate the 4T score

*Occurs 5-14 days after starting heparin*

More rapid onset in patients who have received heparin in past 100 days

*Decreased platelet count*

*Laboratory testing for heparin antibodies*

*Venous or arterial thrombosis*

Treatment:

Immediately discontinue ALL heparin

Begin anticoagulation even with low platelet counts

*Direct thrombin inhibitor*

*Factor Xa inhibitor*

Greatest risk of thrombosis is first few days after HIT occurs

Do not use warfarin alone initially

*Do not initiate Warfarin until platelets recover (>150,000)*

*Warfarin may further increase the risk of thrombosis*

# 4T Score

| Category | 2 points | 1 point | 0 point |
|---|---|---|---|
| Thrombocytopenia | > 50% fall, or nadir ≥ 20 x $10^9$/L | 30–50% fall, or nadir 10-19 x $10^9$/L | < 30% fall, or nadir < 10 x $10^9$/L |
| Timing of the decrease in platelet count | Days 5 to 10, or ≤ day 1 with recent heparin (past 30 days) | > Day 10 or timing unclear, or < day 1 if heparin exposure within past 30-100 days | < Day 4 (no recent heparin) |
| Thrombosis or other sequelae | Proven thrombosis, skin necrosis, or acute systemic reaction after heparin bolus | Progressive, recurrent, or silent thrombosis; erythematous skin lesions | None |
| Other causes of thrombocytopenia | None evident | Possible | Definite |

0 to 3 points: Low probability (risk of HIT <1 percent)
4 to 5 points: Intermediate probability (risk of HIT ~10%)
6 to 8 points: High probability (risk of HIT~50%)

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# Low Molecular Weight Heparins (LMWHs)

Dalteparin (Fragmin®)

Enoxaparin (Lovenox®)

Tinzaparin (Innohep®)

# Low Molecular Weight Heparin (LMWH)

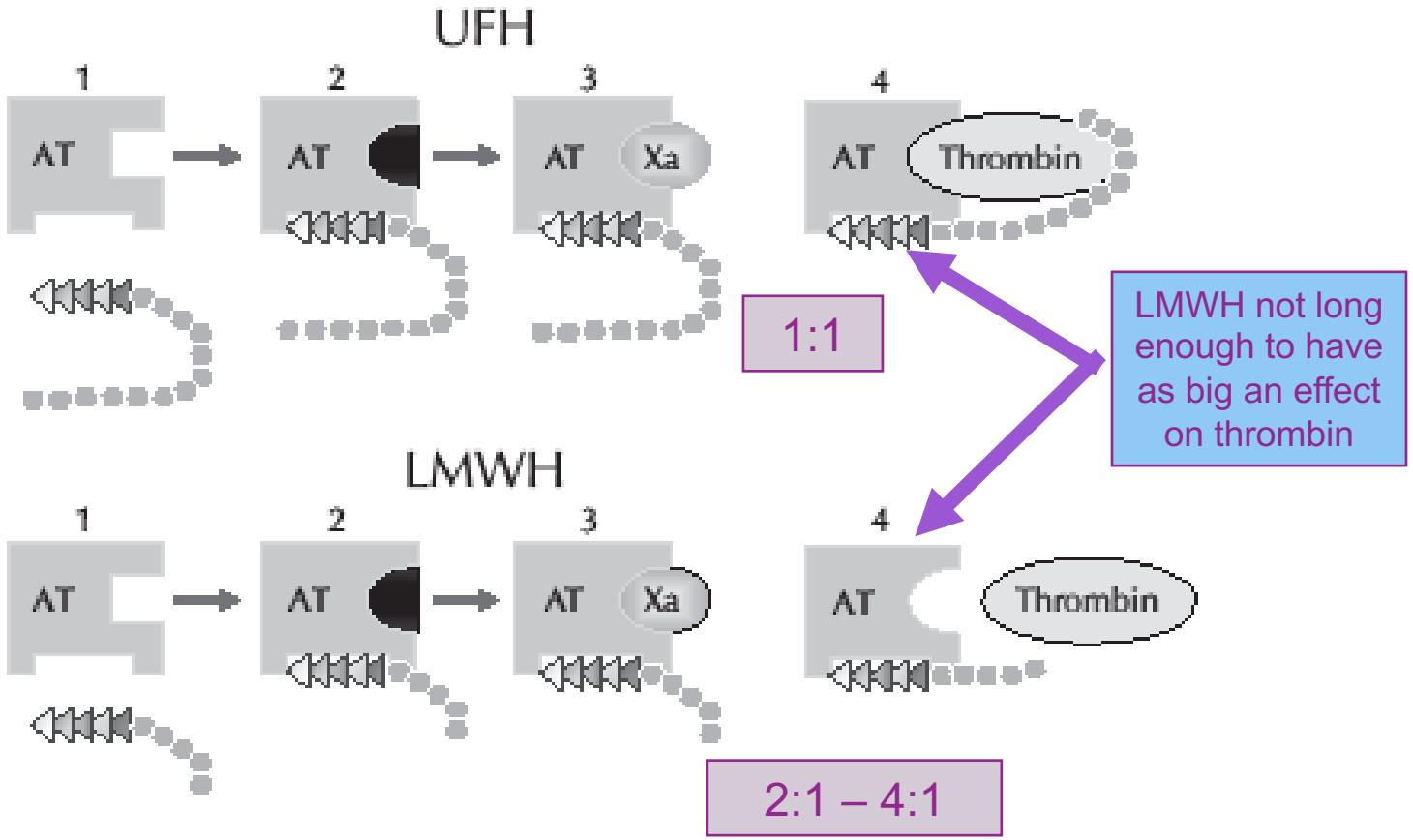
Smaller heparin fragments that contain the portion responsible for anticoagulant effects

- Roughly 1/3 size of heparin
  - *Molecular weight: 4000-5000 daltons*
  - *Undergo chemical depolymerization to achieve lower weights*
- Greater anti-factor Xa activity than heparin
  - *Antifactor Xa/IIa ratio of 2:1 to 4:1*

## Clinical Uses

- Similar to heparin
- More efficacious than heparin in prevention of DVT/PE in trauma and orthopedic patients
- Outpatient treatment of VTE
- Pregnancy

# LMWH Mechanism of Action

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# Enoxaparin PK and Dosing

## PK

Bioavailability almost 100%

- *Administered subcutaneously*
- *Only administered IV in STEMI as one time dose as long as patient <75 years old*

Peak affect in 3-5 hours

Half-life: 2-7 hours

Elimination

- *Primarily renal – requires dose adjustment in renal dysfunction*

## DOSING

Prophylaxis DVT/PE:

- *30 mg subq bid or 40 mg subq once daily*
- *Doses may be adjusted in obesity or underweight patients*
- *May want to consider heparin in patients <40 kg or >190 kg, esp if unable to monitor anti-Xa levels*

Treatment of DVT/PE or ACS:

- *1 mg/kg subq q12h*
- *1.5 mg/kg q24h can be give as outpatient, although not generally preferred*

Decrease treatment dose by 50% in patients with estimated CrCl < 30 mL/min

- *Not FDA approved in hemodialysis*

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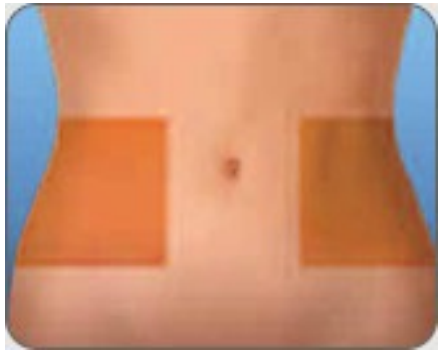
# Enoxaparin Monitoring and Administration

Monitoring

- No routine therapeutic monitoring – has little effect on aPTT
- Antifactor Xa levels may be utilized if needed
  - *May consider levels in pregnancy, obesity, underweight patients, renal failure, patients at high risk for bleed, and trauma patients*

Enoxaparin Administration:

- Deep SQ injection alternating between R and L anterolateral or posterolateral abdominal wall
- Do not rub injection site in order to minimize bruising
- Do not expel air bubble prior to injection to prevent loss of dose



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# LMWH Adverse Effects

Injection-sire reactions

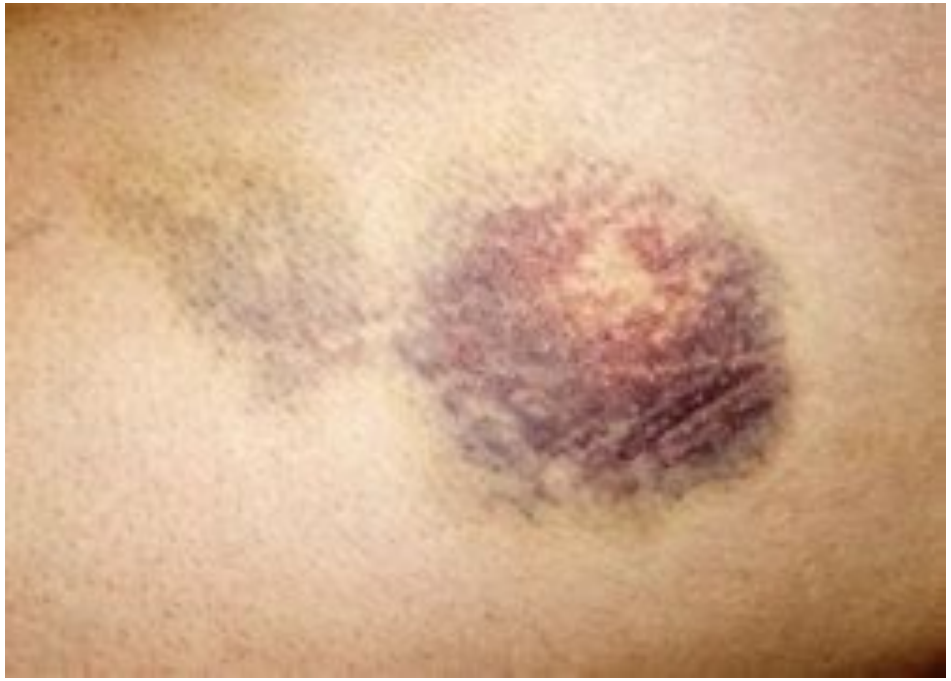
Bleeding and/or hematomas

HIT

*Less than heparin, but still a risk*

Osteoporosis

*Less than heparin*



# LMWH vs UFH

## Advantages over UFH

More consistent PK

Simpler dosing

*Subcutaneously; daily or bid*

Longer half-life (2-7 hrs)

Usually no monitoring needed

## Disadvantages compared to UFH

More costly ($$$)

Significant renal elimination

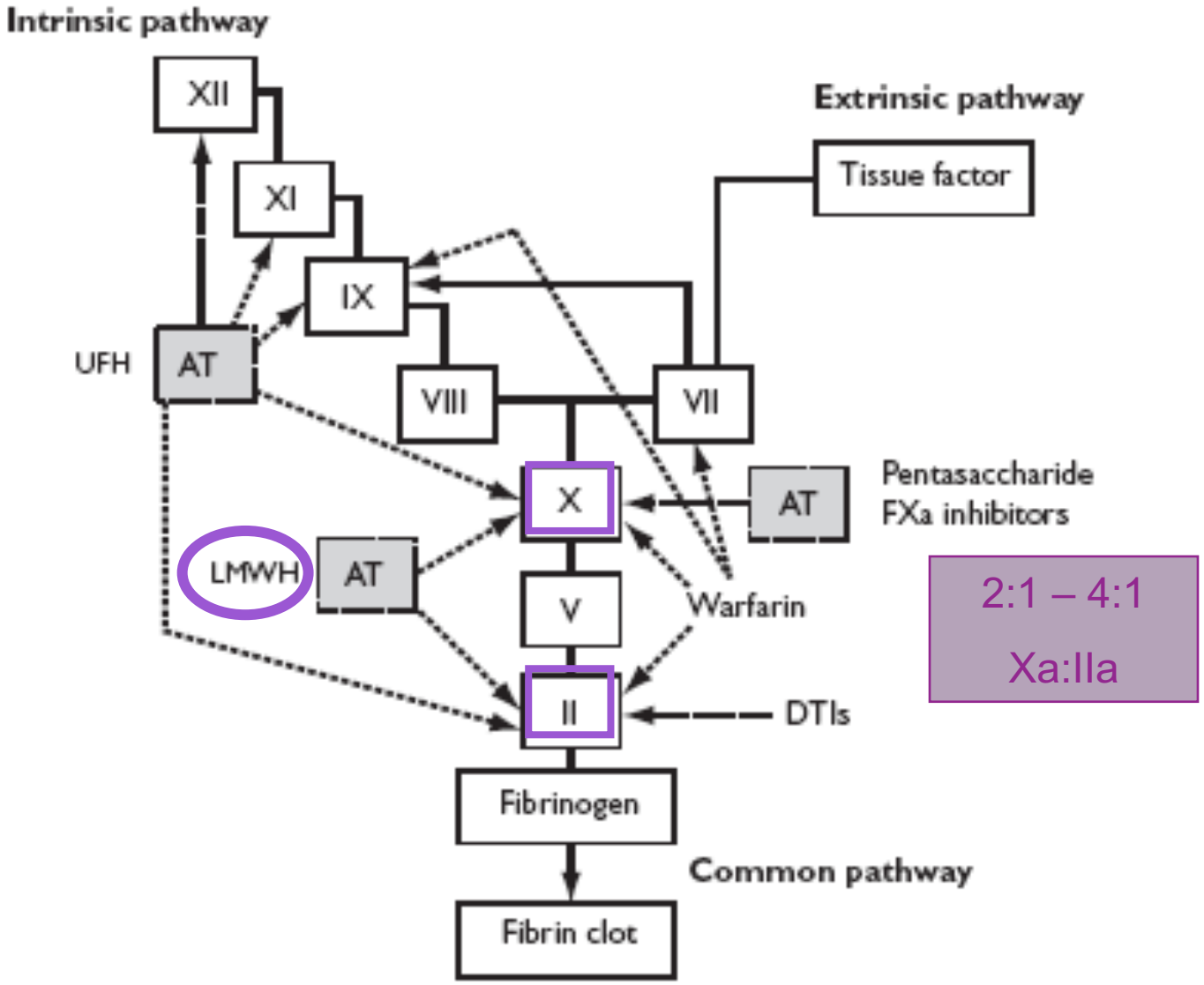
Monitoring may not be readily available → now available most institutions

## Similarities to UFH

Similar rates of bleeding

Also associated with HIT but to lesser degree

# The Coagulation Cascade




2:1 – 4:1

Xa:IIa

Reversal agent for Heparin

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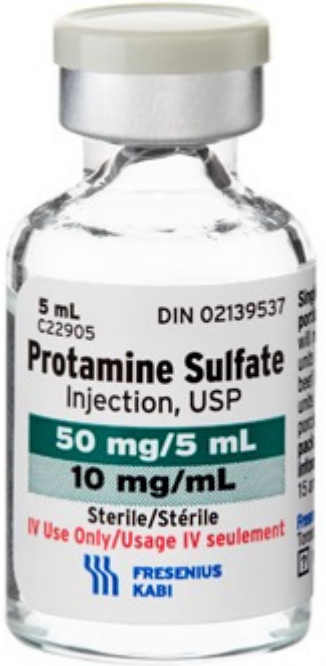
PROTAMINE

Reversal agent for LMWH

=

PROTAMINE?

