DISCLOSURES

CATEGORY	CONFLICT
Employment	No conflict of interest to disclose
Research support	No conflict of interest to disclose
Scientific advisory board	No conflict of interest to disclose
Consultancy	No conflict of interest to disclose
Speakers bureau	No conflict of interest to disclose
Major stockholder	No conflict of interest to disclose
Patents	No conflict of interest to disclose
Honoraria	No conflict of interest to disclose
Travel support	No conflict of interest to disclose
Other	No conflict of interest to disclose

A Look at Antithrombotic Therapy and Novel Anticoagulants

Anne Greist, MD
Indiana Hemophilia & Thrombosis Center
Indianapolis, IN
1-877-CLOTTER

OBJECTIVES

- Review the pharmacology of the novel (target specific) oral anticoagulants
- Explore their indications and use
- Discuss monitoring, management of bleeding, reversal

Incidence of VTE

Adults

- 300,000 – 600,000 cases / year DVT
- 2.5 - 5% of general population
- 100,000 - 200,000 deaths / year PE
- Venous thromboembolism third most common CV disease

1. **The Surgeon General's Call to Action to Prevent Deep Vein Thrombosis and Pulmonary Embolism. Office of the Surgeon General (US); National Heart, Lung, and Blood Institute (US). Rockville (MD): Office of the Surgeon General (US); 2008.**
2. **Beckman M G et al. Am J Prev Med 2010. 38(4 Suppl): S495-501.**

Risk Factors For Venous Thrombosis

ACQUIRED	INHERITED	MIXED/UNKNOWN
Advancing age	Factor V Leiden (FVL)	↑ Homocysteine
Obesity	Prothrombin G20210A	↑ Factor VIII
Prior thrombosis	Protein C deficiency	APC resistance
Immobilization	Protein S deficiency	↑ Factor IX
Major surgery	Antithrombin deficiency	↑ Factor XI
Malignancy	Dysfibrinogenemias (rare)	↓ Free TFPI
Estrogens		
Antiphospholipid antibody syndrome		
Myeloproliferative disorders, Malignancy, IBD, Nephrotic syndrome, Heparin induced thrombocytopenia		

Heit JA. J Thromb Haemost. 2005 Aug;3(8):1611-7. Review.

ATRIAL FIBRILLATION

Most common sustained cardiac arrhythmia

Fivefold increased risk of stroke

Oral anticoagulation is treatment of choice for patients with $CHAD_2$ score =/>2

May be indicated for $CHAD_2$ score = 1

VKA prevent stroke with a RR reduction of 65% compared with placebo

1. **CHEST 2012; 141(2)(Suppl):e531S–e575S**
2. **Chai-Adisaksopha C et al. Blood 2014;124(15):2450-2458.**

DISADVANTAGES OF VKAS

Slow onset and offset of action

Need for INR monitoring

Interactions with diet and many other drugs

Small therapeutic window

Bleeding complications: 1.5-5.2% per year

Chai-Adisaksopha C et al. Blood 2014;124(15):2450-2458.

TARGET-SPECIFIC ORAL ANTICAOGULANTS

Directly inhibit factor Xa:

- rivaroxaban
- apixaban
- edoxaban
- (betrixaban, darexaban)

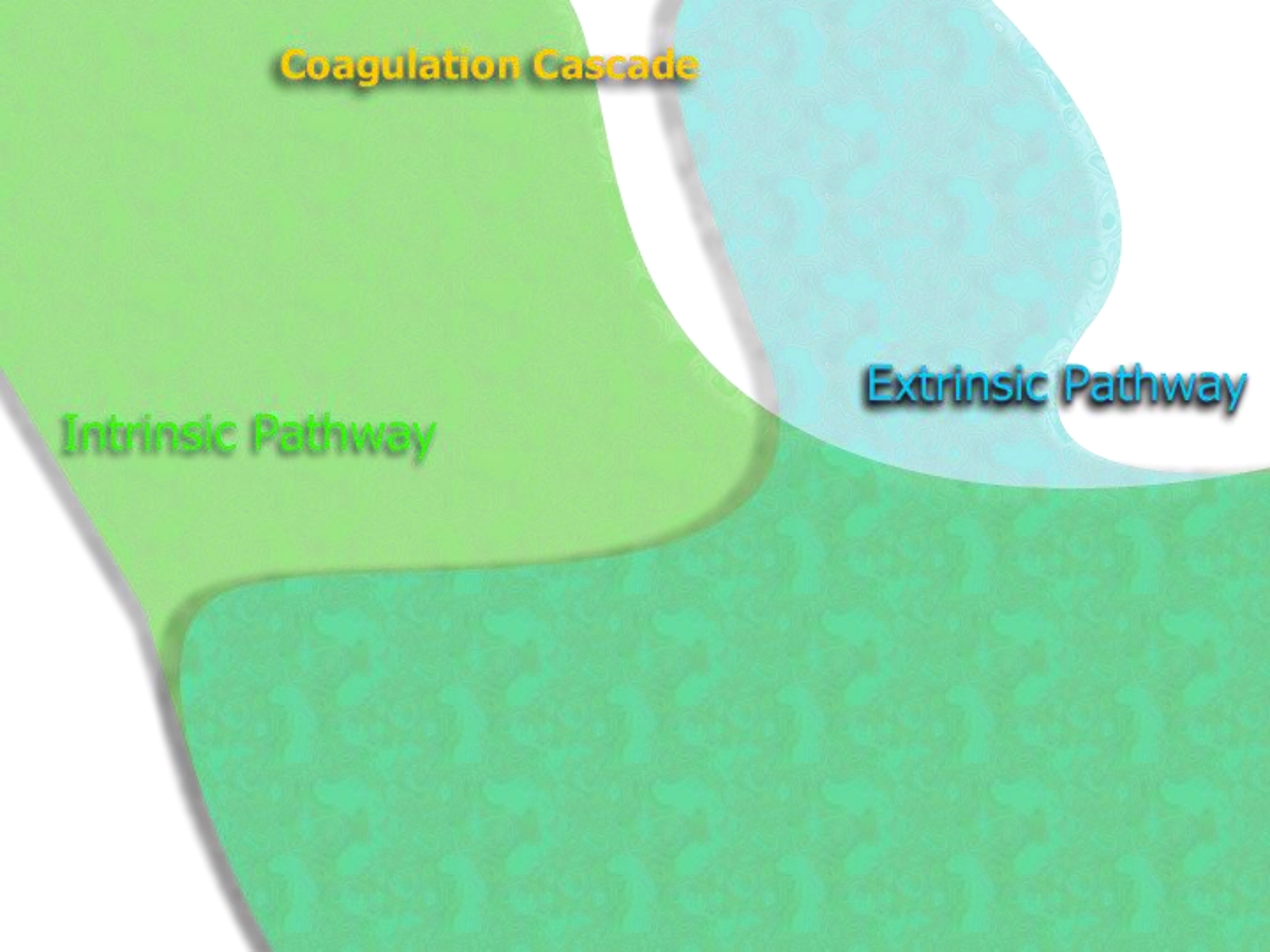
Directly inhibits thrombin:

