Managing Anticoagulants, Antiplatelets, and NSAIDS in the Interventional Radiology Setting

Amy Huggins, BSN, RN

Objectives

1. Recognize bleeding risk based on classes of IR procedures
2. Differentiate between anticoagulants, antiplatelet agents and NSAIDS and how they work
3. Discuss monitoring parameters to evaluate the effects of “blood thinners”
4. Determine how long to hold medications prior to procedure
5. Understand reversal agents and when each would be most appropriate

Consensus Guidelines for Periprocedural Management of Coagulation Status and Hemostasis Risk in Percutaneous Image-guided Interventions

Indravadan J. Patel, MD, Jon C. Davidson, MD, Boris Nikolic, MD, MBA, Gloria M. Salazar, MD, Marc S. Schwartzberg, MD, T. Gregory Walker, MD, and Wael A. Saad, MD, for the Standards of Practice Committee, with Cardiovascular and Interventional Radiological Society of Europe (CIRSE) Endorsement

ABBREVIATIONS

aPTT = activated partial thromboplastin time, DIC = disseminated intravascular coagulation, DTI = direct thrombin inhibitor, FFP = fresh frozen plasma, INR = international normalized ratio, LMWH = low molecular weight heparin, LP = lumbar puncture, NSAID = nonsteroidal antiinflammatory drug, PT = prothrombin time

PREAMBLE

The membership of the Society of Interventional Radiology (SIR) Standards of Practice Committee represents experts in a broad spectrum of interventional procedures from both the private and academic sectors of medicine. Generally, Standards of Practice Committee members dedicate the vast majority of their professional time to performing interventional procedures; as such, they represent a valid broad expert constituency of the subject matter under consideration for standards production.

Technical documents specifying the exact consensus and literature review methodologies, as well as the institutional affiliations and professional credentials of the authors of this document, are available upon request from SIR, 3975 Fair Ridge Dr., Suite 400 N., Fairfax, VA 22033.

METHODOLOGY

SIR produces its Standards of Practice documents by using the following

An in-depth literature search is performed by using electronic medical literature databases. Then, a critical review of peer-reviewed articles is performed with regard to the study methodology, results, and conclusions. The qualitative weight of these articles is assembled into an evidence table, which is used to write the document such that it contains evidence-based data with respect to content, complication rates, outcomes, and thresholds for prompting quality assurance reviews.

When the evidence of literature is weak, conflicting, or contradictory, consensus for the parameter is reached by a minimum of 12 Standards of Practice Committee members by using a modified Delphi consensus method (**Appendix**) (1). For the purposes of these documents, consensus is defined as 80% Delphi participant agreement on a value or parameter.

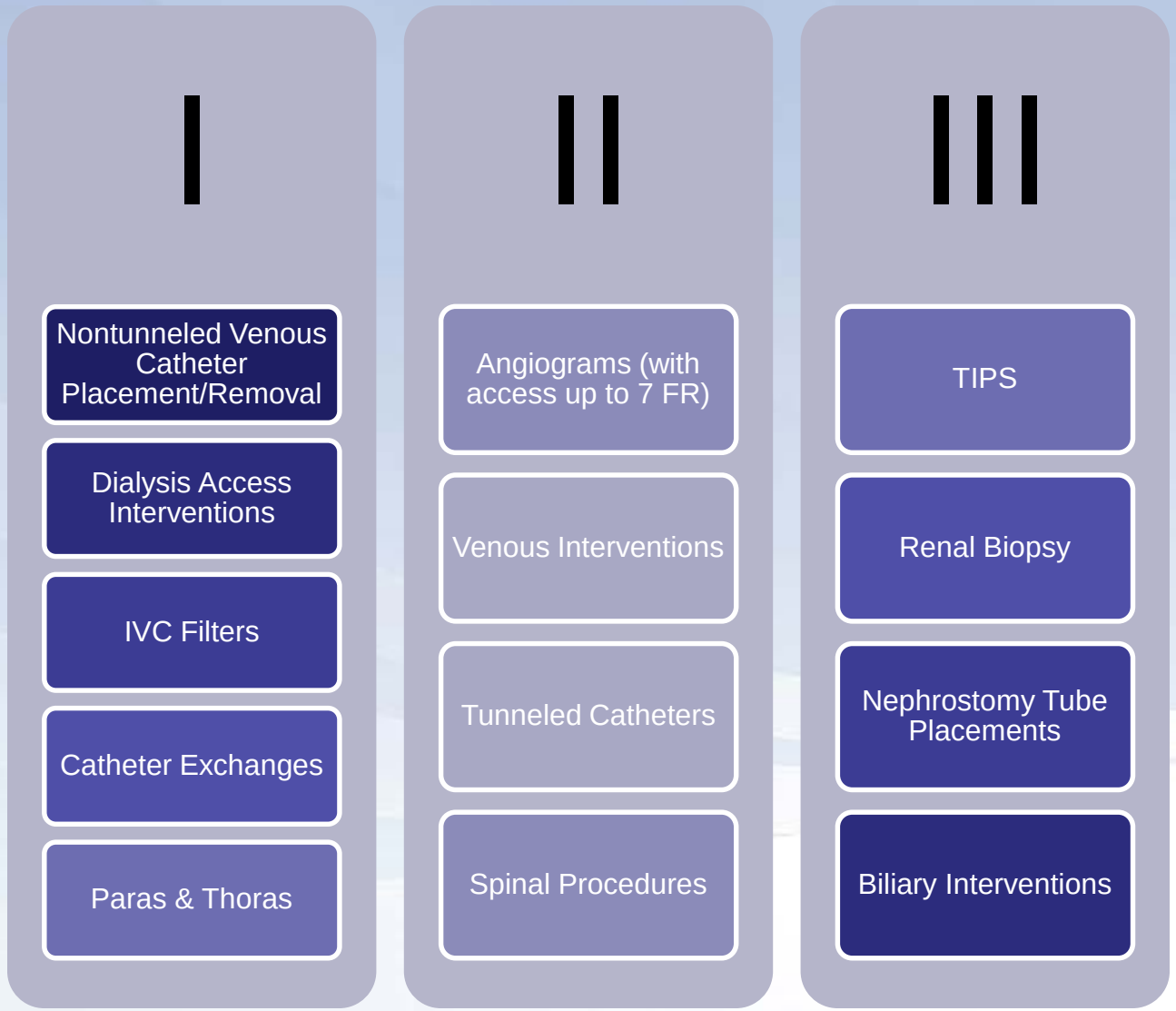
The draft document is critically reviewed by the Standards of Practice Committee members either by telephone conference calling or face-to-face meeting. The finalized draft from the Committee is sent to the SIR membership for further input/criticism during a 30-d comment period.

Procedure Categories

I	II	III
Low Bleeding Risk/Easily Detectable or Controlled	Moderate Bleeding Risk	Significant Bleeding Risk/Bleeding Difficult to Detect of Control

J Vasc Interv Radiol. 2013; 24:641-5.

