

Selection and Dosing of Anticoagulants

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Objectives



Describe anticoagulant mechanisms of action and dosing for FDA approved treatment indications



Understand relative benefits and limitations of available anticoagulants including drug and disease state interactions

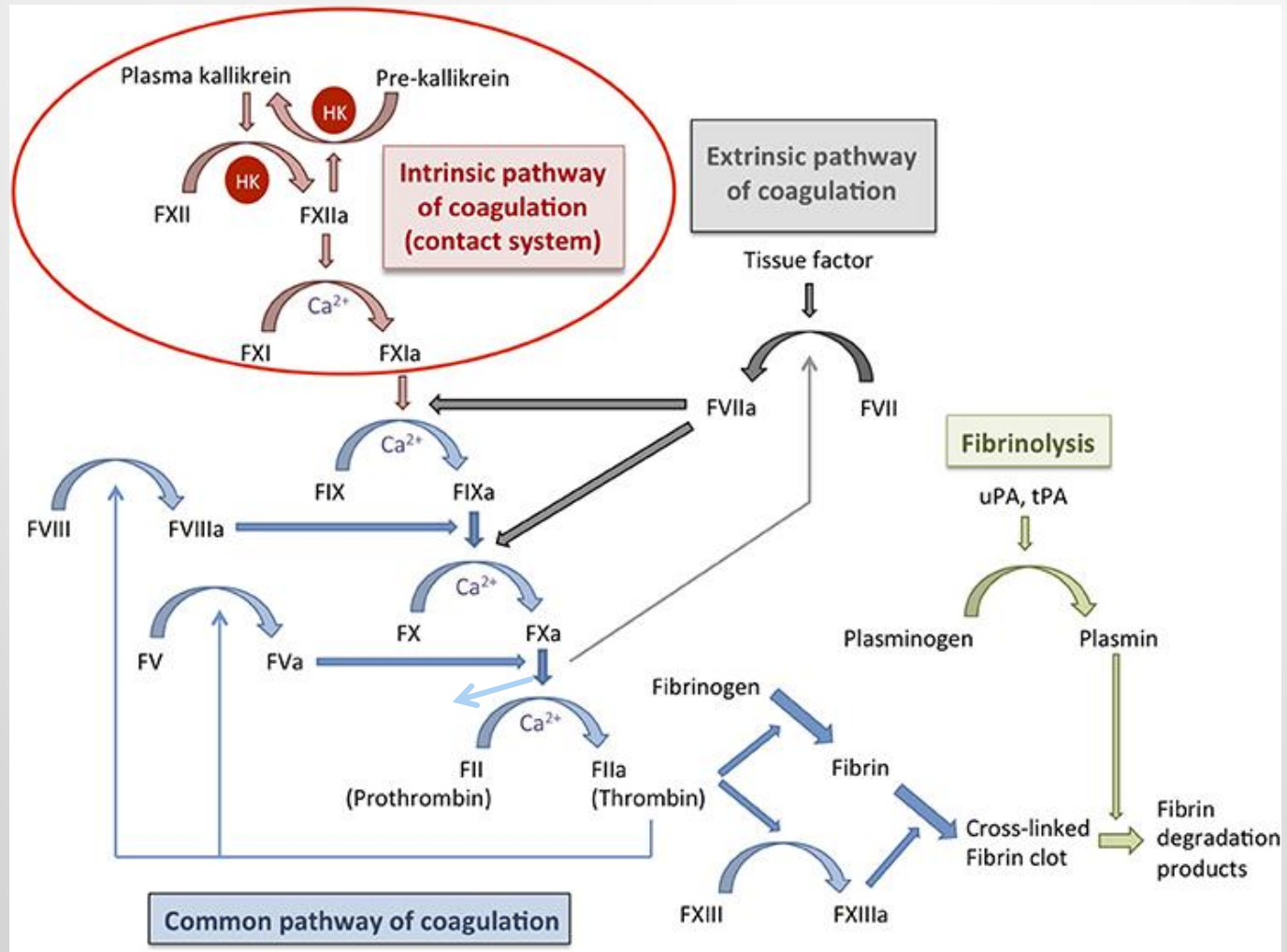


Design an appropriate dosing and monitoring plan for a selected anticoagulant

Anticoagulant Class Review

Class	Agents	Formulation
heparin	unfractionated heparin	IV, SQ injection
low molecular weight heparins	enoxaparin (Lovenox®) dalteparin (Fragmin®)	SQ injection
factor Xa Inhibitors	fondaparinux (Arixtra®)	SQ Injection
	apixaban (Eliquis®) rivaroxaban (Xarelto®) edoxaban (Savaysa®)	tablets
direct thrombin inhibitors	argatroban, bivalirudin dabigatran (Pradaxa®)	IV injection tablet
vitamin K antagonists	warfarin, (Coumadin®, Jantoven®)	tablet

