Warfarin: A Comprehensive Review

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Objectives

- Explain the important pharmacodynamic and pharmacokinetic properties of warfarin
- Describe the role of warfarin in the inpatient setting
- Identify factors that may contribute to variability in the INR with warfarin use
- Discuss warfarin initiation and dose adjustments based on a comprehensive review of the patient

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Disclaimer

Dr. Patel has no actual or potential conflict of interest associated with this presentation

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Coumadin® (Warfarin)

- Clinical Pharmacology
  - Inhibit synthesis of Vitamin K dependent clotting factors
    - II, VII, IX and X
    - Protein C and S
- Mechanism of Action
  - “Vitamin K antagonist” (VKA)
  - Inhibit C1 subunit of vitamin K epoxide reductase (VKORC1) enzyme complex

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Coumadin® (Warfarin)

- Elimination half-lives of vitamin K-dependent proteins

Factor	Half-Life
II	42-72 hours
VII	4-6 hours
IX	21-30 hours
X	27-48 hours
Protein C	8 hours
Protein S	60 hours

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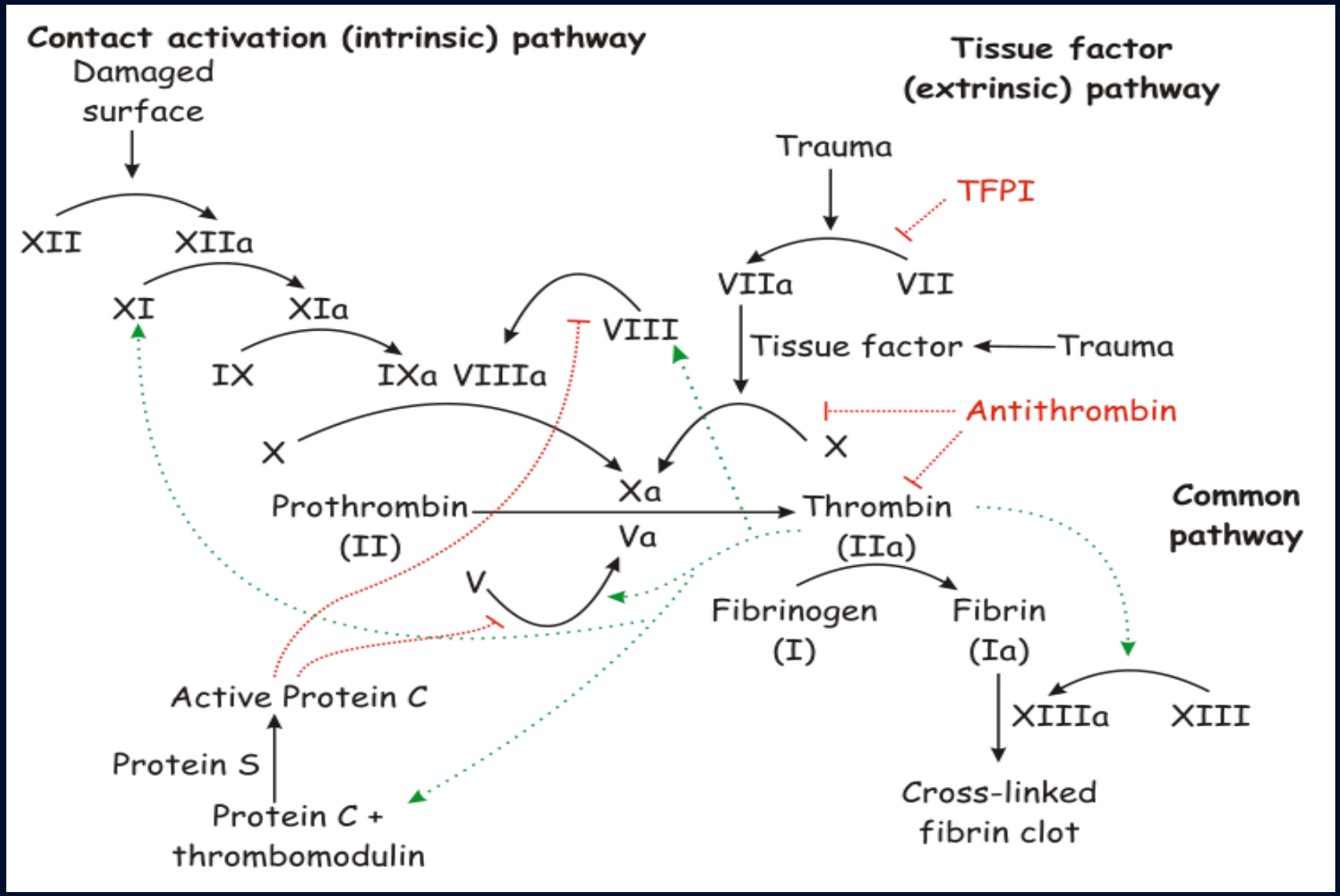