Procedure Examples



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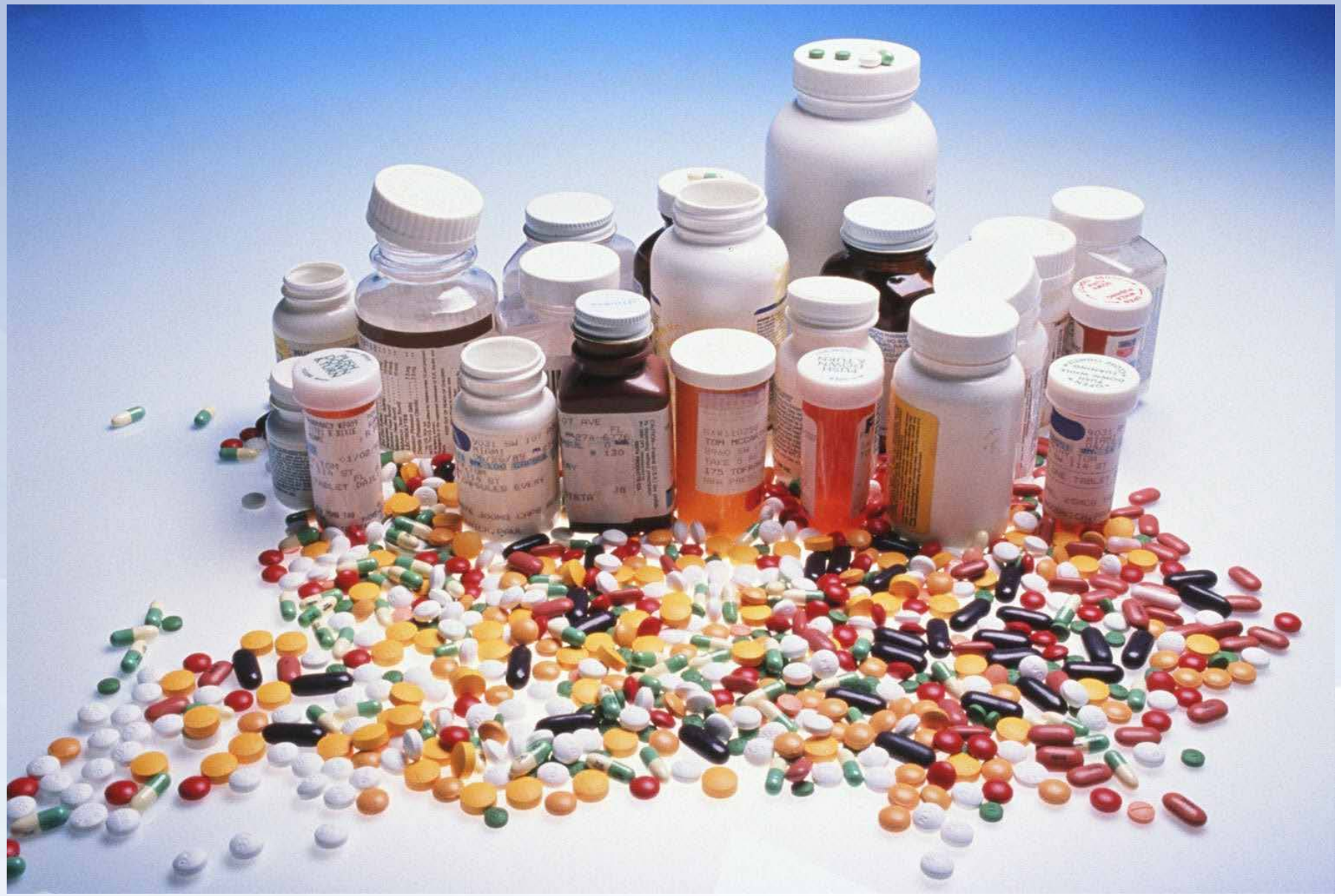
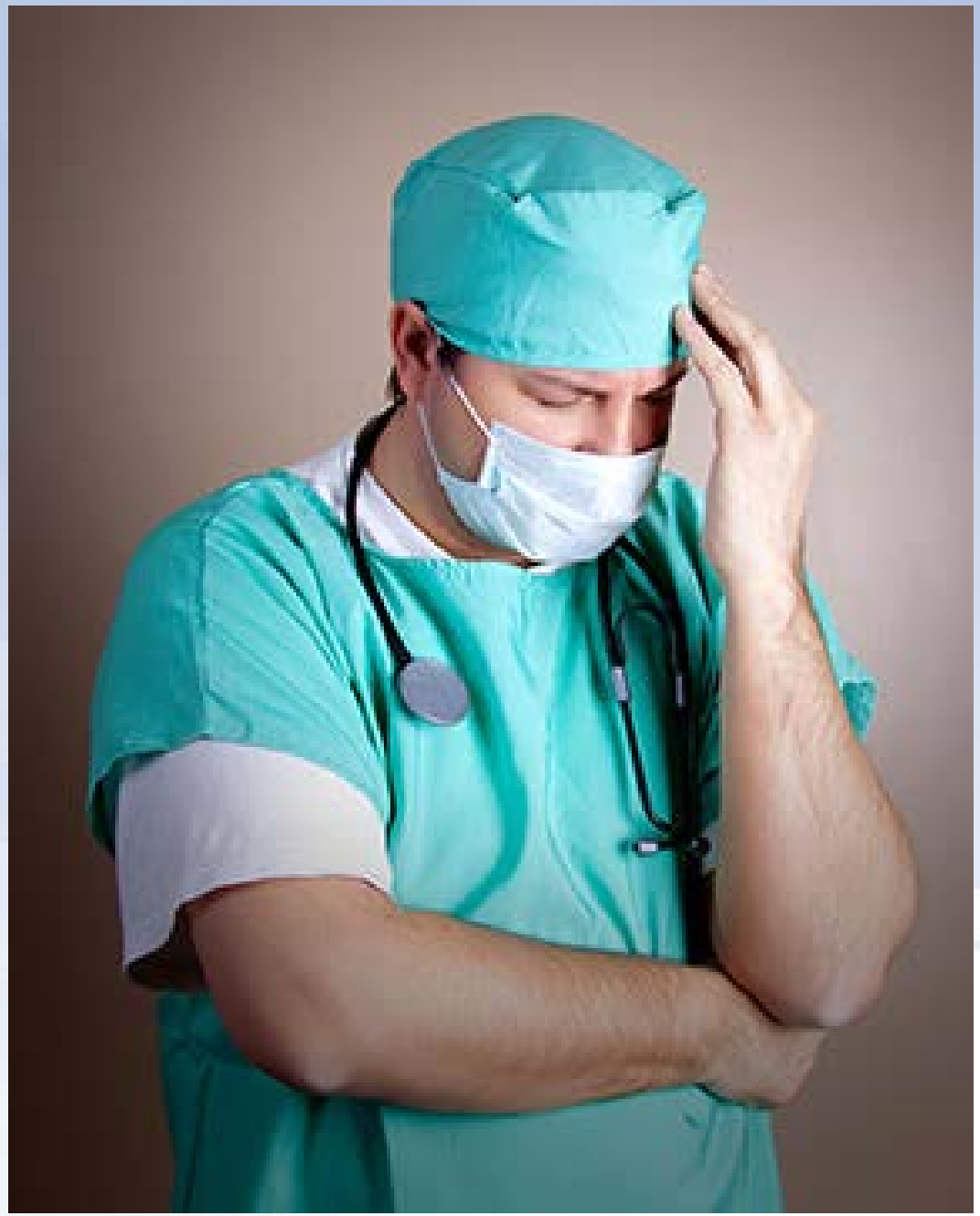
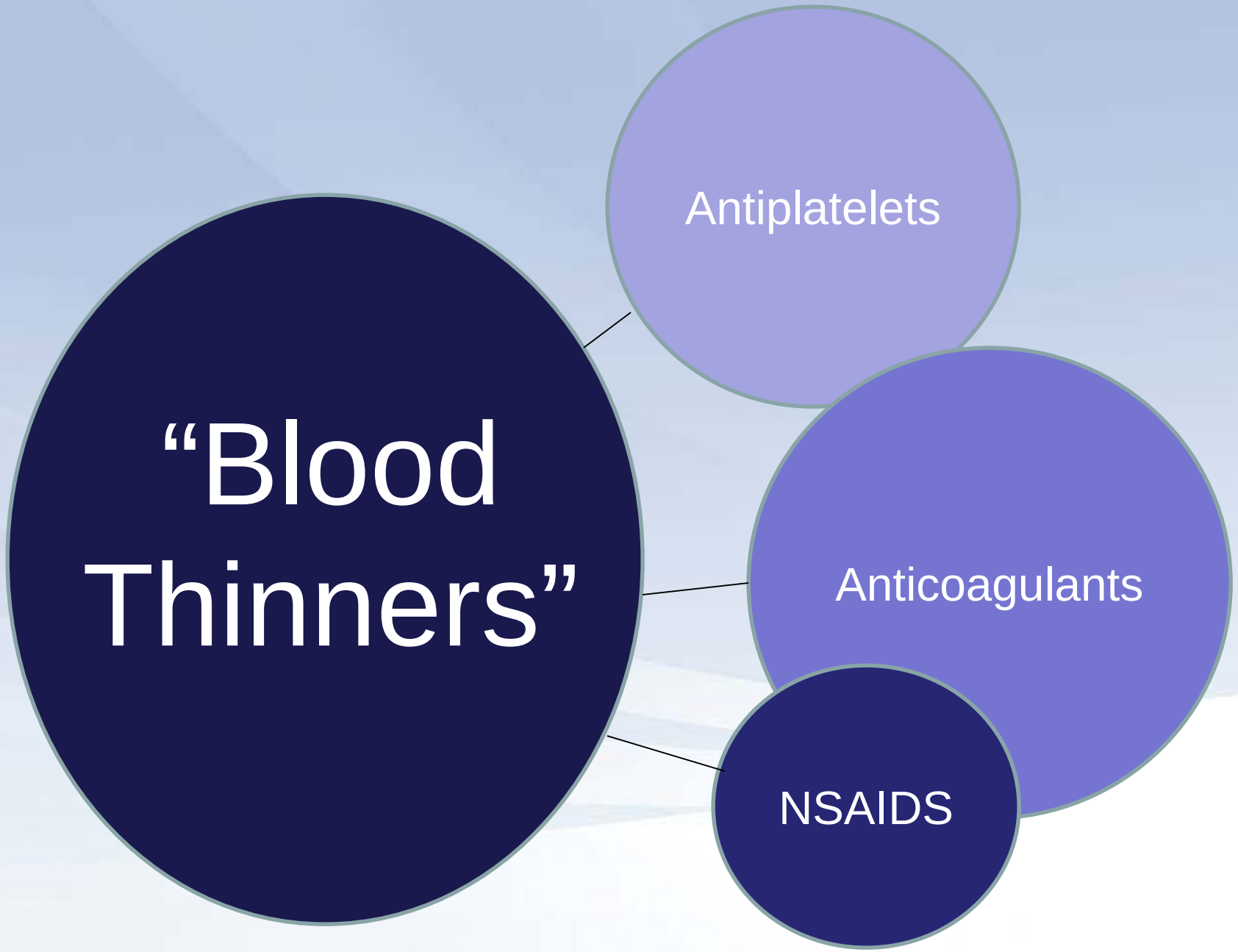
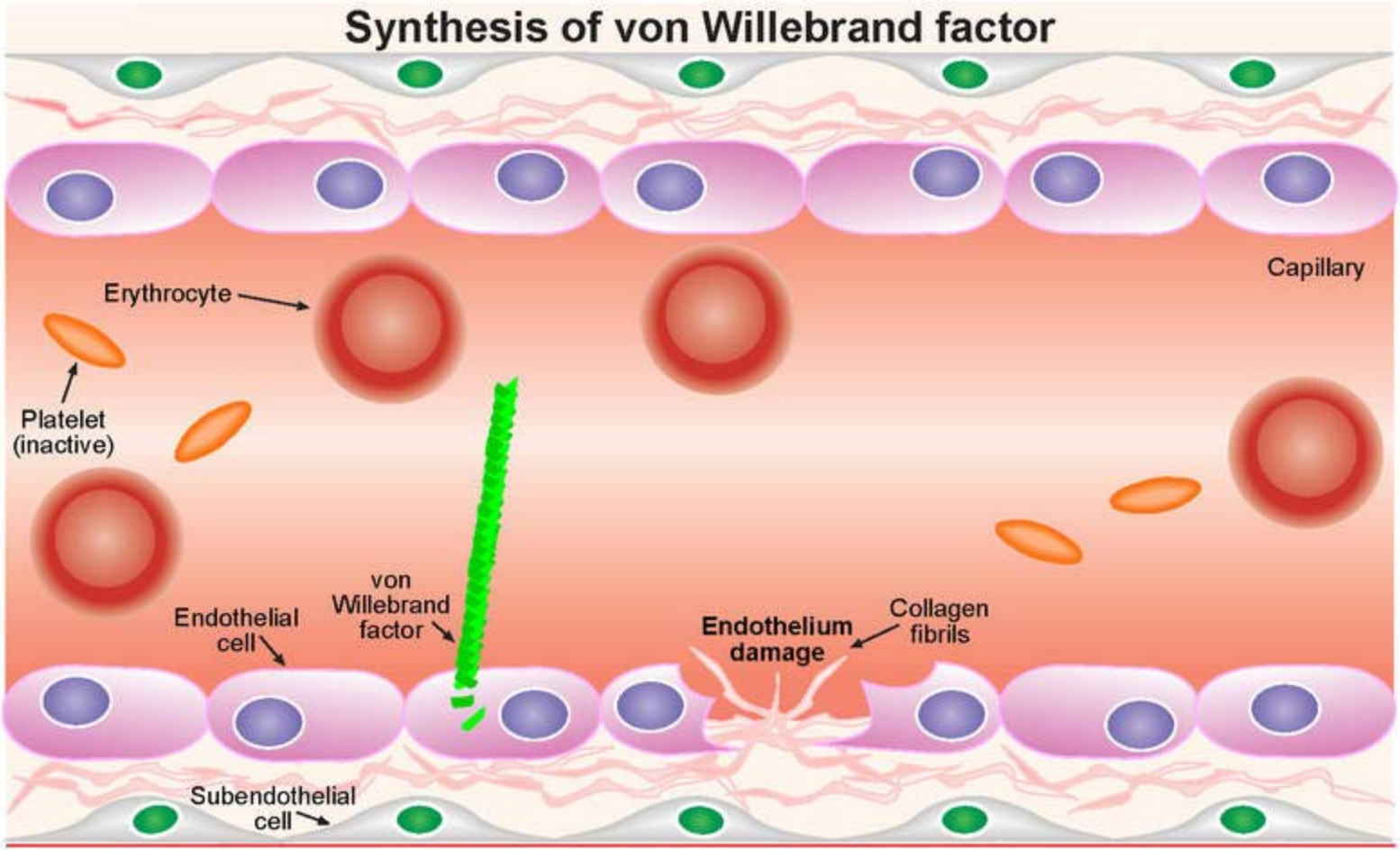