Coagulation Cascade Review



Parenteral Anticoagulants

Heparins

Direct
Thrombin
Inhibitors

Indirect
Factor Xa
Inhibitors

Parenteral Anticoagulants: Heparins

Agent, Route	FDA Labeled Indications	VTE Dosing (Use Total Body Weight)	Dose Adjustments, Notes
unfractionated heparin (UFH), <i>IV, Subcutaneous</i>	<ul style="list-style-type: none"> VTE treatment, prophylaxis ACS 	<p>Therapeutic:</p> <ul style="list-style-type: none"> 80 units/kg IV bolus, then 18 units/kg/hr continuous IV infusion; Titrate to target aPTT/Xa 5,000 units or 333 units/kg as SC bolus, then 250 units/kg SC q12hr <p>Prophylaxis:</p> <ul style="list-style-type: none"> 5000 units q8-12hr 7500 units q8-12hr (obesity) 	<ul style="list-style-type: none"> Hepatic dysfunction: consider reduced initial infusion rate Comorbid conditions which increase risk of bleeding Renal Failure: None AE: heparin antibody development
enoxaparin (Lovenox®), <i>Subcutaneous</i>	<ul style="list-style-type: none"> VTE treatment, prophylaxis ACS 	<p>Therapeutic:</p> <ul style="list-style-type: none"> 1 mg/kg SC Q12hr (preferred) 1.5 mg/kg SC q24hr, 0.8 mg/kg SC q12hr (obesity) <p>Prophylaxis:</p> <ul style="list-style-type: none"> 40 mg SC Q24h 	<ul style="list-style-type: none"> Therapeutic dose: CrCL < 30 ml/min: 1 mg/kg Q 24hr; Avoid in ESRD Prophylactic dose: 30 mg SC q24hr if CrCL < 30 ml/min; Avoid in ESRD No dose adjustment for hepatic dysfunction AE: heparin antibody development
dalteparin (Fragmin®), <i>Subcutaneous</i>	<ul style="list-style-type: none"> VTE treatment, prophylaxis ACS 	<p>Therapeutic:</p> <ul style="list-style-type: none"> 200 units/kg SC q24hr, or 100 units/kg SC q12hr <p>Prophylaxis:</p> <ul style="list-style-type: none"> 5,000 units SC Q24h 	<ul style="list-style-type: none"> CrCL < 30 ml/min: Avoid use Altered dosing recommendations for patients with malignancy-associated VTE

Anti-Xa Monitoring for Low Molecular Weight Heparin Therapy

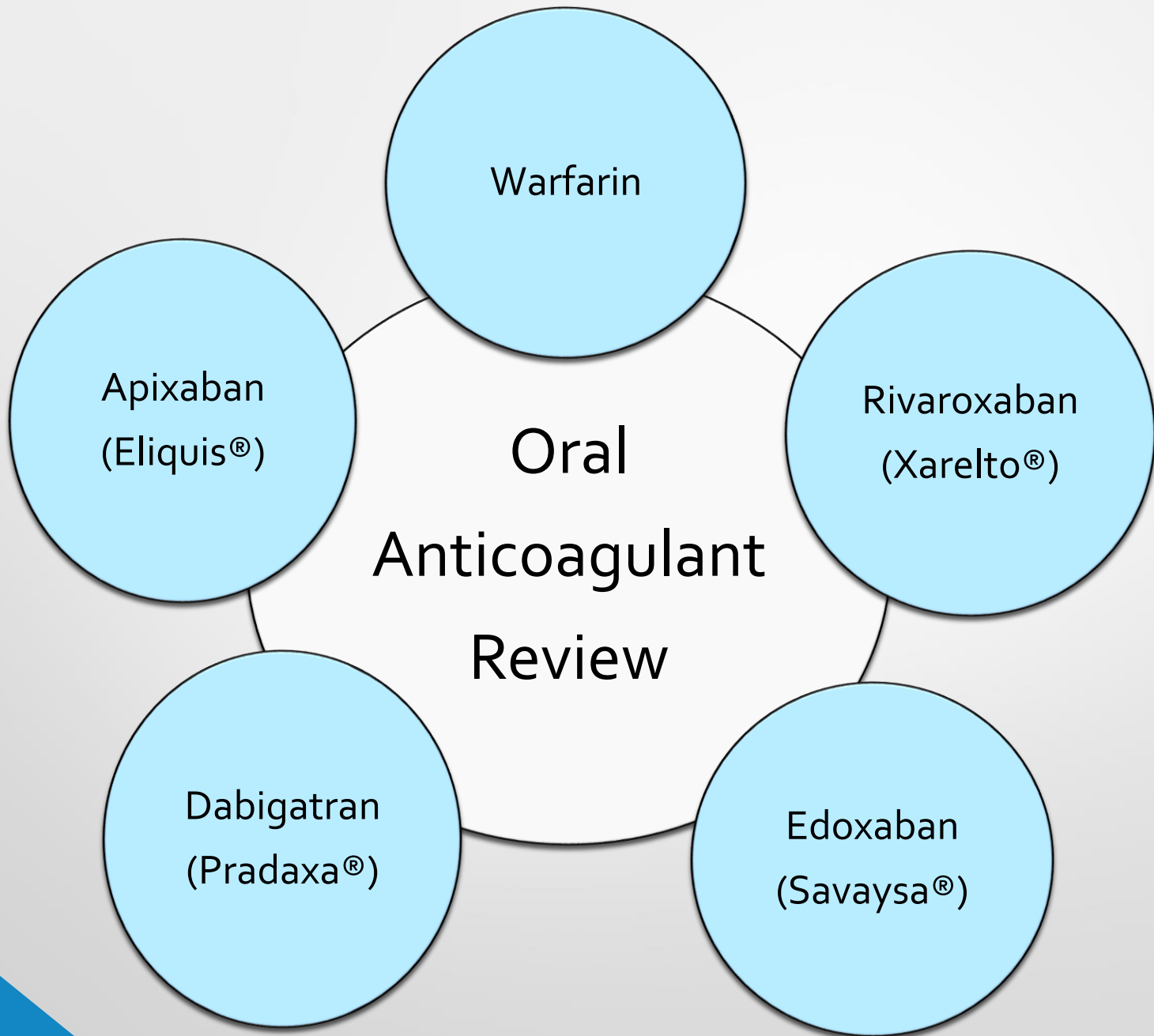
- Potential Indications for Anti-Xa monitoring
 - Extremes of weight
 - Renal impairment
 - Pregnancy
- Anti-Xa Monitoring
 - Peak levels (4h post-dose): obesity
 - Trough levels (1h prior to next dose): renal impairment
 - Dose adjustments by 25% increments