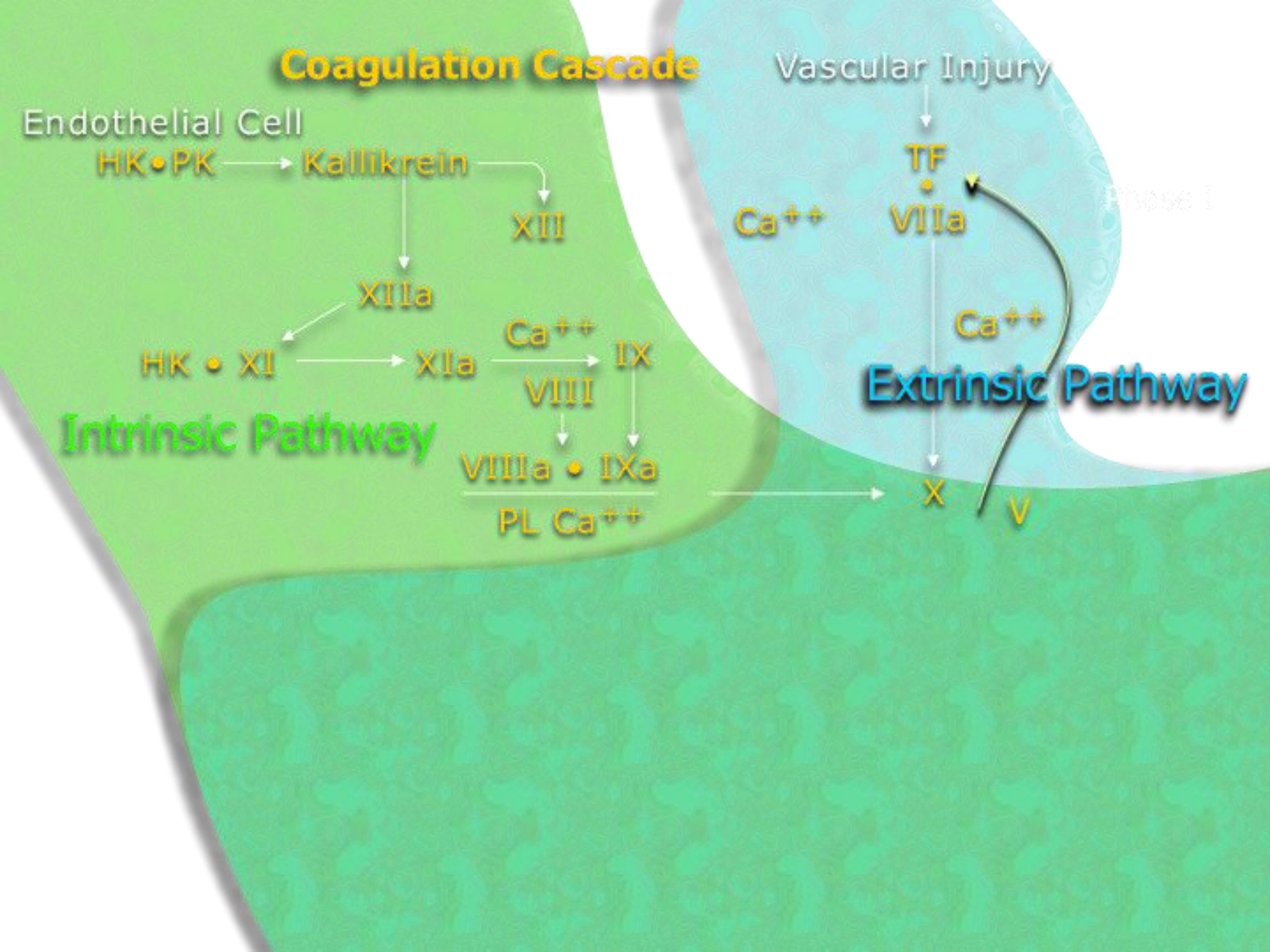
- dabigatran

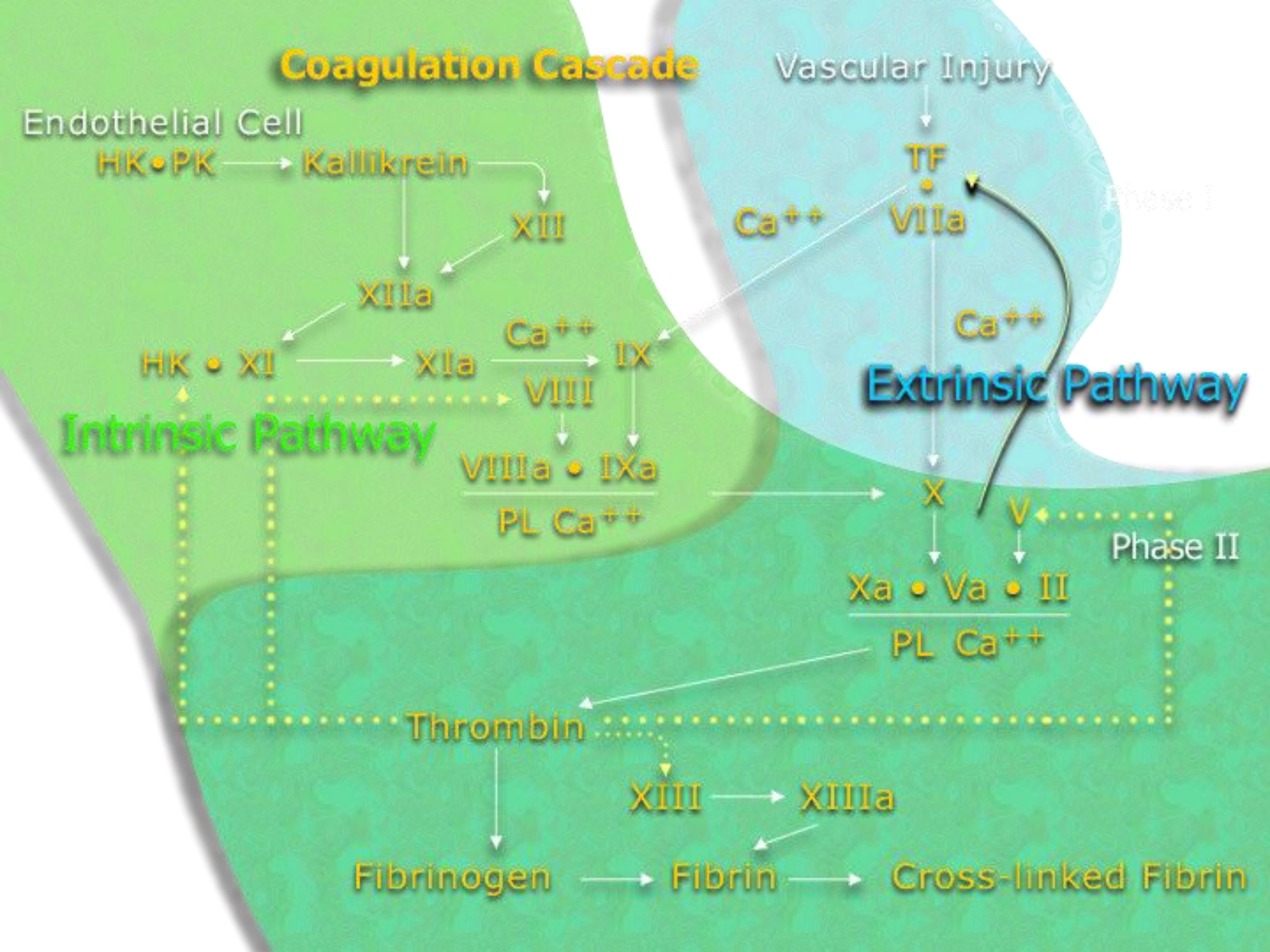
Chai-Adisaksopha C et al. Blood 2014;124(15):2450-2458.