“Blood Thinners”
Antiplatelets
Anticoagulants
NSAIDS

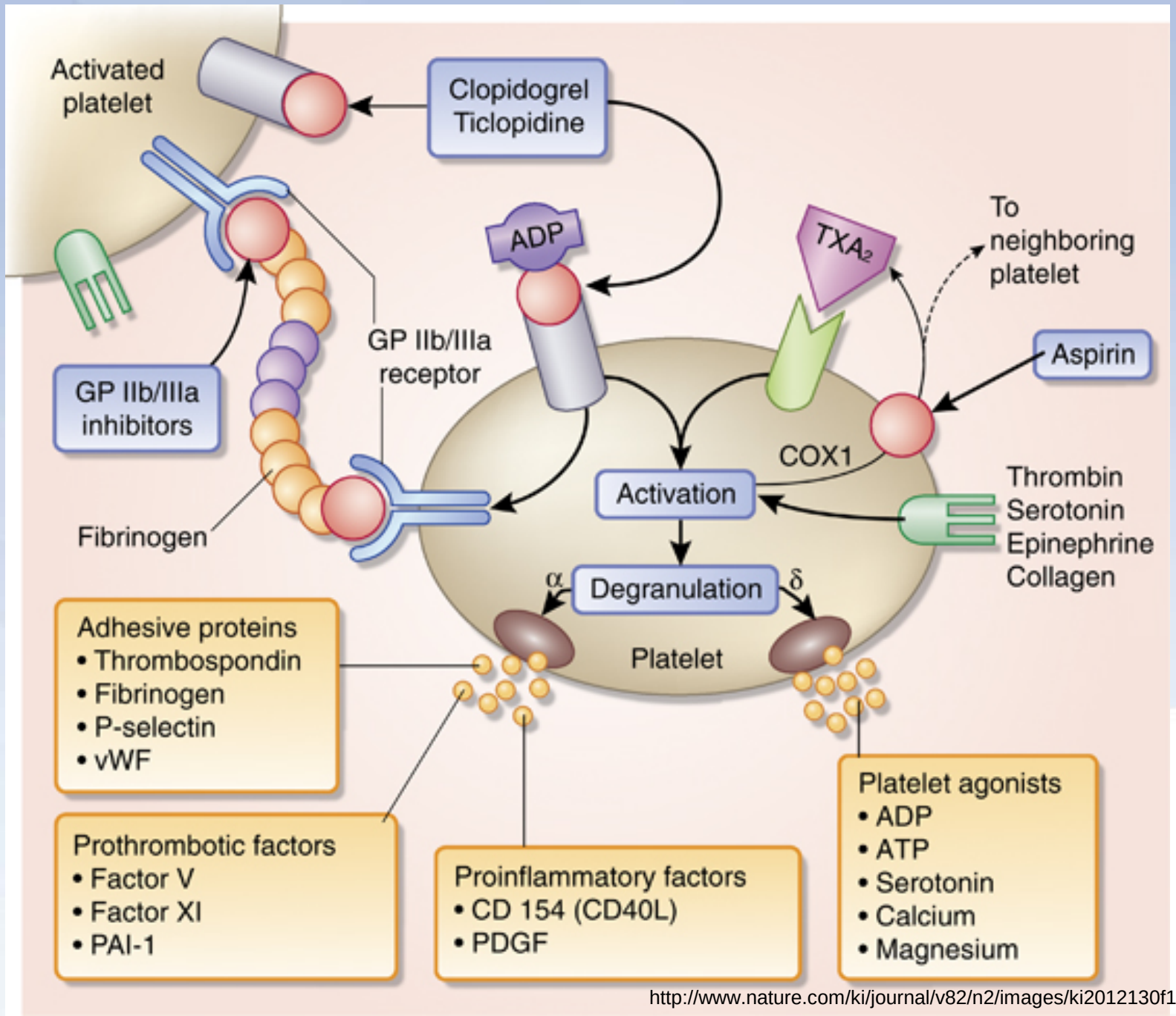
Antiplatelet Agents



Endothelial cells near the site of damage respond by synthesising von Willebrand factor which is secreted in the form of large multimeric chains. Platelets express cell surface receptors, such as GP1b, that allow them to adhere to von Willebrand factor bound to subendothelial collagen fibrils.

immunopaedia.org

http://www.immunopaedia.org.za/index.php?id=689



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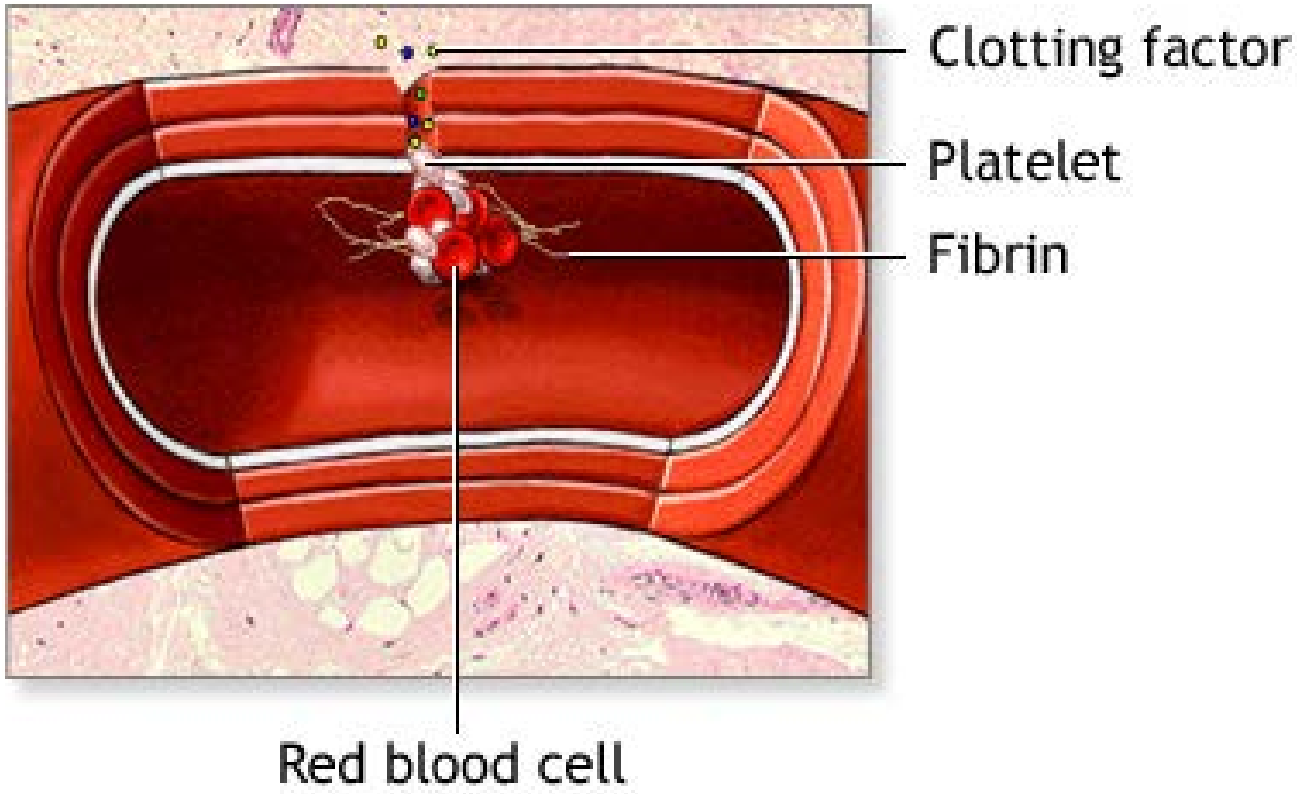
Blood clot formation



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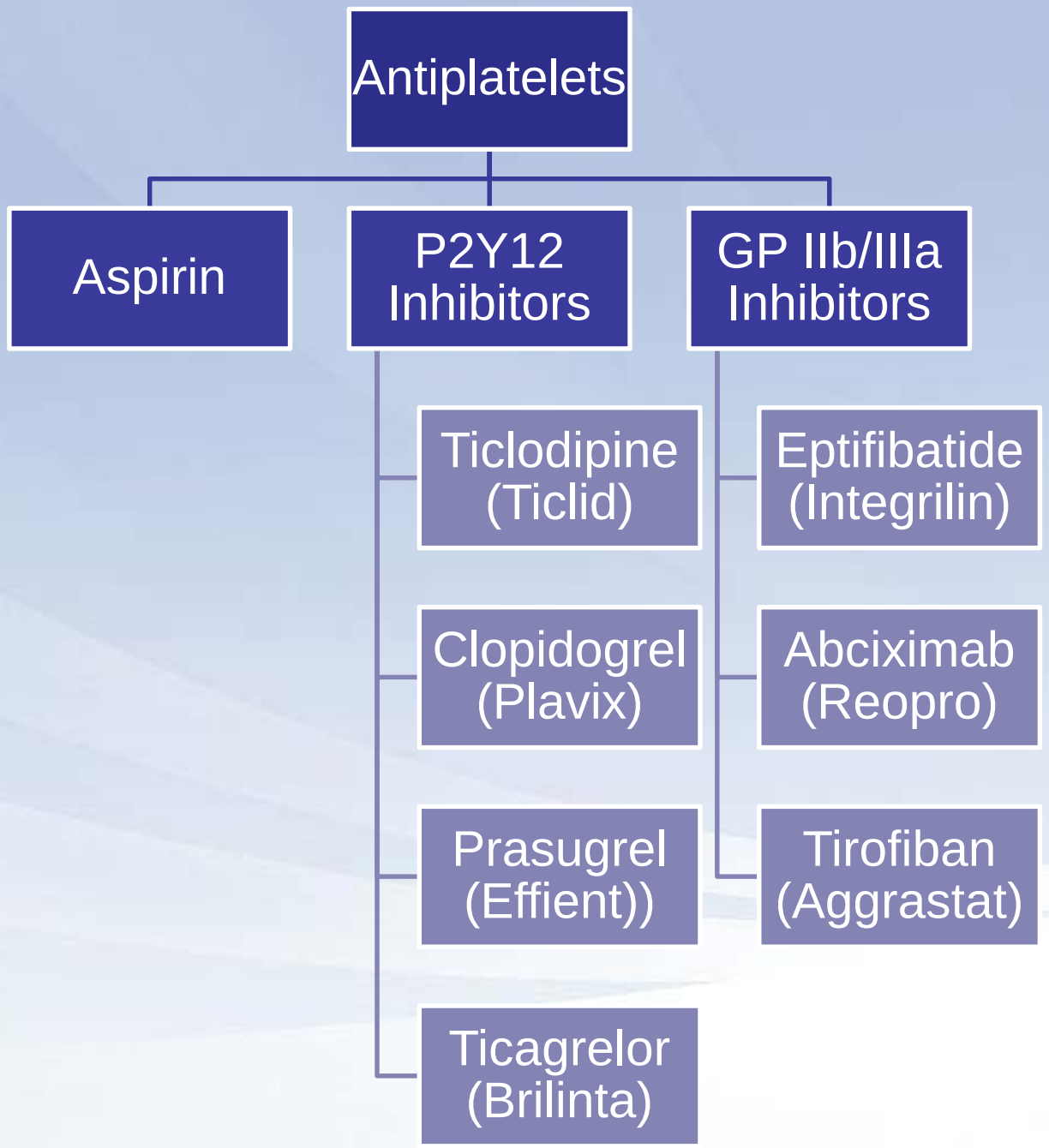
Antiplatelets
Aspirin
P2Y12 Inhibitors
GP IIb/IIIa Inhibitors
Ticlodipine (Ticlid)
Clopidogrel (Plavix)
Prasugrel (Effient))
Ticagrelor (Brilinta)
Eptifibatide (Integrilin)
Abciximab (Reopro)
Tirofiban (Aggrastat)


