Agents Affecting Hemostasis: An Overview

A Companion to the Required Textbook Chapter:
"Pharmacologic Management of Patients with Drug-Related Coagulopathies"
CONTEMPORARY DENTAL PHARMACOLOGY
Evidence-Based Considerations
(A.H. Jeske, Ed., 2019)

PHC 721

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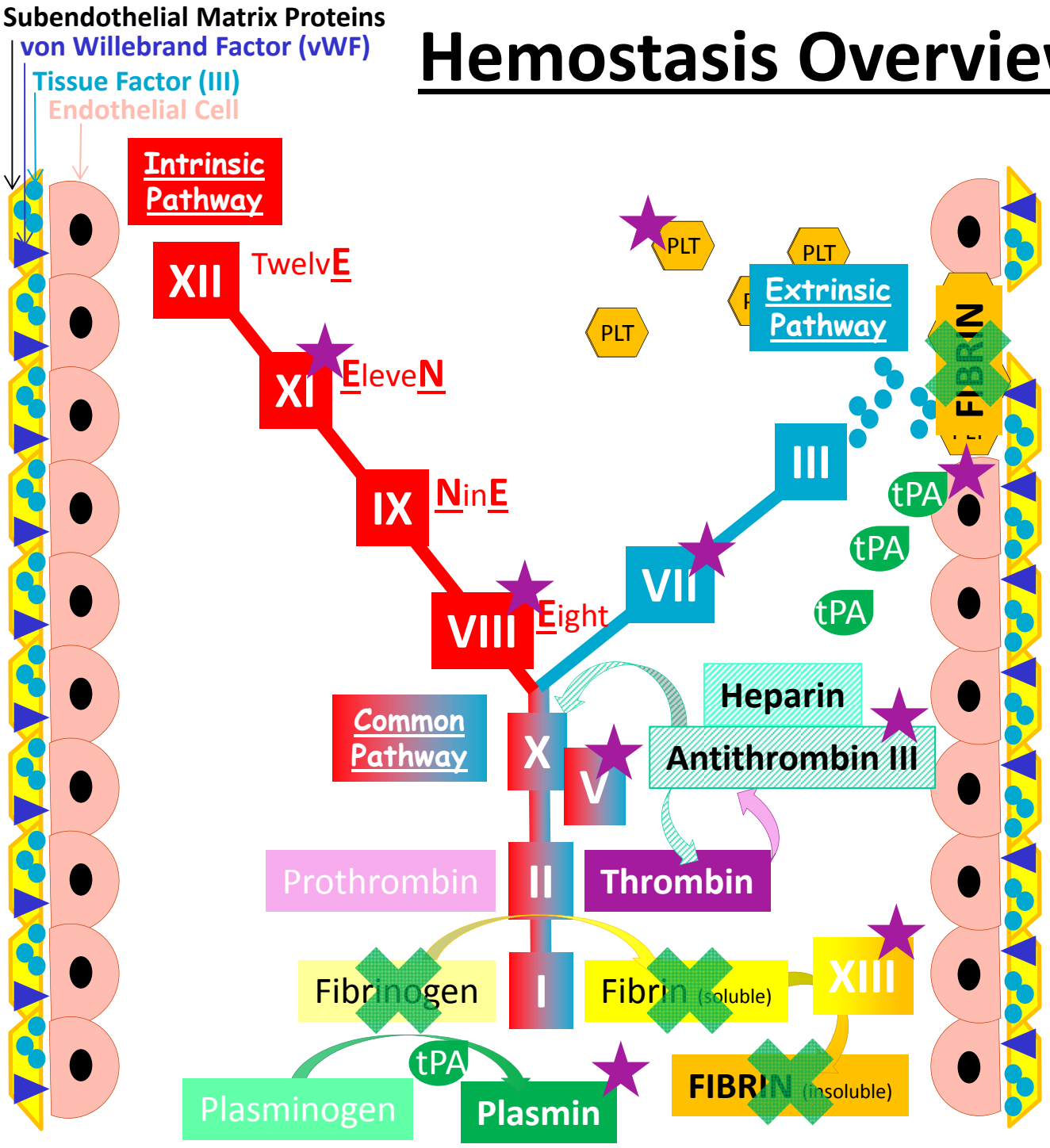
Hemostasis Overview