# Protamine for UFH Reversal




Protamine sulfate

Do NOT use for minor bleeding
- Due to heparin's short half-life, can typically just discontinue infusion
- RAPID REVERSAL ONLY!!

Dosing for IV heparin reversal
- 1 mg of protamine neutralizes ~100 units of heparin
- Should consider only the amount of heparin given in the preceding 2 – 2.5 hours when determining the dose
- Max dose – 50 mg IV over 10 minutes

Monitoring:
- aPTT or ACT
- Cardiac and BP monitoring required during protamine administration

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*Neurocrit Care.* (2016) 24:6–46

# Protamine Mechanism of Action and Adverse Effects

## MECHANISM OF ACTION

Neutralizes the anticoagulant effect of heparin by binding to the drug and forming a stable salt complex

- *Protamine highly alkaline protein that is positively charged with weak anticoagulant effects when given alone*
- *Heparin is strongly acidic with a negative charge*

Protamine + heparin = stable salt → loss of anticoagulation activity

Protamine onset of action: ~5 minutes

## ADVERSE EFFECTS

Hypotension

- *Can be sudden drop*

Bradycardia

Hypersensitivity reactions

- *Black Box Warning*
- *Anaphylactoid reactions from too rapid injection*
  - Histamine release – Facial flushing
- *Can give a small test dose for patients with high risk for allergic reaction*

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*Neurocrit Care.* (2016) 24:6–46

# Protamine Administration

Slow IVP (50 mg over 10 minutes) or IVPB over 30 minutes**

*Rapid infusion causes hypotension*

*Order in EPIC defaults to IVPB over 30 minutes*

Have epinephrine (1:1000) and resuscitation equipment at bedside for hypersensitivity reactions

*Risk factors include:*

- High doses of protamine
- Repeated doses
- Previous protamine administration**
- Fish allergy
- Vasectomy
- NPH Insulin use
  - Neutral protamine Hagedorn
- Severe left ventricular dysfunction


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# Protamine for LMWH Reversal

Off Label Use – Again reserve protamine for significant bleeding or urgent need for OR

Anti-Xa activity is only about 60 – 75% neutralized by protamine

Dosing recommendations for Enoxaparin reversal:

<8 hours since enoxaparin administration: 1 mg of protamine per 1 mg enoxaparin

>8 hours or if bleeding continues: 0.5 mg of protamine per 1 mg enoxaparin

Max single dose: 50 mg

Do not administer protamine if last dose of LMWH given >12 hours ago

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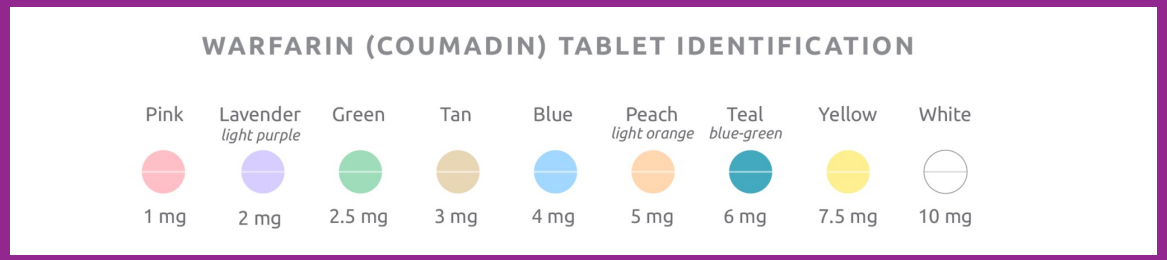
*Neurocrit Care.* (2016) 24:6–46




# Vitamin K Antagonists

## AKA Warfarin (Coumadin®; Jantoven®)

# Warfarin


Only available orally/enterally

*Originally marketed as rat poison*

For the longest time, warfarin was the most frequently used anticoagulant

*Excellent oral bioavailability*

*Now used less frequently as the DOACs become more increasingly popular*

Narrow therapeutic index while a large variability in dosing

Complex pharmacology

Many drug and food interactions

Disadvantages of Warfarin:

*Delayed onset of action*

*Need for regular laboratory monitoring (Anticoagulation Clinics)*

# Warfarin Mechanism of Action and Clinical Uses

## MECHANISM OF ACTION

Depletion of vitamin K dependent coagulation factors

- IIa, VIIa, IXa, Xa
- Inhibits vitamin K epoxide reductase that converts the Vitamin K-dependent clotting factors to their active forms

Inhibits regulatory anticoagulants

- Protein C and Protein S

## CLINICAL USES

Prevention or treatment of VTE ➔ DVT/PE

- Rarely use Warfarin for DVT prophylaxis; may be an alternative following total hip/knee arthroplasty

Secondary stroke prevention/Prevention of systemic embolization

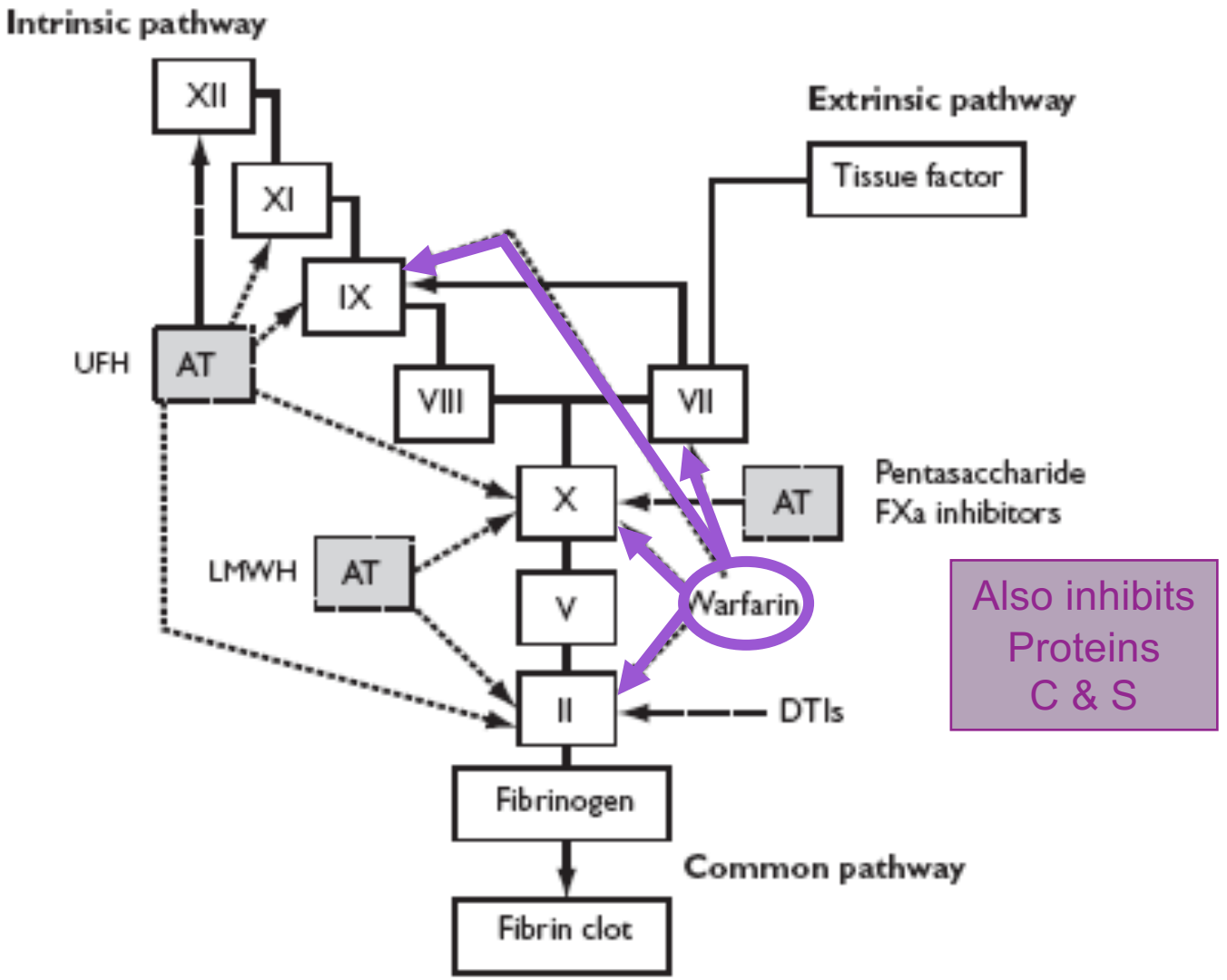
- Atrial Fibrillation
- Previous CVA (secondary prophylaxis)
  - *Rare to use in CVA without concomitant Afib or other indication for anticoagulation*

Prosthetic heart valves

Left ventricular thrombus

Other hypercoagulable states/thrombophilia

- Genetic disorders such as Factor V Leiden, Protein C & S deficiencies, Lupus anticoagulant, etc.




# The Coagulation Cascade

# PK of Clotting Factors

Half-lives of Vitamin K-dependent clotting factors (synthesized in the liver)

VII: 3 – 6 hours
IX: 24 hours
X: 48 hours
II: 60 hours

Protein C: 6 – 9 hours
Protein S: 42 hours

Due to the relatively short half-life of Protein C, Warfarin can result in an initial hypercoagulable state for ~48 – 72 hours

*Requires bridging with another anticoagulant for active thrombus*

# Warfarin PK

Completely absorbed after oral administration

97% bound to albumin
- Patients with nutrition deficiency may be more sensitive to the effects of Warfarin and ultimately may require smaller doses

Warfarin half-life = 36 hours

Peak effects seen in 1-2 weeks
- Need to wait for Factor II to be depleted (half-life 60 hours x5 half-lives)

Rate-limiting step of anticoagulation is depletion of active clotting factors
- Loading dose not of any value

After stopping drug, INR returns close to normal in about 5 days

# Warfarin Dosing

Highly individualized to maintain goal INR (Average dose 5 mg/day; Range 0.5 – 20 mg/day)

*INR goal 2.5 – 3.5 for mechanical mitral valve*

*INR goal 2 – 3 for majority of other indications*

Overlap with IV heparin/SQ LMWH for 5 days in VTE treatment or other **active** clot until two therapeutic INRs (>2 for two consecutive days)

Half life of warfarin 20-60 hours

*However, half life of clotting factors is the true measure of coagulation status*

Half life of Factor II (prothrombin): ~ 60 hours

*5-7 days after starting warfarin to be truly anticoagulated*

Half life of Protein C: ~ 8 hours

*24 hours to reach steady state concentration*

When initiating VKA therapy alone, pro-thrombotic state for 72 hours = ***REASON WE BRIDGE WITH WARFARIN***

OK not to bridge when initiating warfarin therapy for atrial fibrillation if low risk of stroke ($Chads_2vasc < 4$)

Preventing thrombosis, not actively treating

Must bridge if known LAA or apical thrombus

# Warfarin Monitoring

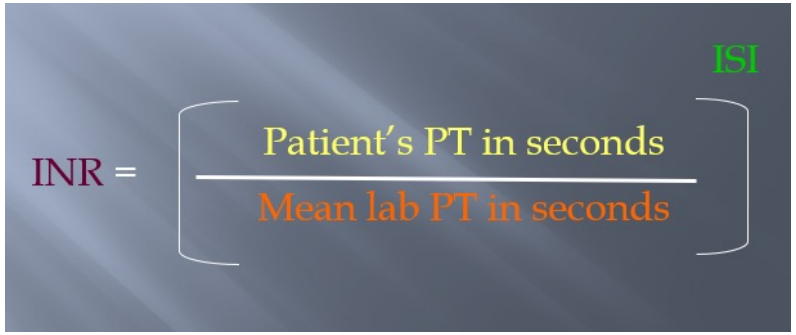
Best guided by the Prothrombin Time (PT)

PT is particularly sensitive to 3 out of the 4 vitamin K dependent clotting factors (II, VII, and X)

Like with aPTT, prothrombin time reagents vary widely in their responsiveness to warfarin-induced decreases in clotting factors

*Not interchangeable between laboratories*

To standardize reporting of Warfarin's affects, the international normalized ratio (INR) was introduced

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# Warfarin Monitoring

Fluctuations in INR can occur for a multitude of reasons, thereby requiring close monitoring of Warfarin therapy

Fluctuations can be caused by changes in diet (leafy greens = Vitamin K), illness (n/v and poor po intake), undisclosed medication changes or initiation of OTC products, poor patient compliance

Patients with underlying liver disease and advanced age typically require lower maintenance doses

*Chronic liver patients unable to produce new clotting factors ➔ higher baseline INR/increased bleeding risk*

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# Warfarin Drug Interactions

Acetaminophen, allopurinol, amiodarone, azathioprine, bosentan, capecitabine, carbamazepine, cimetidine, dicloxacillin, disulfiram, drotrecogin alfa, fluconazole, ginkgo biloba, ginseng, glucosamine, griseofulvin, isoniazid, metronidazole, nafcillin, orlistat, phenytoin, propafanone, quinidine, sucralfate, tigecycline, valproic acid, voriconazole, zafirlukast, acarbose, amoxicillin, argatroban, atenolol, azithromycin, bilberry, borage, cefazolin, cefotetan, chloramphenicol, chlordiazepoxide, cholestyramine, cilostazol, ciprofloxacin, clarithromycin, demeclocycline, cyclosporine, diclofenac, dong quai, doxepin, doxycycline, duloxetine, erythromycin, esomeprazole, ethinyl estradiol, evening primrose, etodolac, exenatide, ezetimibe, feverfew, fluoxetine, fluvoxamine, fosphenytoin, gatifloxacin, glipizide, glyburide, ibuprofen, imipramine, influenza virus vaccine, ketoconazole, ketoprofen, lactulose, lansoprazole, levofloxacin, meloxicam, mercaptopurine, lovastatin, methimazole, methylphenidate, methylprednisolone, minocycline, nabumetone, naproxen, norgestrel, nortriptyline, omeprazole, oxaprozin, pantoprazole, paroxetine, phenobarbital, piroxicam, primidone, propranolol, quetiapine, rabeprazole, ranitidine, raloxifene, rifampin, ritonavir, ropinirole, rosuvastatin, saw palmetto, sertraline, simvastatin, spironolactone, sulfamethoxazole, sulindac, tamoxifen, telithromycin, cephalexin, tetracycline, tolterodine, tramadol, vancomycin, zileuton, amoxapine