ASPIRIN
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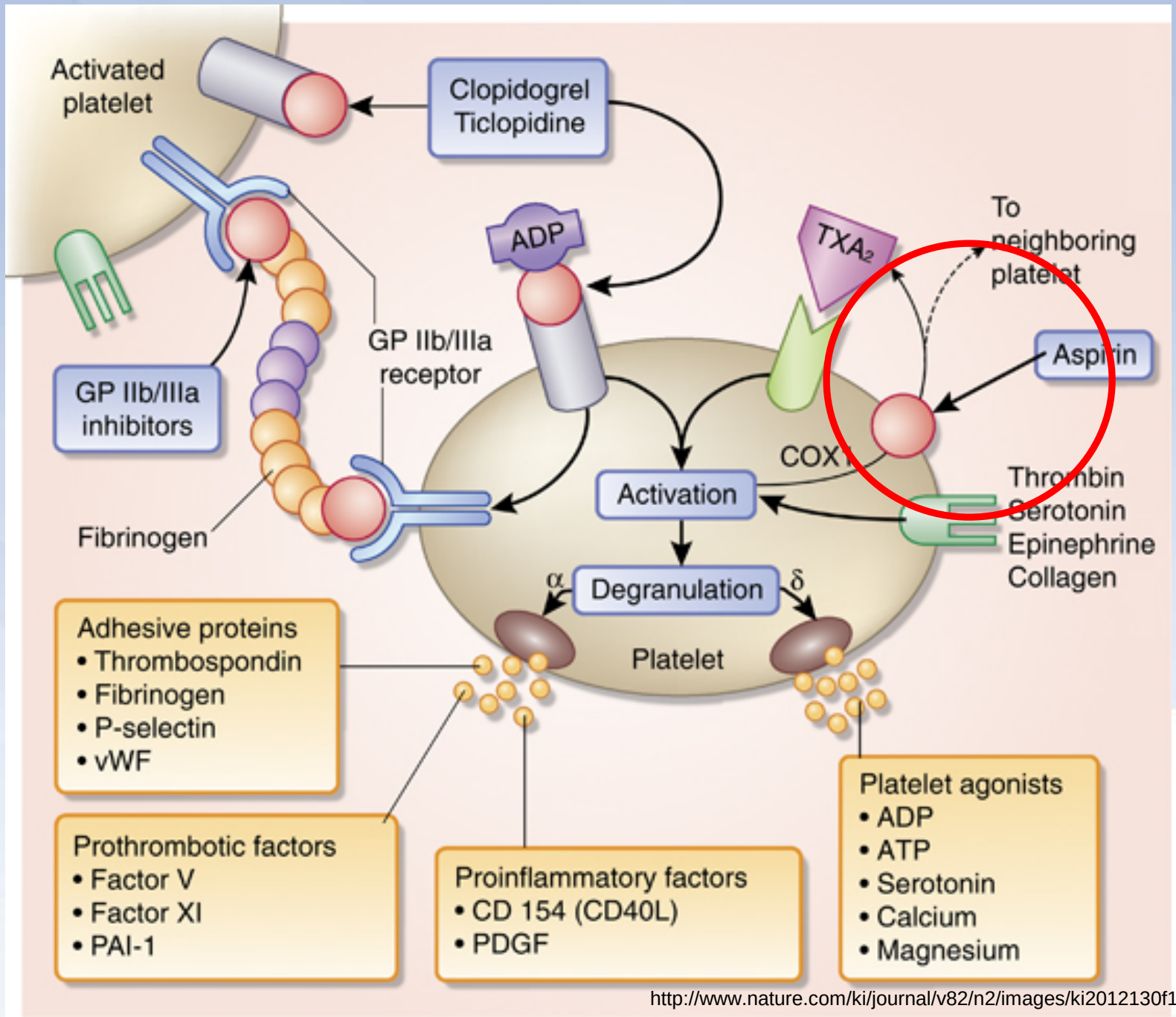
Aspirin

- *Acetylates cyclooxygenase-1 and -2 (COX) enzymes*
  - *Irreversibly binds, inhibits platelet aggregation*

Half-Life	Hold for Class I	Hold for Class II	Hold for Class III
3-6 Hours	Do not withhold	Do not withhold	5 days

J Vasc Interv Radiol. 2013; 24:641-5.



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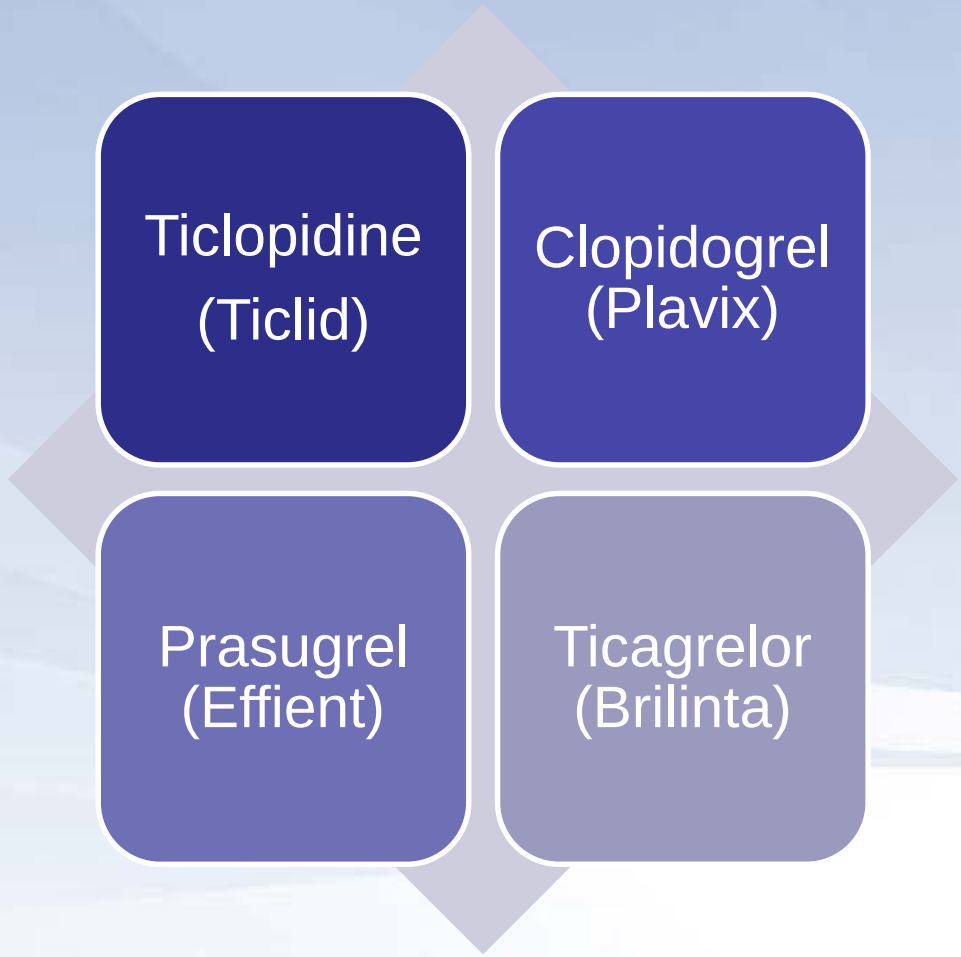
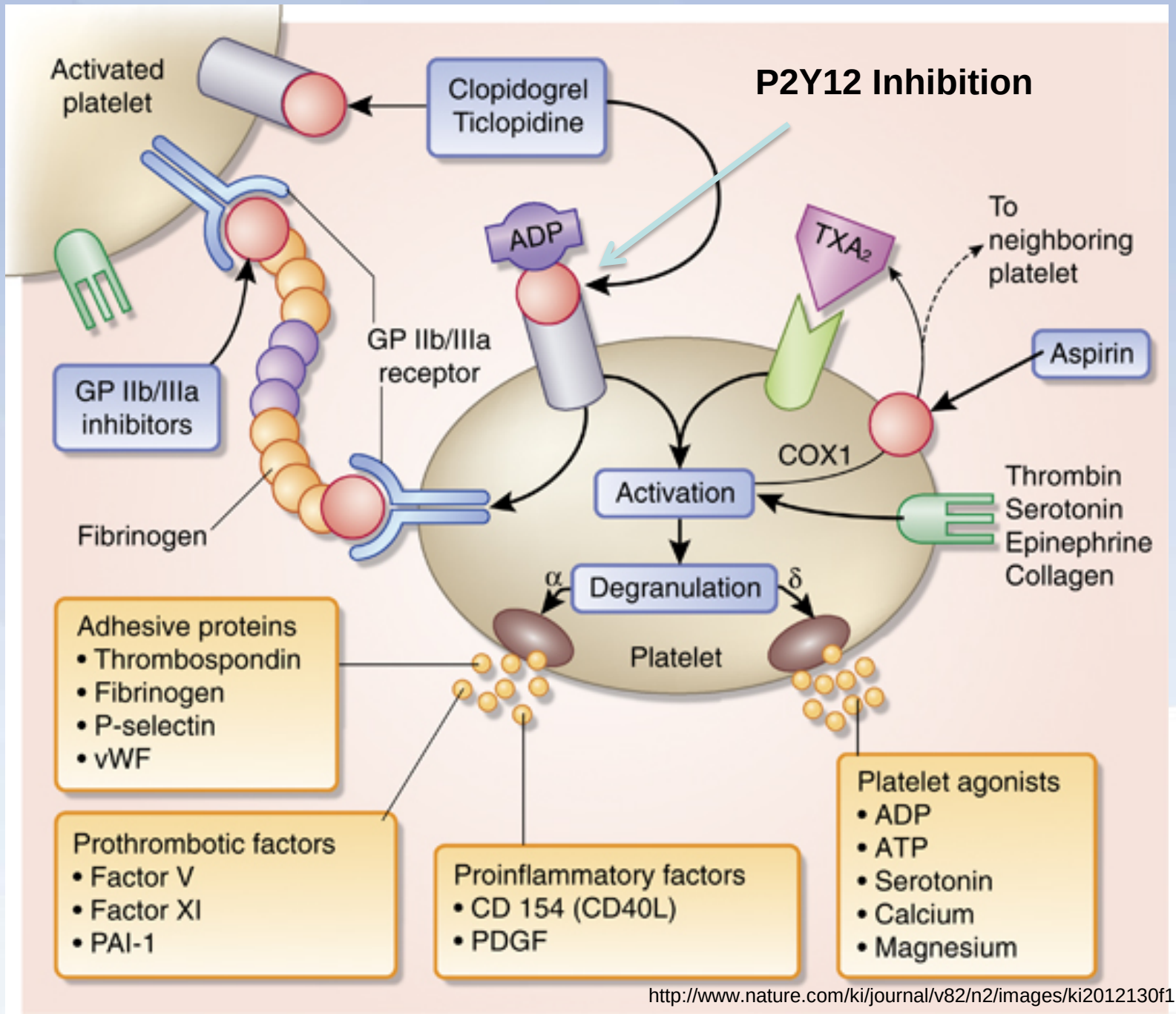
P2Y12 Inhibitors