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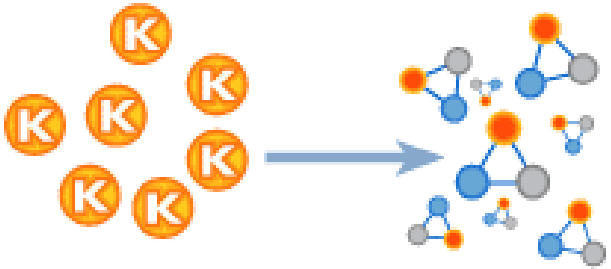
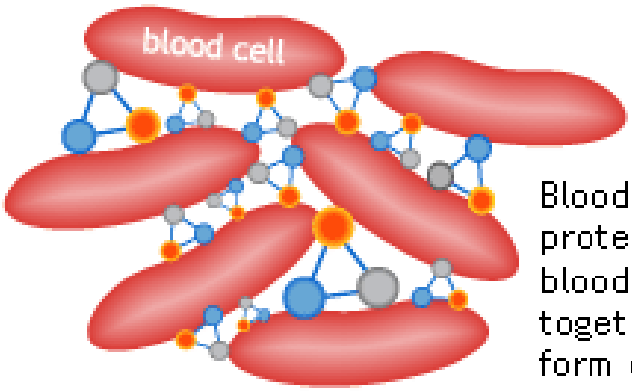
Clotting Cascade.http://medlibes.com/uploads/Screen%20shot%202010-07-30%20at%2012.56.57%20PM.png. Accessed May 15, 2015.

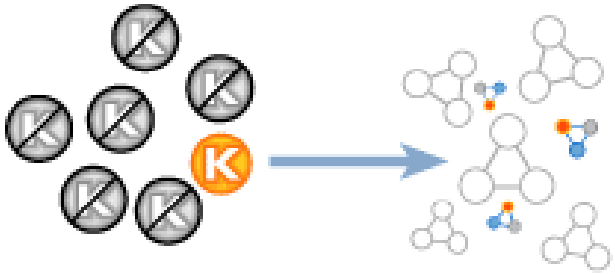
How Warfarin Affects Blood Clotting



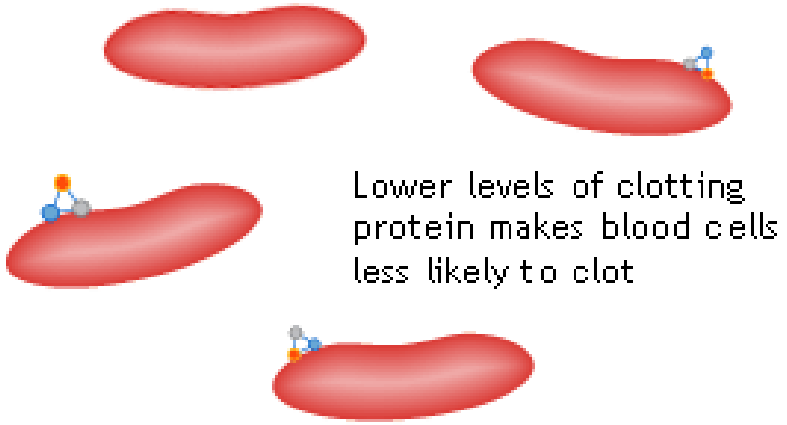
Vitamin K, produced by the body, helps form blood-clotting proteins



Blood-clotting proteins hold blood cells together to form clots



Warfarin reduces the body's ability to make Vitamin K which interferes with protein creation