*Just to name a few….*

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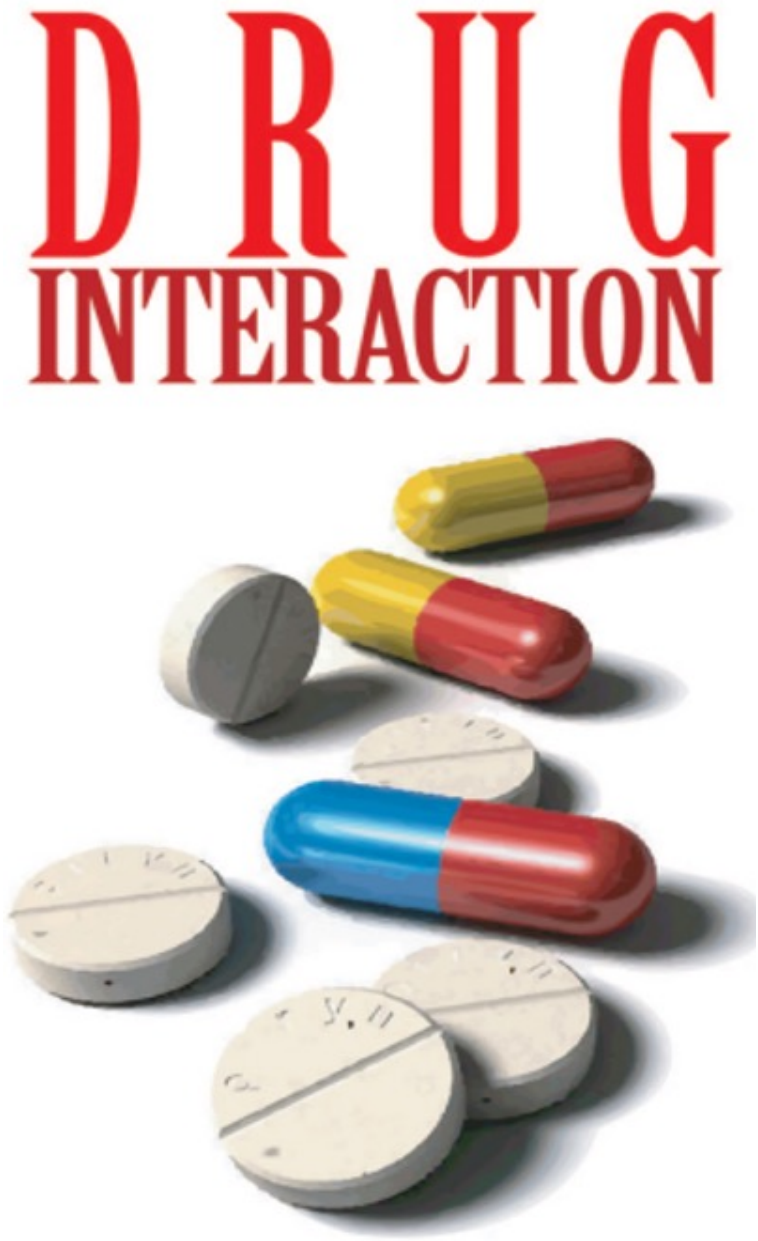
# Warfarin Drug Interactions




Generally broken down by category

- Medications that increase bleeding risk
  - *ASA, antiplatelet agents, other anticoagulants, NSAIDs*
- Medications that affect drug absorption
  - *Sucralfate, bile-acid sequestrants*
- Medications that affect Vitamin K production
  - *Antibiotics*
- Medications that inhibit/induce CYP2C9
  - *Inhibit (↑INR): amiodarone, fluconazole, SMX-TMP, metronidazole*
  - *Induce (↓INR): rifampin*

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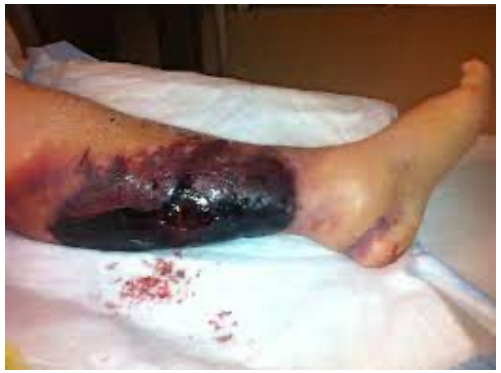
# Warfarin Adverse Effects

Bleeding



Patient risk factors

- *Advanced Age*
- *Interaction medications*
- *History of previous bleed*
- *History of stroke*
- *Reduced platelet count*
- *Comorbid conditions*

Bleeding that occurs when INR <3 is frequently associated with neoplasm or peptic ulcer if no other clear risk factors

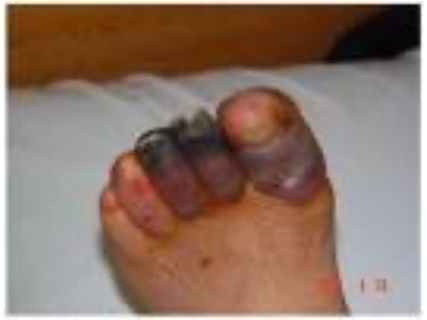
Risk of hemorrhage increases steeply when INR is > 5

Warfarin-induced skin necrosis (rare)

- Usually observed by 3rd to 8th day of therapy
- Extensive thrombosis of venules and capillaries within subcutaneous fat
- Stop warfarin if possible
- Use low doses if continued warfarin treatment required

"Purple Toes" Syndrome

- Cholesterol microembolization
- Stop warfarin



# Preferred management for urgent reversal of Warfarin

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Vitamin K +
4 Factor Prothrombin Complex Concentrate (PCC)

| INR | Significant bleeding? | Recommendation |
|---|---|---|
| 4.5 - 10 | No | Hold warfarin<br>**Vitamin K NOT indicated** |
| > 10 | No | Hold warfarin<br>**Vitamin K orally** |
| Any value | Yes | **Vitamin K 5-10 mg IV and PCC or FFP** |

# Warfarin Reversal: Basic Approach

*CHEST*. (2022), doi: https://doi.org/10.1016/j.chest.2022.07.025.
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# Vitamin K (aka Phytonadione)

Preferred routes of administration: IV for life-threatening bleed or need for immediate reversal; otherwise, Oral

No SQ or IM recommended


Dosing for major bleeding at any elevated INR:

5 – 10 mg IV infused over 20 – 60 minutes

Monitoring:

PT/INR

Mechanism of Action:

Promotes synthesis of clotting factors II, VII, IX, and X by the liver

PK

Onset of IV Vitamin K: 1 – 2 hours; PO Vitamin K: 6 – 10 hours

Normalization of INR with IV: 12 – 14 hours ; PO 24 – 48 hours

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# Vitamin K (aka Phytonadione)

Adverse effects:

- Hypersensitivity Reactions/Anaphylaxis
  - *Black Box Warning*

IV Administration:

- Run IVPB over at least 20 – 30 minutes to reduce incidence of anaphylactic reactions

When resuming warfarin therapy:

- Note high doses of Vitamin K can lead to a period of warfarin resistance ≥1 week

- Depending on indication for anticoagulation, bridging may be needed in the interim for anticoagulation

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# 4 Factor PCC (Kcentra®)


Indications for use:

Urgent reversal of warfarin therapy in adult patients with ACUTE MAJOR BLEEDING or need for URGENT SURGERY ONLY

****Note: IV Vitamin K MUST still be administered along with PCC****

25x more concentrated than FFP

Traditional Dosing per Package Insert:

Note: Dosing based on Factor IX Activity

*INR 2 – <4: 25 Units/kg (Max 2500 Units)*

*INR 4 – 6: 35 Units/kg (Max 3500 Units)*

*INR >6: 50 Units/kg (Max 5000 Units)*

Alternative Low Dose Fixed Dosing - Done frequently off label (ie. 1500 units for intracranial hemorrhage; 1000 units other indications)

Monitoring:

INR pre-treatment

INR 30 -60 minutes post-dose

Note: Make sure you flush the line!

Kcentra® Package Insert.

# 4 Factor PCC (Kcentra®)

## Mechanism of Action:

Provides the inactive Vitamin K-dependent clotting factors II, VII, IX, X as well as Protein C and S

## PK:

Onset of action:

*Significant INR decline within 10 minutes*

Duration of action:

*~6 – 8 hours*

## Adverse effects:

Thromboembolic complications

*Boxed Warning*

Hypersensitivity reactions

*Derived from human plasma*

## Precautions:

Formulation contains small amounts of heparin

*Heparin allergy*

*Heparin Induced Thrombocytopenia (HIT)*

Kcentra® Package Insert.

# Administration of 4 Factor PCC (Kcentra®)

Administer at room temperature at a rate of 0.12 mL/kg/minute (~3 **units**/kg/minute)

Do **not** exceed 8.4 mL/minute (~210 **units**/minute)

ie. Max dose of 5000 units can be given in ~25 minutes

Hang a 50 - 100 mL bag of NS behind the Kcentra dose at the same rate to ensure the entire dose reaches the patient and none of the dose remain in the IV tubing

Avoid infusing other medications through same IV line

**Reminder:** IV Vitamin K should also be administered

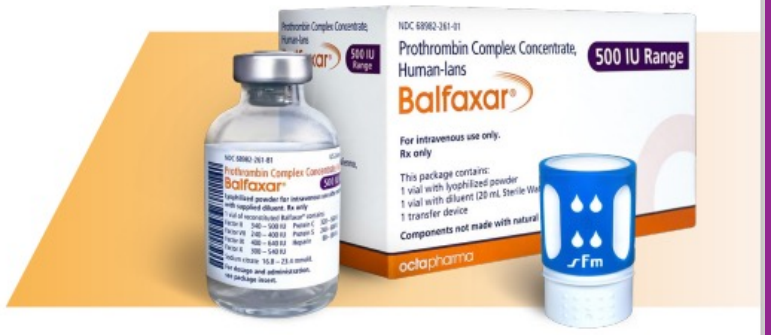
Kcentra® Package Insert.

Balfaxar®
Prothrombin Complex Concentrate, Human-Ians

# BALFAXAR Dosing and Ordering Information

## BALFAXAR Is a Non-Activated Human-Plasma Derived 4F-PCC

- BALFAXAR contains coagulation factors II, VII, IX, and X and antithrombotic proteins C and S.[1]
- The actual potency per vial of factor X is stated on the carton. The potencies of factors II, VII, IX, and X, as well as proteins C and S, are indicated as ranges.[1]




## BALFAXAR Dosage for Reversal of VKA Anticoagulation[1]

Individualize BALFAXAR dosing based on the patient's body weight and predose International Normalized Ratio (INR) value.[1a]

| Pretreatment INR | 2-<4 | 4-6 | >6 |
|---|---|---|---|
| Dose[b] of BALFAXAR (units[c] of factor IX) per kg body weight | 25 | 35 | 50 |
| Maximum dose[d] (units of factor IX) | Not to exceed 2500 | Not to exceed 3500 | Not to exceed 5000 |

[a]Repeat dosing is not recommended because its safety and effectiveness have not been established.

[b]Dosing is based on body weight. Dose based on actual potency is stated on the vial, which will vary from 20-32 factor IX units/mL after reconstitution. The actual potency for a 500-unit vial ranges from 400-640 units/vial. The actual potency for a 1000-unit vial ranges from 800-1280 units/vial.

[c]Units refer to International Units.

[d]Dose is based on body weight up to but not exceeding 100 kg. For patients weighing more than 100 kg, maximum dose should not be exceeded.

### Administer BALFAXAR[1]:

- By intravenous infusion at a rate of 0.12 mL/kg/min (~3 units/kg/min), up to a maximum rate of 8.4 mL/min (~210 units/min)
- Concurrently with vitamin K through a separate infusion line

# Newly approved PCC - Balfaxar®

Balfaxar_Order_Dosing_Information.pdf

# Alternative management for urgent reversal of Warfarin

=

Vitamin K +/-

Fresh Frozen Plasma (FFP)

# Fresh Frozen Plasma (FFP)

A unit of FFP provides plasma proteins and clotting factors to support adequate hemostasis

- Often used to treat or prevent bleeding

FFP contains an average of 1 IU/mL of each coagulation factor

FFP provides the patient with clotting factors immediately and the Vitamin K allows him/her to synthesize more factors


Medscape.com [Internet]. Fresh frozen plasma information.

# Direct-Acting Oral Anticoagulants (DOACs)

DIRECT THROMBIN INHIBITORS

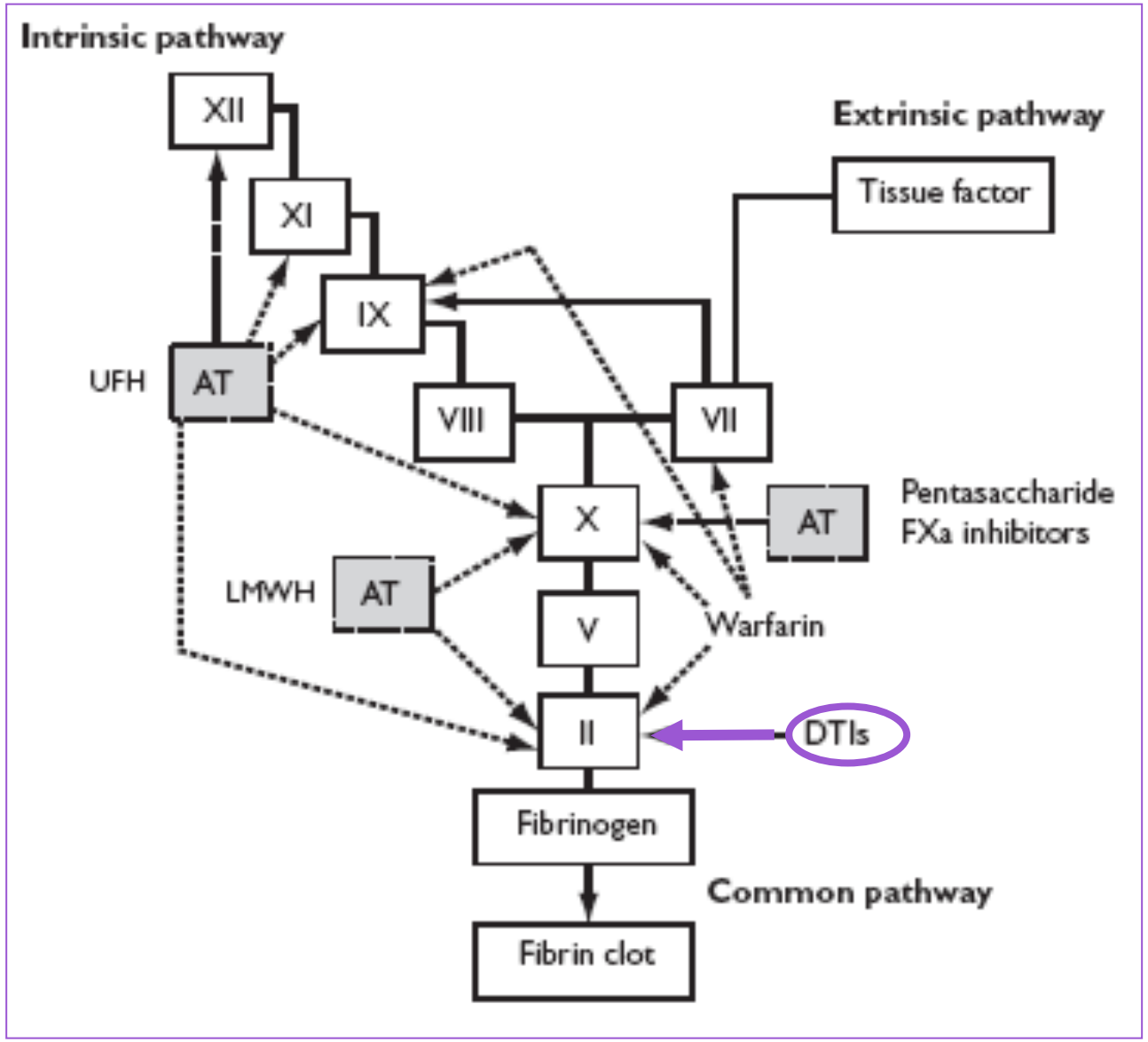
Dabigatran (Pradaxa®)