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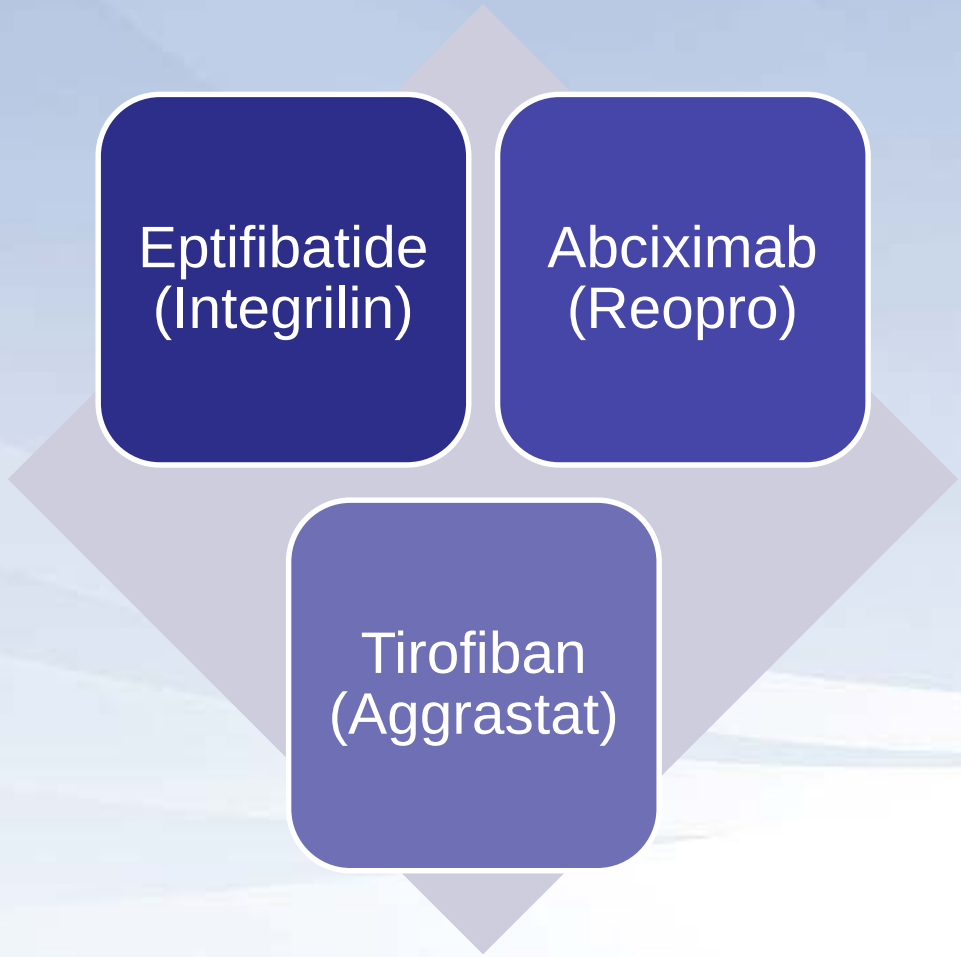
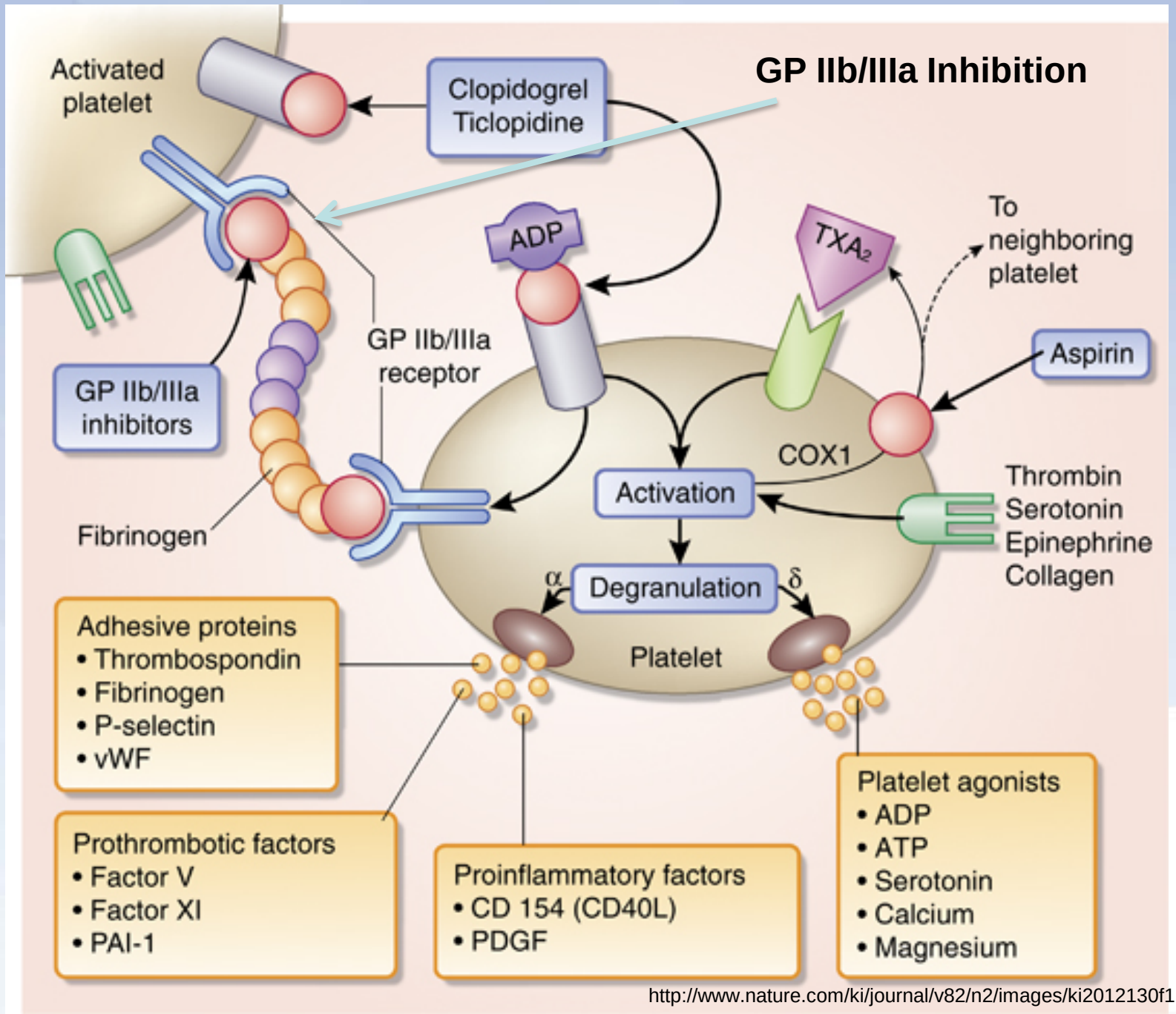
P2Y12 Inhibitors*

Medication	Half-Life	Hold for Class I	Hold for Class II	Hold for Class III
Clopidogrel (Plavix)	6 hours	0-5 days	5 days	5 days
Ticlopidine (Ticlid)	12.5 hours	0-5 days	7 days	7 days
Prasugrel (Effient)	2-15 hours, avg appx 7	0-5 days	5 days	5 days
Ticagrelor (Brilinta)	7 hours	0-5 days	5 days	5 days

J Vasc Interv Radiol. 2013; 24:641-5.
Dtsch Arztebl Int. 2013;110(31-32):525-32

GP IIb/IIIa Inhibitors





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GP IIb/IIIa Inhibitors

Medication	Half-Life	Hold for Class I	Hold for Class II	Hold for Class III
Abciximab (Reopro)	30 minutes	12-24 hours aPTT ≤ 50 s ACT ≤ 150 s	24 hours aPTT ≤ 50 s ACT ≤ 150 s	24 hours aPTT ≤ 50 s ACT ≤ 150 s
Eptifibatide (Integrilin)	2.5 hours	Immediately prior to procedure	4 hours	4 hours
Tirofiban (Aggrastat)	2 hours	Immediately Prior to Procedure	4 hours	4 hours

J Vasc Interv Radiol. 2013; 24:641-5.

Cilostazol (Pletal)

- *Inhibits thrombosis and platelet aggregation*
- Less potent platelet inhibitor than Plavix
- Half Life: 11-13 hours
- Not listed in SIR CPG

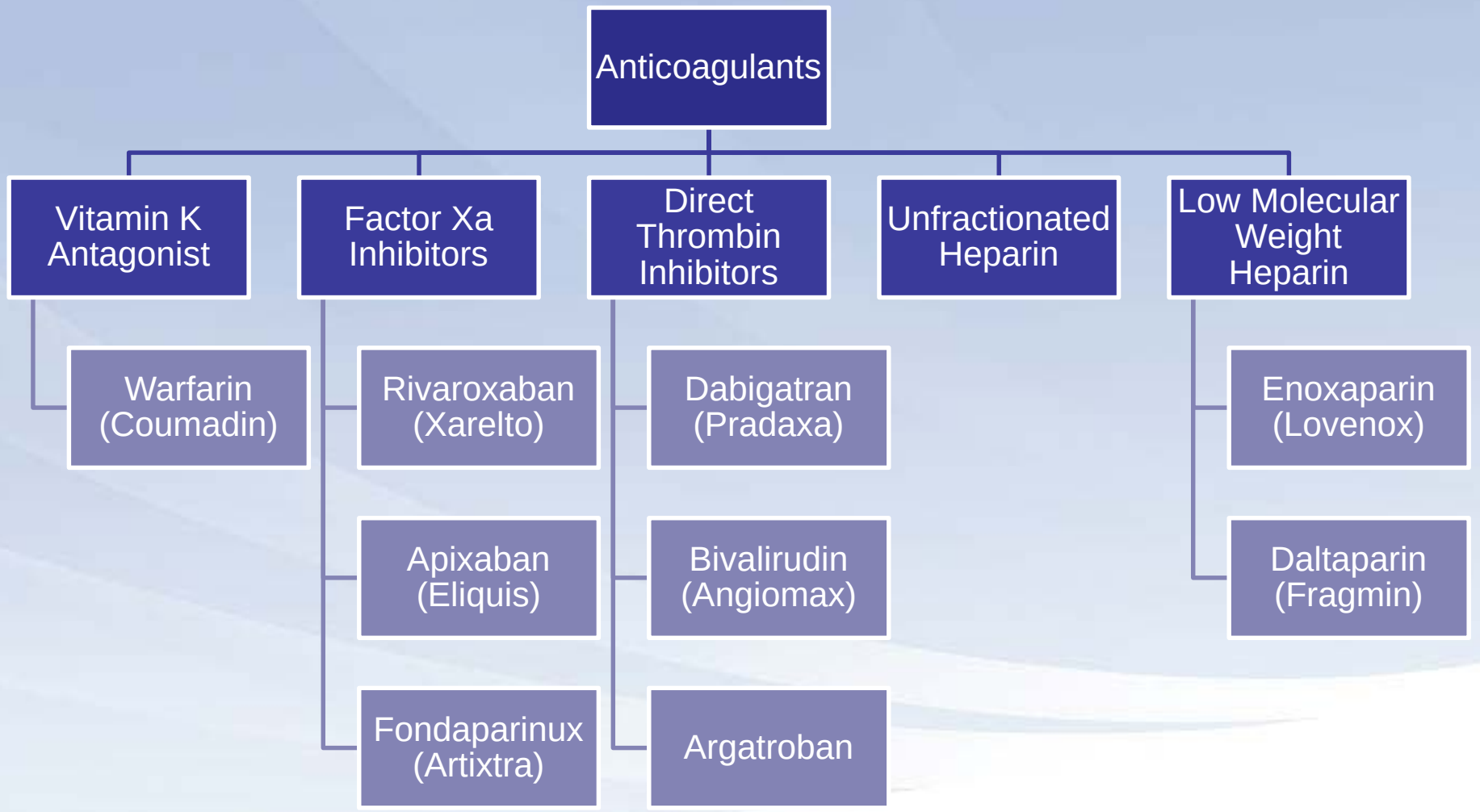
J Vasc Interv Radiol. 2013; 24:641-5.

Reinitiation of Antiplatelets

- When postoperative bleeding risk has subsided
- Aspirin takes effect almost immediately after it is taken
- P2Y12 Inhibitors can have a delayed impact
  - Could consider a loading dose
    - Plavix 300-600 mg
    - Prasugrel 60 mg