Lower levels of clotting protein makes blood cells less likely to clot

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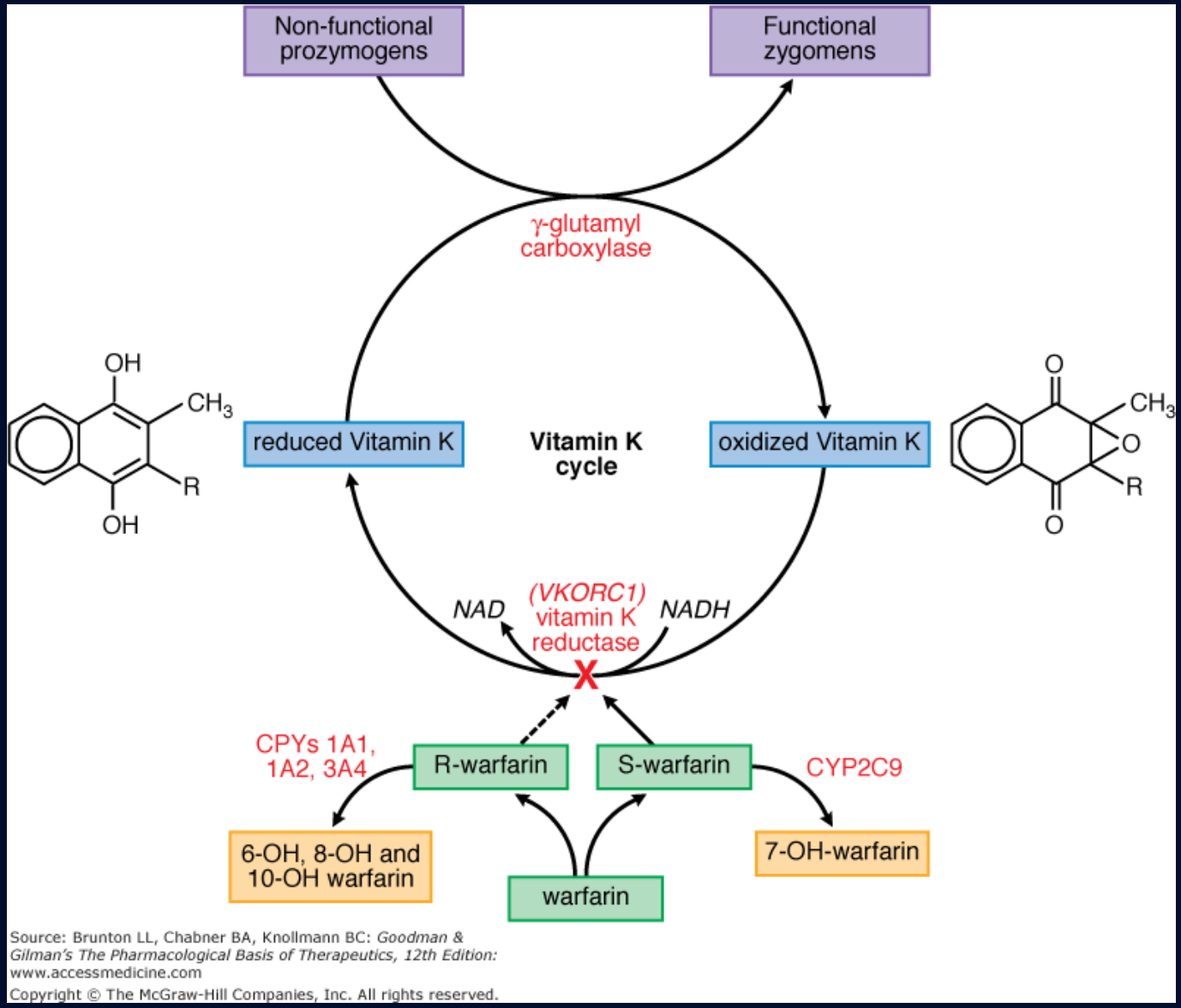
Warfarin Response. El Camino Hospital. http://elcaminogmi.dnadirect.com/img/content/tests/drug_response/howWarfarinAffectsBloodClotting.gif. Date Accessed May 14, 2015.



