Emergent Reversal of Anticoagulation in the ED and ICU Settings

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Disclosures

- None

Objectives

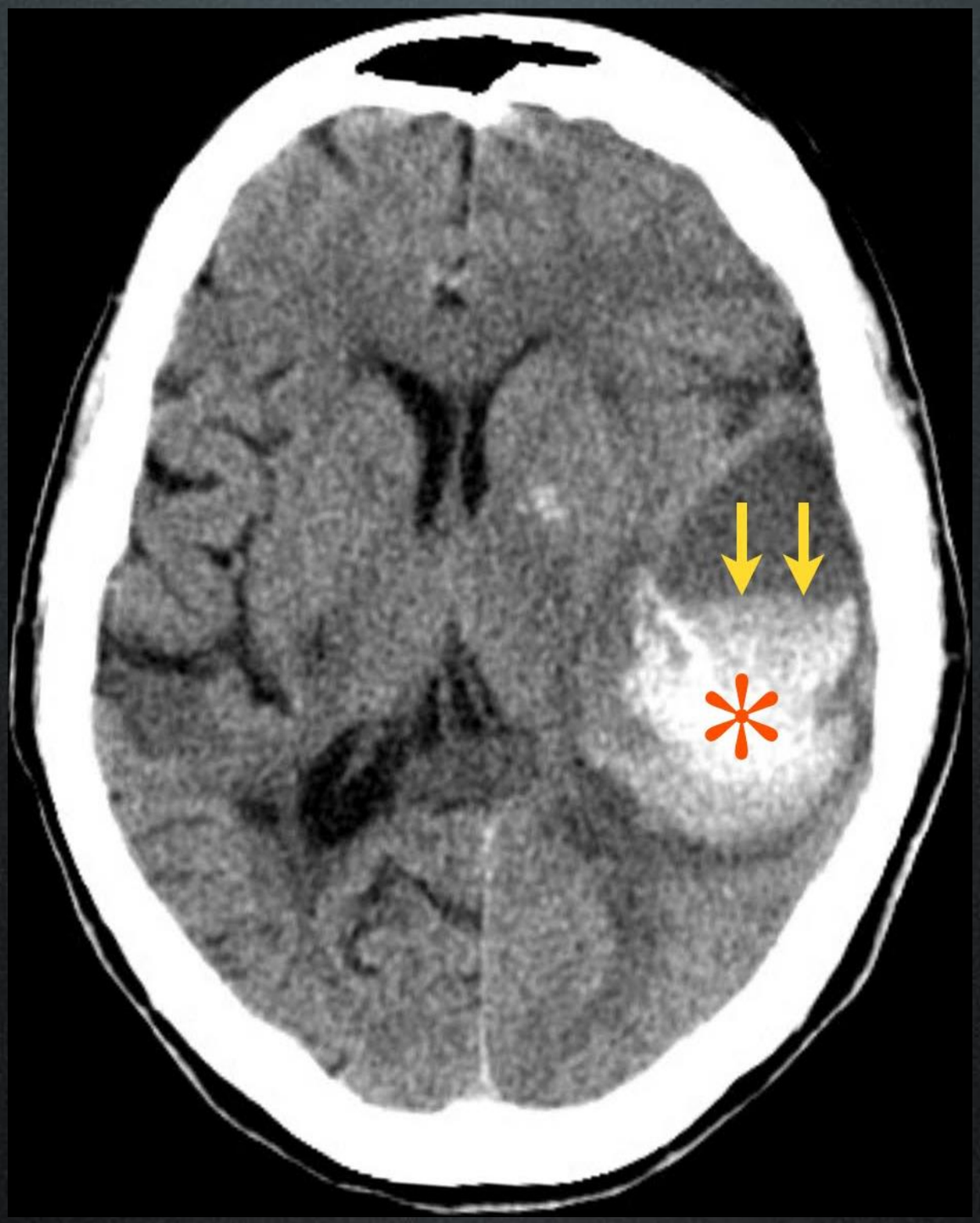
- Review coagulation cascade, common parenteral and oral anticoagulants
- Discuss reversal agents and strategies for emergent reversal of anticoagulation
- Consider laboratory monitoring and potential reversal agents of new oral anticoagulants
- Discuss anticoagulant and reversal drugs in development