Indication	Dose frequency	Timing of level	Anti-Xa Goal (IU/mL)
VTE treatment	Q12h* (1 mg/kg)	Peak	0.6 – 1.2
VTE treatment	Q24h (1.5 mg/kg)	Peak	1 - 2
VTE prophylaxis	Q12h – q24h	Peak	0.3 – 0.5
VTE treatment	Q24h	Trough	0.3 – 0.5

*Q24h if CrCL < 30 ml/min

Parenteral Heparin Alternatives

Agent, Route	Class	Indications	VTE Dosing (Total Body Weight)	Dose Adjustments
Argatroban, <i>IV</i>	direct thrombin inhibitor	<ul style="list-style-type: none"> VTE treatment and prevention in patients with heparin allergy Heparin Induced Thrombocytopenia (HIT) (off label) 	<p>0.5 – 2 mcg/kg/min IV continuous, Titrates to goal aPTT 1.5-2x baseline (60 – 85sec)</p> <p>No Bolus Dose</p>	<ul style="list-style-type: none"> ↓ starting drip rate to 0.5 mcg/kg/min with hepatic or renal dysfunction <i>Avoid if liver failure</i> False INR elevation
Bivalirudin, <i>IV</i>	direct thrombin inhibitor	<ul style="list-style-type: none"> HIT Percutaneous Coronary Intervention 	<p>0.15 mg/kg/hr IV continuous, Titrates to goal aPTT (60-85 sec)</p>	<ul style="list-style-type: none"> CrCl < 30 ml/min: 0.08 mg/kg/h Dialysis: 0.02 mg/kg/h FALSE INR ELEVATION
Fondaparinux (Arixtra), <i>Subcutaneous</i>	Antithrombin inhibitor	<ul style="list-style-type: none"> VTE treatment, prophylaxis HIT (off label) 	<p>VTE treatment, HIT</p> <ul style="list-style-type: none"> >100 kg: 10 mg Q24h 50 – 100 kg: 7.5 mg q24h < 50 kg: 5 mg Q24h <p>Prophylaxis, Superficial VTE</p> <ul style="list-style-type: none"> 2.5 mg Q24h 	<ul style="list-style-type: none"> CrCl < 30 ml/min: Avoid use < 50 kg: Avoid use as prophylactic agent