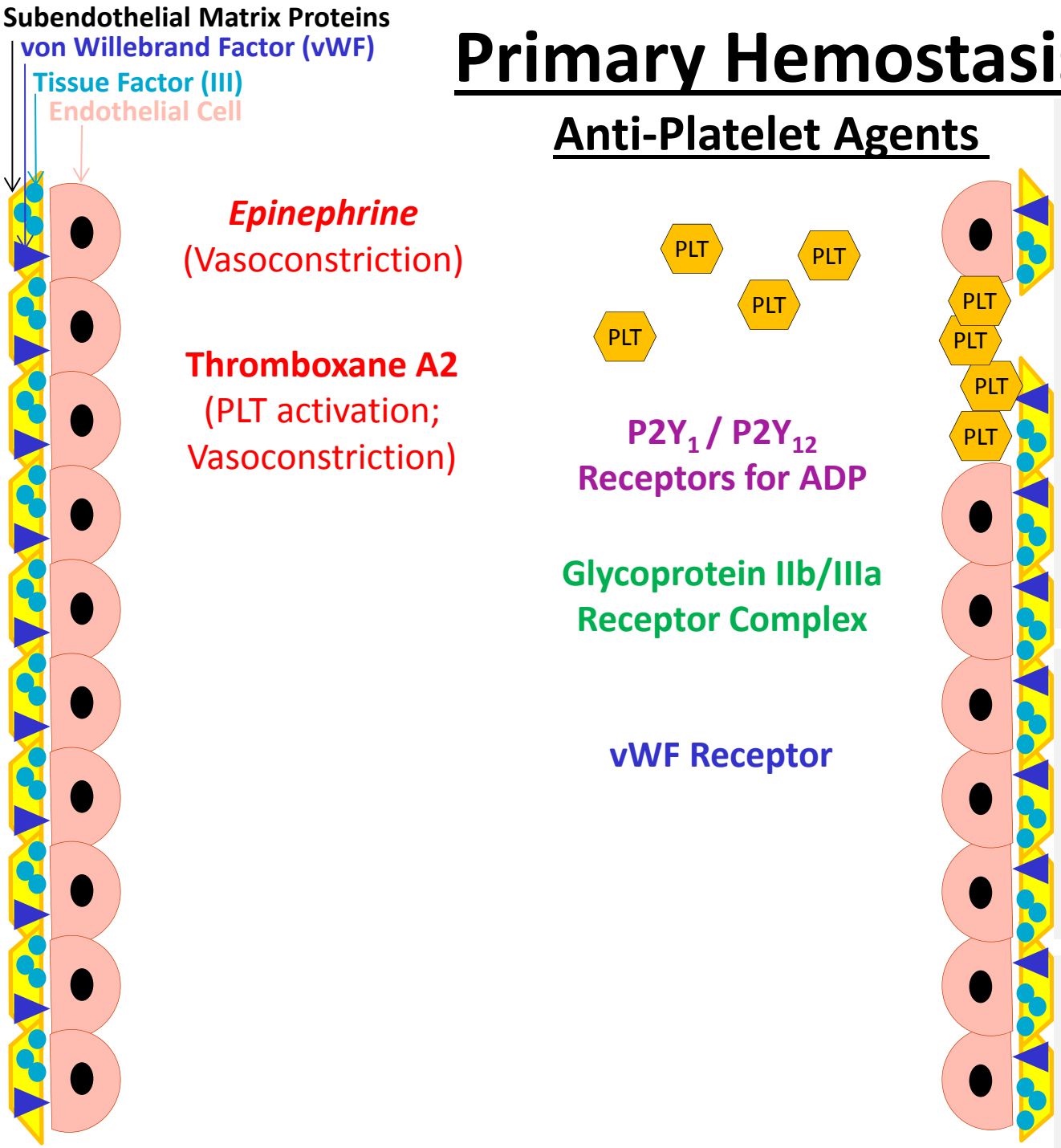
I. Vasoconstriction
↓ NO/Prostacyclin secretion