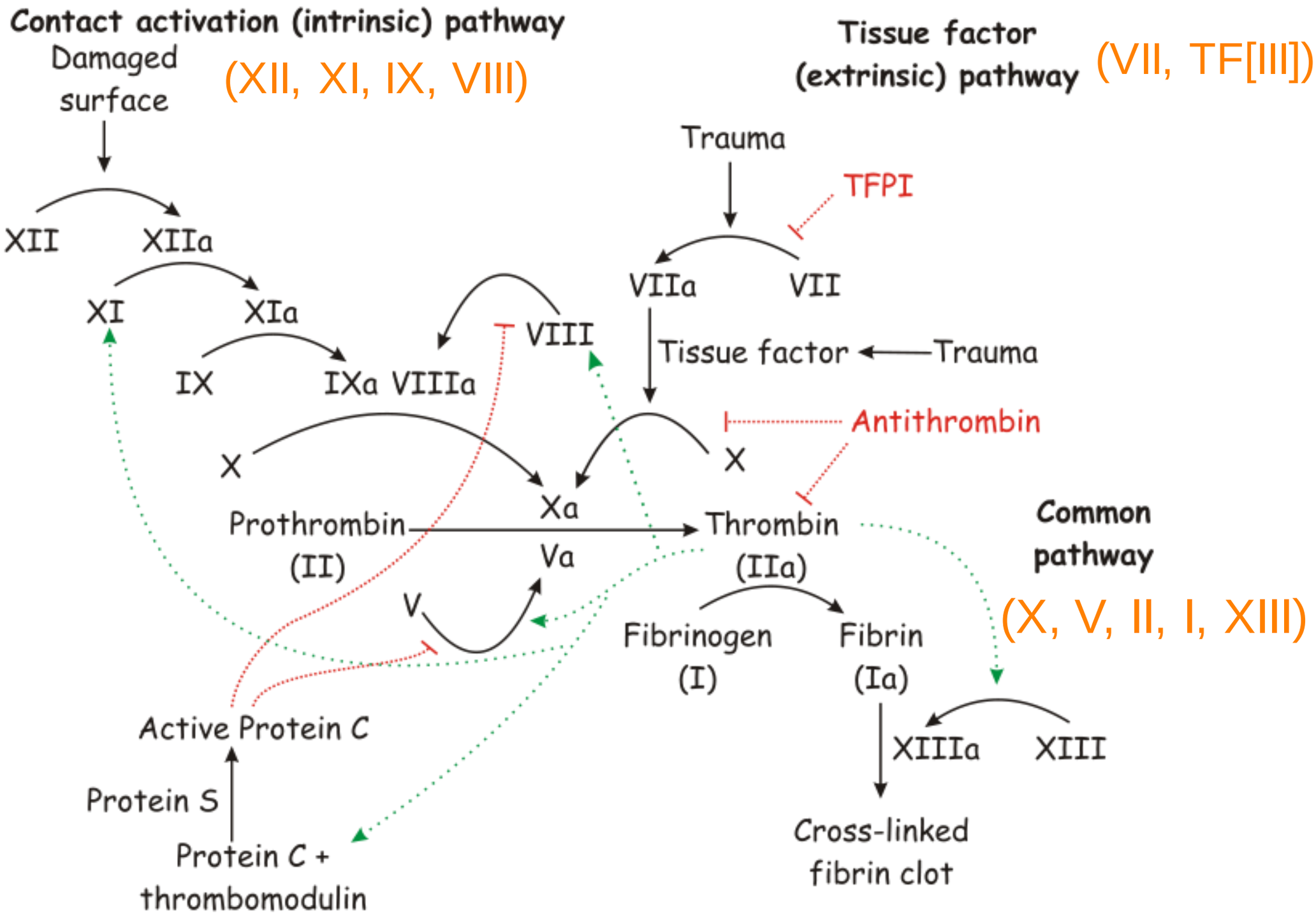
Warfarin (coagulopathy)-related ICH

- 30-day mortality up to 67% (without coagulopathy, 35-52%)
- tend to be larger than non-warfarin-related ICH
- increased risk of expansion: 50% (vs. 30%)
- mean ICH expansion in warfarin-associated 21hrs (up to 7 days) vs. 8-24 hrs

Neurology 2008;71:1084.
Neurology 2004;63:1059.