Recommendations for Anticoagulant Selection

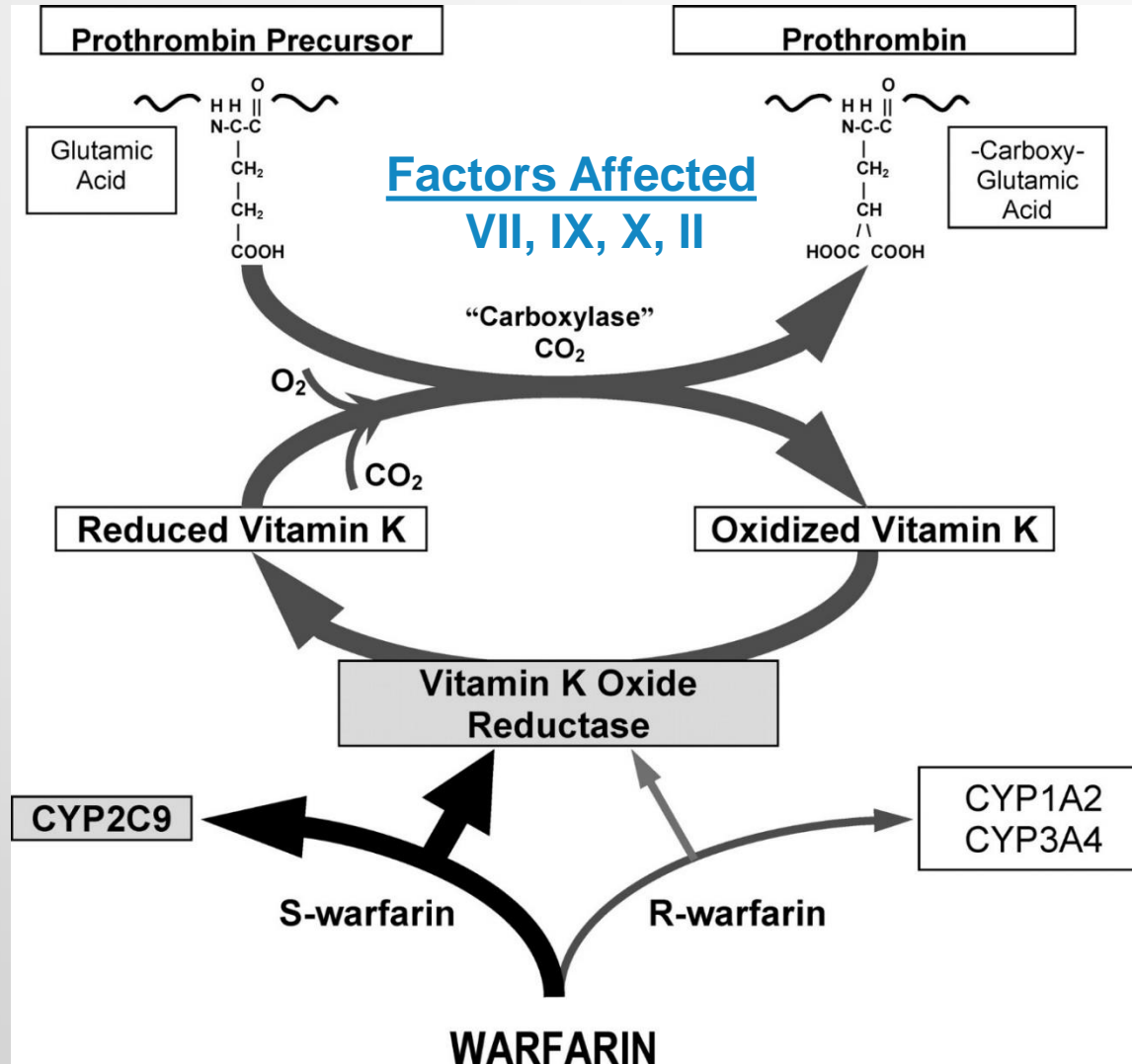
VTE without cancer: DOAC > LMWH/warfarin

VTE with active cancer: DOAC > LMWH/warfarin

Atrial Fibrillation: DOAC > warfarin

Mechanical heart valves: warfarin

Warfarin Management



Clotting Factor Metabolism and Onset of Warfarin Effect

	Half-Life (hours)	90% Inhibition (Days)	Steady State (Days)
Factor VII	4-6	0.5	1
Factor IX	24	4	5
Factor X	48-72	6-9	10-15
Factor II	60-72	7.5-9	13-15
Protein C	8	1	2
Protein S	30	4	6

Warfarin Initiation and Monitoring

INR Goal 2-3

- DVT / PE
- Aortic Mechanical Valve
- Hypercoagulable states

INR Goal 2.5 – 3.5

- Mitral Mechanical Valve
- > 1 Mechanical Valve
- Repeat thrombotic event while on therapeutic warfarin
- Aortic Mechanical Valve + Additional Risk Factor for Stroke*

**AF, Anterior-apical STEMI, left atrial enlargement, hypercoagulable state, heart failure with reduced ejection fraction*

Warfarin Initiation Dosing Strategies

5 mg daily

Standard Dose

- Majority of patients
- Desired INR increase by 0.2 – 0.3 per day

2.5 – 3 mg daily

Reduced Dose

- Advanced age, malnourished, debilitated, heart failure, hepatic or renal insufficiency, recent major surgery, presence of major drug interactions

7.5 – 10 mg daily

Increased Dose

- May consider in select patients: obesity without advanced age or comorbid renal or hepatic impairment
- Avoid loading dose strategy

Select Common Warfarin Drug Interactions

INCREASES INR

- Fluconazole
- Metronidazole
- Sulfamethoxazole/
trimethoprim
- Amiodarone
- Fluoroquinolones
- Macrolides
- Doxycycline
- Corticosteroids
- Phenytoin