FACTOR XA INHIBITORS

Rivaroxaban (Xarelto®)

Apixaban (Eliquis®)

Edoxaban (Savaysa®)


Intrinsic pathway
XII
XI
IX
UFH
AT
VIII
Extrinsic pathway
Tissue factor
VII
X
AT
Pentasaccharide
FXa inhibitors
LMWH
AT
V
Warfarin
II
DTIs
Fibrinogen
Common pathway
Fibrin clot

# Dabigatran

# Dabigatran


The first DOAC to come to market in 2010

MOA: A prodrug converted in vivo to active dabigatran, a specific, reversible oral direct thrombin inhibitor that inhibits both free and fibrin-bound thrombin, ultimately preventing the conversion of fibrinogen to fibrin

- Prevents final step of coagulation cascade

Clinical Uses

- Nonvalvular atrial fibrillation
- VTE (DVT/PE) treatment and prophylaxis

# Dabigatran Dosing

Nonvalvular Afib 150 mg PO BID

*If high bleeding risk can consider decreased dose of 100 mg PO BID (off-label)*

VTE treatment 150 mg PO BID

*Per package label, can initiate dabigatran in hemodynamically stable patients after at least 5 days of a parenteral anticoagulant administration*

VTE prophylaxis in THA/TKA

*Give 110 mg 1 – 4 after completion of surgery and hemostasis present*

*Or if initiating following day with hemostasis present – give 220 mg PO daily for at least 10 – 14 days; can be extended up to 35 days*

Dosage adjustments needed in renal dysfunction

VTE treatment and prophylaxis (THA/TKA)

*CrCl ≤30 mL/min and hemodialysis: avoid use*

Nonvalvular Afib

*CrCl 15 to ≤30 mL/min: 75 mg PO BID*

*CrCl ≤15 mL/min and hemodialysis: Avoid use*

Generally not recommended in obese patients with a BMI ≥40 kg/$m^2$ (Class 3 obesity)

Pharmacology & Physiology in Anesthetic Practice –6th ed. 2022

LexiComp®

# Dabigatran Administration and Adverse Effects

Oral administration

- Do not break, chew or open capsules as this will lead to a 75% increase in absorption and potentially serious adverse effects (ie bleeding)

Adverse effects

- Bleeding
  - *Risk of major hemorrhage ≤6%*
  - *Risk of major gastrointestinal hemorrhage ≤3%*

# Emergent reversal of Dabigatran in life-threatening bleed

=

Idarucizumab (Praxbind®)

# Dabigatran Reversal

Activated charcoal may be used if ingestion <2 hours

Discontinue dabigatran

*Half-life 12 – 17 hours; severe renal impairment 28 hours*

*What if it has been longer than 48 hours since their last dose??*

Consider thrombin time (TT) for qualitative assessment

If normal thrombin time, dabigatran not present

Can also check aPTT and ecarin clotting time

Administer Idarucizumab (Praxbind®)


Hemodialysis??

~60% dialyzable

Dager WE. *Am J Health-Syst Pharm*. 2013; 70: S21-S31.
Kalus JS. *Am J Health-Syst Pharm*. 2013; 70: S12-S21.
Schulman S, *et al. British J of Hematology*. 2014; 164(2): 308-10.

# Idarucizumab (Praxbind®)

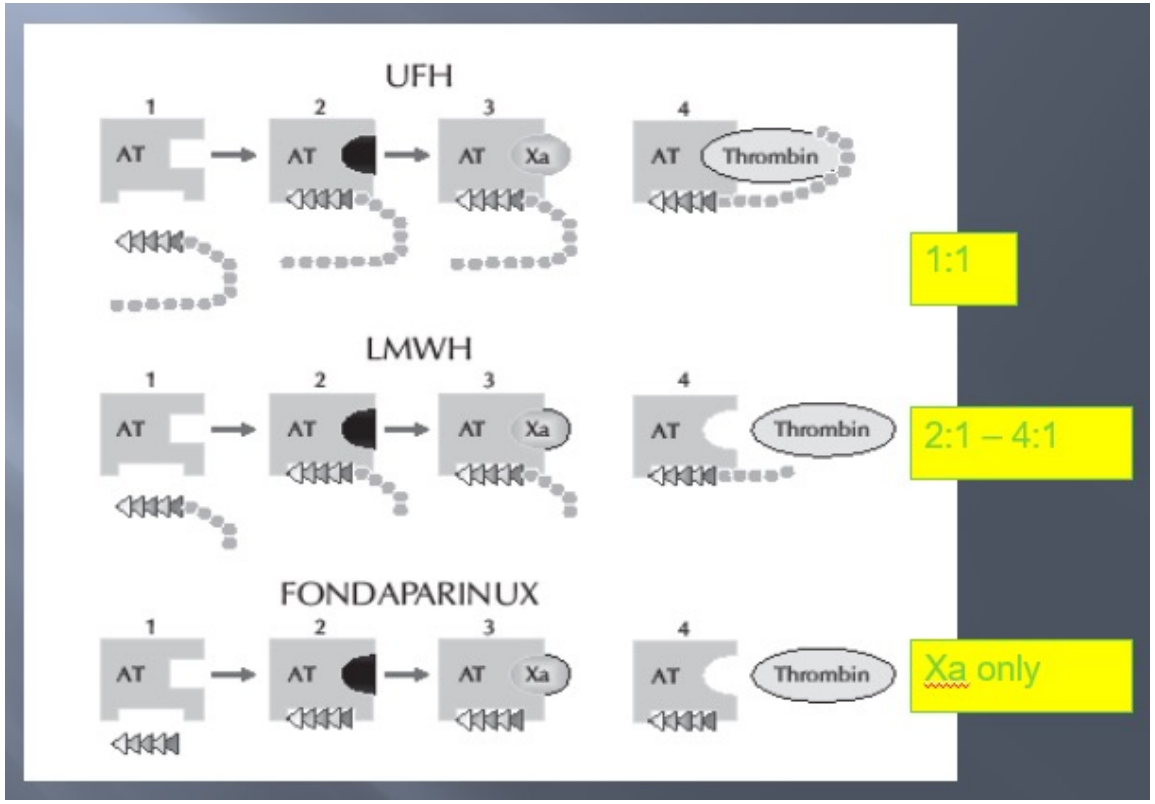
Approved by the FDA in October 2015

Mechanism of Action: A monoclonal antibody that binds to dabigatran with 350 times more affinity than thrombin, thus neutralizing the anticoagulant effect of dabigatran

Dosing: 5 gm total (administered as two separate 2.5 gm doses no more than 15 minutes apart)

***If coagulation parameters re-elevate (ie aPTT) and/or clinically relevant bleeding occurs, may consider an additional 5 gm dose (limited data to support)***

Pollack CV, *et al. N Engl J Med*. 2015; 373: 511-520.
Lexicomp Online®



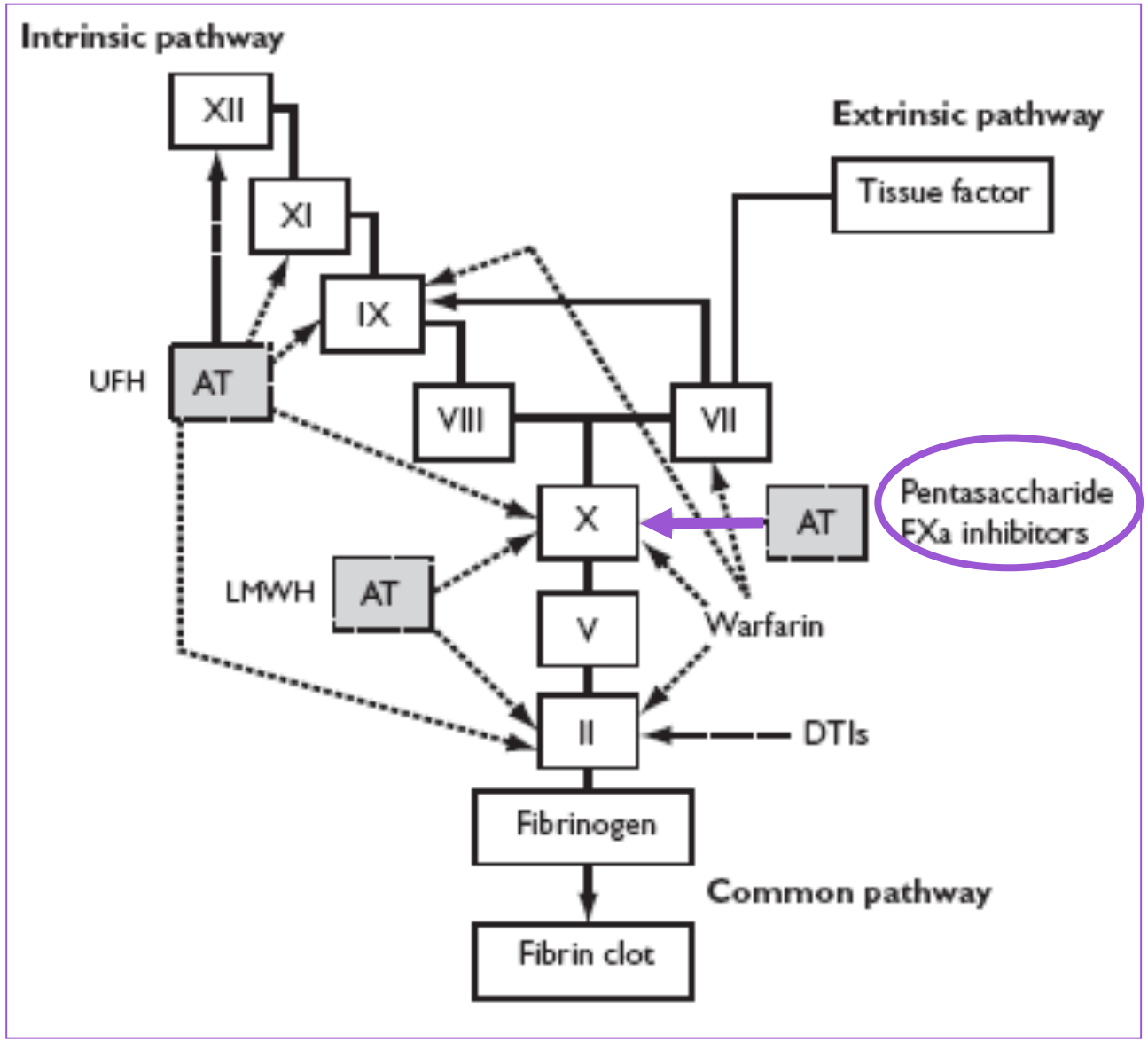

# Factor Xa Inhibitors

Fondaparinux (Arixtra®)

Rivaroxaban (Xarelto®)

Apixaban (Eliquis®)

Edoxaban (Savaysa®)




# Factor Xa Inhibitors

# Rivaroxaban (Xarelto®)

Clinical uses

- DVT/PE prevention for hip/knee replacement and acutely ill medical patients
- Treatment of DVT/PE
- Non-valvular atrial fibrillation
- HIT
- Peripheral artery disease (stable; low bleeding risk)
- CAD after stabilization with initial management as add-on to clopidogrel

Pharmacokinetics

- Onset of action: 2-4 hours
- Half-life: 5-9 hours
- Renal elimination
  - *Dosage adjustments needed based upon CrCl*
- Hepatic metabolism
  - *Avoid use in moderate-severe hepatic disease*

Approved July 1, 2011

# Rivaroxaban Mechanism of Action

An oral direct Xa inhibitor with >10,000-fold selectivity for factor Xa than for other related serine proteases

Unlike LMWH and fondaparinux, rivaroxaban does NOT require antithrombin as a cofactor

Can inhibit free factor Xa, clot-bound factor Xa, and factor Xa bound to the prothrombinase complex

# Rivaroxaban

## DOSING

Nonvalvular Afib: 20 mg PO once daily with evening meal

VTE treatment: 15 mg PO BID with food for 21 days followed by 20 mg PO once daily with food

VTE prophylaxis 10 mg PO once daily (without regard to meals)

**Requires renal dose adjustment

## MONITORING

No therapeutic monitoring

Safety monitoring: PT / aPTT/anti-Xa level

# Rivaroxaban

## ADVERSE EFFECTS

Bleeding

*No difference in bleeding when compared to enoxaparin*


## DRUG INTERACTIONS

CYP3A4 inducers may decrease the serum concentration of rivaroxaban

*Phenobarbital, phenytoin, rifampin, St. John's Wort*

CYP3A4 inhibitors may increase the serum concentration of rivaroxaban

*Clarithromycin, diltiazem, itraconazole, ritonavir, verapamil, and grapefruit*

Avoid combined P-gp and strong CYP3A inhibitors and inducers

Pharmacology & Physiology in Anesthetic Practice –6th ed. 2022

LexiComp®

# Apixaban (Eliquis®)

## Clinical Uses

- Nonvalvular Afib
- HIT
- VTE treatment
- VTE prophylaxis (THA/TKA only)
- Left Ventricular Thrombus Treatment/Prophylaxis (off-label)

## Pharmacokinetics

- Peak onset: 3-4 hours
- Half-life: 12 hours
- Extensively metabolized by CYP3A4
  - *Use not recommended in patients with severe hepatic impairment*

## Approved December 28, 2012

# Apixaban Dosing


Nonvalvular Afib 5 mg PO BID

*UNLESS patient has at least 2 of the following:*

SCr ≥1.5 mg/dL

Body weight ≤60 kg

Age ≥80 years old

*THEN 2.5 mg PO BID*

VTE treatment 10 mg PO BID x7 days, then 5 mg PO BID

*No dosage adjustment required for renal dysfunction*

VTE prophylaxis 2.5 mg PO BID beginning 12 – 24 hours post-op

# Apixaban

## Monitoring

No therapeutic monitoring

Safety monitoring: PT / aPTT/ Anti-Xa levels

## Adverse effects

Bleeding

## Drug Interactions

For patients receiving apixaban 5 mg or 10 mg BID, the dose should be decreased by 50% when coadministered with drugs that are combined P-gp and strong CYP3A4 inhibitors (ketoconazole, itraconazole, ritonavir)

*For 2.5 mg BID dose, avoid coadministration*

Avoid concomitant use of apixaban with combined P-gp and strong CYP3A4 inducers (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) due to decreased exposure to apixaban

**Table 19**. Recommended Doses of Currently Approved DOACs According to Renal Function (Table view)

| | CrCl (mL/min) | | | | |
|---|---|---|---|---|---|
| DOAC | >95 | 51-95 | 31-50 | 15-30 | <15 or on dialysis |
| Apixaban | 5 or 2.5 mg twice daily* | 5 or 2.5 mg twice daily* | 5 or 2.5 mg twice daily* | 5 or 2.5 mg twice daily* | 5 or 2.5 mg twice daily* |
| Dabigatran | 150 mg twice daily | 150 mg twice daily | 150 mg twice daily | 75 mg twice daily | Contraindicated |
| Edoxaban | Contraindicated | 60 mg once daily | 30 mg once daily | 30 mg once daily | Contraindicated |
| Rivaroxaban | 20 mg once daily | 20 mg once daily | 15 mg once daily | 15 mg once daily | 15 mg once daily† |

Note that other, nonrenal considerations such as drug interactions may also apply. The gray area indicates doses not studied in the pivotal clinical trials of these agents.