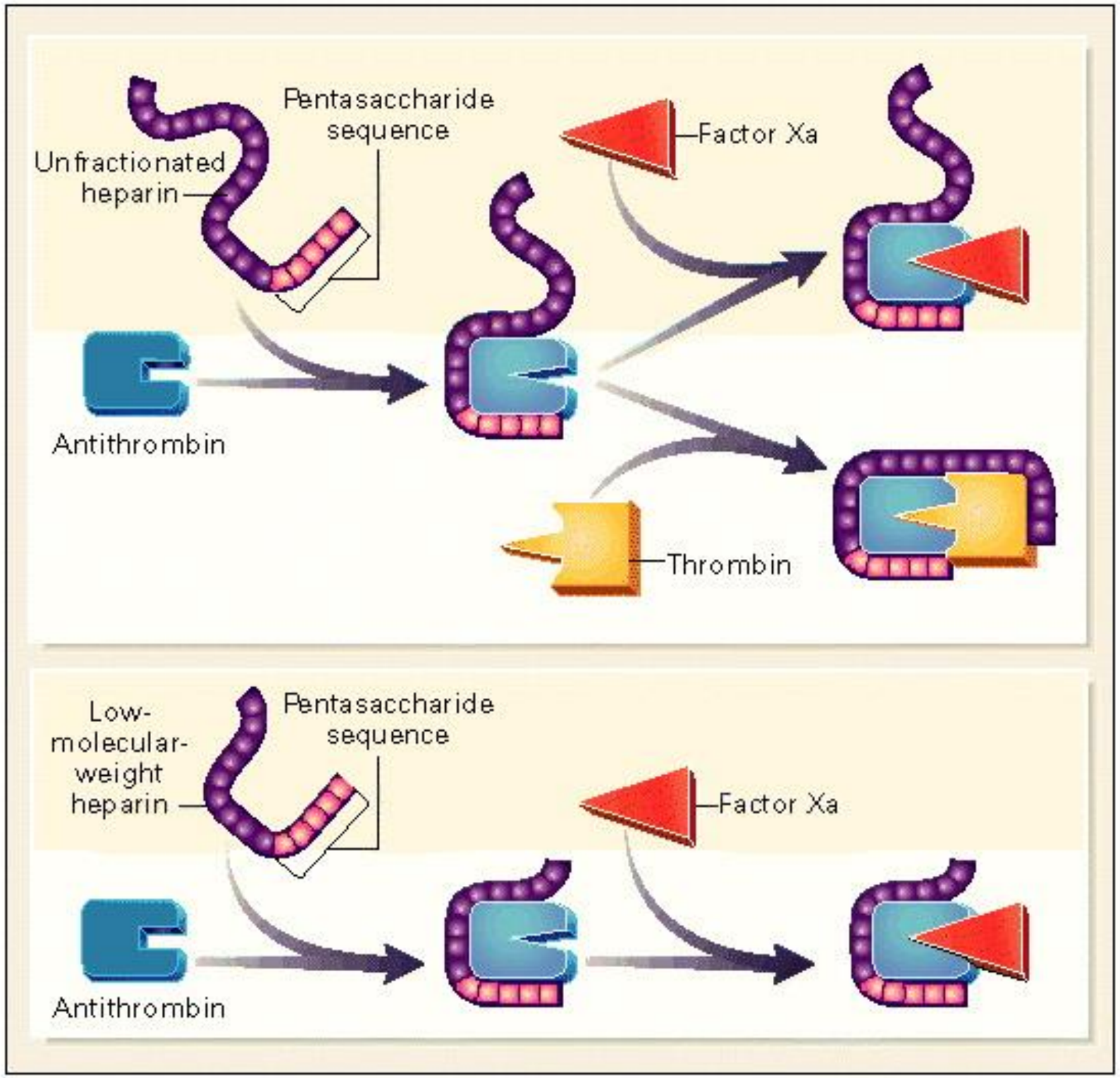
Coagulopathy-related ICH




Contact activation (intrinsic) pathway
Damaged surface
(XII, XI, IX, VIII)
Tissue factor (extrinsic) pathway
(VII, TF[III])
Trauma
TFPI
XII
XIIa
XI
XIa
IX
IXa
VIIIa
VIII
VIIa
VII
Tissue factor
Trauma
Antithrombin
X
X
Xa
Prothrombin (II)
Thrombin (IIa)
Va
V
Common pathway
(X, V, II, I, XIII)
Fibrinogen (I)
Fibrin (Ia)
XIIIa
XIII
Cross-linked fibrin clot
Active Protein C
Protein S
Protein C + thrombomodulin

Common Parenteral Anticoagulants

- Indirect FXa inhibitors
  - Unfractionated heparin
  - LMWH
    - enoxaparin (Lovenox)
    - dalteparin (Fragmin)
    - tinzaparin (Innohep)
- Pentasaccharides
  - Fundaparinux (Arixtra)



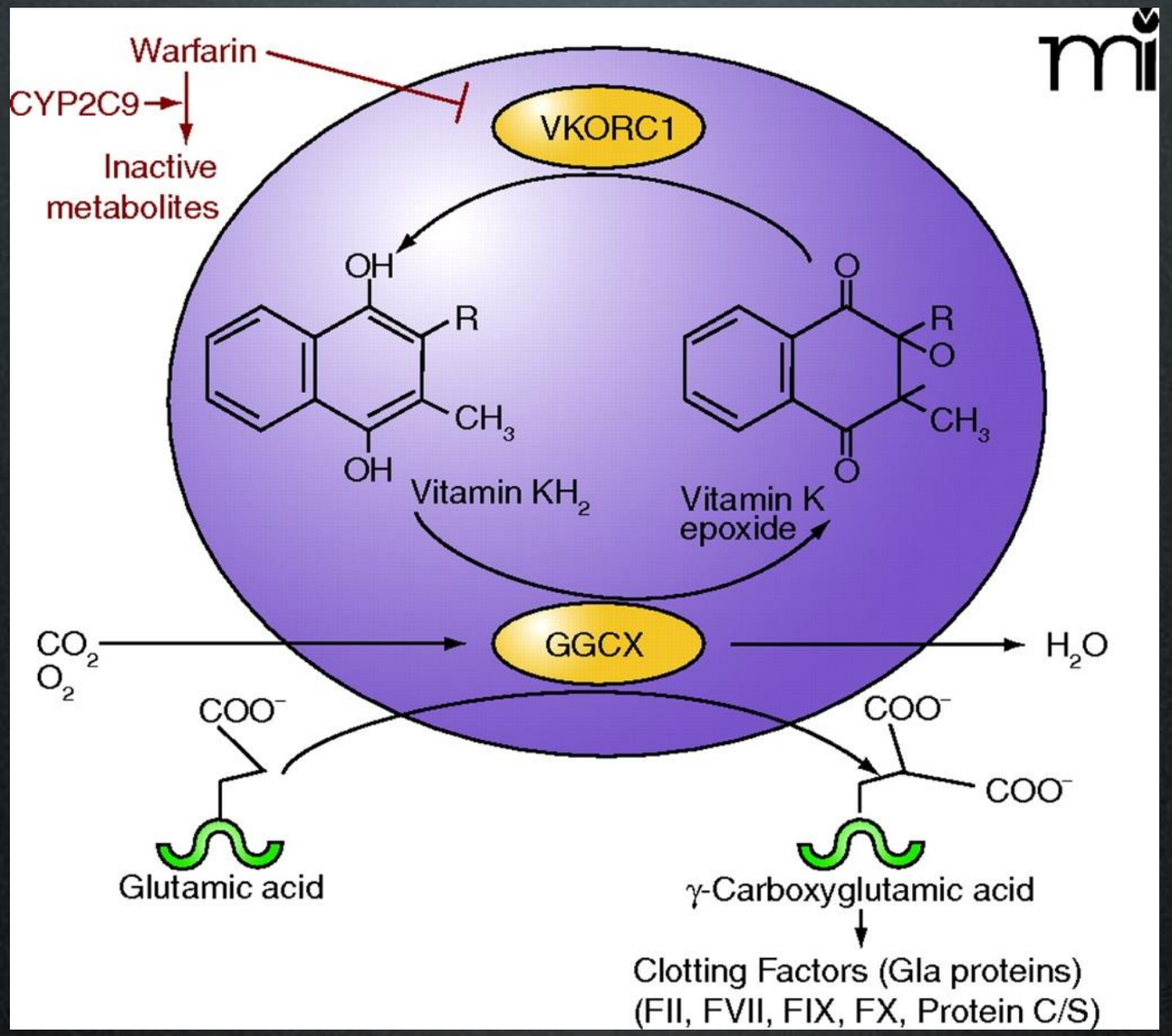
NEJM 1997;337:688-699.