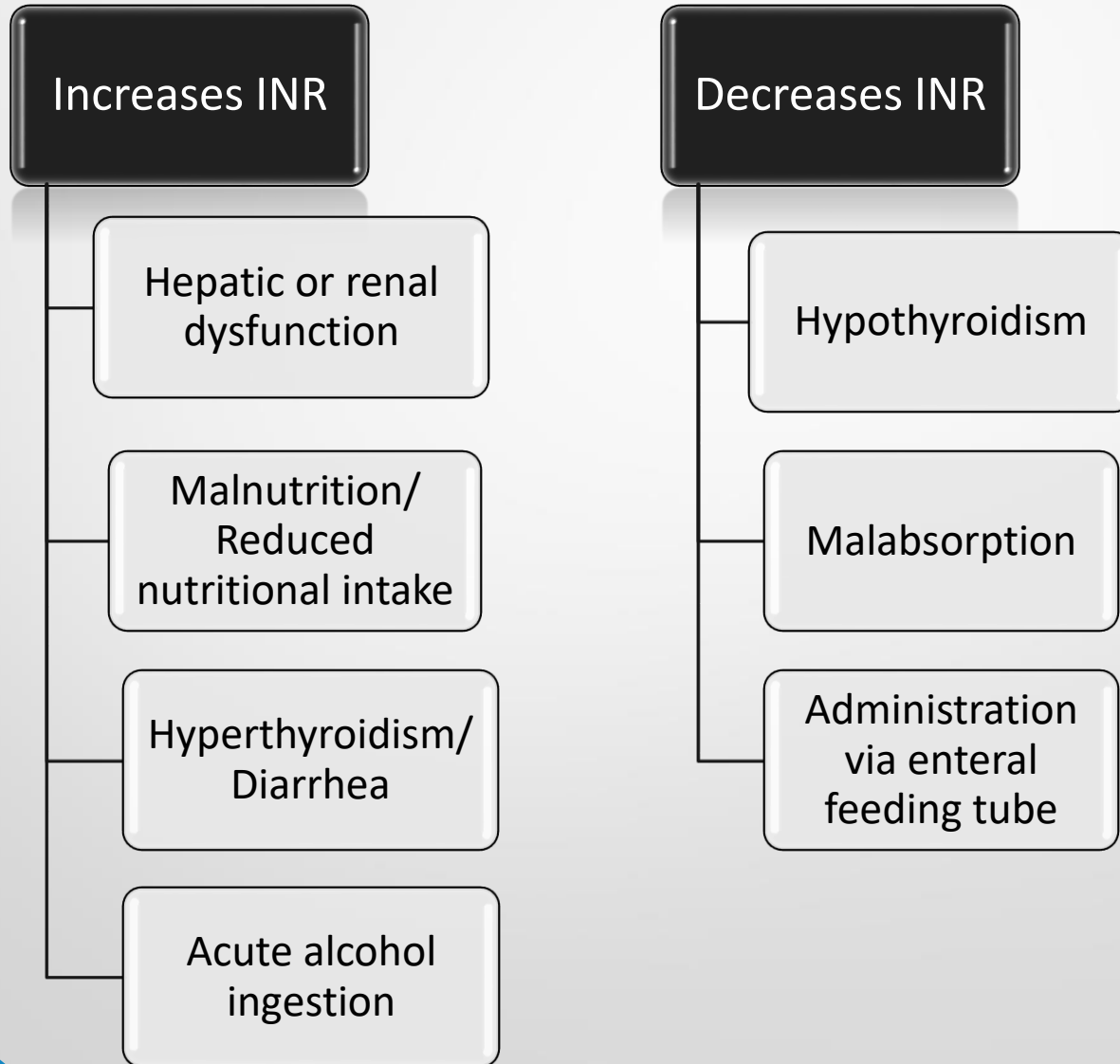
DECREASES INR

- Vitamin K
- Nafcillin
- Carbamazepine
- Phenytoin
- Sucralfate
- Cholestyramine
- Oral magnesium
- Rifampin
- St. John's Wort

INCREASES BLEEDING RISK WITHOUT INR EFFECT

- Aspirin
- NSAIDs
- P2Y12 inhibitors
- SSRIs
- Vitamin E
- Garlic
- Ginger
- Gingko biloba

Common Warfarin-Disease State Interactions



Warfarin Management: INR Out of Range

INR < 5, no bleeding	INR 5-9, no bleeding	INR > 9, no bleeding	Bleeding at ANY INR
<ul style="list-style-type: none"> • Lower dose by 10-20% • High bleeding risk: hold x1 dose, then begin lower daily dose • Daily INR in hospital 	<ul style="list-style-type: none"> • Hold x 1-2 doses, restart at lower dose when INR at goal • High bleeding risk: hold x1 dose, Vitamin K PO 1-2.5mg, restart at lower dose when INR at goal <p><u>Surgery needed:</u> Hold warfarin, give Vitamin K PO 5mg x 1, repeat INR in 12-24h</p>	<ul style="list-style-type: none"> • Hold warfarin • Give vitamin K 2.5-5mg PO x1 dose • Expect large drop in INR at 24-48h • Consider more frequent INR checks • May repeat oral vitamin K in 24 hours if needed 	<ul style="list-style-type: none"> • Hold warfarin • Give Vitamin K 10 mg IV • +/- FFP • Repeat Vitamin K q12-24h prn <p><u>Life Threatening or emergent surgical intervention needed:</u> Vitamin K 10 mg IV x 1 + prothrombin complex concentrate +/- FFP</p>