Blood. 2012 Dec 6; 120(24):4699-705

Anticoagulant Agents

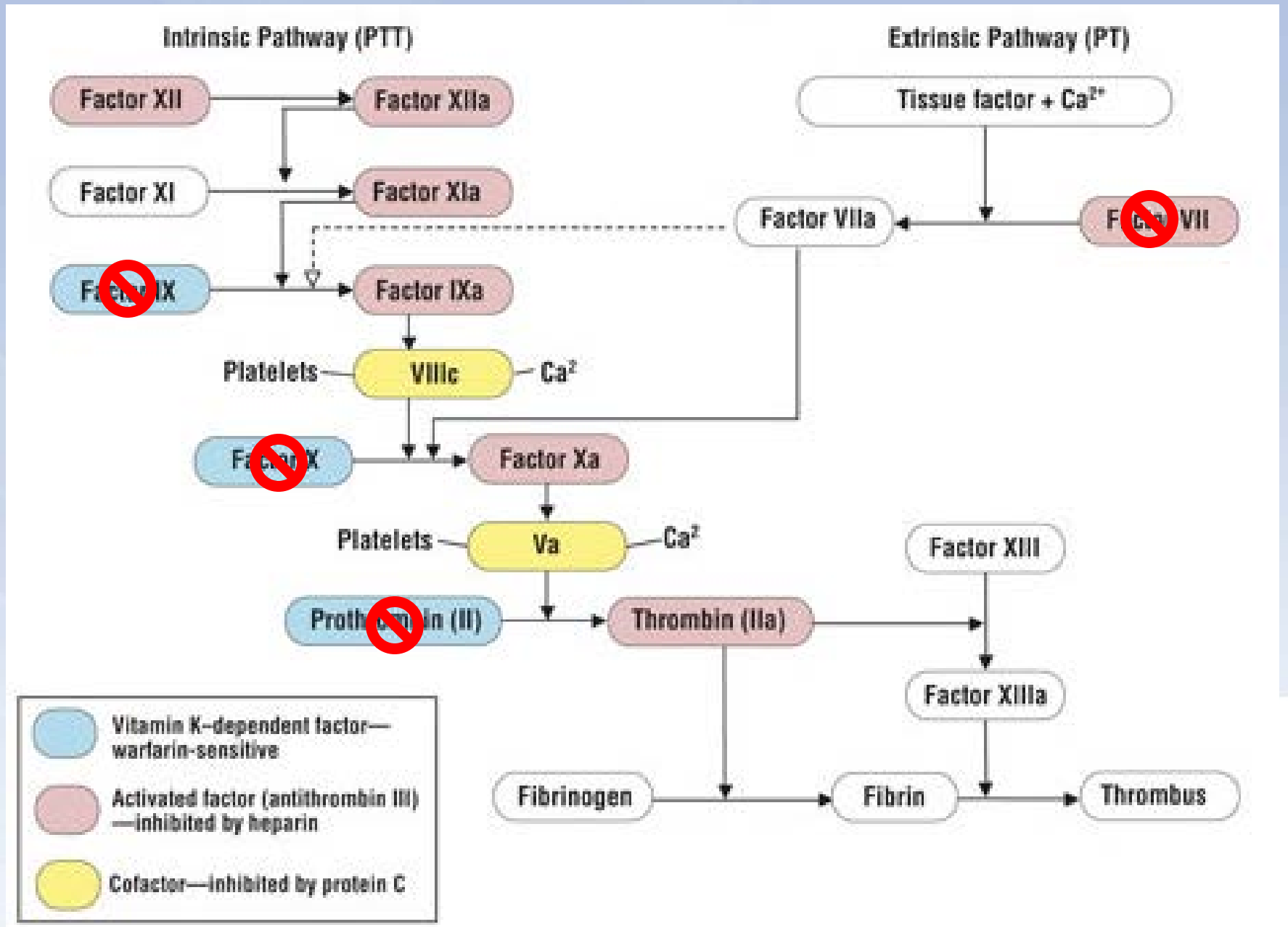

Anticoagulants
Vitamin K Antagonist
Factor Xa Inhibitors
Direct Thrombin Inhibitors
Unfractionated Heparin
Low Molecular Weight Heparin
Warfarin (Coumadin)
Rivaroxaban (Xarelto)
Apixaban (Eliquis)
Fondaparinux (Artixtra)
Dabigatran (Pradaxa)
Bivalirudin (Angiomax)
Argatroban
Enoxaparin (Lovenox)
Daltaparin (Fragmin)

Warfarin

- Vitamin K Antagonist
  - Inhibits Vitamin K Clotting Factors
    - II, IX, X, and VII
- Delayed onset based on half life of the affected factors
- Drug Interactions affect INR

Half-Life	Hold for Class I	Hold for Class II	Hold for Class III
20-60 hours	3-5 days INR ≤ 2.0	5 days INR ≤ 1.5	5 days INR ≤ 1.5

J Vasc Interv Radiol. 2013; 24:641-5.



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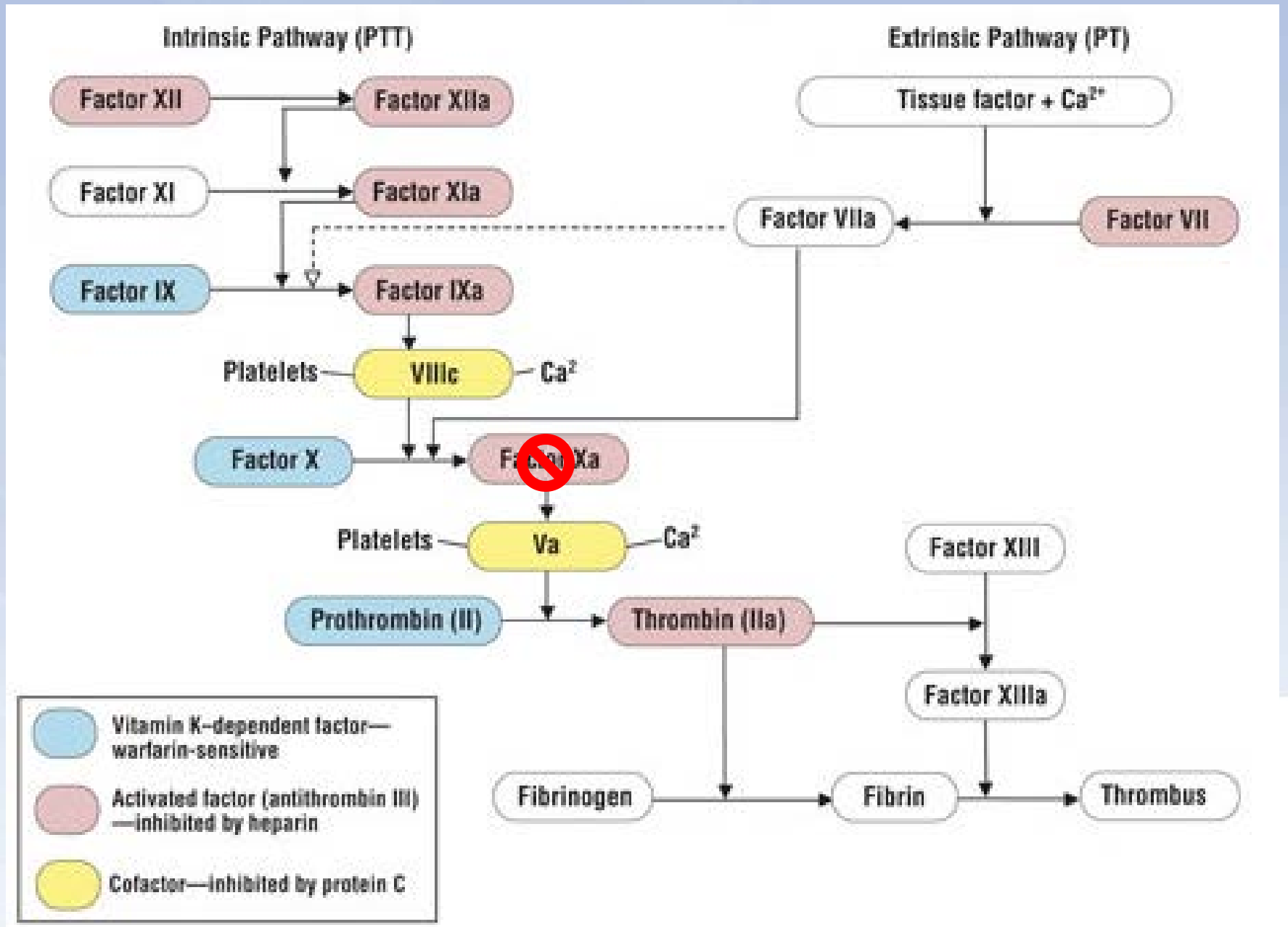
Factor Xa Inhibitors

Fonadparinux (Arixtra)

Apixaban (Eliquis)

Rivaroxaban (Xaralto)



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Factor Xa Inbibitors

Medication	Half-Life	Renal Elimination	Hold for Class I	Hold for Class II	Hold for Class III
Fonadparinux (Arixtra)	17-21 hours	77%	Do not withhold	2-3 days (CrCl >50 mL) 3-5 days (CrCl <50 mL)	2-3 days (CrCl >50 mL) 3-5 days (CrCl <50 mL)
Apixaban (Eliquis)	8-15 hours	27%	1-2 days	2-4 days	2-4 days
Rivaroxaban (Xaralto)	5-9 hours, 11-13 hours in the elderly	66%	1-2 days	2-4 days	2-4 days

Am J Health-Syst Pharm. 2013 May;70:S3-11
J Vasc Interv Radiol. 2013; 24:641-5.

Rivaroxaban and Apixaban

Hold times mildly dependent on renal function

Creatinine Clearance	Last Dose before Minor Procedure	Last Dose before Major Procedure
> 50 mL/min	1	2
31-50 mL/min	1-2	3-4
≤ 30 mL/min	2	4

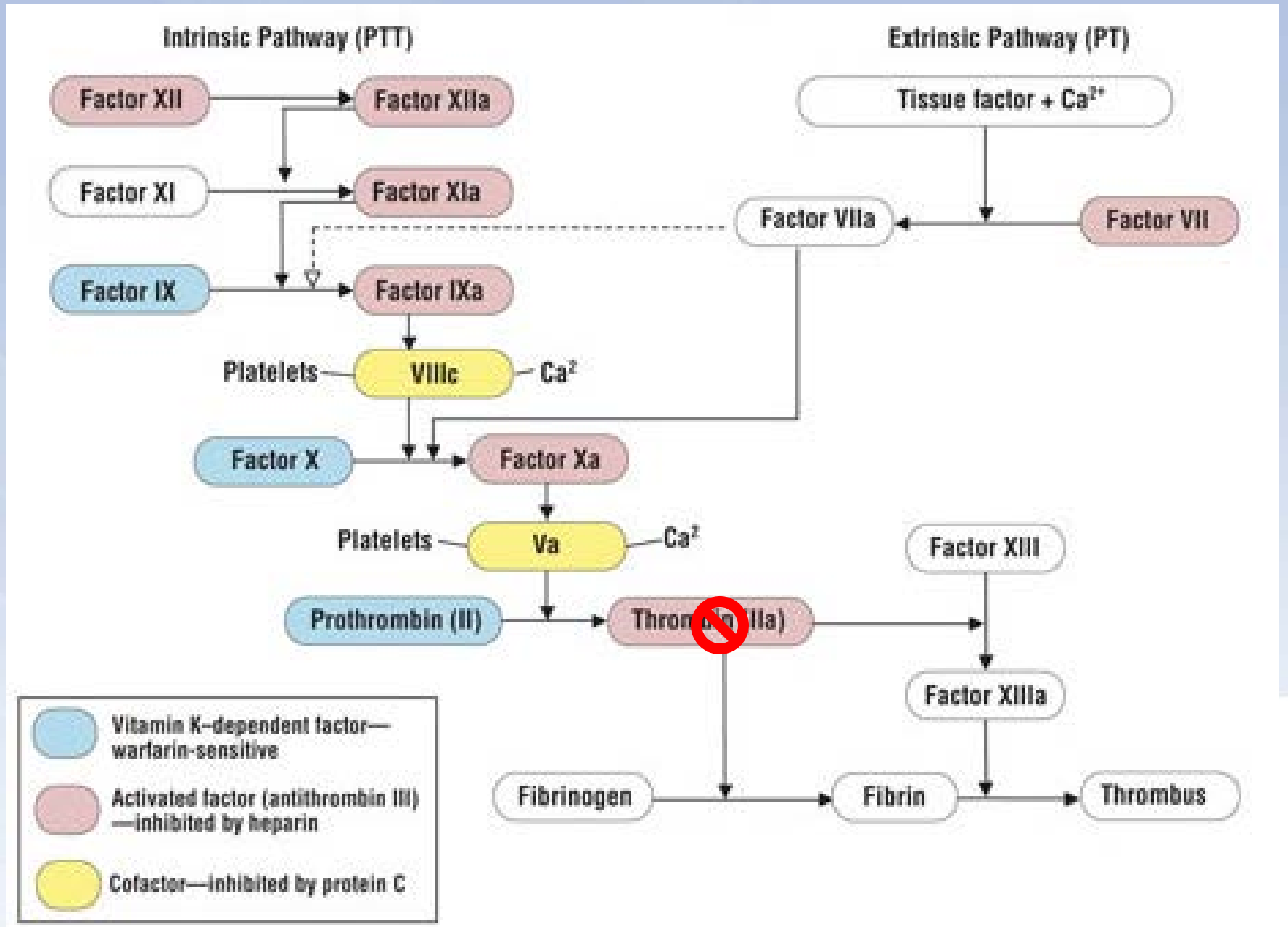
Am J Health-Syst Pharm. 2013 May;70:S3-11
Am J Health-Syst Pharm. 2012 Sept;69:1473-84

Direct Thrombin Inhibitors

Dabigatran (Pradaxa)

Bivalirudin (Angiomax)