Oral Anticoagulants

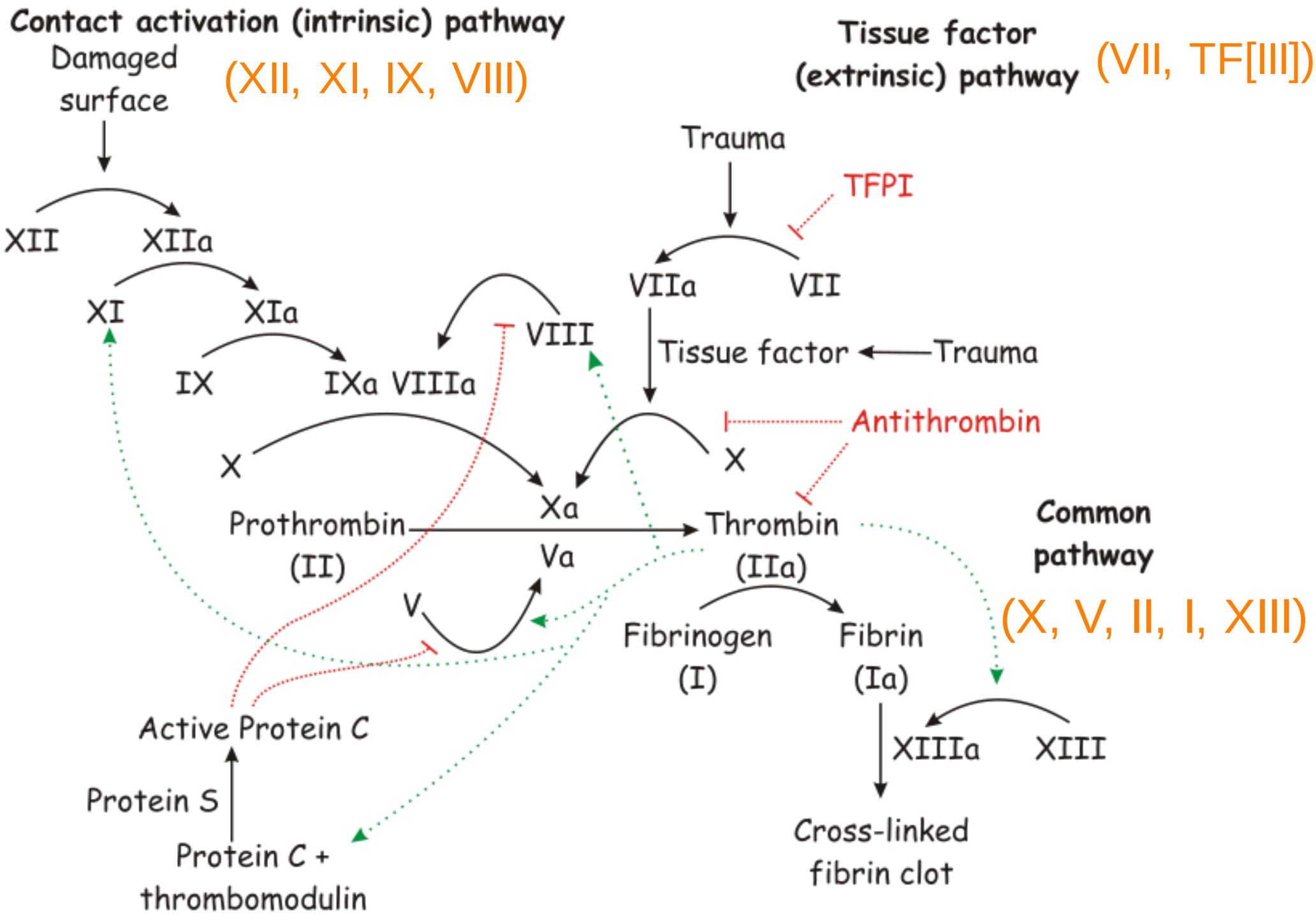
- Warfarin (Coumadin, Jantoven)
- Direct Thrombin Inhibitors
  - Dabigatran (Pradaxa)
- Direct FXa Inhibitors
  - Rivaroxaban (Xarelto)
  - Apixaban (Eliquis)
  - Edoxaban (Savaysa)
  - In development: Betrixaban, Letaxaban, Darexaban, Erixaban

Expert Opin Investig Drugs 2013;22(11):1465-72.
Discov med 2012;13(73):445-450.