* If at least 2 of the following are present: serum creatinine ≥1.5 mg/dL, age ≥80 y, or body weight ≤60 kg, the recommended dose is 2.5 mg twice daily. The ARISTOTLE trial excluded patients with either a creatinine of >2.5 mg/dL or a calculated CrCl <25 mL/min.

† Rivaroxaban is not recommended for other indications in patients with a CrCl <15 mL/min, but such a recommendation is not made for the AF indication. However, pharmacokinetic data are limited.

AF indicates atrial fibrillation; ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; CrCl, creatinine clearance; and DOAC, direct oral anticoagulant.

# Dosing of DOACs with Afib and Renal Dysfunction

2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

Circulation. 2024;149:e1–e156. DOI: 10.1161/CIR.0000000000001193

## 10.4. Anticoagulation Considerations in Patients With Class III Obesity

**Recommendations for Anticoagulation Considerations in Patients With Class III Obesity**
**Referenced studies that support the recommendations are summarized in the Online Data Supplement.**

| COR | LOE | Recommendations |
|---|---|---|
| 2a | B-NR | 1. In patients with AF and class III obesity (BMI ≥ 40 kg/m$^2$), DOACs are reasonable to choose over warfarin for stroke risk reduction.[1–5] |
| 2b | C-LD | 2. In patients with AF who have undergone bariatric surgery, warfarin may be reasonable to choose over DOACs for stroke risk reduction in view of concerns about DOAC drug absorption.[6,7] |

# Dosing of DOACs with Afib and Obesity

2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

Circulation. 2024;149:e1–e156. DOI: 10.1161/CIR.0000000000001193

# Reversal of Factor Xa Inhibitors

=

Supportive Care;
Andexanet Alfa? PCC? aPCC?

# Factor Xa Inhibitors

Rivaroxaban (Xarelto®), Apixaban (Eliquis®), Edoxaban (Savaysa®)

Onset of action:

- Apixaban 3 – 4 hours
- Rivaroxaban 2 – 4 hours
- Edoxaban 1 – 2 hours

Half–life elimination:

- Apixaban ~12 hours
- Rivaroxaban 5 – 13 hours
- Edoxaban 10 – 14 hours

LexiComp®

# Factor Xa Inhibitor Reversal

Activated charcoal may be used if ingestion <2 hours
- For apixaban, may use activated charcoal up to 6 hours after ingestion
- For rivaroxaban, some data to support using activated charcoal up to 8 hours after last dose

Supportive care
- Discontinue agent
  - Consider anti-Xa level for qualitative assessment
    - At majority of institutions, anti Xa levels are not calibrated for apixaban or rivaroxaban
  - If normal anti-Xa level, apixaban/rivaroxaban not present
- Fluids/blood products
  - *Note: FFP will not reverse the medication's effects*
- Stop source of bleeding
- Not dialyzable

PCC and Activated PCC (aPCC) have been studied off label for this indication

Andexanet Alfa approved by the FDA in 2018

Dager WE. *Am J Health-Syst Pharm*. 2013; 70: S21-S31.
Kalus JS. *Am J Health-Syst Pharm*. 2013; 70: S12-S21.

# Factor Xa Inhibitor Reversal with PCC


If life-threatening bleed, can consider 4 Factor PCC or activated PCC (aPCC → FEIBA)

- Off label use
- PCC dosing: 25 - 50 Units/kg (Max dose 5000 Units)
- Some institutions used fixed dosing
- Dosing as high as 90 units/kg have been suggested in the literature

- aPCC dosing: Anywhere from 25 – 100 Units/kg has been studied in the literature
  - *FEIBA (Factor Eight Inhibitor Bypass Activity)*
    - Non-activated factors II, IX, and X
    - **ACTIVATED** factor VII

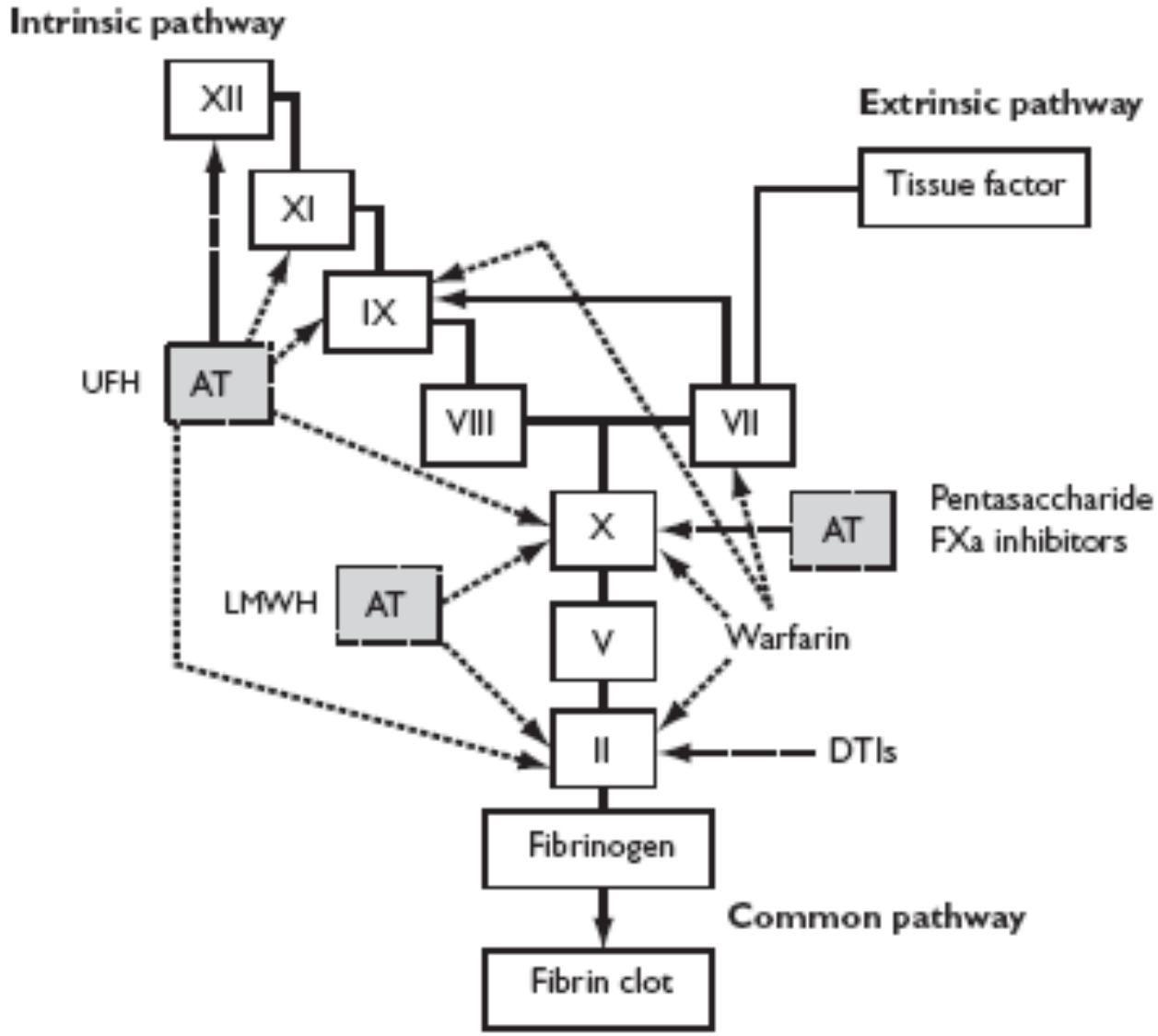
*LexiTox®*

*Neurocrit Care.* (2016) 24:6–46.

# Factor Xa Inhibitor Reversal with PCC

Providing factors IX, VII, and X should be ineffective due to the MOA of the Factor Xa inhibitor

Theory for use: Overwhelm the pharmacologic activity with clotting factors




*Am J Health-Syst Pharm* . 2016; 73(10S2):S5-S13.

# Comparison of PCC products available

| Clotting Factors | Nonactivated 4-Factor PCC | Fresh Frozen Plasma (FFP) | Activated 4-Factor PCC (Factor VIII bypassing agent) | 3-Factor PCC | Recombinant Factor VIIa |
|---|---|---|---|---|---|
| II | X | X | X | X | |
| VII | X | X | X (activated) | marginal | X (activated) |
| IX | X | X | X | X | |
| X | X | X | X | X | |
| Protein C | X | X | | | |
| Protein S | X | X | | | |

# Andexanet-Alfa (Andexxa®)

MOA: Structurally similar to Factor Xa, Andexanet alfa acts as a decoy that sequesters the Factor Xa inhibitors or LMWH in the blood. This prevents these agents from binding to native Factor Xa, thus allowing continuation of the coagulation cascade and clot formation to occur.

Dosing:

Low Dose: 400 mg IV bolus over ~15 minutes (30 mg/min), followed by 480 mg over 2 hours (4 mg/min)

High dose: 800 mg IV bolus over ~30 minutes (30 mg/min), followed by 960 mg over 2 hours (8 mg/min)


Andexxa® Package Insert.

**Table 1: ANDEXXA Dosing Regimens**

| Dose* | Initial IV Bolus | Follow-On IV Infusion | Total Number of 200 mg Vials |
|---|---|---|---|
| Low Dose | 400 mg at a target rate of 30 mg/min | 4 mg/min for up to 120 minutes (480 mg) | 5 (2 vials bolus + 3 vials infusion) |
| High Dose | 800 mg at a target rate of 30 mg/min | 8 mg/min for up to 120 minutes (960 mg) | 9 (4 vials bolus + 5 vials infusion) |

*The safety and effectiveness of more than one dose have not been evaluated.

The recommended dosing of ANDEXXA is based on the specific FXa inhibitor, dose of FXa inhibitor, and time since the patient's last dose of FXa inhibitor (see Table 2).

**Table 2: ANDEXXA Dose Based on Rivaroxaban or Apixaban Dose (Timing of Last Dose of FXa Inhibitor before ANDEXXA Initiation)**

| FXa Inhibitor | FXa Inhibitor Last Dose | < 8 Hours or Unknown | ≥ 8 Hours |
|---|---|---|---|
| Rivaroxaban | ≤ 10 mg | Low Dose | Low Dose |
| | > 10 mg or Unknown | High Dose | |
| Apixaban | ≤ 5 mg | Low Dose | |
| | > 5 mg or Unknown | High Dose | |

# Andexanet -Alfa Dosing

Andexxa® Package Insert.

# ANNEXA – 4 TRIAL

Prospective, open-label, single group (no comparator arm)

Final analysis had 352 patients, including 227 intracranial bleeds*

>80% of patients on DOAC for atrial fibrillation

Co-primary study outcomes

- % reduction in anti-factor Xa activity
  - *% reduction of anti-factor Xa activity measured after the bolus, at the end of the 2hr infusion, at 4hrs and 8hrs*
- "Clinical hemostatic efficacy" at 12hrs after infusion

*Efficacy population excluded patients with a baseline anti-Factor Xa activity <75 ng/mL or who did not have major bleeding when adjudicated*

Secondary safety outcomes

- Thrombosis
- Mortality

*Safety population included all patients receiving andexanet-alfa*

Slide Credit: Paul Miller, PharmD, BCPS

Connolly, S. J. (2019). New England Journal of Medicine

# ANNEXA – 4 Trial Inclusion and Exclusion Criteria

## INCLUSION CRITERIA

Age >18 yo

Acute major bleeding

- Life-threatening with evidence of hemodynamic compromise
- Hgb decrease ≥2 g/dL
- Critical area (ie ICH)

Apixaban, Rivaroxaban, Edoxaban, Enoxaparin

Last dose of Factor Xa inhibitor within 18 hours

## EXCLUSION CRITERIA

GCS < 7 or ICH hematoma size > 60mL

- Or SDH hematoma thickness > 10mm

Expected mortality within 1 month, irrespective of cause

Any planned/scheduled procedure within 12hrs

- Not studied in surgical patients (minimally invasive surgery allowed)!!