Argatroban



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Direct Thrombin Inhibitors

Medication	Half-Life	Hold for Class I	Hold for Class II	Hold for Class III
Argatroban	40-60 minutes	Do not withhold	Hold 4 hours, defer procedure if possible	Hold 4 hours, defer procedure if possible
Bivalirudin (Angiomax)	25-60 minutes	Do not withhold	2-3 hours (CrCl >50 mL/min) 3-5 hours (CrCl <50 mL/min)	2-3 hours (CrCl >50 mL/min) 3-5 hours (CrCl <50 mL/min)
Dabigatran (Pradaxa)	12-17 hours	Do not withhold	2-3 days (CrCl >50 mL/min) 3-5 days (CrCl <50 mL/min)	2-3 days (CrCl >50 mL/min) 3-5 days (CrCl <50 mL/min)

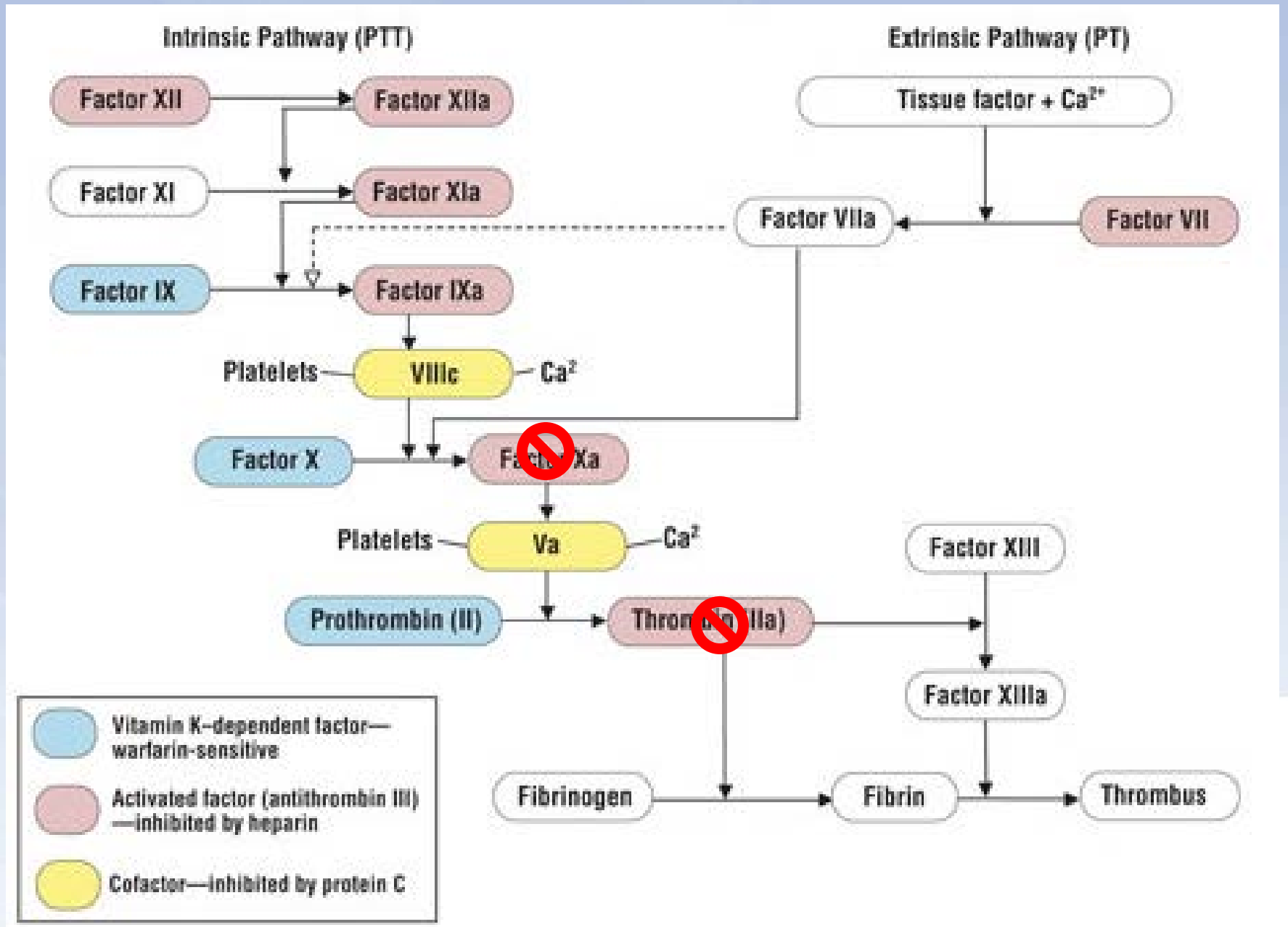
Am J Health-Syst Pharm. 2013 May;70:S3-11
Am J Health-Syst Pharm. 2012 Sept;69:1473-84

Unfractionated Heparin

- Combines with antithrombin III (Heparin cofactor)
  - Prevents the conversion of prothrombin to thrombin
  - Inactivates the activated Factor X

Half-Life	Hold for Class I	Hold for Class II	Hold for Class III
30-60 minutes	No consensus, check aPTT	No consensus, check aPTT	Withhold 2-4 hours before procedure, aPTT ≤ 1.5 x control

J Vasc Interv Radiol. 2013; 24:641-5.



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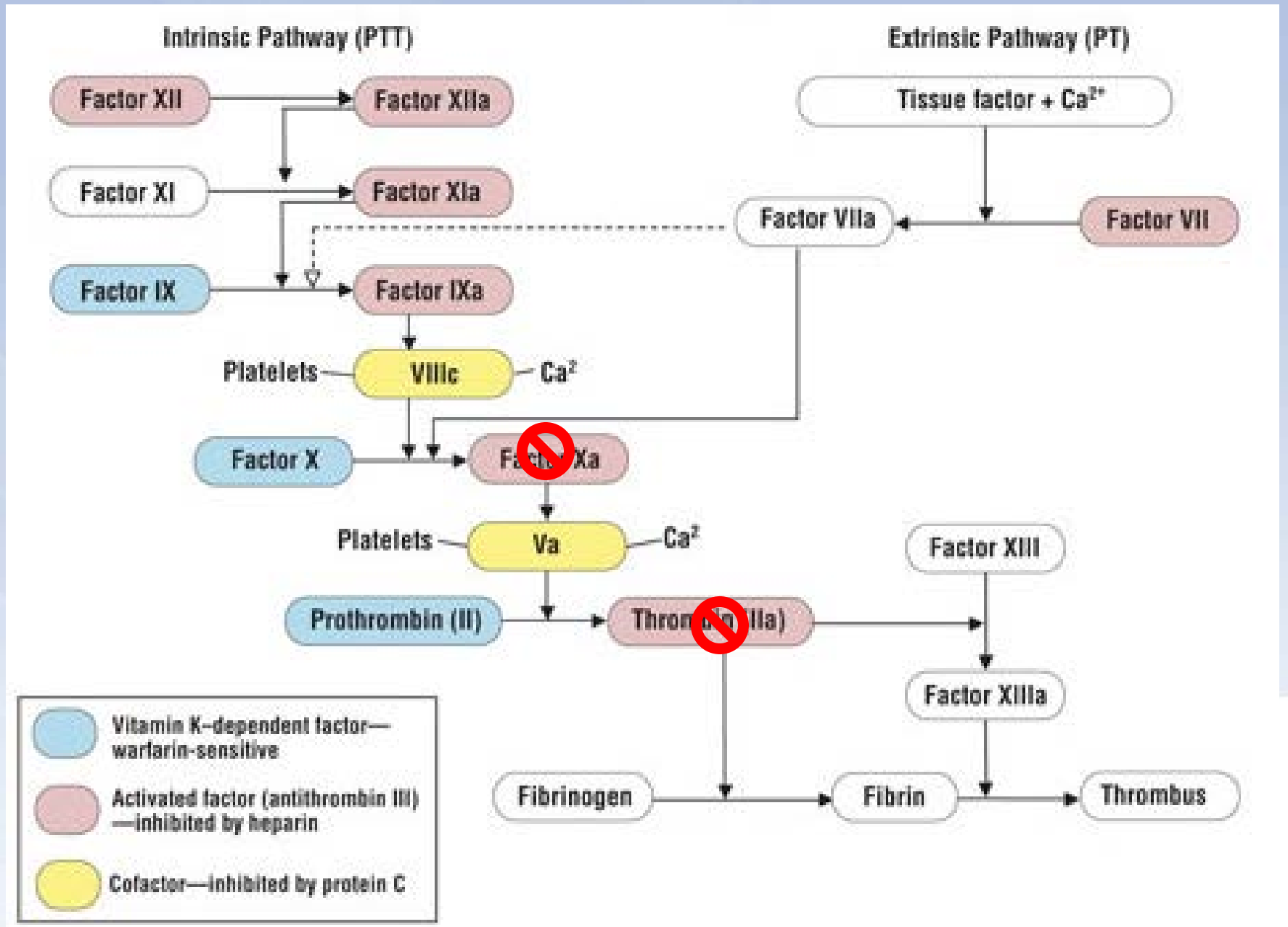
Low Molecular Weight Heparins

Enoxaparin (Lovenox)

Dalteparin (Fragmin)



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Low Molecular Weight Heparins

Medication	Half-Life	Hold for Class I	Hold for Class II	Hold for Class III
Enoxaparin (Lovenox)	4.5-7 hours	1 dose or 12 hours	1 dose or 12 hours	2 doses or 24 hours
Dalteparin (Fragmin)	2-7 hours	1 dose or 12 hours	1 dose or 12 hours	2 doses or 24 hours

J Vasc Interv Radiol. 2013;24:641-5

Could use as “Bridge” Therapy

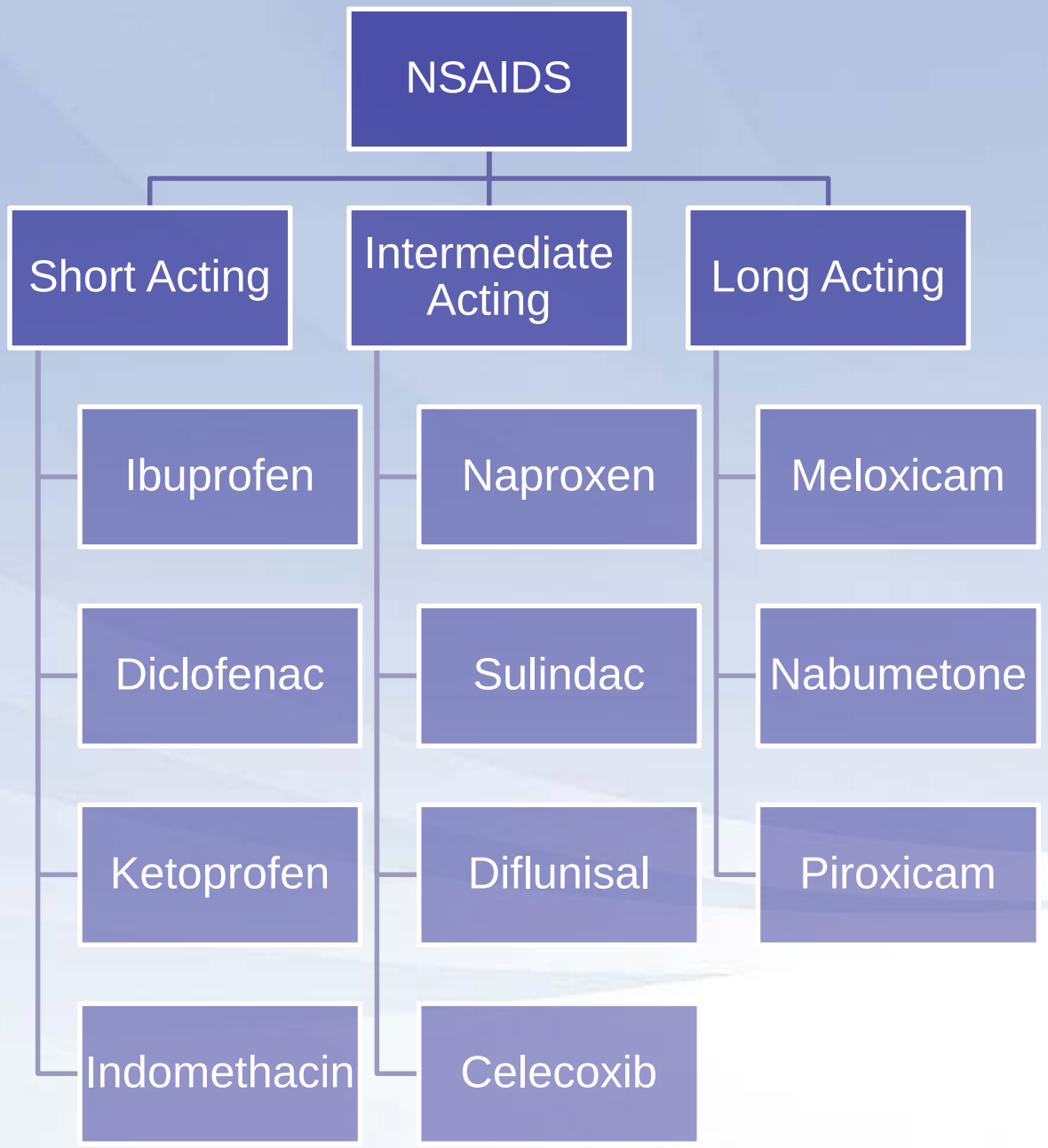
- For patients with high risk when off anticoagulation
- Stop Coumadin 3-5 days prior and use Lovenox up until 12-24 hours before procedure
- Restart the Coumadin post and continue Lovenox until goal INR is reached