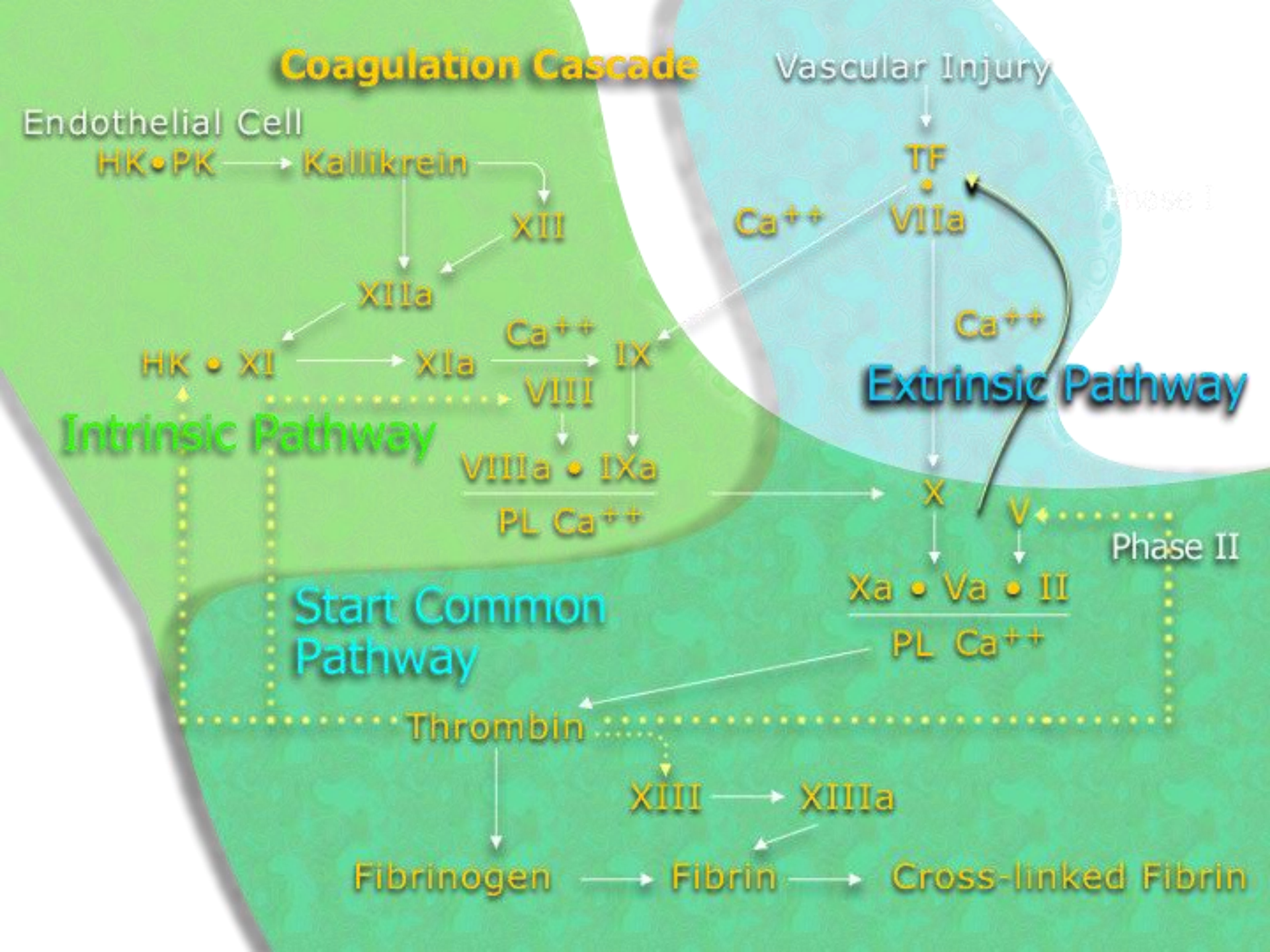
Coagulation Cascade

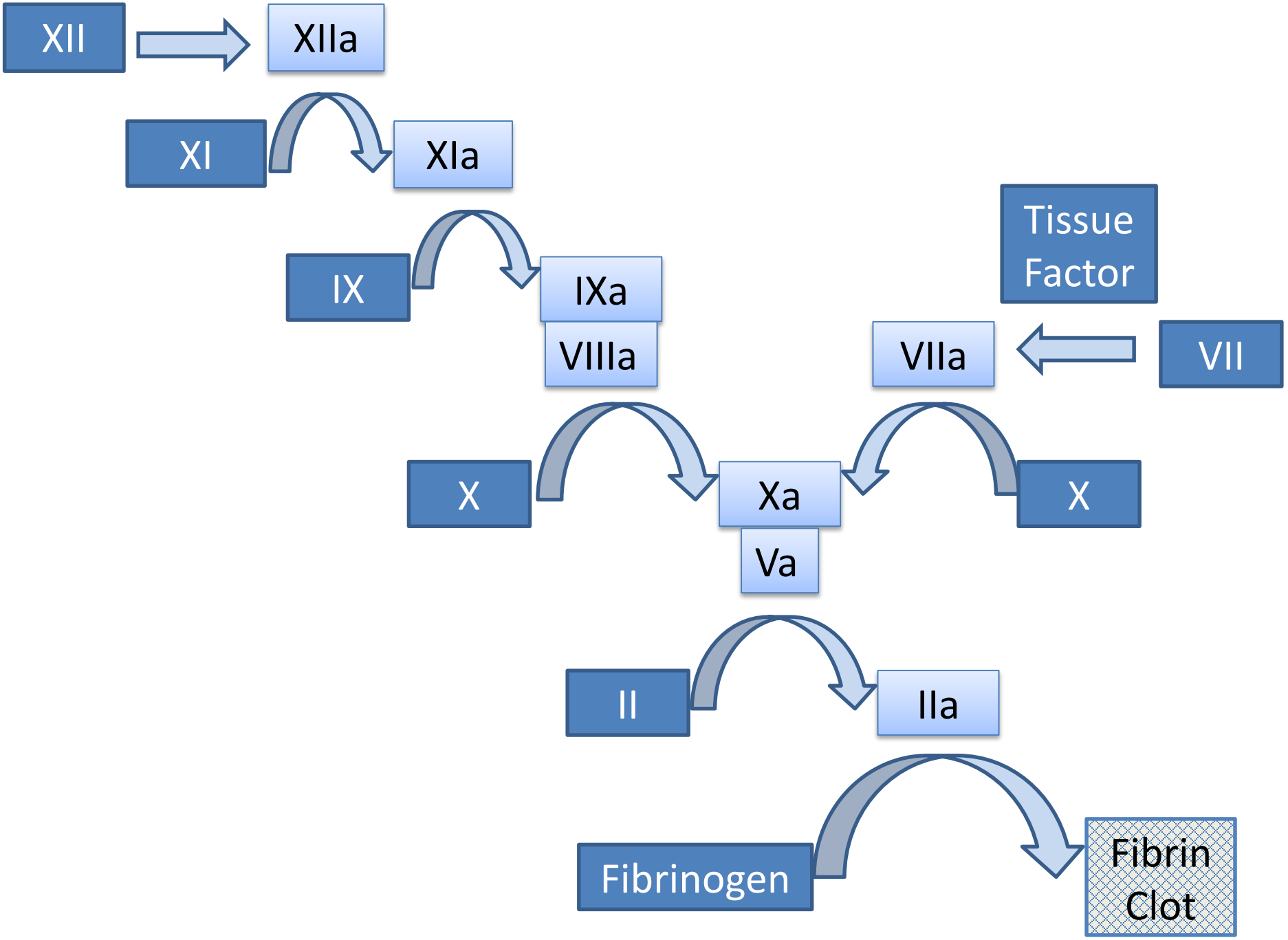
Intrinsic Pathway

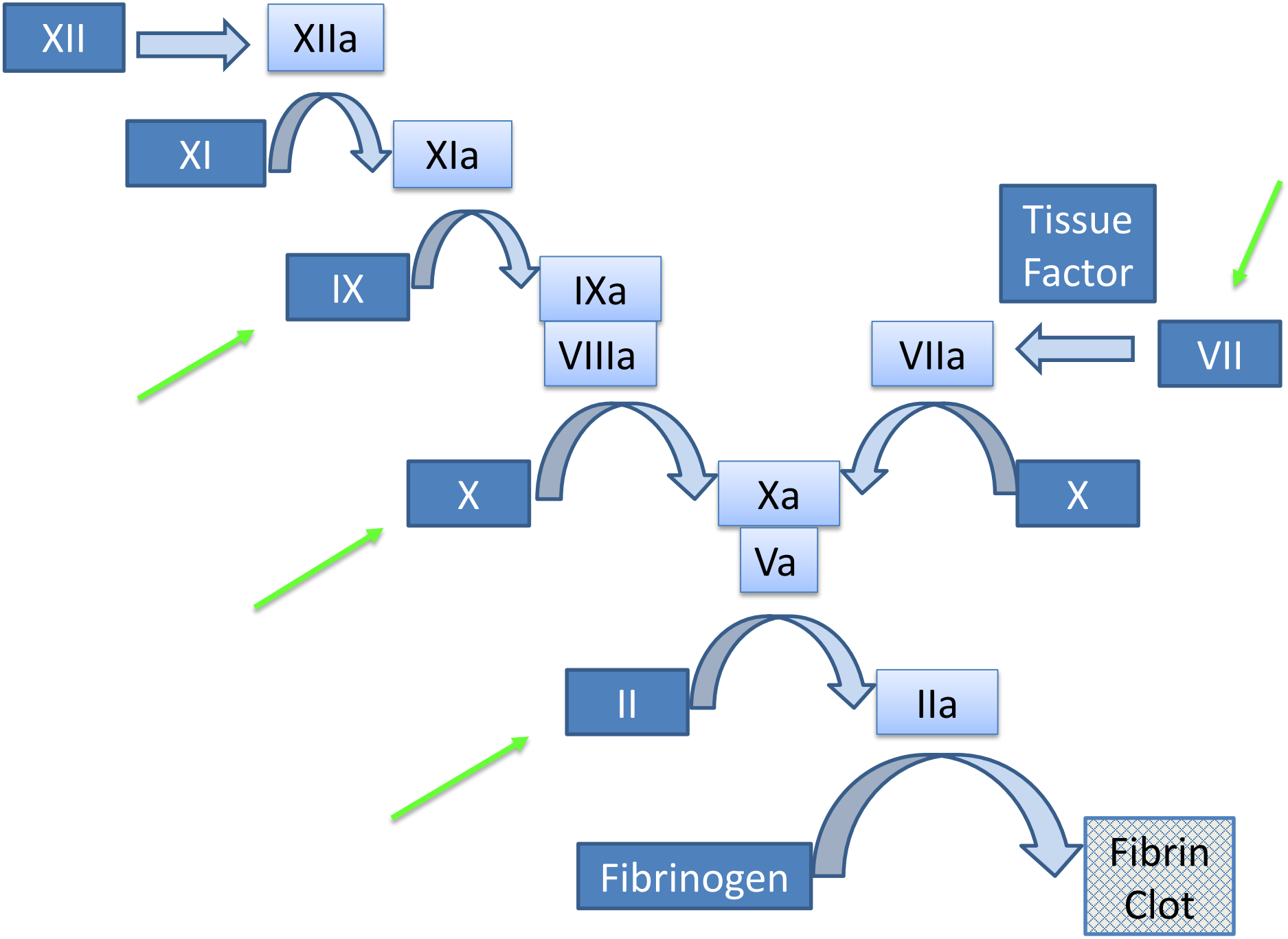

Coagulation Cascade
Extrinsic Pathway
Intrinsic Pathway