A thrombotic event within 2 weeks before enrollment

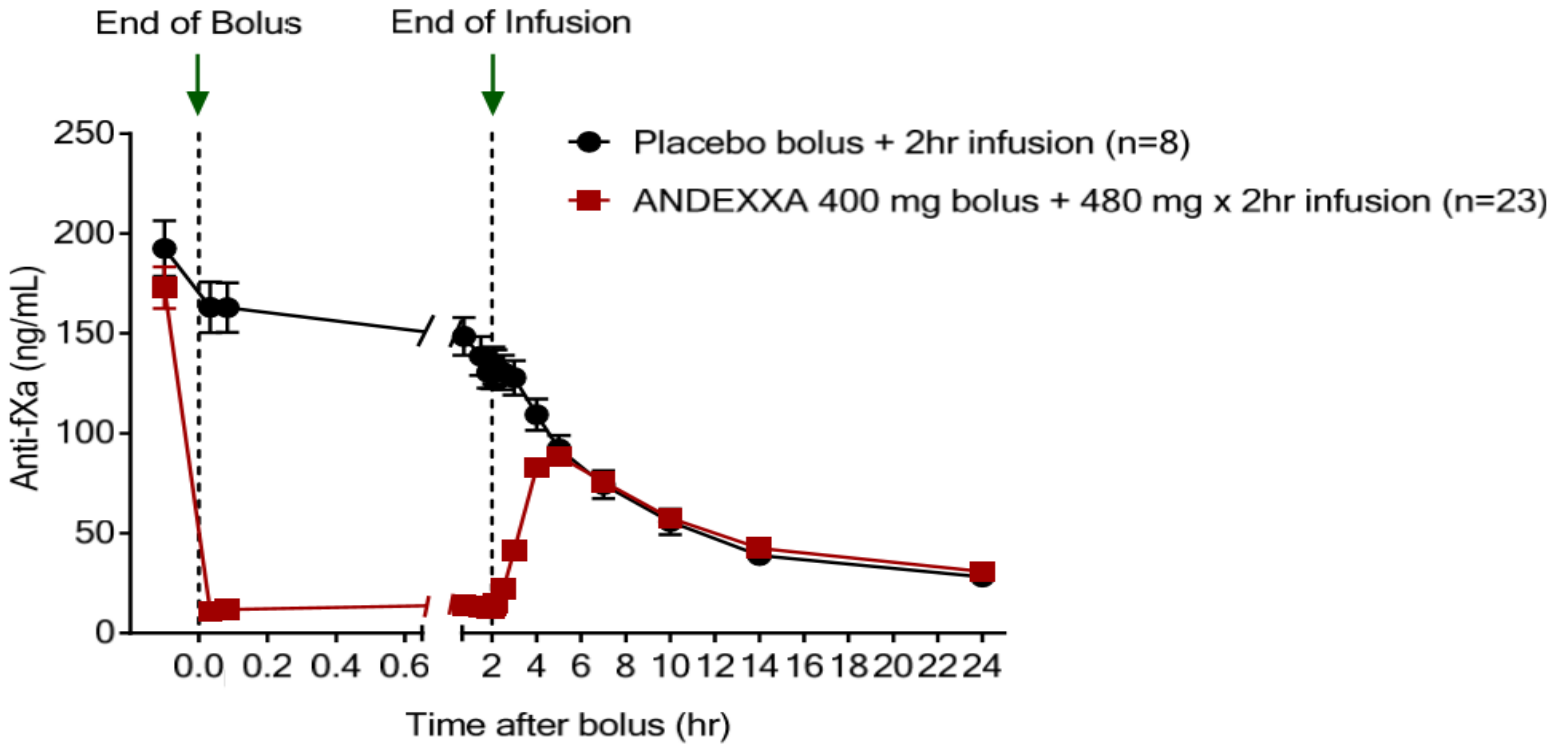
Use of any of the following agents within the previous 7 days: vitamin K antagonist, dabigatran, prothrombin complex concentrate, recombinant factor VIIa, whole blood, or plasma

Connolly, S. J. (2019). New England Journal of Medicine

# ANNEXA – 4 Trial Results

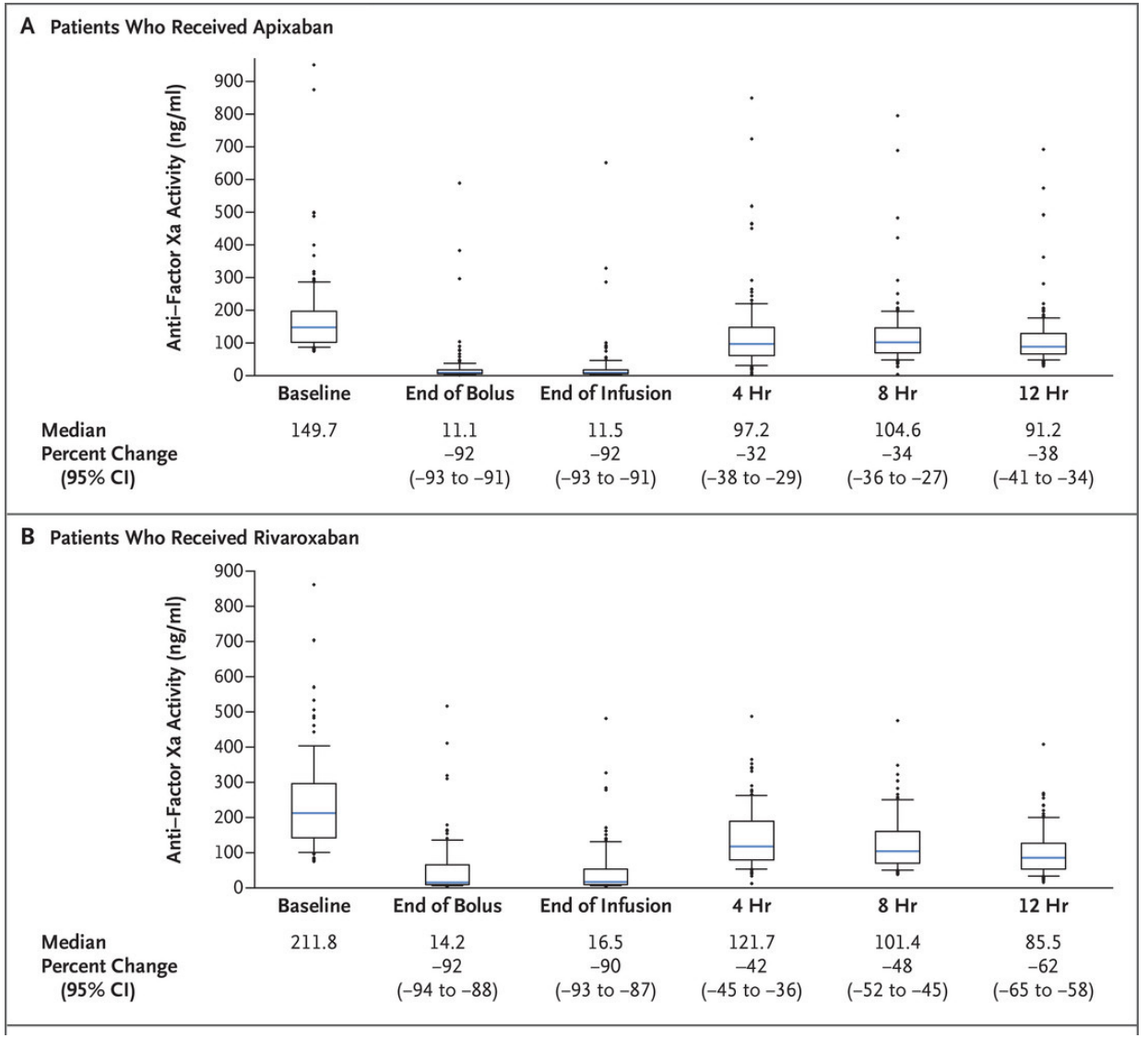
90% reduction of anti-factor Xa activity at end of 2hr infusion

Anti Xa activity returned to pre-treatment levels within 2hr after infusion




Slide Credit: Paul Miller, PharmD, BCPS

Connolly, S. J. (2019). New England Journal of Medicine




Connolly, S. J. (2019). New England Journal of Medicine

# ANNEXA – 4 Trial Results

80% achieved good or excellent “clinical hemostatic efficacy”

15% mortality rate

**10% rate of thrombosis**

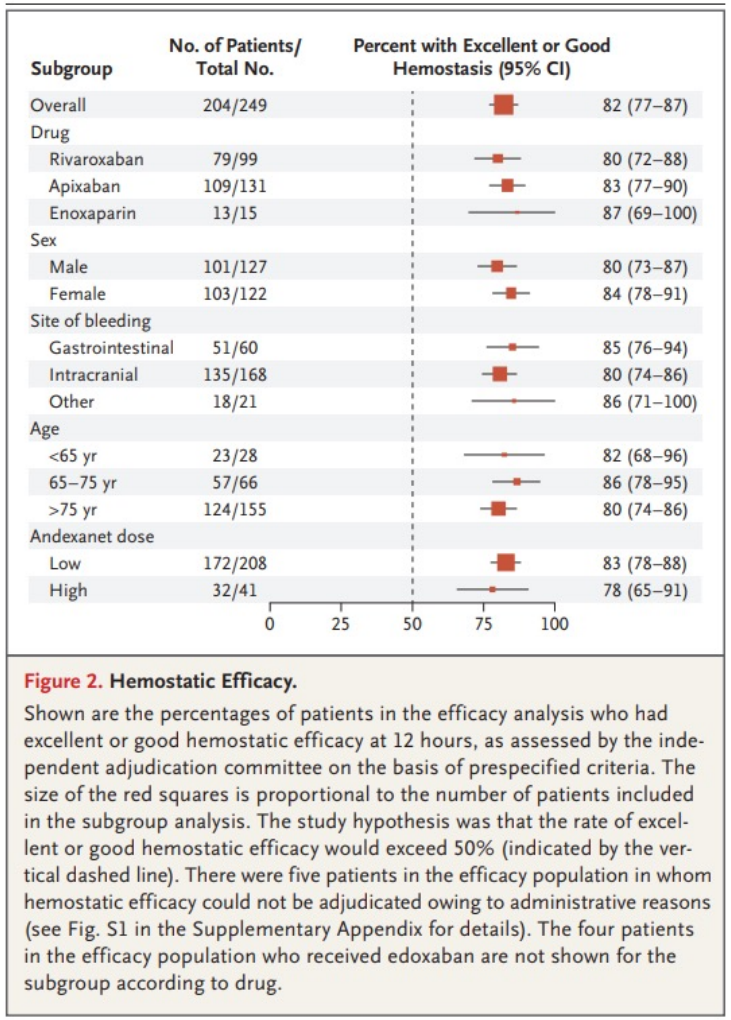



**Figure 2. Hemostatic Efficacy.**

Shown are the percentages of patients in the efficacy analysis who had excellent or good hemostatic efficacy at 12 hours, as assessed by the independent adjudication committee on the basis of prespecified criteria. The size of the red squares is proportional to the number of patients included in the subgroup analysis. The study hypothesis was that the rate of excellent or good hemostatic efficacy would exceed 50% (indicated by the vertical dashed line). There were five patients in the efficacy population in whom hemostatic efficacy could not be adjudicated owing to administrative reasons (see Fig. S1 in the Supplementary Appendix for details). The four patients in the efficacy population who received edoxaban are not shown for the subgroup according to drug.

Connolly, S. J. (2019). New England Journal of Medicine

**Table 2. Timing of Thrombotic Event and Restarting of Anticoagulation.***

| Variable | Safety Population (N = 352) | | | |
|---|---|---|---|---|
| | Total | <6 Days after Bolus | 6–14 Days after Bolus | 15–30 Days after Bolus |
| | *number of patients (percent)* | | | |
| ≥1 Thrombotic event within 30 days† | 34 (10) | 11 | 11 | 12 |
| Myocardial infarction | 7 | 6 | 1 | 0 |
| Ischemic stroke or stroke of uncertain classification | 14 | 5 | 6 | 3 |
| Transient ischemic attack | 1 | 0 | 0 | 1 |
| Deep-vein thrombosis | 13 | 1 | 5 | 7 |
| Pulmonary embolism | 5 | 1 | 0 | 4 |
| Death within 30 days‡ | 49 (14) | 8 | 21 | 20 |
| Cardiovascular cause | 35 | 7 | 15 | 13 |
| Noncardiovascular cause | 12 | 1 | 5 | 6 |
| Uncertain cause | 2 | 0 | 1 | 1 |
| Restart of any anticoagulation§ | 220 (62) | 145 (41) | 46 (13) | 29 (8) |
| Thrombotic event before restart¶ | 26 (7) | | | |
| Thrombotic event after restart | 8 (2) | | | |
| Restart of oral anticoagulation‖ | 100 (28) | 31 (9) | 37 (11) | 32 (9) |
| Thrombotic event before restart¶ | 34 (10) | | | |
| Thrombotic event after restart | 0 | | | |

80% of patients in trial on DOAC for atrial fibrillation

Why such high proportion of DVT/PE/MI?

Connolly, S. J. (2019). New England Journal of Medicine

## Abstract

**IMPORTANCE** Direct oral anticoagulant (DOAC)–associated intracranial hemorrhage (ICH) has high morbidity and mortality. The safety and outcome data of DOAC reversal agents in ICH are limited.

**OBJECTIVE** To evaluate the safety and outcomes of DOAC reversal agents among patients with ICH.

**DATA SOURCES** PubMed, MEDLINE, The Cochrane Library, Embase, EBSCO, Web of Science, and CINAHL databases were searched from inception through April 29, 2022.

**STUDY SELECTION** The eligibility criteria were (1) adult patients (age ≥18 years) with ICH receiving treatment with a DOAC, (2) reversal of DOAC, and (3) reported safety and anticoagulation reversal outcomes. All nonhuman studies and case reports, studies evaluating patients with ischemic stroke requiring anticoagulation reversal or different dosing regimens of DOAC reversal agents, and mixed study groups with DOAC and warfarin were excluded.

**DATA EXTRACTION AND SYNTHESIS** Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines were used for abstracting data and assessing data quality and validity. Two reviewers independently selected the studies and abstracted data. Data were pooled using the random-effects model.

**MAIN OUTCOMES AND MEASURES** The primary outcome was proportion with anticoagulation reversed. The primary safety end points were all-cause mortality and thromboembolic events after the reversal agent.

**RESULTS** A total of 36 studies met criteria for inclusion, with a total of 1832 patients (967 receiving 4-factor prothrombin complex concentrate [4F-PCC]; 525, andexanet alfa [AA]; 340, idarucizumab). The mean age was 76 (range, 68-83) years, and 57% were men. For 4F-PCC, anticoagulation reversal was 77% (95% CI, 72%-82%; $I^2$ = 55%); all-cause mortality, 26% (95% CI, 20%-32%; $I^2$ = 68%), and thromboembolic events, 8% (95% CI, 5%-12%; $I^2$ = 41%). For AA, anticoagulation reversal was 75% (95% CI, 67%-81%; $I^2$ = 48%); all-cause mortality, 24% (95% CI, 16%-34%; $I^2$ = 73%), and thromboembolic events, 14% (95% CI, 10%-19%; $I^2$ = 16%). Idarucizumab for reversal of dabigatran had an anticoagulation reversal rate of 82% (95% CI, 55%-95%; $I^2$ = 41%), all-cause mortality, 11% (95% CI, 8%-15%, $I^2$ = 0%), and thromboembolic events, 5% (95% CI, 3%-8%; $I^2$ = 0%). A direct retrospective comparison of 4F-PCC and AA showed no differences in anticoagulation reversal, proportional mortality, or thromboembolic events.


(continued)

### Key Points

**Question** What outcomes are associated with direct oral anticoagulant (DOAC) reversal agents in intracranial hemorrhage (ICH)?