Source: Brunton LL, Chabner BA, Knollmann BC: *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th Edition:* www.accessmedicine.com

Accessed May 14, 2015

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Question 1

- Warfarin, through the inhibition of VKOR, inhibits the production of which factors?
  A. II, VIII, XII, Protein C and Protein S
  B. I, II, III, and X
  C. XI, Protein C and Protein S
  D. II, VII, IX, X, Protein C and Protein S

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Pharmacokinetics

- Racemic mixture of R- and S- enantiomers
  - S- 2 to 5 times more anticoagulant activity
- Completely absorbed after oral administration
- Small volume of distribution
  - ~0.14 L/Kg

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Pharmacokinetics

- Approximately 99% protein bound
- Extensive hepatic metabolization
  - CYP2C9, 2C19, 2C8, 2C18, 1A2 and 3A4
    - S- enantiomer 2C9
    - R- enantiomer 1A2/3A4
  - Minimally active metabolites excreted mainly in urine and lesser extent in bile
- Singe dose terminal half-life ~ 1 week
- Effective half life 20-60 hours

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Question 2

- Which entantiomer is a more potent anticoagulant and is primarily metabolized by CYP2C9?
  A. R-enantiomer
  B. S-enantiomer

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Warfarin Initiation – CHADS2

Table-2a: CHADS2.

Condition		Points
C	Congestive heart failure	1
H	Blood pressure consistently above 140/90mmHg (or treated hypertension on medication)	1
A	Age ≥75 years	1
D	Diabetes mellitus	1
S_2	Prior Stroke or Transient Ischaemic Attack or Thromboembolism	2

Table-2b:

CHADS2 score	Risk	Anticoagulation therapy	
0	Low	None or ASA	ASA daily
1	Moderate	ASA or warfarin	ASA or warfarin with INR 2-
3			
2 or more	High	Warfarin	Warfarin with INR 2-3

ASA: Acetylsalicylic Acid or Aspirin.
INR: International Normalised Ratio.

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Lamichhane, D. Update on secondary prevention of ischaemic stroke. http://jpma.org.pk/images/July2014/Update%20on%20secondary%20table2.jpg Published July, 2014. Accessed May 14, 2015.

FDA Approved Indications

- Prophylaxis and/or treatment of
  - Venous thrombosis and its extension, and pulmonary embolism
  - Thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement
- Reduce risk of death, recurrent myocardial infarction (MI), and thromboembolic events such as stroke or systemic embolism after MI

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Other Uses of Warfarin

- Orthopedic, general or urological surgery
  - Hip or knee arthroplasty
  - Hip fracture surgery
  - Abdominal or pelvic surgery
  - Prevention of transient ischemic attacks

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Warfarin Dosing Inpatient

- Initiation overlap for heparin/low molecular weight heparin (LMWH) and VKA
  - Historically
    - Unfractionated heparin (UFH) 5-7 days then co-administer VKA
  - Contemporary practice
    - VKA therapy initiated day 1 or 2 UFH/LMWH

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Warfarin Dosing Inpatient

- Initial dose selection
  - Doses should be individualized based on a comprehensive review of the patient
  - General recommendations
    - 5 mg daily for healthy individuals
    - 2.5mg daily for individuals with concomitant factors

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Patient Factors

- Increased age
- Varying size
- Nutritional status
- Drug-drug interactions
- Chronic heart failure
- Elevated baseline INR
- Diarrhea
- Thyroid disorders
- Hepatic/renal dysfunction
- Genomic variants*
  - CYP2C9 (*2 or *3 alleles)
  - VKORC1 polymorphism

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*The American College of Chest Physicians recommends against the use of routine pharmacogenomic testing to guide dosing

Question 3

- Which of the following patient factors can influence initial warfarin dosing and INR variability?
  A. Age
  B. Diarrhea
  C. Nutritional status
  D. Chronic heart failure exacerbation
  E. All of the above

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Target INR

- International normalized ratio (INR)
  - (Patient PT/Mean normal PT)^{ISI}
  - ISI = International Sensitivity Index
    - Responsiveness of given thromboplastin to reduction of the vitamin K-dependent coagulation factors
    - More responsive agent ➔ low ISI

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Recommended Target INR

Indication	INR	Duration
Antiphospholipid Syndrome		
No additional risk factors	2 to 3	Indefinite
Recurrent events with therapeutic INRs	2.5 to 3.5	Indefinite
DVT and PE		
Transient/reversible risk factor	2 to 3	3 Months
Unprovoked	2 to 3	3 Months
Second episode unprovoked	2 to 3	Long-term
With active cancer or LMWH for 3-6 months	2 to 3	Indefinite
Atrial Fibrillation		
With prior CVA or TIA or systemic embolism	2 to 3	Long-term
With mitral stenosis	2 to 3	Long-term
Following open heart surgery	2 to 3	4 weeks