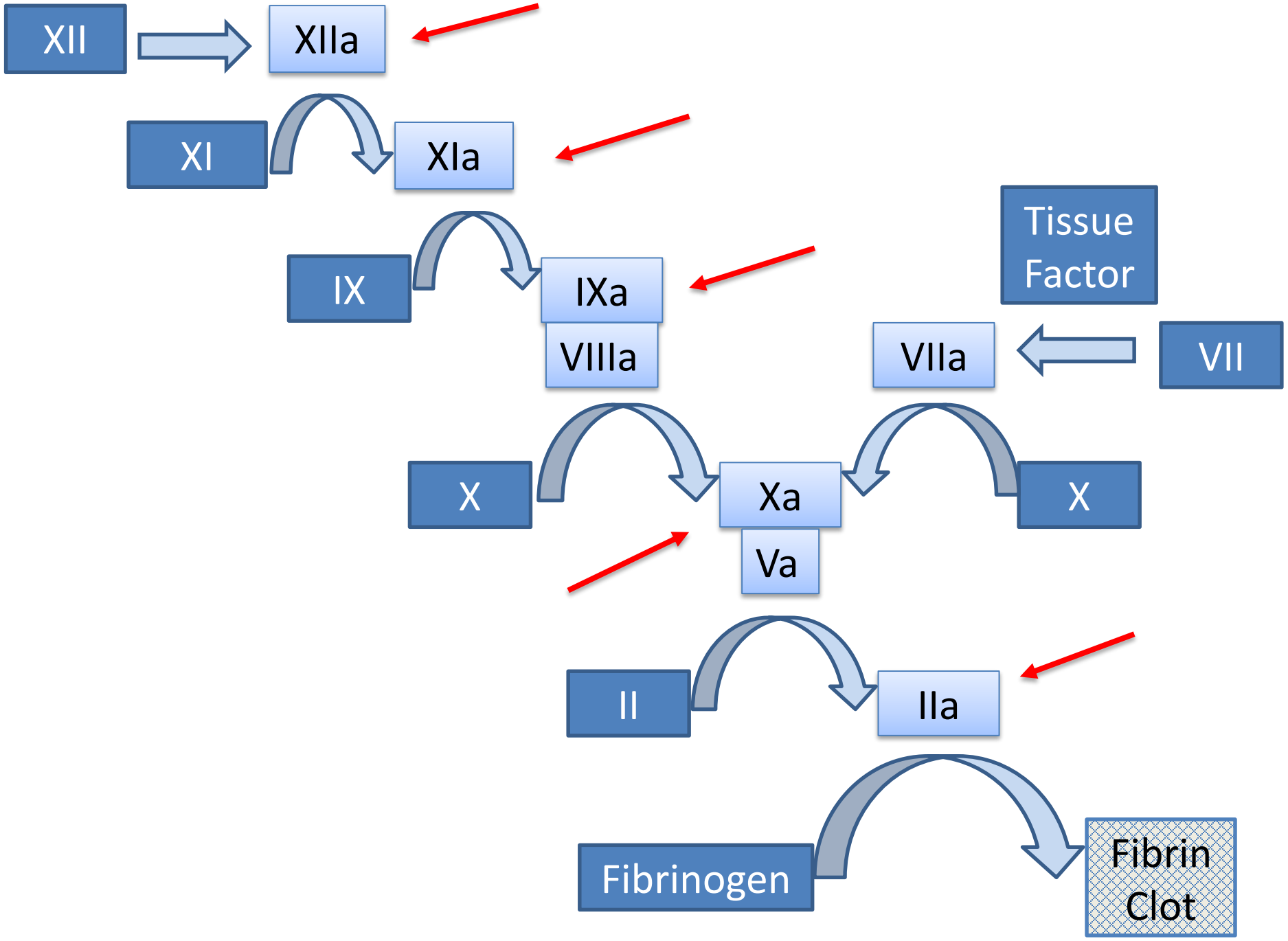

Coagulation Cascade
Endothelial Cell
HK • PK
Kallikrein
XII
XIIa
HK • XI
XIa
Ca++
IX
VIII
Intrinsic Pathway
VIIIa • IXa
PL Ca++
Vascular Injury
TF
Ca++
VIIa
Ca++
Extrinsic Pathway
X
V