**Findings** In a meta-analysis of 32 studies including 1832 patients with ICH, 4-factor prothrombin complex concentrate (4F-PCC), andexanet alfa (AA), and idarucizumab were associated with a successful anticoagulation reversal in 77%, 75%, and 82% of patients, respectively; all-cause mortality rates were 26%, 24%, and 11%, respectively; and thromboembolic event rates were 8%, 14%, and 5%, respectively. A direct retrospective comparison of 4F-PCC with AA showed no differences in successful anticoagulation reversal, all-cause mortality, or thromboembolic events.

**Meaning** In this study, factor Xa inhibitor reversal agents for ICH had similar safety profiles and outcomes, but the lack of head-to-head comparison warrants cautious interpretation.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

# Evaluation of Direct Oral Anticoagulant Reversal Agents in Intracranial Hemorrhage: A Systematic Review and Meta-analysis

*JAMA Network Open.* 2022;5(11):e2240145. doi:10.1001/jamanetworkopen.2022.40145

# Evaluation of Direct Oral Anticoagulant Reversal Agents in Intracranial Hemorrhage: A Systematic Review and Meta-analysis

Conclusions:

Reversal, mortality, and thromboembolic event rates appeared similar between reversal agents

Majority of studies retrospective

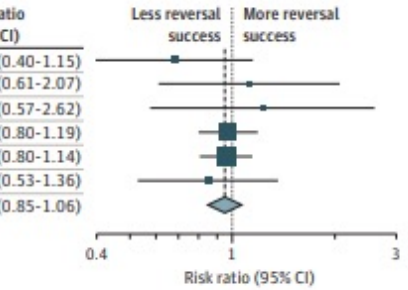
Significant heterogeneity

**Figure 4. Comparison of 4-Factor Plasma Concentrate Complex (4F-PCC) vs Andexanet Alfa (AA) for Proportion of Anticoagulation Reversed, Mortality, and Thromboembolic Outcomes Among Patients Receiving Factor Xa Inhibitors With Intracranial Hemorrhage**

**A** Anticoagulation reversed

| Study | 4F-PCC Reversed | 4F-PCC Total | AA Reversed | AA Total | Risk ratio (95% CI) |
|---|---|---|---|---|---|
| Barra et al,[35] 2020 | 6 | 10 | 16 | 18 | 0.68 (0.40-1.15) |
| Ammar et al,[37] 2021 | 6 | 10 | 15 | 28 | 1.12 (0.61-2.07) |
| Stevens et al,[39] 2021 | 7 | 10 | 4 | 7 | 1.23 (0.57-2.62) |
| Pham et al,[40] 2022 | 46 | 58 | 31 | 38 | 0.97 (0.80-1.19) |
| Parsels et al,[41] 2022 | 23 | 26 | 24 | 26 | 0.96 (0.80-1.14) |
| Vestal et al,[44] 2022 | 17 | 31 | 11 | 17 | 0.85 (0.53-1.36) |
| Random-effects model | | 145 | | 134 | 0.95 (0.85-1.06) |

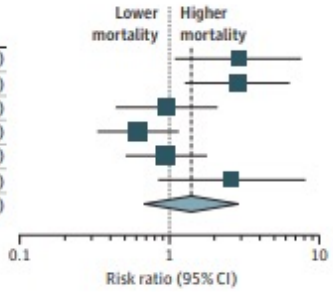
Heterogeneity: $\tau^2 = 0$ ($P = .76$); $I^2 = 0\%$




**B** Mortality

| Study | 4F-PCC Reversed | 4F-PCC Total | AA Reversed | AA Total | Risk ratio (95% CI) |
|---|---|---|---|---|---|
| Barra et al,[35] 2020 | 7 | 11 | 4 | 18 | 2.86 (1.08-7.58) |
| Coleman et al,[36] 2021 | 43 | 170 | 6 | 67 | 2.82 (1.26-6.32) |
| Ammar et al,[37] 2021 | 6 | 16 | 11 | 28 | 0.95 (0.44-2.09) |
| Pham et al,[40] 2022 | 13 | 62 | 16 | 47 | 0.62 (0.33-1.15) |
| Milioglou et al,[42] 2022 | 10 | 22 | 11 | 23 | 0.95 (0.51-1.78) |
| Vestal et al,[44] 2022 | 13 | 35 | 3 | 21 | 2.60 (0.84-8.07) |
| Random-effects model | | 316 | | 204 | 1.40 (0.68-2.86) |

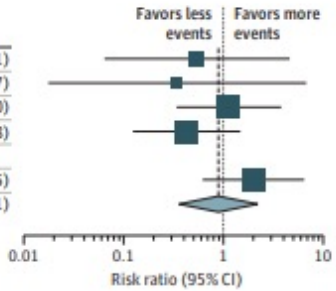
Heterogeneity: $\tau^2 = 0.3069$ ($P = .01$); $I^2 = 65\%$




**C** Thromboembolic outcomes

| Study | 4F-PCC Reversed | 4F-PCC Total | AA Reversed | AA Total | Risk ratio (95% CI) |
|---|---|---|---|---|---|
| Barra et al,[35] 2020 | 1 | 11 | 3 | 18 | 0.55 (0.06-4.61) |
| Ammar et al,[37] 2021 | 0 | 16 | 2 | 28 | 0.35 (0.02-6.77) |
| Pham et al,[40] 2022 | 6 | 62 | 4 | 47 | 1.14 (0.34-3.80) |
| Parsels et al,[41] 2022 | 3 | 26 | 7 | 26 | 0.43 (0.12-1.48) |
| Milioglou et al,[42] 2022 | 0 | 22 | 0 | 23 | |
| Vestal et al,[44] 2022 | 10 | 35 | 3 | 21 | 2.00 (0.62-6.45) |
| Random-effects model | | 172 | | 163 | 0.89 (0.36-2.21) |

Heterogeneity: $\tau^2 = 0.1176$ ($P = .42$); $I^2 = 0\%$




*JAMA Network Open.* 2022;5(11):e2240145. doi:10.1001/jamanetworkopen.2022.40145

## ABSTRACT

**BACKGROUND** Direct oral anticoagulants (DOACs) have shown a positive benefit-risk balance in both clinical trials and real-world data, but approximately 2% to 3.5% of patients experience major bleeding annually. Many of these patients require hospitalization, and the administration of reversal agents may be required to control bleeding.

**OBJECTIVES** The aim of this study was to investigate clinical outcomes associated with the use of 4-factor prothrombin complex concentrates, idarucizumab, or andexanet for reversal of severe DOAC-associated bleeding.

**METHODS** The investigators systematically searched for studies of reversal agents for the treatment of severe bleeding associated with DOAC. Mortality rates, thromboembolic events, and hemostatic efficacy were meta-analyzed using a random effects model.

**RESULTS** The investigators evaluated 60 studies in 4,735 patients with severe DOAC-related bleeding who were treated with 4-factor prothrombin complex concentrates (n = 2,688), idarucizumab (n = 1,111), or andexanet (n = 936). The mortality rate was 17.7% (95% confidence interval [CI]: 15.1% to 20.4%), and it was higher in patients with intracranial bleedings (20.2%) than in patients with extracranial hemorrhages (15.4%). The thromboembolism rate was 4.6% (95% CI: 3.3% to 6.0%), being particularly high with andexanet (10.7%; 95% CI: 6.5% to 15.7%). The effective hemostasis rate was 78.5% (95% CI: 75.1% to 81.8%) and was similar regardless of the reversal agent considered. The rebleeding rate was 13.2% (95% CI: 5.5% to 23.1%) and 78% of rebleeds occurred after resumption of anticoagulation. The risk of death was markedly and significantly associated with failure to achieve effective hemostasis (relative risk: 3.63; 95% CI: 2.56 to 5.16). The results were robust regardless of the type of study or the hemostatic scale used.

**CONCLUSIONS** The risk of death after severe DOAC-related bleeding remains significant despite a high rate of effective hemostasis with reversal agents. Failure to achieve effective hemostasis strongly correlated with a fatal outcome. Thromboembolism rates are particularly high with andexanet. Comparative clinical trials are needed.

(J Am Coll Cardiol 2021;77:2987-3001) © 2021 by the American College of Cardiology Foundation.

# Meta-Analysis of Reversal Agents for Severe Bleeding Associated With Direct Oral Anticoagulants

*J Am Coll Cardiol.* 2021; 77:2987-3001

# Meta-Analysis of Reversal Agents for Severe Bleeding Associated With Direct Oral Anticoagulants

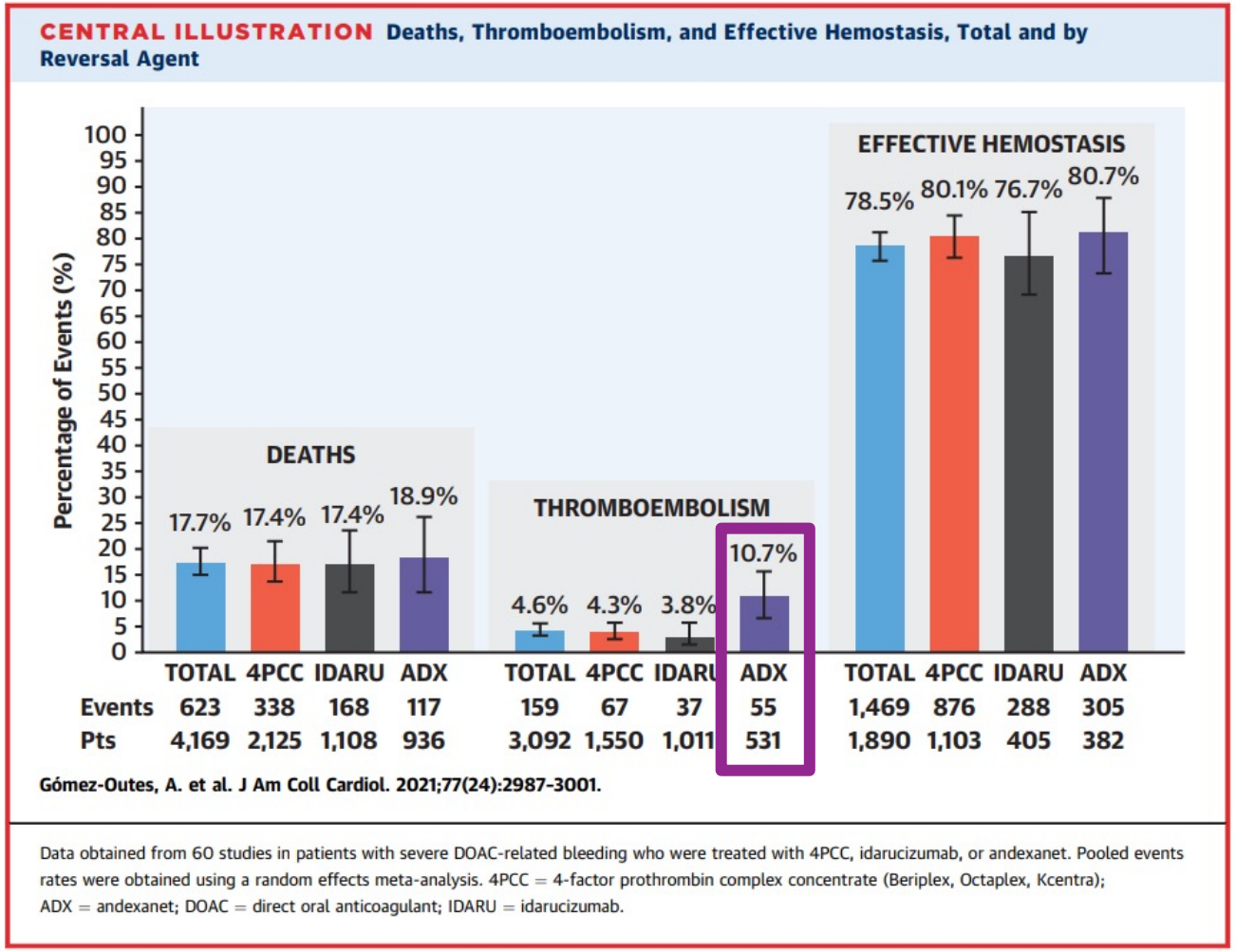
Conclusions:

Risk of death remains high with DOAC-related bleeding despite effective hemostasis

Failure to achieve hemostasis is predictor of mortality

Majority of studies retrospective

Significant heterogeneity




*J Am Coll Cardiol.* 2021; 77:2987-3001

# Lower Mortality with Andexanet Alfa vs 4-Factor Prothrombin Complex Concentrate for Factor Xa Inhibitor-related Major Bleeding in a U.S. Hospital-based Observational Study


## Abstract

**Background:** Well-designed studies with sufficient sample size comparing andexanet alfa vs 4-factor prothrombin complex concentrate (4F-PCC) in routine clinical practice to evaluate clinical outcomes are limited.

**Objectives:** To compare in-hospital mortality in patients hospitalized with rivaroxaban- or apixaban-related major bleeding who were treated with andexanet alfa or 4F-PCC.

**Methods:** An observational cohort study (ClinicalTrials.gov identifier: NCT05548777) was conducted using electronic health records between May 2018 and September 2022 from 354 U.S. hospitals. Inclusion criteria were age ≥18 years, inpatient admission with diagnosis code D68.32 (bleeding due to extrinsic anticoagulation), a record of use of the factor Xa inhibitors rivaroxaban or apixaban, andexanet alfa or 4F-PCC treatment during index hospitalization, and a documented discharge disposition. Multivariable logistic regression on in-hospital mortality with andexanet alfa vs 4F-PCC was performed. The robustness of the results was assessed via a supportive propensity score-weighted logistic regression.

**Results:** The analysis included 4395 patients (andexanet alfa, $n$ = 2122; 4F-PCC, $n$ = 2273). There were 1328 patients with intracranial hemorrhage (ICH), 2567 with gastrointestinal (GI) bleeds, and 500 with critical compartment or other bleed types. In the multivariable analysis, odds of in-hospital mortality were 50% lower for andexanet alfa vs 4F-PCC (odds ratio [OR], 0.50; 95% CI, 0.39-0.65; $P < .01$) and were consistent for both ICH (OR, 0.55; [0.39-0.76]; $P < .01$) and GI bleeds (OR, 0.49 [0.29-0.81]; $P$ = .01). Similar results were obtained from the supporting propensity score-weighted logistic regression analyses.

**Conclusion:** In this large observational study, treatment with andexanet alfa in patients hospitalized with rivaroxaban- or apixaban-related major bleeds was associated with 50% lower odds of in-hospital mortality than 4F-PCC. The magnitude of the risk reduction was similar in ICH and GI bleeds.