Warfarin



Molecular Interventions 2006;6(4):223.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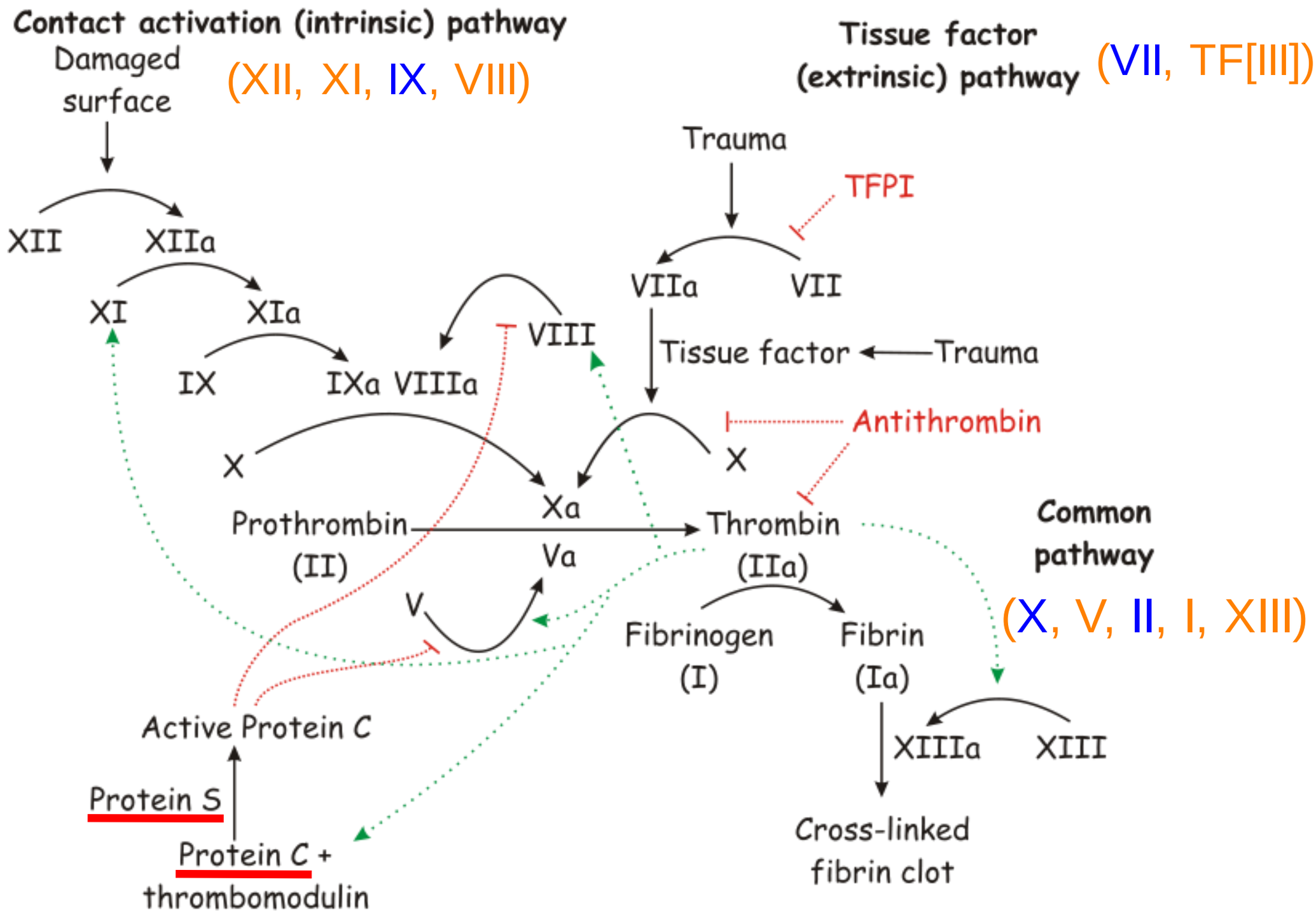
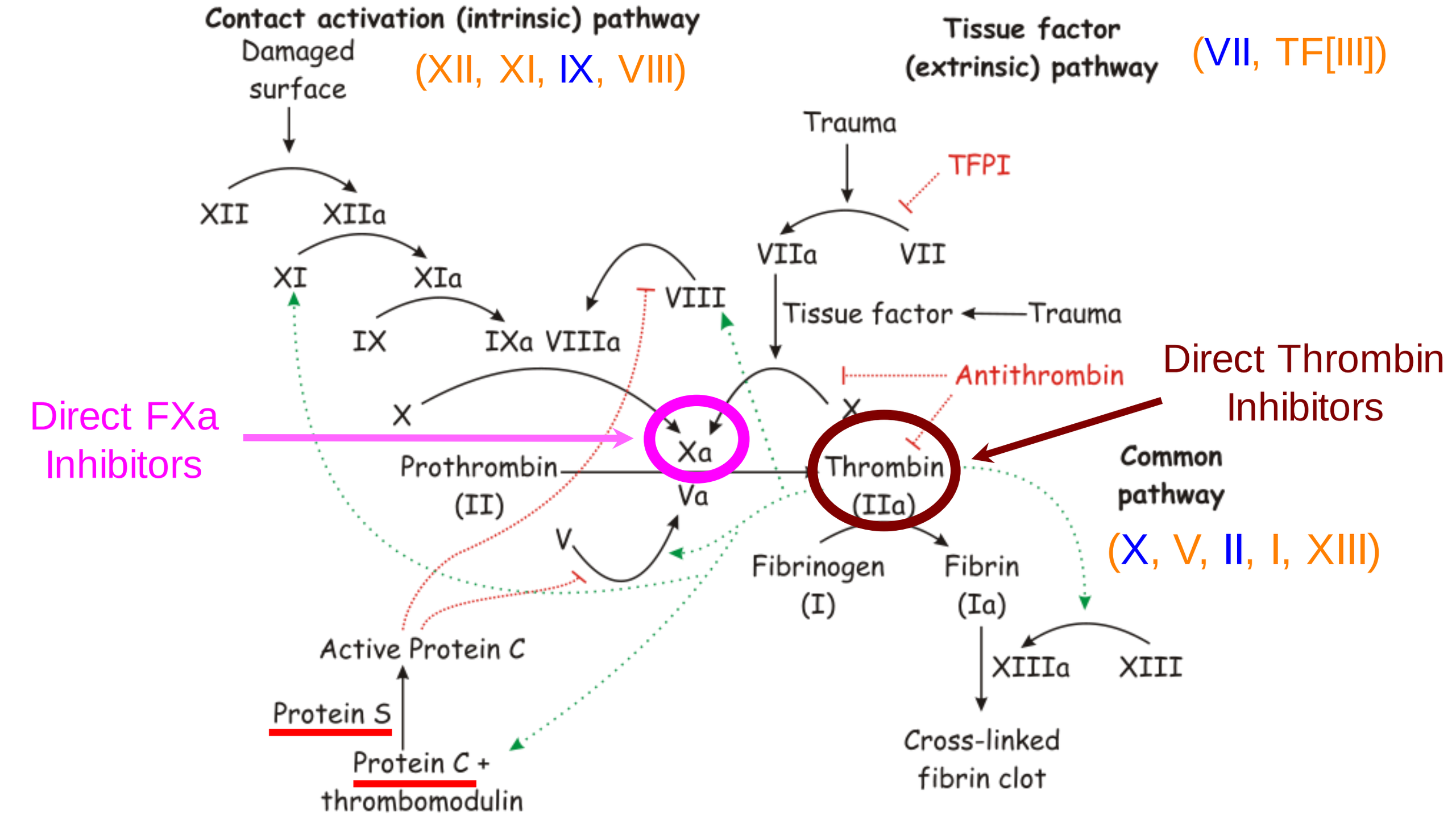