- AVOID SUBCUTANEOUS VITAMIN K
- ORAL ROUTE MOST APPROPRIATE IF NO ACTIVE BLEEDING

Pitfalls of warfarin management

- Failure to recognize major drug interactions
- Failure to recognize factors that may cause sensitivity
- Aggressive dose titration early in therapy
 - INR increase by > 0.3 in 24 hours should prompt dose reduction by 10-20%
 - INR increase by 0.5 – 1, consider holding warfarin
 - DAILY INRs during hospitalization
- Use contraindicated in pregnancy

Direct Oral Anticoagulants

apixaban
(Eliquis®)

rivaroxaban
(Xarelto®)

dabigatran
(Pradaxa®)

edoxaban
(Savaysa®)

Management of Direct Oral Anticoagulants (DOAC)

- Safe, efficacious, convenient
 - Simplistic dosing
 - No monitoring or dietary restrictions
- Limitations
 - Severe renal insufficiency (rivaroxaban), mod-severe liver disease
 - Contraindicated with mitral valvular Afib, mechanical cardiac valves
 - Limited data for intracranial and portal vein thromboses
 - Drug interactions: strong inducers/inhibitors of CYP3A4, PGP
 - Avoid in pregnancy, lactation
 - Cost

Direct Oral Anticoagulant Pharmacokinetics

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Onset	1 h	2h	3h	1h
Half-life	12-17h	5-9h	12h	10-14h
Renal Elimination	80%	36%	27%	50%

Direct Oral Anticoagulant Dosing By Indication

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Atrial Fibrillation	150 mg twice daily	20 mg daily w/supper	5mg twice daily	60mg daily
VTE	150mg BID <i>After 5-10d of parenteral anticoagulant</i>	15mg BID x21d, then 20mg QD w/supper Extended Therapy: 10 mg daily	10mg BID x 7d, then 5mg BID Extended Therapy: 2.5 mg BID	60mg daily <i>After 5-10d of parenteral anticoagulant</i>
CAD/PAD	Not studied	2.5 mg twice daily	Not Studied	Not studied

Direct Oral Anticoagulant Dose Adjustments

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Atrial Fibrillation	<p>CrCl 15-30: 75 mg BID</p> <p>CrCl < 15: AVOID USE</p>	<p>CrCl 15-50: 15 mgQ24</p> <p>CrCl < 15: AVOID USE</p>	<p>2.5 mg BID if 2 of the following: Scr ≥ 1.5, age ≥ 80y, ≤ 60 kg</p>	<p>CrCl 15-50: 30 mg/d</p> <p>Weight < 60kg: 30 mg/day</p> <p>Contraindicated: CrCl > 95</p>
VTE	<p>No dose adjustment</p> <p>CRCL < 30: Avoid use</p>	<p>No dose adjustment</p> <p>CrCL < 30: Avoid use</p>	<p>No Dose Adjustment</p> <p>CrCL < 25: Avoid use</p>	<p>No Dose Adjustment</p> <p>CrCL < 15: Avoid use</p>

DOAC Contraindications

Mechanical
Cardiac Valves

Valvular Atrial
Fibrillation

Bioprosthetic
Valve
Replacement
within ≤ 3 months

Antiphospholipid
Antibody
Syndrome

Ordi-Ros et al. Rivaroxaban versus Vitamin K Antagonist in Antiphospholipid Syndrome: A Randomized Noninferiority Trial. *Annals of Internal Medicine*. 2019;171(10):685-694.
Otto et al. 2020 ACC/AHA Guideline for Management of Patients with Valvular Heart Disease. *Circulation*. 2020;143(5):e72-227.
Stevens et al. Antithrombotic Therapy for VTE Disease: 2021

DOAC Drug Interactions

	PGP	CYP3A4	Notes
Apixaban	✓	✓	<ul style="list-style-type: none"> Do not combine with strong CYP3A4+PGP inducers* Dose modification if combined with strong inhibitor of PGP+CYP3A4**: 50% apixaban dose reduction in patients who would otherwise receive 5 or 10 mg twice daily; avoid in patients who would otherwise receive 2.5 mg twice daily
Rivaroxaban	✓	✓	<ul style="list-style-type: none"> Do not combine with strong inducers or inhibitors of CYP3A4*,¥
Dabigatran	✓		<ul style="list-style-type: none"> Avoid with PGP inducers
Edoxaban	✓		<ul style="list-style-type: none"> Monitor closely if combined with PGP inducers/inhibitors