II. Primary Hemostasis
- Platelet (PLT)
  - Adhesion
  - Activation (ADP, TXA_2)
  - Aggregation (GP IIb/IIIa, P2Y)
- von Willebrand Factor

III. Secondary Hemostasis
Coagulation Cascade
- Extrinsic Pathway (Initiator):
  - *Tissue Injury / Inflammation*
  - *Tissue Factor III*
- Intrinsic Pathway (Propagator):
  - *Platelet-derived factors*
  - *Subendothelial Collagen*
  - *Bacterial Endotoxins/LPS*

IV. Fibrinolysis
- Tissue Plasminogen Activator (tPA)
- Plasmin

Primary Hemostasis



Anti-Platelet Agents

Anti-Platelet Therapy

Indications:

↑ Risk of Thrombosis
- Virchow's Triad

Drugs:

- ***COX inhibitors*** *(Aspirin, Ibuprofen & related drugs)*
- ***ADP Receptor Inhibitors*** *(Clopidogrel)*
- ***GP IIb/IIIa Inhibitors*** *(Abciximab, Eptifibatide)*

von Willebrand Disease

-vWF deficient or defective:
- Factor VIII stabilization
- PLT adhesion
- PLT aggregation (GP IIb/IIIa)

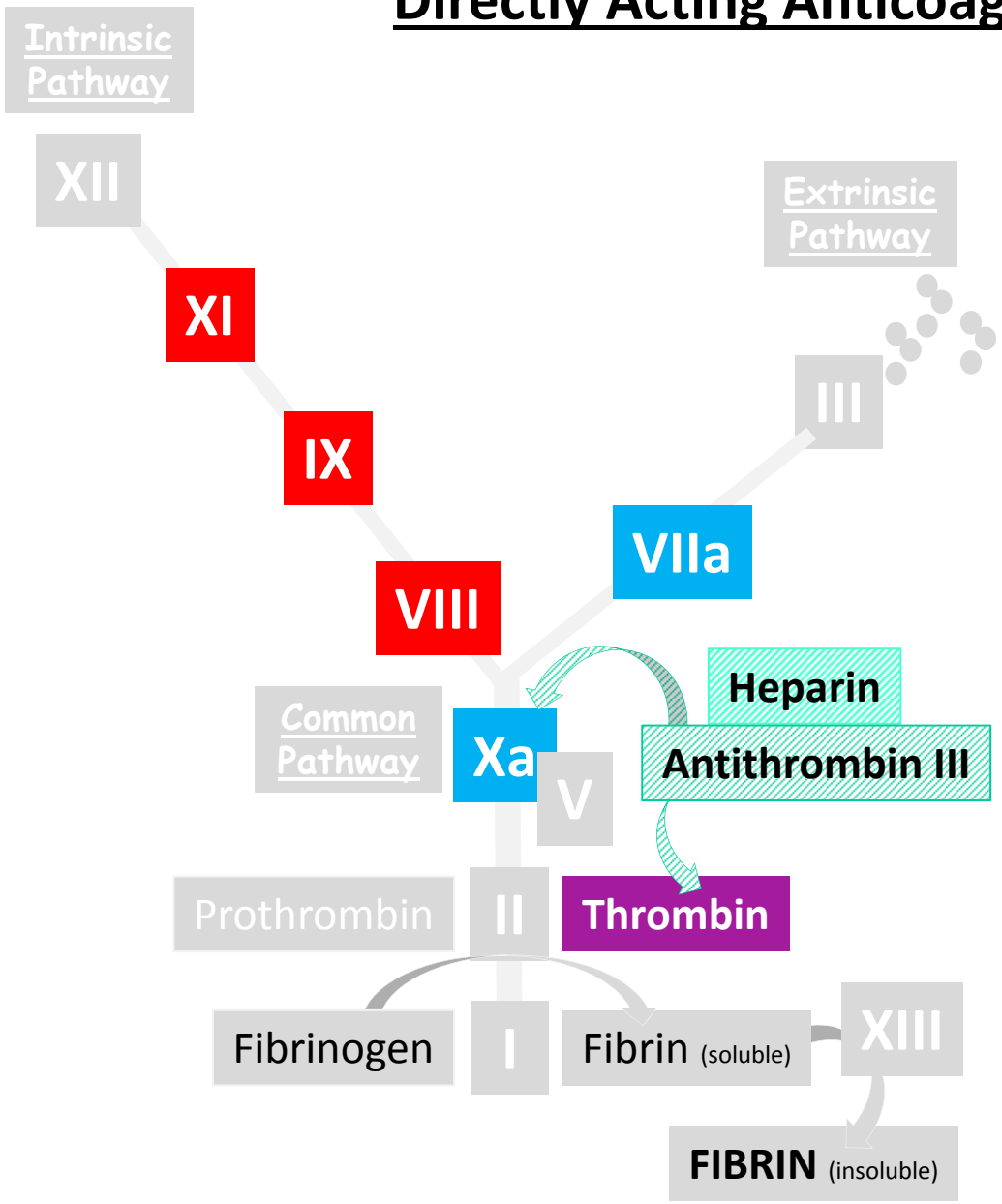
-Factor VIII/vWF replacement

Thrombocytopenia – causes:

- Liver Cirrhosis / Alcoholism
- Myelogenous diseases, HIV
- Drug-Induced

Secondary Hemostasis

Directly Acting Anticoagulants



Genetic Disorders:

- Hemophilia A (VIII), B (IX), C (XI)
- von Willebrand Disease

Treatment:

Factor Replacement Products; Desmopressin; Factor VIIa

Directly Acting Anticoagulants

- ***Heparins*** *(↓Thrombin & ↓Factor Xa)*
- ***Low-Molecular Weight Heparins***
  (↓Factor Xa)
  Enoxaparin, Dalteparin
  Antidote: Protamine Sulfate

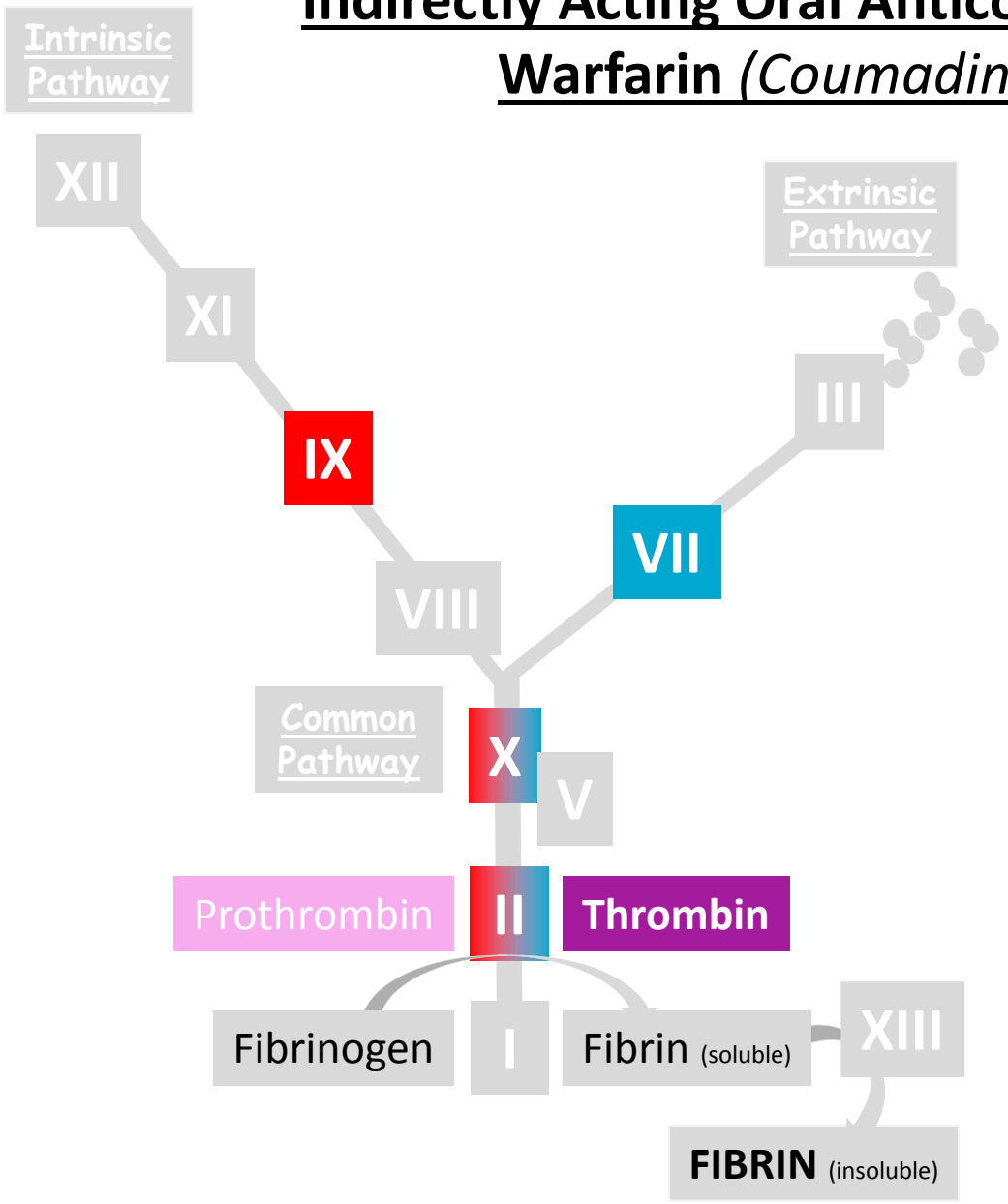
- ***Direct Oral Anticoagulants (DOAC):***
- ***Direct Thrombin Inhibitors***
  Hirudin (from leeches), Bivalirudin
  Dabigatran- Pradaxa®
  Antidote: Idarucizumab- Praxbind®