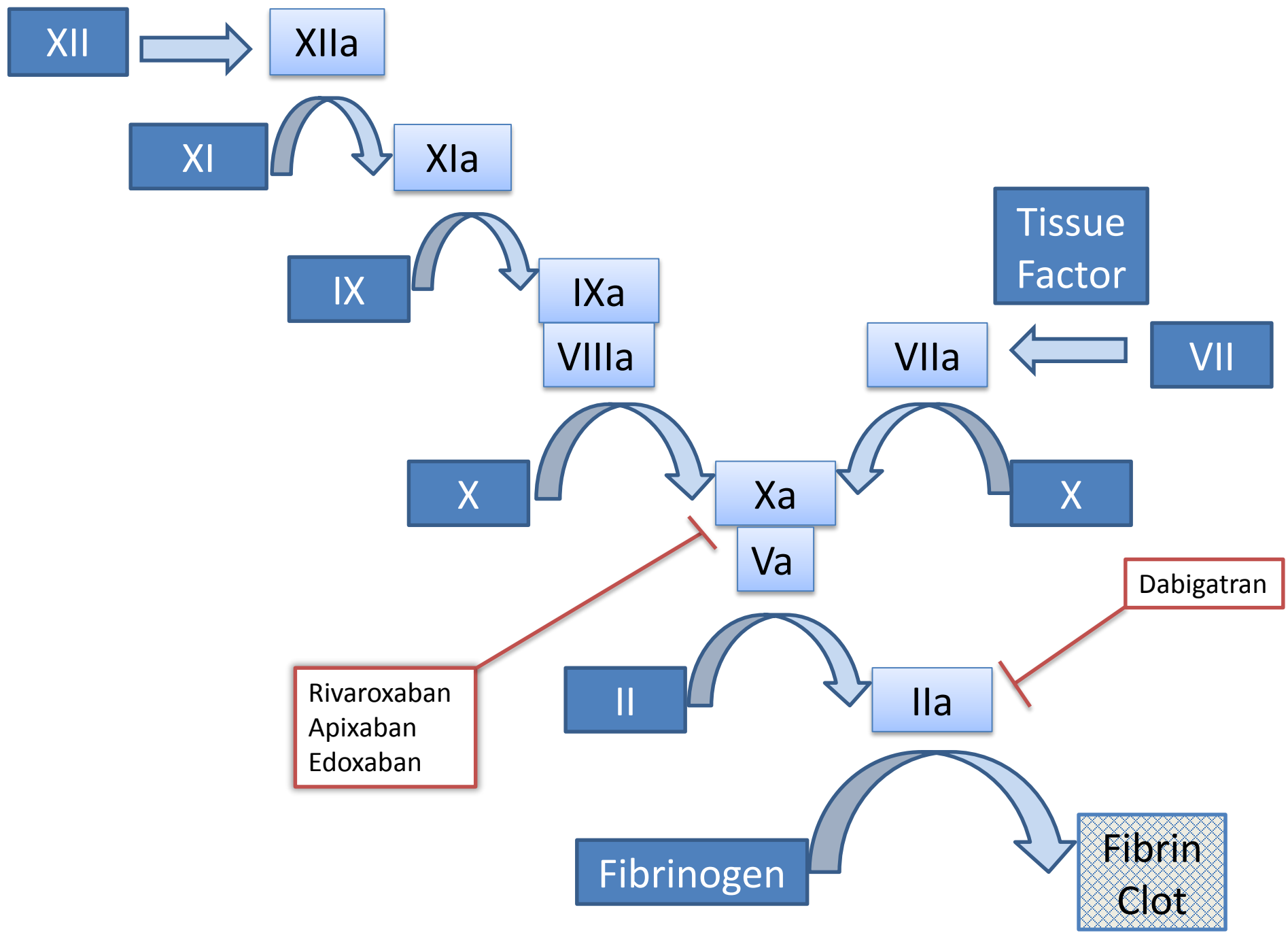

Coagulation Cascade
Vascular Injury
Endothelial Cell
HK • PK
Kallikrein
XII
XIIa
TF
Ca++
VIIa
HK • XI
XIa
Ca++
IX
VIII
Ca++
Extrinsic Pathway
Intrinsic Pathway
VIIIa • IXa
PL Ca++
X
V
Phase II
Xa • Va • II
PL Ca++
Thrombin
XIII
XIIIa
Fibrinogen
Fibrin
Cross-linked Fibrin


Coagulation Cascade
Vascular Injury
Endothelial Cell
HK • PK
Kallikrein
XII
XIIa
TF
Ca++
VIIa
HK • XI
XIa
Ca++
IX
VIII
Ca++
Extrinsic Pathway
Intrinsic Pathway
VIIIa • IXa
PL Ca++
X
V
Phase II
Start Common Pathway
Xa • Va • II
PL Ca++
Thrombin
XIII
XIIIa
Fibrinogen
Fibrin
Cross-linked Fibrin


XII
XIIa
XI
XIa
IX
IXa
VIIIa
Tissue Factor
VIIa
VII
X
Xa
Va
X
II
IIa
Fibrinogen
Fibrin Clot


XII
XIIa
XI
XIa
IX
IXa
VIIIa
Tissue Factor
VII
VIIa
X
Xa
Va
X
II
IIa
Fibrinogen
Fibrin Clot


XII
XIIa
XI
XIa
IX
IXa
VIIIa
Tissue Factor
VIIa
VII
X
Xa
X
Va
II
IIa
Fibrinogen
Fibrin Clot


XII
XIIa
XI
XIa
IX
IXa
VIIIa
Tissue Factor
VIIa
VII
X
Xa
X
Va
Dabigatran
Rivaroxaban
Apixaban
Edoxaban
II
IIa
Fibrinogen
Fibrin Clot

Novel Oral Anticoagulants

- Directly inhibit either Xa or IIa without requiring antithrombin
  - All heparinoids and pentasaccharides require antithrombin to function
- Do not require routine monitoring of levels
- No reliable method to reverse critical bleeding
- Short half-life so missed doses result in lack of protection

Comparison of RR

Event	Dabigatran	Rivaroxaban	Apixaban
Embolism/stroke	0.77 (0.61-0.99)	0.93 (0.74-1.16)	0.96 (0.77-1.20)
VTE	1.1 (0.66-1.84)	0.70 (0.46-1.07)	1.13 (0.76-1.69)
Intracranial hemorrhage	0.26 (0.14-0.5)	0.58 (0.37-0.92)	0.51 (0.35-0.75)
GI bleeding	1.5 (0.99-2.28)	1.46 (1.19-1.78)	0.88 (0.68-1.14)
Major bleeding	0.90 (0.60-1.37)	1.03 (0.89-1.18)	0.70 (0.61-0.81)

* RR all relative to warfarin = 1.0

Adam SS, McDuffie JR, *et al.* Ann Intern Med 2012;157:796.

DABIGATRAN

- Avoid if CrCl <30
- Use 75 mg bid if CrCl 15-30
- Food delays but does not reduce absorption
- Affects TT>PTT>PT
- 85% renal clearance