*PGP+CYP3A4 Inducers: phenytoin, carbamazepine, rifampin

¥PGP+CYP3A4 Inhibitors: ketoconazole, itraconazole, ritonavir

DOAC Use in Special Populations



DOAC Use in ESRD

- Concern for lack of large, well-designed studies examining efficacy and safety data
- Available literature and guidance limited to prospective studies of pharmacokinetic evaluations, retrospective safety evaluations, large insurance registry data
- Lack of robust clinical studies of DOACs in ESRD population
 - Avoid rivaroxaban if CrCL < 15-30 ml/min
 - Apixaban labeling states that no dose adjustment is necessary with ESRD unless age \geq 80 years, or weight \leq 60 kg

DOAC Use in Obesity

Use of direct oral anticoagulants in patients with obesity for treatment and prevention of venous thromboembolism: Updated communication from the ISTH SSC Subcommittee on Control of Anticoagulation

Karlyn A. Martin¹  | Jan Beyer-Westendorf² | Bruce L. Davidson³ |
Menno V. Huisman⁴ | Per Morten Sandset⁵  | Stephan Moll⁶

- Best evidence: DOACs appropriate for BMI ≤ 40 , weight ≤ 120 kg
- IF DOAC used with BMI > 40 , weight > 120 kg:
 - Standard doses rivaroxaban, apixaban appropriate regardless of BMI, weight
 - Avoid dabigatran, edoxaban
 - Do not monitor anti-Xa or drug-specific levels

Martin et al. Use of direct oral anticoagulants in patients with obesity for treatment and prevention of venous thromboembolism: Updated communication from the ISTH SSC Subcommittee on Control of Anticoagulation. *J Thromb Haemo*.2021.19(8):1874-82.

Sebaaly J, Kelley D. Direct Oral Anticoagulants in Obesity. *Annals of Pharmacotherapy*.2020.54(11):1144-1158.

DOAC Use after Major GI Surgery

- Rivaroxaban
 - pH dependent absorption in stomach, proximal bowel
 - Metabolism via PGP efflux pumps, CYP384
 - Do not administer via J-tube
 - Avoid use after gastric bypass, small bowel resection
- Apixaban
 - Proximal and distal absorption (50% in distal bowel)
 - Limited impact of gastric bypass or gastrectomy on drug absorption
 - Avoid after colectomy, SBS, bowel resection
- Dabigatran
 - pH dependent absorption
 - Avoid after gastric bypass due to documented therapeutic failures, small bowel resection

When should a DOAC *NOT* be considered first line?

Severe Renal Impairment
(Except Apixaban)

Moderate-Severe Hepatic Impairment

Clinically significant drug interactions
(CYP3A4 + PGP)

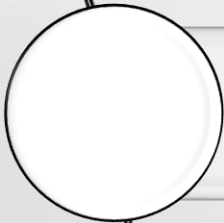
Prohibitive Cost

Antiphospholipid Antibody Syndrome

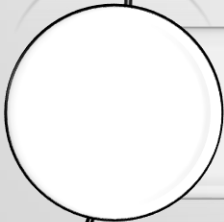
Pitfalls of DOAC Management



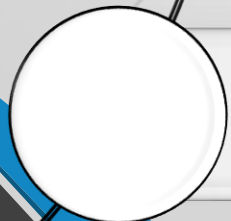
Dosing varies by indication for use
(VTE treatment, Prophylaxis, Afib, ACS)



Renal dosing cutoffs vary by agent and indication



Use in severe hepatic, severe renal disease, major GI surgery, antiphospholipid antibody syndrome