Vitamin K Dependent
(II, VII, IX, X, Protein C and S)



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Potential Reversal Agents

- Protamine sulfate
- Vitamin K
- FFP
- rFVIIa
- PCC (Prothrombin (FIX) Complex Concentrate)
- FEIBA (“activated” PCC)
- Idarucizumab (Praxbind)
- In development: Andexanet alfa, Aripazine, modified thrombin molecules

Heparin Reversal

- Protamine sulfate
  - Adjust for time elapsed since last dose:
    - < 30 min → 1 mg/100 U
    - 30-120 min → 0.5 mg/100 U
    - > 120 min → 0.25 mg/100 U
- continuous infusion: 1mg/100U heparin given in previous 2-3 hours
- max rate 5mg/min, max dose 50mg (hypotension, bradycardia)

2011 Clinical Practice Guide on Anticoagulant Dosing and Management of Anticoagulant-Associated Bleeding Complications in Adults.

LMWH (Enoxaparin) Reversal

- Protamine sulfate (30-60% reversal)
- 1mg/100 U, adjust for time elapsed since last dose:
  - < 8 hr → 1 mg/100 U
  - > 8 hr → 0.5 mg/100 U
  - max rate 5mg/min, max dose 50mg (hypotension, bradycardia)

Lovenox (enoxaparin sodum injection) [prescribing information]. 2013 Oct.
Thromb Haemost 2015;113:931.

Fondaparinux Reversal

- Fondaparinux
- no reversal agent
- protamine ineffective
- may consider FEIBA/aPCC (20 U/kg)

Neurocrit Care 2016;24:6.

Warfarin Reversal

- Vitamin K
  - 10 mg IV (4-24hrs for reversal)
    - PO/SC (~24 hrs)
      - slow, but important for sustained correction of coagulopathy
      - risk of anaphylactoid reaction (slow IV, 1mg/min)
      - do not give alone

Warfarin Reversal

- FFP
  - 15-20 mL/kg (30 mL/kg)
  - 1 unit ~250mL
  - large volume, long infusion time (3-6 hrs), transfusion reactions, variability of clotting factors
  - normalization of INR takes ~30 hrs

Calculating FFP or PCC Dose to Target INR

	INR	Approximate %
Overanticoagulation	>5	5
	4.0-4.9	10
Therapeutic Range	2.6-3.2	15
	2.2-2.5	20
Subtherapeutic Range	1.9-2.1	25
	1.7-1.8	30
	1.4-1.6	40
Complete reversal to normal	1.0	100

[Target level (%) - Current level (%)] x Weight (kg) = mL FFP or IU of PCC

NEJM 2003;349:675.