PPX = prophylaxis; VT = venous thrombosis

Recommended Target INR

Indication	INR	Duration
Mechanical Heart Valve		
Aortic bileaflet or tilting disk	2 to 3	Long-term
Mitral bileaflet or tilting disk	2.5 to 3.5	Long-term
Aortic or mitral caged ball or caged disk	2.5 to 3.5	Long-term
Any valve with additional risk factor	2.5 to 3.5	Long-term
Bioprosthetic Heart Valve		
Aortic	N/A	Aspirin 50-100mg
Mitral	2 to 3	3 months
W/ prior history of systemic embolism	2 to 3	3 months
W/ left atrial thrombus	2 to 3	Until resolves
Cardioembolic Ischemic Stroke	2 to 3	Long-term

Factors Influencing INR Variability

- Other medications
  - Antibiotics
  - CYP450 inducers/inhibitors
- Diet
- Increased/decreased activity
- Increased/decreased weight

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Factors Influencing INR Variability

- Antibiotics
  - Disrupt vitamin K-producing intestinal flora
    - Increased effect of warfarin
- Inhibit metabolism of warfarin
  - Generally within one week

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Factors Influencing INR Variability

- CYP450 Inducers
  - Rifampin
  - Phenobarbital
  - Phenytoin
  - Prednisone
  - St. John’s Wort
  - Ritonavir
  - Smoking
- CYP450 Inhibitors
  - Antifungals
  - Macrolides
  - Fluoroquinolones
  - Antiretrovirals
  - Amiodarone
  - Propafenone
  - Isoniazid
  - Fluvastatin
  - Grapefruit

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Factors Influencing INR Variability

- Other medications
  - Amiodarone
  - Ascorbic acid
  - Acetaminophen
  - Corticosteroids
  - Sucralfate
  - Statins

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Factors Influencing INR Variability

- Foods high in vitamin K
  - Leafy, green vegetables
    - Kale
    - Spinach
    - Brussel sprouts
    - Asparagus
    - Basil
- Malnutrition
- Diet ordered in house
  - NPO

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Dose Adjustments

Target INR Goal of 2 -3			
Day	**Warfarin Starting Dose (mg)**	**INR Value**	**Warfarin Increased Sensitivity Starting Dose**
Day 1	5 mg	< 1.5	2.5 mg
Day 2	5 mg	< 1.5	2.5 mg
	2.5mg	1.5 – 1.9	1 – 1.5 mg
	1 – 2.5 mg	2 – 2.5	0.5 – 1 mg
	0 mg	> 2.5	0 mg
Day 3	5 – 10 mg	< 1.5	2.5 – 5 mg
	2.5 – 5 mg	1.5 – 1.9	1 – 2.5 mg
	0 – 2.5 mg	2 – 3	0 – 1 mg
	0 mg	> 3	0 mg

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Dose Adjustments

	Warfarin Starting Dose	INR Value	Warfarin Increased Sensitivity Starting Dose
Day 4	10 mg	< 1.5	5 mg
	5 – 7.5 mg	1.5 – 1.9	3 – 5 mg
	0 – 5 mg	2 - 3	0 – 2.5 mg
	0 mg	> 3	0 mg
Day 5	10 mg	< 1.5	5 mg
	7.5 – 10 mg	1.5 – 1.9	3 – 5 mg
	0 – 5 mg	2 - 3	0 – 2.5 mg
	0 mg	> 3	0 mg
Day 6	7.5 – 12.5 mg	< 1.5	3 – 7.5 mg
	5 – 10 mg	1.5 – 1.9	2.5 – 5 mg
	0 – 7.5 mg	2 – 3	0 – 4 mg
	0 mg	> 3	0 mg

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Increased Bleeding Risk

- Current antiplatelet therapy
- Elevated PT
  - Normal: 9.4 – 12.5 seconds
- Thrombocytopenia
  - Platelet <75 K/uL
- Significant hepatic disease
  - Cirrhosis or total bilirubin >2.4 mg/dL
- Alcohol abuse history
- End stage renal disease
- GI bleed w/in past 30 days
- Surgery w/in past 2 weeks
- Intracranial bleed w/in past 30 days
- Medications

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Signs and Symptoms of Bleeding

- Low hemoglobin/hematocrit
- Blood in urine, stool, or sputum
- Intracranial bleeding
  - Confusion
  - Weakness
  - Loss of vision
- Lightheadedness
- Weakness
- Black, tarry stools
- Bleeding gums
- Severe abdominal pains