**KEYWORDS**

4-factor prothrombin complex concentrate, andexanet alfa, anticoagulant reversal agents, cerebral hemorrhage, factor Xa inhibitors, gastrointestinal hemorrhage



*Res Pract Thromb Haemost*. 2023;7:e102192

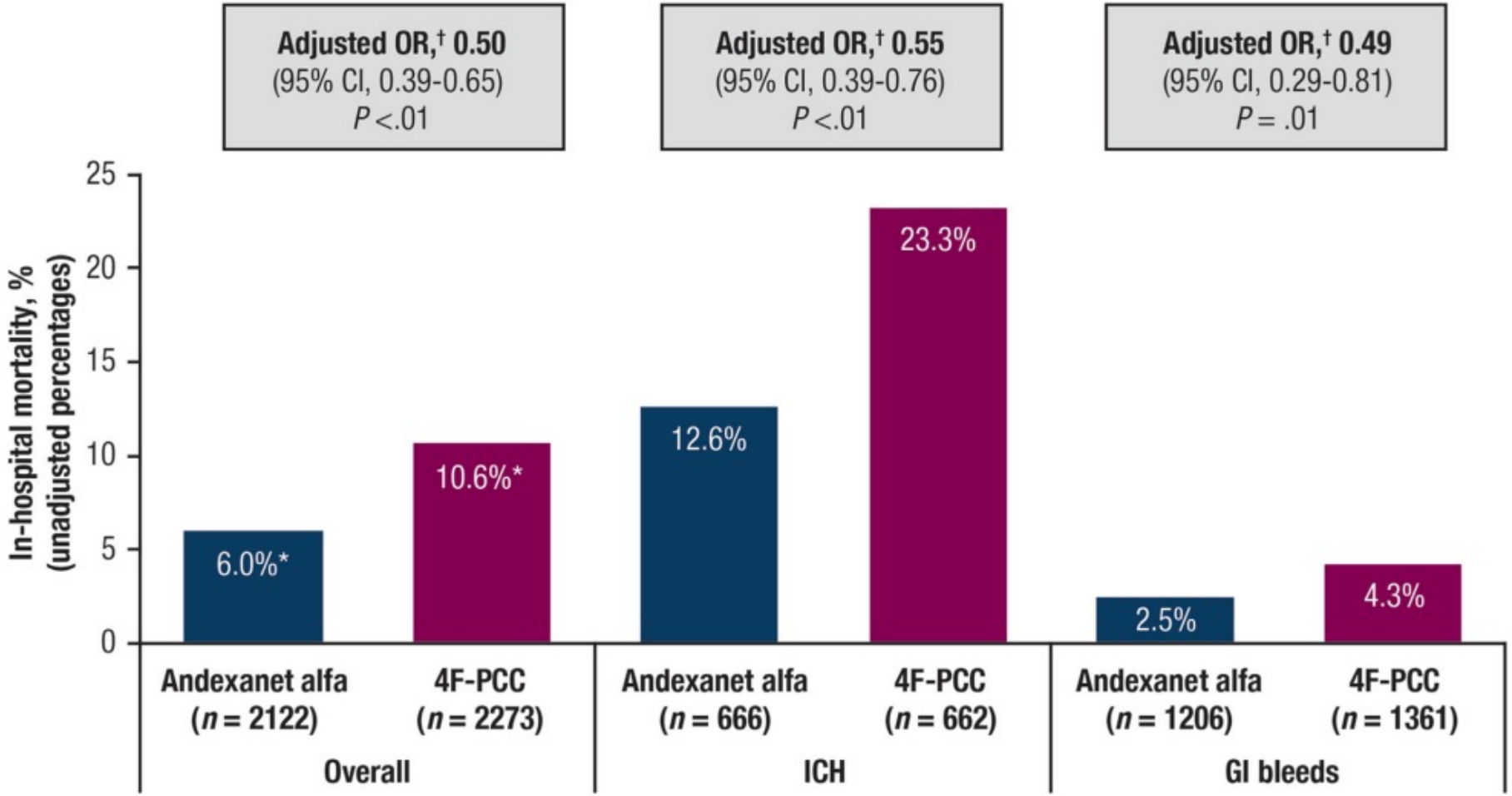



**FIGURE 1** In-hospital mortality with andexanet alfa vs 4-factor prothrombin complex concentrate (4F-PCC) in patients with rivaroxaban- or apixaban-associated major bleeding overall and separately for gastrointestinal (GI) bleeds and intracranial hemorrhage (ICH). *Unadjusted percentages of in-hospital mortality were calculated in the overall population, including those with "other bleed" types and missing mental status (*N* = 4395). †Adjusted for age, sex, bleed location (in analyses of overall bleeds), traumatic vs spontaneous ICH (in analyses of overall bleeds and ICH), systolic blood pressure, impaired mental status, do-not-resuscitate order, liver disease, chronic kidney disease, heart failure, diabetes, time since last factor Xa inhibitor dose, time from arrival to administration, and timing of data collection. Patients with "other bleed" types (*n* = 80) were excluded from the overall bleeds category in the adjusted logistic regression analysis. Patients with missing mental status were also excluded (*n* = 187 in the overall bleeds category; *n* = 45 in ICH; *n* = 110 in GI bleeds). Thus, the resulting patient counts (and number of events) in the adjusted logistic regression analyses were as follows: overall, *N* = 4128 (352 events); ICH, *N* = 1283 (235 events); GI bleeds, *N* = 2457 (85 events). OR, odds ratio.

Conclusions:

Patients with Factor Xa bleeds treated with andexanet-alfa were at 50% lower odds of in-hospital mortality when compared to 4-Factor PCC*

Retrospective and nonrandomized

*Focus on in-hospital mortality only; hemostatic efficacy and thrombosis were not assessed

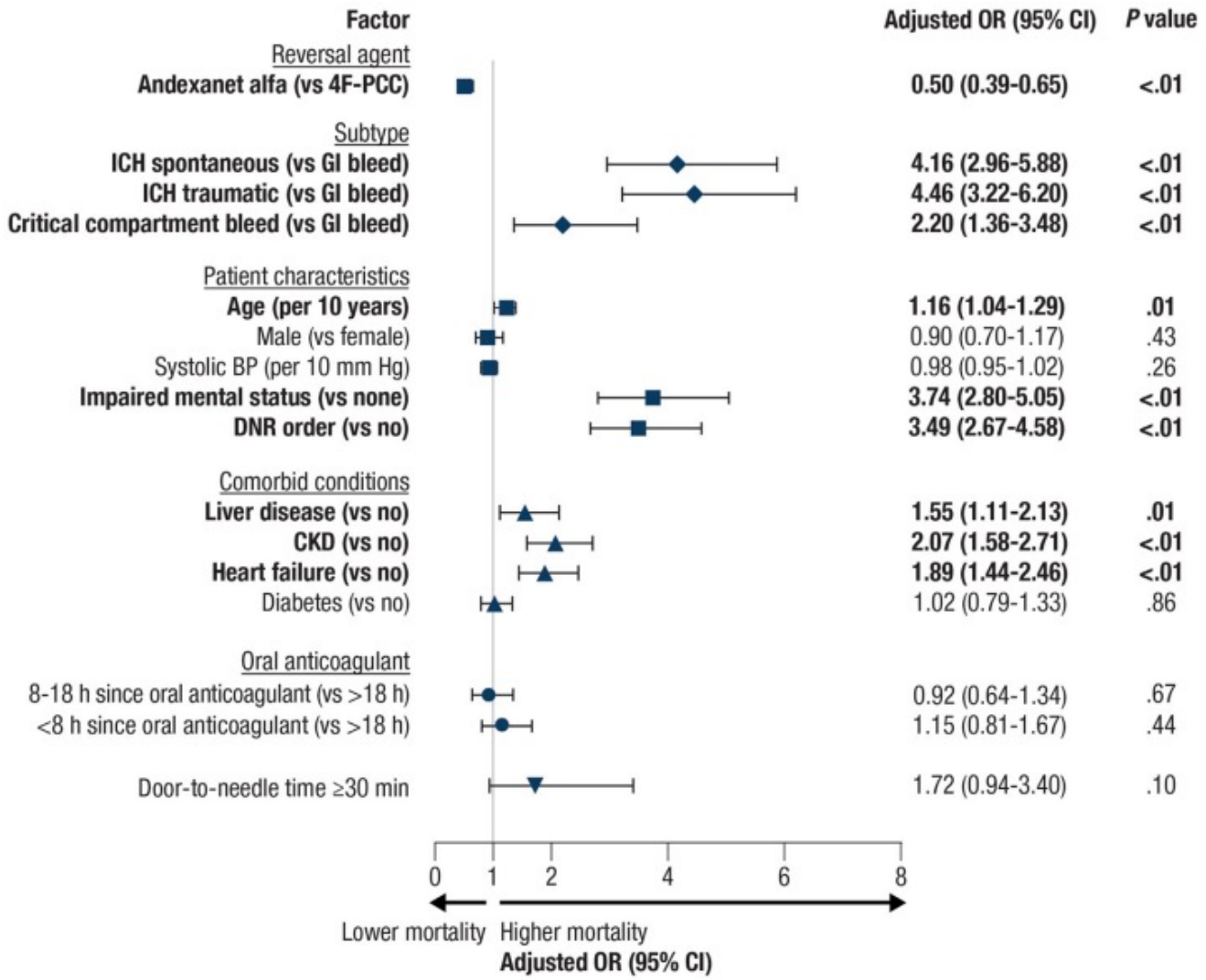



**FIGURE 2** Adjusted logistic regression analysis of clinical factors associated with odds of in-hospital mortality. Models were adjusted for bleed location, intracranial hemorrhage (ICH) bleed cause (trauma vs spontaneous), age, sex, systolic blood pressure (BP), mental status, do-not-resuscitate (DNR) status, comorbid liver disease, chronic kidney disease (CKD), heart failure, and diabetes, time since last anticoagulant dose, door-to-needle time, and timing of data collection. Patients with "other bleed" types ($n$ = 80) and missing mental status ($n$ = 187) were excluded from the adjusted logistic regression analysis, resulting in $N$ = 4128; events = 352. 4F-PCC, 4-factor prothrombin complex concentrate; GI, gastrointestinal; OR, odds ratio.

*Res Pract Thromb Haemost*. 2023;7:e102192

# ANNEXA-1

A randomized, open-label, multicenter clinical trial aimed to determine the safety and efficacy of andexanet alfa vs usual care for the treatment of ICH within 6 hours of symptom onset to baseline scan and within 15 hours of taking an oral Factor Xa inhibitor

*Note: Usual care consists of any other treatment (including no treatment) administered within 3 hours of randomization that the investigator and/or treating prescriber deemed appropriate*

Primary endpoint: A measure of effective hemostasis, which was defined as:

- *A National Institutes of Health Stroke Scale (**NIHSS**) change of +6 or less from baseline to 12 hours*
- *A hematoma volume increase of 35% or less at 12 hours compared with baseline on a repeat CT or MRI scan*
- *No rescue therapies given between 3 and 12 hours after randomization*

Secondary endpoint: Andexanet alfa's effect on anti-Factor Xa activity, defined as the percent change from baseline to nadir in anti-Factor Xa activity in the first 2 hours following randomization

Safety endpoints: Thrombotic events at 30 days and 30-day mortality

ANNEXA-I: Andexanet Alfa Shows Efficacy, Safety for Factor Xa Reversal in Acute ICH (ajmc.com)

# ANNEXA-1

The phase 4 ANNEXA-I trial was **stopped early** based on the achievement of prespecified criteria (450 patients; efficacy set at p<0.031) for superior hemostatic efficacy and the capability to limit potentially life-threatening brain bleeding compared with usual care in patients on oral Factor Xa inhibitors

*Study showed similar demographics, including median time from symptom onset to baseline scan (2.2 hrs in andexanet alfa group vs. 2.4 hrs in usual care group)*

**Results for Primary and Secondary Endpoints:**

"The median reduction in anti-Factor Xa activity with andexanet alfa was 94.4%, while patients treated with usual care saw a 23.5% reduction (*P* < .0001)"

"The median reduction in anti-Factor Xa activity with andexanet alfa was 94.4%, while patients treated with usual care saw a 23.5% reduction (*P* < .0001)"

**Results for Safety Endpoints:**

No statistically significant difference in mortality

"Regarding safety, 10.3% of patients (n = 27) experienced at least 1 thrombotic event (TE) following treatment with andexanet alfa vs 5.6% (n = 15) in the usual care group. The increase in TE incidence with andexanet alfa was 4.6 per 100 patients (*P* = .048)."

Data presented during a plenary session at the 15th World Stroke Congress (WSC) held in Toronto, Canada, from October 10-12, 2023

Study not yet published in peer-reviewed journal

ANNEXA-I: Andexanet Alfa Shows Efficacy, Safety for Factor Xa Reversal in Acute ICH (ajmc.com)

# Andexanet-alfa vs. PCC

ANDEXANET-ALFA

Pros

-Clear, FDA approved dosing
-Superior hemostatic efficacy?
-Improved inpatient mortality?

Cons

-Difficult to prepare and administer
-$$
-Increased thrombotic risk?

PCC

Pros

-Easier preparation and administration
-Fixed-dosing option
-Cheaper
-Less thrombosis?

Cons

-Most data available is retrospective
-Dosing varies widely
-Inferior hemostatic efficacy?

# Guidelines Recommendations on Reversal

Neurocritical Care 2016 Guideline for Reversal of Antithrombotics in Intracranial Hemorrhage

*Recommends 4 factor PCC or aPCC (Note: These guidelines were written PRIOR to approval of andexanet-alfa)*

2019 Anticoagulation Forum Reversal of DOAC Guidance Document

*If reversal is warranted for rivaroxaban or apixaban reversal, we suggest treatment with andexanet-alfa dosed according to the US FDA label. If unavailable, we suggest treatment with 4-Factor PCC 2000 units*

2019 European Stroke Organization on Reversal of Oral Anticoagulant in Acute Intracerebral Hemorrhage

*We recommend using andexanet-alfa, if available for ICH with rivaroxaban or apixaban. When specific reversal agents are not available, we recommend considering the use of 4-Factor PCC (37.5 – 50 units/kg) to normalize coagulation tests*

*Am J Hematol*. 2019; 94(6): 697-709.
*European Stroke* Journal. 2019; 4(4): 294-306.
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# Guidelines Recommendations on Reversal

AHA/ASA 2022 Guideline for Spontaneous Intracerebral Hemorrhage (ICH)

*In patients with Factor Xa-associated spontaneous ICH:*

*-Andexanet-alfa is reasonable to reverse the anticoagulant effect of factor Xa*

*-4Factor PCC or aPCC may be considered to improve hemostasis*

2022 American College of Gastroenterology-Canadian Association of Gastroenterology Clinical Practice Guideline for Acute Gastrointestinal Bleeding and the Periendoscopic Period

*Suggest AGAINST use of both andexanet-alfa and PCC*

*Am J Gastroenterol*. 2022; 117(4): 542-558.
*Stroke*. 2022; 53:e282-e361.

# Bottom Line: Still **NO** consensus on Factor Xa Reversal

# Any Questions?

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