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Ex: Target level 1.4, Current level 3.0, weight 75 kg

NEJM 2003;349:675.

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Complete reversal to normal	1.0	100

[Target level (%) - Current level (%)] x Weight (kg) = mL FFP or IU of PCC

Ex: Target level 1.4, Current level 3.0, weight 75 kg

(40-15) x 75 = 1875 mL FFP or 1875 IU PCC (~150mL)

NEJM 2003;349:675.

4 Factor PCC

- Kcentra (Beriplex in Europe)
  - FII 380-800 U
  - FVII 200-500 U
  - FIX 400-620 U
  - FX 500-1020 U
  - Protein C 420-820 U
  - Protein S 240-680 U
  - small amount of heparin, human albumin, antithrombin III

Kcentra (Prothrombin Complex Concentrate) [prescribing information]. 2013 Dec.

4 Factor PCC

- Kcentra
  - currently the only 4 PCC available in US
  - approved for urgent reversal of Vit K antagonist (warfarin) in acute major bleeding
  - thromboembolic events ~5-9% (vs. ~4-6% for FFP)
  - reversal can be achieved in 10-30 min

Kcentra (Prothrombin Complex Concentrate) [prescribing information]. 2013 Dec.

4 Factor PCC

- Kcentra Dosing:
  - INR 2-4, 25 IU/kg (max 2500 IU)
  - INR 4-6, 35 IU/kg (max 3500 IU)
  - INR > 6, 50 IU/kg (max 5000 IU)

Kcentra (Prothrombin Complex Concentrate) [prescribing information]. 2013 Dec.

“activated” PCC

- FEIBA (Factor Eight (VIII) Inhibitor Bypassing Activity)
  - FVII (mainly activated) + FII, IX, X (non-activated)
  - 500 U, 1000 U, 2500 U (50-100 U/kg)
  - approved for use in hemophilia A or B patients with inhibitors (control of bleeding, perioperative, routine prophylaxis)

FEIBA [prescribing information]. 2013 Nov.

“activated” PCC

- FEIBA (Factor Eight (VIII) Inhibitor Bypassing Activity)
  - limited off-label experience for Warfarin reversal
    - compared w FFP, faster INR correction, goal INR 50% vs. 33%
    - thromboembolic events 7%
  - animal models - lower dose probably just as effective as higher dose

P&T 2013;38(11):696-701.
Int J Emerg Med 2009;2:217-25.

Warfarin-Reversal

- rFVIIa
  - onset in minutes
  - half-life only 2.6 hrs
  - thromboembolism, expensive
  - improves INR reversal and decreases FFP requirements (as ADJUNCT to Vit K + FFP)
    - alone, not adequate for warfarin reversal
  - ? dose

Neurocrit Care 2005;2:263-7.

Warfarin Reversal

- rFVIIa
  - INR reversal w/o adequate hemostasis?
  - animal studies suggest despite INR normalization, bleeding time and thrombin generation not as good as with PCC (four factor repletion)
- alone, NOT recommended for Warfarin reversal

Ann Intern Med 2003;139:791.
Thromb Res 2007;119:643-51.

Potential Thrombotic Events

(rFVIIa and PCC)

- Arterial thromboembolic events:
  - MI, stroke, retinal artery thrombosis, limb/bowel infarct
- Caution: DIC, advanced atherosclerotic disease, crush injury, septicemia, concomitant use of rFVIIa and PCC (circulating TF or predisposing coagulopathy)

Potential Thrombotic Events

(rFVIIa and PCC)

- Possible RF:
  - multiple dosing
  - high dose
  - immobility s/p orthopedic procedures
  - hepatic disease
  - severe vascular disease

British J Haematology 2002;116:619-24.
Blood Reviews 1998;12:35-44.

Proposed Protocol: Warfarin Reversal

- Vitamin K 10mg IV>PO>SC daily x 3 days

+

- 4-Factor PCC (Kcentra) based on INR:
  - 2-4 → 25 IU/kg (max 2500)
  - 4-6 → 35 IU/kg (max 3500)
  - > 6 → 50 IU/kg (max 5000)
- Alternative to PCC: FEIBA
  - INR < 5 → 500 Units
  - INR > 5 → 1000 Units
  - (alternatively 50 U/kg)
- Recheck INR in 10-30-min, give additional FFP if adequate reversal not achieved

Dabigatran Reversal

- Idarucizumab (Praxbind)
  - monoclonal antibody fragment
  - binds to thrombin binding site of dabigatran (free and thrombin-bound)
  - 5g IV (two 50mL bolus infusions)
  - mild adverse affects (headache, erythema)
  - reversal (dTT, ECT, aPTT, TT) within minutes, sustained at least 24hrs
  - ? hemostatsis - 11h

NEJM 2015;373:511-520.
Neurocrit Care 2016;24:6.