- $T_{1/2}$: 12-17h; mild-moderate CKD 15-18h; severe CKD 28h
- Protein binding 35%

1. **Pradaxa Prescribing Information. Boehringer Ingelheim Pharmaceuticals. Updated 04/2014.**
2. **Lexi-Comp Online, Lexi-drugs. Hudson, Ohio: Lexi-Comp, Inc.; 2014.**
3. **Crowther M et al. Arterioscler Thromb Vasc Biol. 2015; 35:1736-1745**

Factor Xa Inhibitors

Rivaroxaban

- Approved for VTE, AF and VTE prophylaxis
- Take with food
- Affects anti-Xa>PT>PTT
- 66% renal clearance
  - VTE: Avoid if CrCl <30 mL/min
  - AF: 15 mg daily if CrCl 15-50
- $T_{1/2}$: 5-9h or 11-13h if elderly
- Not influenced by extremes of body weight

Apixaban

- Approved for VTE, AF and VTE prophylaxis
- Not affected by food
- Affects anti-Xa levels
- 27% renal clearance
  - Reduce dose if 2 of: age >80, creatinine >1.5, weight <60 kg
- $T_{1/2}$: ~12h

1. **Eliquis Prescribing Information. Bristol-Meyers Squibb. Updated 03/2014.**
2. **Xarelto Prescribing Information. Janssen Pharmaceuticals. Updated 03/2014.**
3. **Lexi-Comp Online, Lexi-drugs. Hudson, Ohio: Lexi-Comp, Inc.; 2014.**

PHARMACOKINETICS

	Warfarin	Dabigatran	Apixaban	Rivaroxaban	Edoxaban
Bioavailability	100%	6.5%	50%	80-100%	60%
Max concentration	4h	0.5-2h	3-4h	2-4h	1.5h
Half-life	20-60h	12-14h	12h	11-13h 5-9h (young)	10-14h
Renal clearance	0%	85%	27%	66%	33%
Protein binding	99%	35%	87%	92-95%	40-59%

Crowther M et al. Arterioscler Thromb Vasc Biol. 2015; 35:1736-1745

Dosing Considerations

Condition	Dabigatran	Rivaroxaban	Apixaban
Liver disease	Use caution	Contraindicated if Child's B or C	Caution if Child's B; Contraindicated if Child's C
CrCl 15-30	Adjust dose if used for AF (contraindicated in Canada)	Not recommended	Caution*
CrCl <15	Contraindicated	Contraindicated	Not recommended‡
Pregnancy	Category C; not recommended	Category C	Category B; still not recommended
Lactation	Unknown if excreted in breast milk; not recommended	Unknown if excreted	Unknown if excreted; not recommended

* Reduce dose if at least 2 are true: creatinine ≥1.5, age ≥80 years, or weight <60 kg.