Blood. 2012 Dec 6; 120(24):4699-705

Restarting Anticoags

- When post procedure risk has subsided

NSAIDS



J Vasc Interv Radiol. 2013;24:641-5

NSAIDS

- Like ASA, NSAIDs block the COX Receptors
- Unlike ASA, NSAIDS diminish over time as they circulate

Medication	Half-Life	Hold for Class I	Hold for Class II	Hold for Class III
Short Acting	2-6 hours	Do not withhold	Do not withhold	24 hours
Intermediate Acting	7-15 hours	Do not withhold	Do not withhold	2-3 days
Long Acting	> 20 hours	Do not withhold	Do not withhold	10 days

J Vasc Interv Radiol. 2013;24:641-5

Monitoring for Efficacy

Lab Values

Lab Value	Description
PT	Time in seconds for plasma to coagulate after addition of thromboplastin
INR	Calculation of PT that accounts for manufacturer's sensitivity index
Dilute PT (dPT)	Similar to PT, dilution increases the sensitivity
aPTT	Reflects activity of Factors II, V, VIII-XII
Thrombin Time (TT)	Activity of thrombin in plasma
Ecarin Clotting Time (ECT)	Measures thrombin generation
Chromogenic Assays	Color changes of substrate specific for a certain factor
Heptest	Measures the inhibition of exogenous Factor Xa
Prothrombinase--induced clotting time (PiCT)	Involves phospholipids, Fxa, & enzymes to activate factor V to measures time & effect of anticoagulant

Lab Values—Rivaroxaban (Xaralto)

Lab Value	Utility	Comments
PT	☑	Widely available, more sensitive at higher concentrations
Dilute PT (dPT)	-----	Reagent variability, not widely available
aPTT	-----	Less sensitive than PT, not ideal
Thrombin Time (TT)	-----	No effect
Ecarin Clotting Time (ECT)	-----	Unlikely to have an effect
Chromogenic Anti Factor IIa Assays	☑	Accurate & Precise, most promising
Heptest	☑	Sensitive at low and high concentrations. Not widely available
Prothrombinase--induced clotting time (PiCT)	☑	Not widely available, not FDA approved

Am J Health-Syst Pharm. 2012 Sept; 69:1473-84
Am J Health-Syst Pharm. 2013 May; 70:S21-31
Blood. 2013 Dec 6; 120(24):4699-705

Lab Values—Apixaban (Eliquis)

Lab Value	Utility	Comments
PT	☑	Widely available, more sensitive at higher concentrations
Dilute PT (dPT)	☑	More sensitive than PT, not widely available or FDA approved
aPTT	-----	Less sensitive than PT, not ideal
Thrombin Time (TT)	-----	No effect
Ecarin Clotting Time (ECT)	-----	Unlikely to have an effect
Chromogenic Anti Factor IIa Assays	☑	Accurate & Precise, most promising
Heptest	☑	Sensitive at low and high concentrations. Not widely available
Prothrombinase--induced Clotting time (PiCT)	☑	Not widely available, not FDA approved

Am J Health-Syst Pharm. 2012 Sept; 69:1473-84
Am J Health-Syst Pharm. 2013 May; 70:S21-31
Blood. 2013 Dec 6; 120(24):4699-705

Lab Values—Dabigatran (Pradaxa)

Lab Value	Utility	Comments
PT	-----	Not ideal, but widely available
Dilute PT (dPT)	-----	More sensitive than PT, not widely available
aPTT	☑	Availability & sensitivity support use
Thrombin Time (TT)	☑	Limited utility in quantifying extent of anticoagulation
Ecarin Clotting Time (ECT)	☑	Sensitive at all concentrations, limited availability
Chromogenic Anti Factor IIa Assays	-----	Minimal data, not available
Heptest	-----	Poor correlation, not useful
PiCT	-----	Not studied, not likely to be useful

Am J Health-Syst Pharm. 2012 Sept; 69:1473-84
Am J Health-Syst Pharm. 2013 May; 70:S21-31
Blood. 2013 Dec 6; 120(24):4699-705

Strategies for Reversals

Blood Products

Packed Red Blood Cells

- Maintain oxygenation and hemoglobin
- Will increase Hgb by appx 1

Fresh Frozen Plasma

- Contains clotting factors contained in human plasma
- 20-30% increase in plasma clotting factors

Platelets

- Human platelet concentrates
- May give in combo with DDAVP

Prothrombin Complex Concentrate (PCC)

Profilnine

- 3 factors
  - II, IX, X
- May use multiple doses
- No max dose

Kcentra

- 4 factors
  - II, VII, IX, X
- Repeat dosing not recommended
- Max dosing weight = 100kg

<u>Dosing is the same for both:</u>

- INR <4: 25 units/kg
- INR 4-6: 35 units/kg
- INR > 6: 50 units/kg

Am J Health-Syst Pharm. 2013 May;70:S3-11

FFP vs. PCC

	FFP	PCC
Dose	•Commonly appx 2 unites • 10-30 mL/kg (appx 200-250 mL/unit)	•Expressed as Factor IX •25-50 units/kg
Adverse Reactions	•Hemolytic Reaction •Acute Lung Injury •Hypersensitivity	•Hypersensitivity •Thrombosis (1-2%)
Price	$40/pack	$1.27 per unit
Advantages	Contains all factors found in human plasma	•Fast administration •No type and cross needed
Disadvantages	•Large Volume •Need to be thawed •Risk for transmission of disease	•Expensive •Risk of infectious disease transmission

Factor VIIa – NovoSeven RT

- Recombinant Activated Factor VII
- Dose 10-20 mcg/kg, max 100 mcg/kg
  - Higher risk for thrombosis with higher dosing
  - Dosing regimen evidence isn’t clear
- Activated products carry a higher risk of arterial thrombosis

Vitamin K

- Can be used to reverse Warfarin
- Can be used if patient cannot wait for Warfarin to wear off or if they are actively bleeding

Route	Reversal Time	Dose
IV	12-16 hours	5-10 mg
PO	24 hours	2-5 mg

Protamine Sulfate

- Used to reverse heparin (unfractionated and low molecular weight)
- Max dose of 50 mg
- As time passes from heparin administration, dose needed drops

	Unfractionated Heparin	Low Molecular Weight Heparin	Dalteparin (Fragmin)
1 mg Protamine Neutralizes	100 units	1 mg	100 anti-Xa units

Desmopressin (DDAVP)

- *De-amino d-arginin vasopressin*
- Often given in addition to platelets
- Increases Von Willebrand Factor and Factor XIII
- Dosing
  - 0.3 mcg/kg in 100 mL of saline administered over 30 minutes
  - Effect is immediate

J Thromb Haemost 2011;9:1705-12
J Thromb Haemost 2003;1:682-9

Reversal of Selected Agents

Drug Class	Antidote	Dialysis	Recommendations
Antiplatelets	Desmopressin (DDAVP)	Acute ASA toxicity only	• Platelets - ASA only – 1 pack - Combo Therapy – 2 packs • Factor VIIa • pRBC
Vitamin K Antagonists Warfarin (Coumadin)	Vitamin K	No	• Vitamin K +/- PCC • FFP •pRBCs
Dabigatran (Pradaxa)	In Development	Yes	• PCC 50 units/kg IV • Factor VIIa 90 mcg/kg IV • FFP • pRBC

Reversal of Selected Agents

Drug Class	Antidote	Dialysis	Recommendations
Factor Xa Inhibitors	In Development	No	• PCC 50 units/kg IV • Factor VIIa 30 mcg/kg IV • FFP • pRBC
Heparin & Low Molecular Weight Heparins	Protamine Sulfate	No	• FFP • pRBC

Possible New Agents on the Horizon

- Potential Future Reversals
  - Dabigatran monoclonal antibody fragment
  - Rivaroxaban, apixaban, LMWH antidote
    - Factor X Fragment

- New Agents being Studied
  - Cangrelor—P2Y12 Inhibitor, IV Route with Rapid Onset
  - Endoxaban—Factor Xa Inhibitor, PO Route

Blood. 2012 Dec 6; 120(24):4699-705
Best Pract Res Clin Haematol. 2013 Jun;26(2):191-202

Questions

- How urgent is the procedure? Can it wait for the agent to wear off on its own?
- What reversal strategy is most appropriate for the agent in use?
- Will the patient need to restart the medication? If so, what would be the safest way to do so?

Thank you to…

- Carlion Clinic Pharmacy

  Joleen Bierlein, Pharm.D.

References

1) Patel IJ, Davidson JC, Nikolic B, et al. Addendum of newer anticoagulants to the SIR consensus guideline. J Vasc Interv Radiol. 2013; 24:641-5.

2) Schlitt A, Jambor C, Spannagl M, et al. The perioperative management of treatment with anticoagulants and platelet aggregation inhibitors. Dtsch Arztebl Int. 2013;110(31-32):525-32.

3) Ortel TL. Perioperative management of patients on chronic antithrombotic therapy. Blood. 2012 Dec 6; 120(24):4699-705.

4) Nutescu EA. Oral anticoagulant therapies: Balancing the risks. Am J Health-Syst Pharm. 2013 May; 70:(S3-11)

5) Miyares MA, Davis K. Newer oral anticoagulants: A review of laboratory monitoring options and reversal agents in the hemorrhagic patient. Am J Health-Syst Pharm. 2012 Sept; 69:1473-84

6) Dager WE. Developing a management plan for oral anticoagulant reversal. Am J Health-Syst Pharm. 2013 May; 70:(S21-S31)

7) Levi M, Eerenberg E, Kamphuisen PW. Bleeding risk and reversal strategies for old an new anticoagulants and antiplatelet agents. J Thromb Haemost 2011; 9:1705-12

8) Kalus JS. Pharmacologic interventions for reversing the effects of oral anticoagulants. Am J Health-Syst Pharm. 2013 May; 70:(S12-S21).

9) Kaufmann JE, Vischer UM. Cellular mechanisms of the hemostatic effects of desmopression (DDAVP). J Thromb Haemost 2003;1:682-9.

10) Majeed A, Schulman S. Bleeding and antidotes in new oral anticoagulants. Best Pract Res Clin Haematol. 2013 Jun;26(2):191-202.