- ***Direct Factor Xa Inhibitors***
  *Rivaro**xa**ban- Xarelto®*
  *Api**xa**ban- Eliquis®*
  Antidote: Andexanet Alfa- Andexxa®

Secondary Hemostasis

Indirectly Acting Oral Anticoagulants:

Warfarin *(Coumadin®)*



- A competitive **inhibitor of Vitamin K epoxide reductase**, an enzyme restoring Vitamin K back to its active state, so it can serve as cofactor in synthesis of clotting factors (**II**, **VII**, **IX**, **X**).

Pharmacokinetic considerations:
- 99% plasma protein bound
- Vitamin K bioavailability
  - diet, antibiotic therapy, etc.
- CYP2C9-mediated metabolism

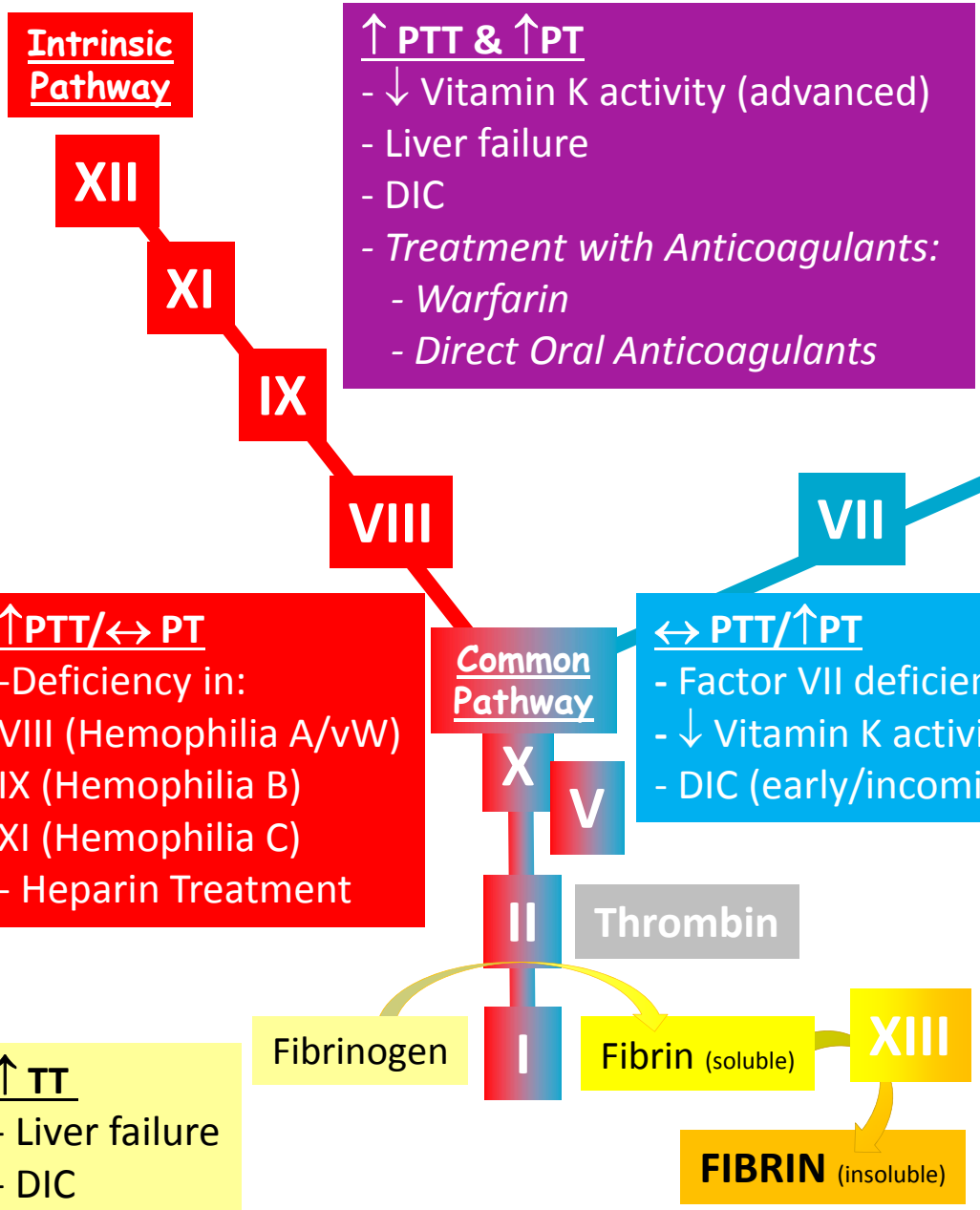
Other interactions:
- Risk of uncontrolled bleeding with anti-platelet treatment (Aspirin, Ibuprofen, Clopidogrel)

Antidote: Vitamin K

- *The most sensitive* test ⇒ **depression of Factor VII** (half-life 4-6 hrs *versus* 2-3 days for Factor II, Prothrombin).

PT / INR is the test of choice.

PT [INR] – aPTT – TT



↑ PTT & ↑PT
- ↓ Vitamin K activity (advanced)
- Liver failure
- DIC
- *Treatment with Anticoagulants:*
  - *Warfarin*
  - *Direct Oral Anticoagulants*

↑PTT/↔ PT
-Deficiency in:
VIII (Hemophilia A/vW)
IX (Hemophilia B)
XI (Hemophilia C)
- Heparin Treatment

↔ PTT/↑PT
- Factor VII deficiency
- ↓ Vitamin K activity (early)
- DIC (early/incoming)

↑ TT
- Liver failure
- DIC

The time it takes for blood clot to form after activation of…

…Extrinsic → Common Pathway

Prothrombin Time (PT)

[Citrated Plasma + Tissue Factor (III)]

International Normalized Ratio (INR):

$$\frac{PT_{\text{Anticoagulant Tx}}}{PT_{\text{Healthy Subjects}}}$$

…Intrinsic → Common Pathway

(activated) Partial Thromboplastin Time (aPTT, PTT)