‡ Label approves use in ESRD, but American Heart Association recommends against use.

Selected Drug Interactions

Medications	Dabigatran	Rivaroxaban	Apixaban
Antacids	Not recommended, May reduce absorption	—	—
Azole antifungals (excludes fluconazole)	Not recommended	Avoid combination	Avoid combination
HIV/HCV antivirals	Monitor therapy	Avoid combination	Avoid combination
Rifamycins	Avoid combination	Avoid combination	Avoid combination
Quinidine	Not recommended	Monitor therapy	Monitor therapy
Dronedarone	Not recommended	Avoid combination	Monitor therapy
Amiodarone	Consider alternative, monitor therapy	Monitor therapy	Monitor therapy
Clarithromycin	May increase levels, monitor therapy	May increase levels, monitor therapy	Avoid combination

Lexi-Comp Online, Lexi-Interact. Hudson, Ohio: Lexi-Comp, Inc.; 2014.

How to address bleeding in patients taking target specific oral anticoagulants

PUTTING THE BRAKES ON

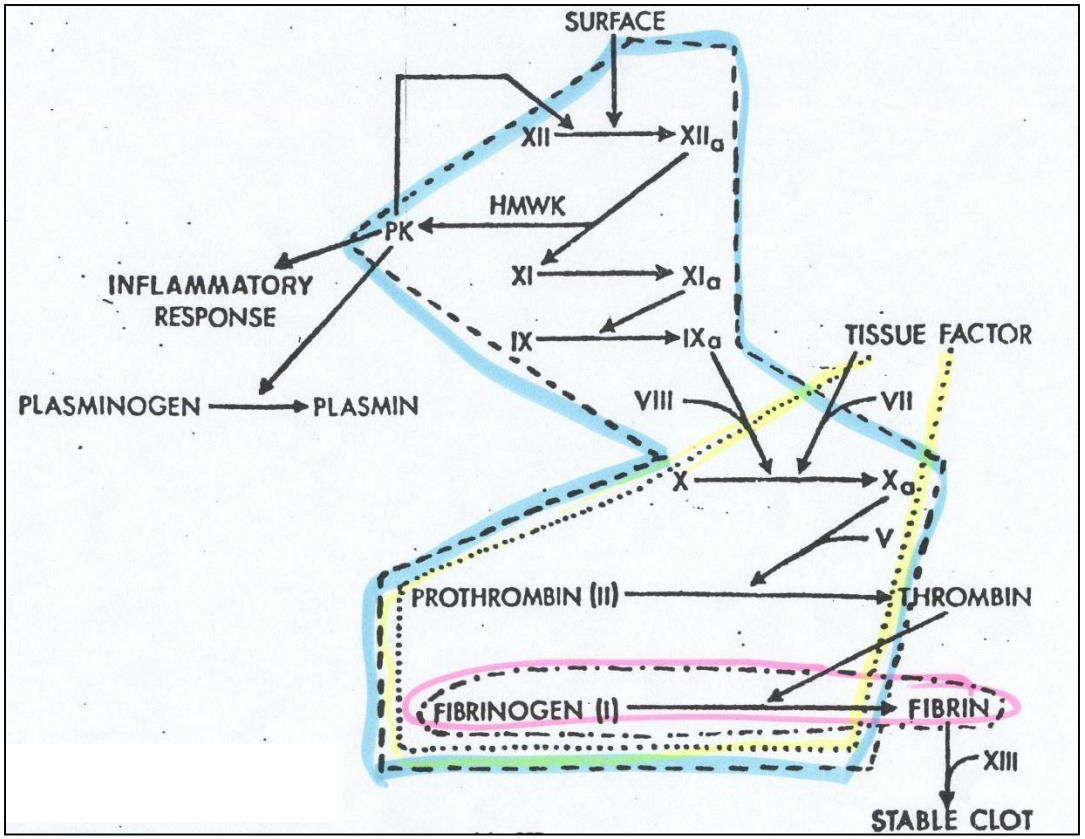
DRUG MONITORING

	PT	aPTT	TT	Dilute TT	Anti-Xa
Dabigatran	**+/-**	**↑**	**↑↑↑**	**↑↑**	**NA**
Rivaroxaban	**↑**	**+/-**	**NA**	**NA**	**↑↑**
Apixaban	**↑**	**+/-**	**NA**	**NA**	**↑↑**
Edoxaban	**↑**	**↑↑**	**Unclear**	**Unclear**	**Unclear**

+/-	May increase or produce no change. Reagent and individual dependent.
↑	Variable Increase
↑ ↑	Predictable increase that may be calibrated
↑ ↑ ↑	Highly sensitive increase, often exceeding upper limit of assay

1. **Siegal DM, Garcia DA*, et al.* Blood 2014;123:1152.**
2. **Crowther M et al. Arterioscler Thromb Vasc Biol. 2015; 35:1736-1745**

Procoagulants Measured by Screening Tests



APTT sensitive to intrinsic and common pathway factors or inhibition of the coagulation process

PT sensitive to extrinsic and common pathway factors or inhibition of the coagulation process

TT sensitive to quantity and quality of fibrinogen or inhibition of the fibrin clot formation

Risk Factors for Bleeding with Anticoagulant Therapy & Estimated Risk of Major Bleeding in Low-, Moderate-, & High-Risk Categories

Risk Factors

- Age > 65 years
- Age >75 years
- Previous bleeding
- Cancer
- Metastatic cancer
- Renal failure
- Liver failure
- Thrombocytopenia
- Previous stroke
- Diabetes
- Anemia
- Antiplatelet therapy
- Poor anticoagulant control
- Comorbidity & reduced functional capacity
- Recent surgery
- Frequent falls
- Alcohol use

	Estimated Absolute Risk of Major Bleeding %		
Categorization of Risk of Bleeding	Low Risk (0 Risk Factors)	Moderate Risk (1 Risk Factor)	High Risk (≥ 2 Risk Factors)
Anticoagulation 0-3 months			
Baseline risk (%)	0.6	1.2	4.8
Increased risk (%)	1.0	2.0	8.0
Total risk (%)	1.6	3.2	12.8
Anticoagulation after first 3 months			
Baseline risk (% per year)	0.3	0.6	≥ 2.5
Increased risk (% per year)	0.5	1.0	≥ 4.0
Total risk (% per year)	0.8	1.6	≥ 6.5

Kearon C et al American College of Chest Physicians. Chest. 2012 Feb;141(2 Suppl):e419S-94S. Erratum in: Chest. 2012 Dec;142(6):1698-1704. Adapted from Table 2 [Section 2.3, 3] pg 2432S.