Emergent Reversal

- Direct Thrombin Inhibitors (Dabigatran)
  - Idarucizumab (Praxbind)
  - maintain diuresis (80% renal elimination)
  - lipophilic - if ingestion within 1-2 h, give activated charcoal PO
  - consider hemodialysis (4hrs, removal of 48% at 200mL/min, 60% at 400mL/min)
  - consider FEIBA (50 U/kg), PCC

Thromb Haemost 2010;103: 1116-27.
Thromb Haemost 2012;108(4):625-32.

Emergent Reversal

- Direct FXa Inhibitors
  - Rivaroxaban
    - if within 8h ingestion, give activated charcoal
    - maintain adequate diuresis (66% renal elimination)
  - Apixaban
    - if within 4h ingestion, give activated charcoal

Am J Health-Syst Pharm 2012;69:e28-39.

Emergent Reversal

- NOACs
  - overall, limited to animal studies, healthy volunteers
  - FFP, FVIIa don’t appear to be effective
  - PCC, aPCC show possible promise, probably reasonable to consider in emergent situations

Clin Cardiol 2012;35(12):730-7.

Monitoring Adequate Reversal

- PT, INR for Warfarin
- aPTT for Heparin
- anti-FXa level for LMWH (renal failure, obese, long-term anticoagulation)
- But what about the new oral anticoagulants?
  - Dabigatran
  - Rivaroxaban
  - Apixaban
  - Edoxaban

Coagulation Studies

- Novel Oral Anticoagulants (NOACs)
  - Assays demonstrate high variability in sensitivity to the new oral anticoagulants, depending on what reagent is used
  - Thus no standardization from lab to lab

Coagulation Studies

- Direct Thrombin Inhibitors (Dabigatran)
  - PT/INR - little effect
  - aPTT
    - relatively insensitive but still may provide qualitative indication of anticoagulant activity
    - prolonged aPTT = presence of activity (does not quantify how much)
    - normal aPTT = no pharmacologically relevant anticoagulant activity

Thromb Haemost 2010;103:1116-27.

Coagulation Studies

- Direct Thrombin Inhibitors (Dabigatran)
  - ECT (ecarin clotting time)
    - specific assay for thrombin generation
    - direct measure of direct thrombin inhibitor activity
    - not readily available everywhere, reagents in different labs not standardized
  - Others: dilute thrombin time (dTT), ecarin chromogenic assay

Thromb Haemost 2010;103:1116-27.
Arterioscler Thromb Vasc Biol 2015;35:1736.

Coagulation Studies

- Direct Thrombin Inhibitors (Dabigatran)
  - TT, TCT (thrombin clotting time)
    - extremely sensitive
    - prolonged TT = presence of drug
    - normal TT = no pharmacologically relevant anticoagulant activity
    - Hemoclot Thrombin Inhibitor assay (Hyphen BioMed) - research only in US

Thromb Haemost 2010;103:1116-27.

Coagulation Studies

- Direct Thrombin Inhibitors (Dabigatran)
  - By decreasing sensitivity:
    - TT > ECT > aPTT
  - in animal models, even when clinical bleeding reduced, no changes in above lab values noted

Thromb Haemost 2010;103:1116-27.
Circulation 2011;123:1436-50

Coagulation Studies

- Direct FXa Inhibitors (Rivaroxaban, Apixaban)
  - prolong PT > aPTT
    - varying response depending on reagent
      - INR cannot be applied
  - no effect on TT
  - modified chromogenic anti-Xa assays can be used, but must use reagents standardized to specific drug

Hematology Am Soc Hematol Educ Program 2012;: 460-5.
Am J Health-Syst Pharm 2012;69:e28-39.

Reversal Agents in Development

- Andexanet alfa
  - modified, recombinant FXa
  - binds to and inactivates FXa inhibitors and antithrombin activated by heparin/LMWH/fondaparinux, oral direct FXa inh
- 400mg IV bolus, 4mg/min continuous infusion

Arterioscler Thromb Vasc Biol 2015;35:1736-1745..

Reversal Agents in Development

- Aripazine
  - small molecule
  - binds to and inhibits heparin, LMWH, fondaparinux, direct FXa inhibitors, direct thrombin inhibitor
  - may require different doses for reversal of Apixaban and Rivaroxaban
  - unclear mechanism of action

Thromb Haemost 2015;113:931-942.

Summary

- Warfarin-related ICH is associated with high morbidity and mortality rates
- Rapid reversal of coagulopathy is crucial in preventing hematoma expansion
- High quality trials lacking in comparing various modalities, and demonstrating improvement in outcome

Summary

- Vitamin K should be given with one of the following, for emergent Warfarin reversal:
  - FFP (widely available but slow, unpredictable, large volume)
  - 4-Factor PCC (rapid, physiologic correction, thrombotic events)
  - FEIBA/aPCC (off-label, rapid, limited experience)

Summary

- NOACs - even less evidence for effective reversal strategy, but more to come..
  - Dabigatran - Idarucizumab, support diuresis, consider HD, activated charcoal within 1-2h ingestion
  - Rivaroxaban - support diuresis, activated charcoal within 8h ingestion
  - Apixaban - activated charcoal within 4h ingestion
  - in all, consider PCC, FEIBA/aPCC - FFP and rFVIIa probably not as effective

Summary

- NOACs - but more to come..
  - Future directions:
    - Andexanet alpha (direct FXa inh, LMWH, Fondaparinux)
    - Aripazine (heparin, LMWH, Dabigatran, direct FXa inh)


Wake Up!
Break Time
COFFEE
TEA