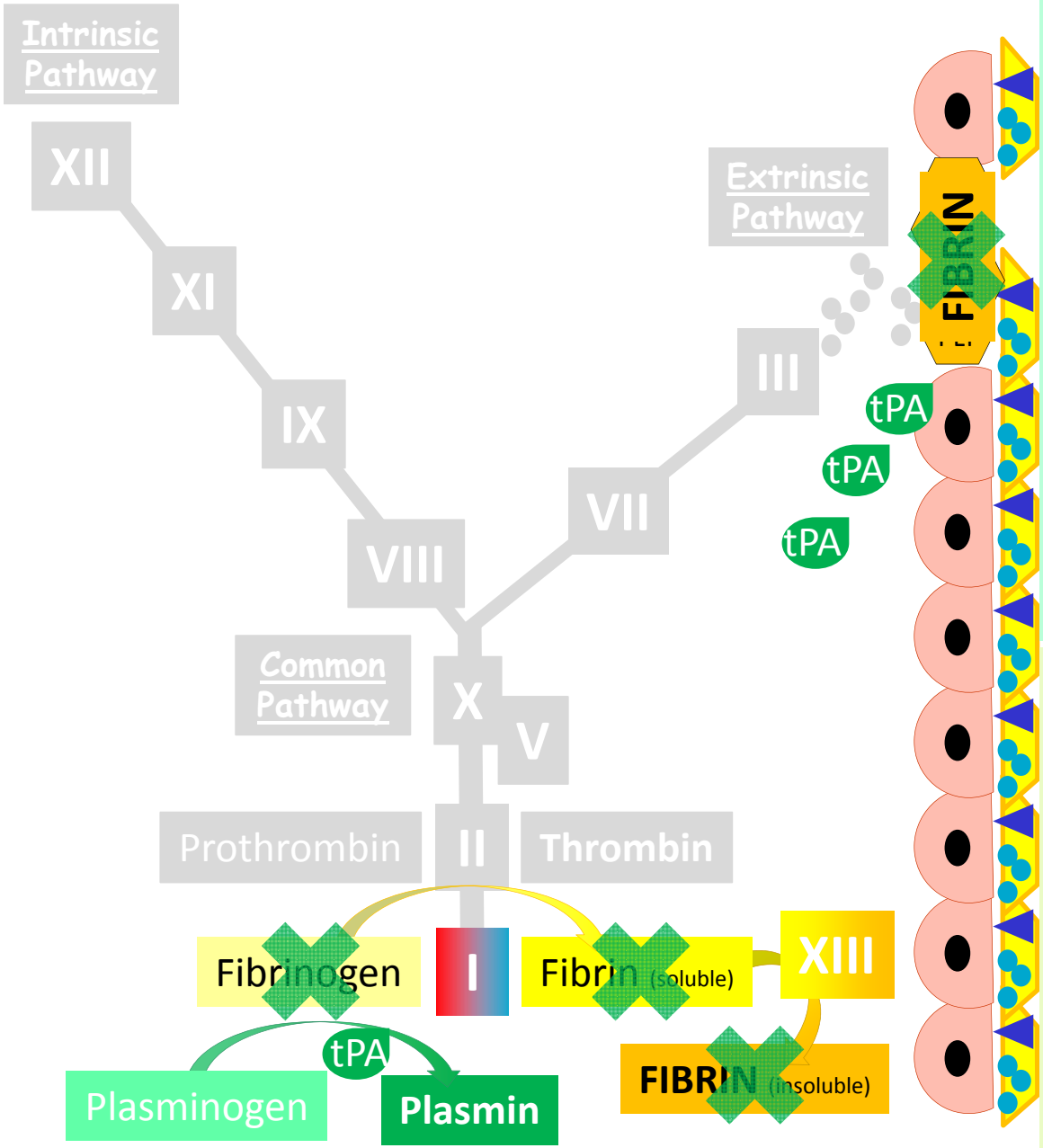
[Citrated Plasma + Activator (e.g., silica)]

Thrombin Time (TT)

Measures the amount/function of Fibrinogen

Thrombin added in excess

Fibrinolysis



Fibrinolytics

Mechanism of action:

Stimulate 'plasminogen → plasmin' conversion.

Indications: Relieving thromboses (e.g., acute myocardial infarction, pulmonary embolism, ischemic stroke, deep vein thrombosis).

Drugs:

- Recombinant tPA (Alteplase) – AHA-recommended in myocardial thrombosis;
- A mutation variant of tPA (Reteplase);
- Streptokinase (exotoxin ⇒ allergies).

Anti-fibrinolytics

Mechanism of action:

Competitive inhibition of Plasminogen and plasminogen activators from binding to Fibrin ⇒ limited fibrinolysis.

Indications: Oozing sockets after dental extractions; post-surgery in hemophilics).

Drugs:

- Aminocaproic Acid
- Tranexamic Acid (Cyklokapron, Lysteda)