Anticoagulation Reversal

- Blocking absorption
- Removing the circulating drug
- Increasing excretion
- Inactivating the drug
- Increasing the targeted clotting factor
- Promoting coagulation

Anticoagulation Reversal

- Increasing the target
  - PCC: Kcentra® 50 units/kg
  - aPCC: FEIBA® 50 units/kg
- Promoting coagulation
  - rFVIIa: NovoSeven® 90 mcg/kg

SPECIFIC ANTIDOTES

- Idarucizumab: RE-VERSE AD
- Andexanet alfa
- PER977

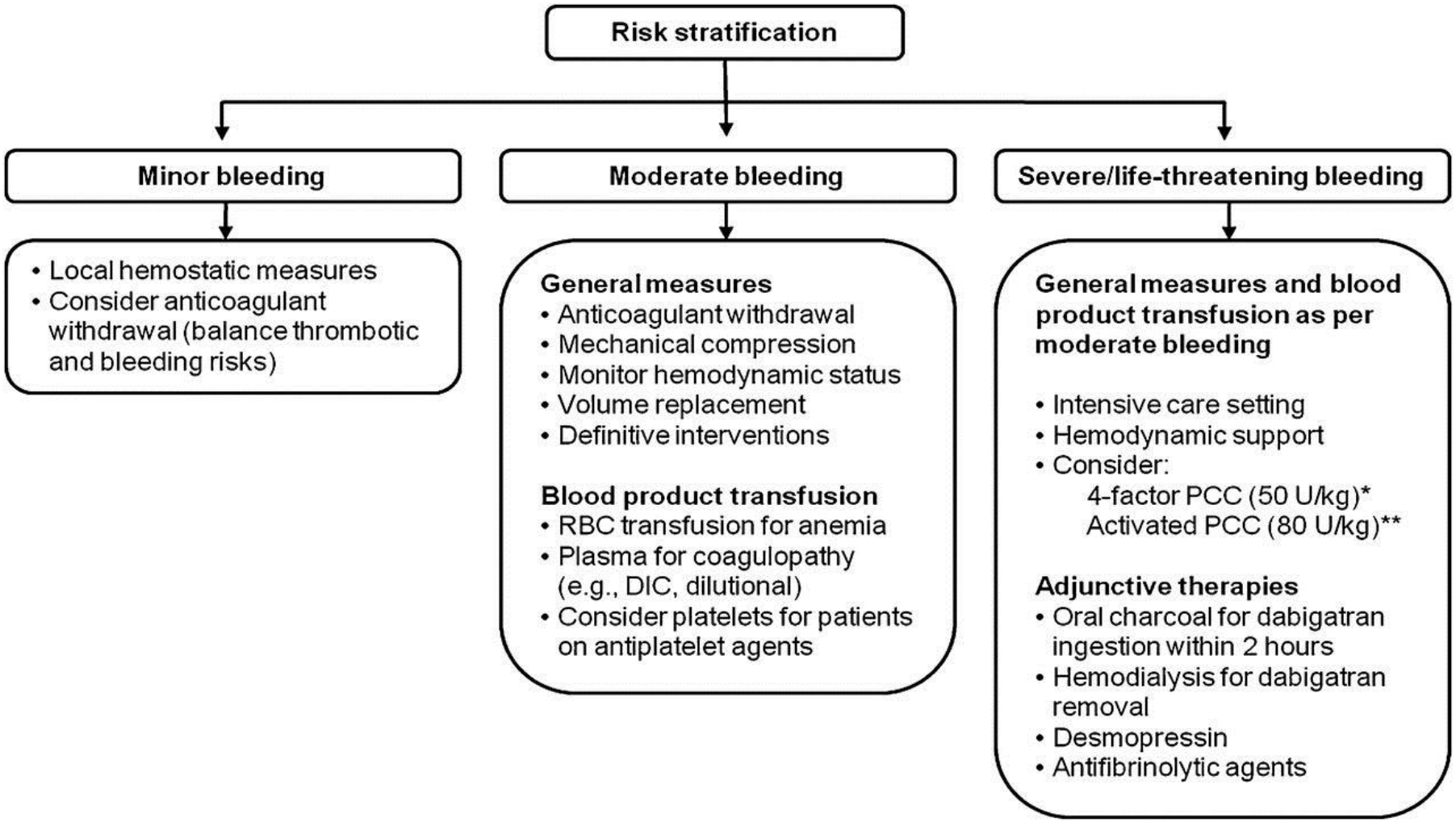
Crowther M et al. Arterioscler Thromb Vasc Biol. 2015; 35:1736-1745

REVERSE-AD

- A Study of the RE-VERSal Effects of Idarucizumab on Active Dabigatran
- Patients on dabigatran
  - Active major bleeding
  - Needing emergency surgery
  - Given idarucizumab 5 gm IV
  - Data obtained on bleeding, clotting assays and dabigatran levels

Pollack, Jr CV et al. N Engl J Med 2015;373:511-20

Suggested strategy for management of TSOAC-associated bleeding.



Siegal D M et al. Blood 2014;123:1152-1158

blood

CONCLUSIONS

1. These drugs seem to have comparable efficacy when compared with warfarin, with fewer intracranial hemorrhages
2. Risk of major bleeding is reduced with apixaban, but equivalent with rivaroxaban and dabigatran
3. Dabigatran and rivaroxaban seem to increase the rate of GI bleeding
4. We cannot measure levels to adjust for drug interactions
5. The recommendations for reversal of these drugs are based on studies in animals and healthy volunteers, or nonrandomized trials
6. Long term side effects may still be unknown

SUMMARY

- Novel anticoagulants are appealing, but should be used with caution
- As TSOACs become more widespread, automated testing will be needed in routine hospital laboratories
- Bleeding from novel anticoagulants is primarily supportive unless life threatening, in which case PCC or aPCC could be used; there are specific antidotes in development