Failure to recognize financial barriers before prescribing

Preoperative DOAC Interruption

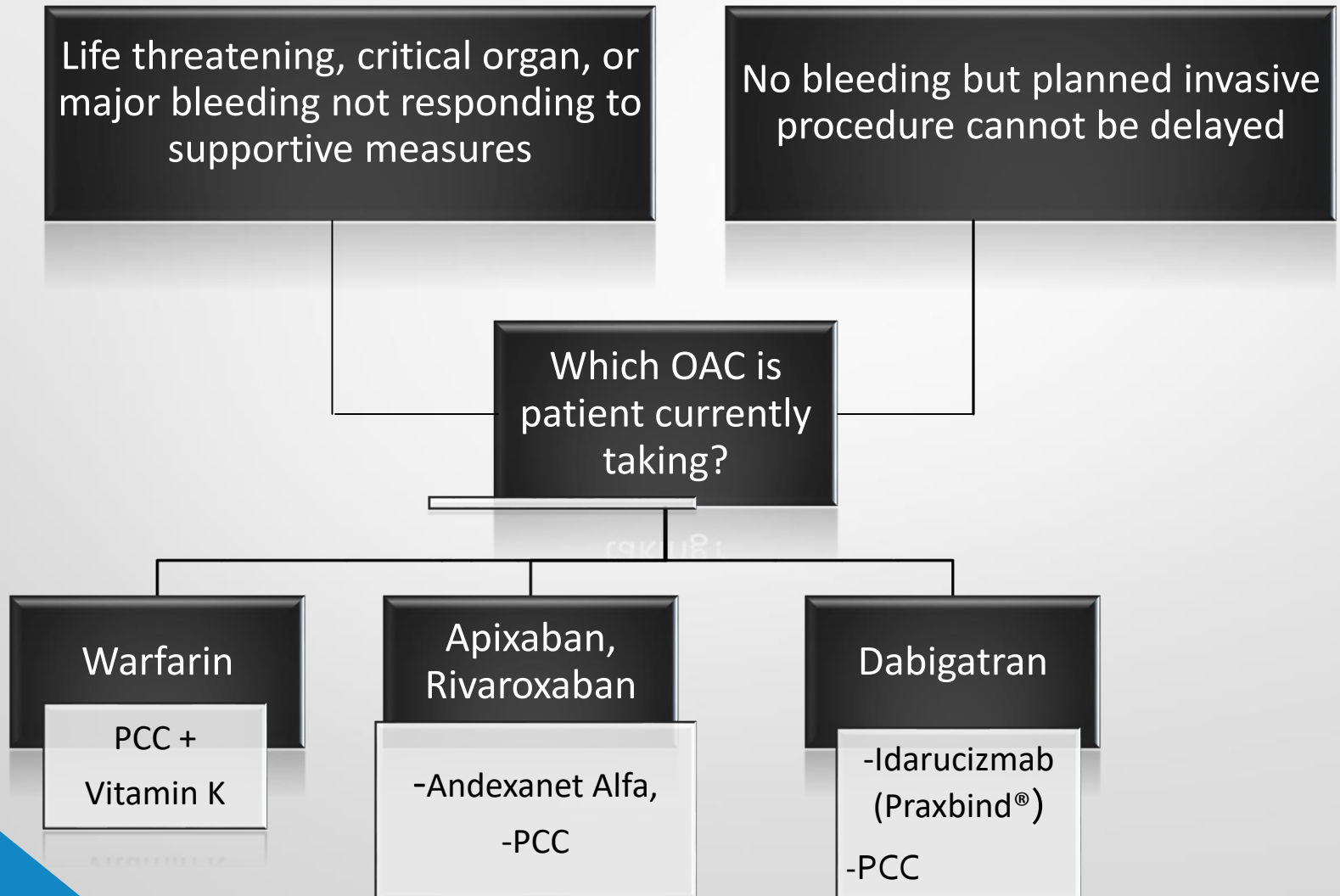
TABLE 2 Recommended Durations for Withholding DOACs Based on Procedural Bleed Risk and Estimated CrCl When There Are No Increased Patient Bleed Risk Factors

CrCl, mL/min	Dabigatran					Apixaban, Edoxaban, or Rivaroxaban		
	≥80	50-79	30-49	15-29	<15	≥30	15-29	<15
Estimated drug half-life, h	13	15	18	27	30 (off dialysis)	6-15	Apixaban: 17 Edoxaban: 17 Rivaroxaban: 9	Apixaban: 17 (off dialysis) Edoxaban: 10-17 (off dialysis) Rivaroxaban: 13 (off dialysis)
Procedural bleed risk								
Low	≥24 h	≥36 h	≥48 h	≥72 h	No data. Consider measuring dTT and/or withholding ≥96 h.	≥24 h	≥36 h	No data. Consider measuring agent-specific anti Xa level and/or withholding ≥48 h
Uncertain, intermediate, or high	≥48 h	≥72 h	≥96 h	≥120 h	No data. Consider measuring dTT.	≥48 h	No data. Consider measuring agent-specific anti Xa level and/or withholding ≥72 h.	

NOTE: The duration for withholding is based upon the estimated DOAC half-life withholding times of 2 to 3 half-lives for low procedural bleeding risk and 4 to 5 drug half-lives for uncertain, intermediate, or high procedural bleeding risk (46,60-67).

CrCl = creatinine clearance; DOAC = direct-acting oral anticoagulant; dTT = dilute thrombin time.

OAC Reversal Agents



Summary and Major Takeaways



Providers should be aware of specific monitoring requirements of parenteral anticoagulant therapies, and look to institutional protocols for guidance



Oral anticoagulant dosing, including adjustments for renal and hepatic impairment vary by agent and also indication for therapy



A thorough knowledge of potential oral anticoagulant drug interactions and clinical significant of these is key in avoiding unsafe combinations that may increase the risk of bleeding or therapy failure



End-stage renal disease, obesity, and major gastrointestinal surgery are areas requiring more research with use of DOACs



Oral anticoagulant reversal agents may be considered in cases of serious, life-threatening bleeding or when invasive procedures cannot be delayed.



Anticoagulation 101

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