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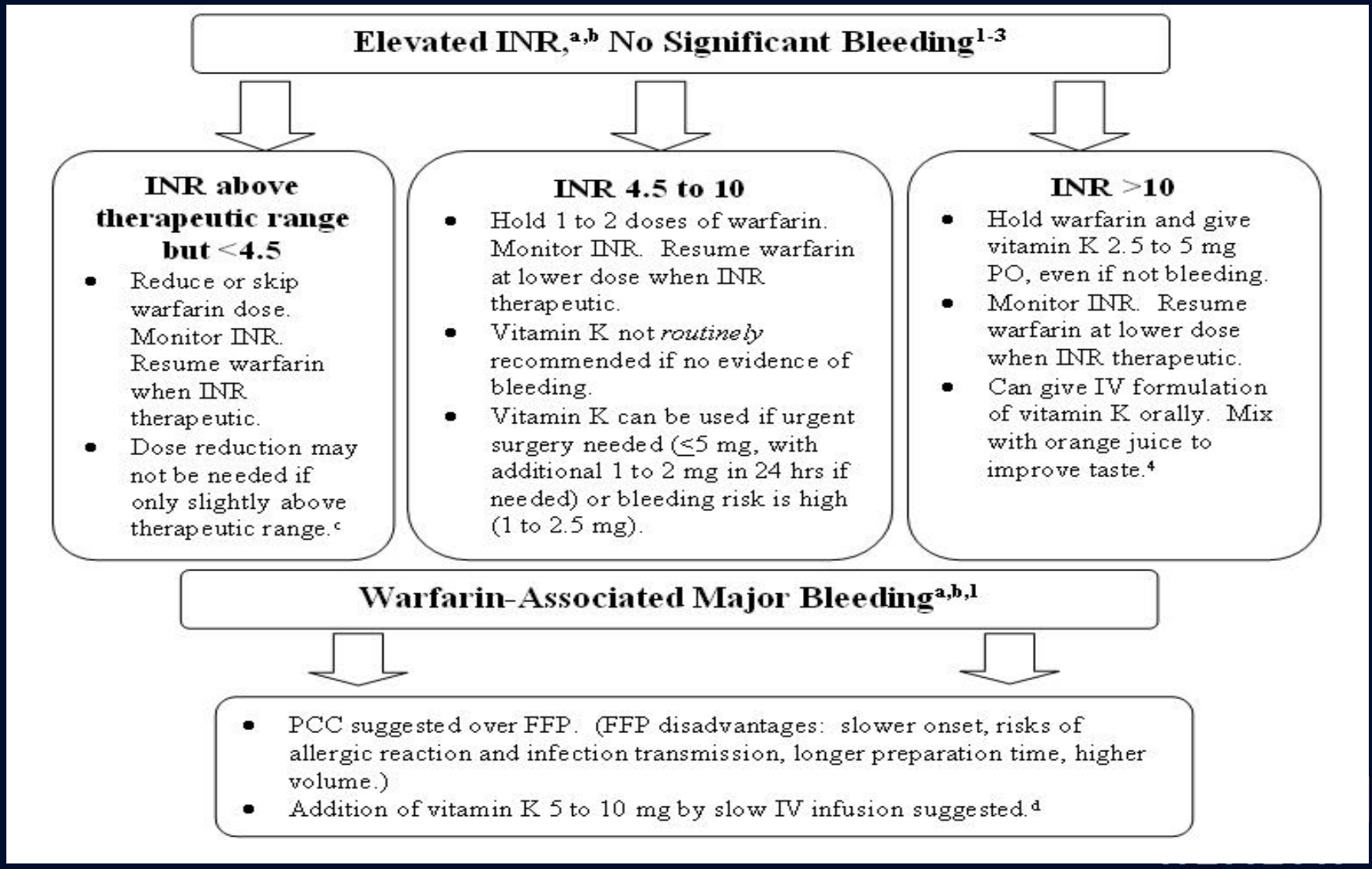
Warfarin Reversal



FFP = fresh frozen plasma, PCC = prothrombin complex concentrate

Warfarin Reversal

- Kcentra® (prothrombin complex concentrate)
  - Factors II, VII, IX, and X
  - Proteins C and S
- Urgent reversal of acquired coagulation factor deficiency induced by Vitamin K Antagonist therapy in adults with:
  - Acute major bleeding
  - Need for an urgent surgery/invasive procedure

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Warfarin Reversal

- Kcentra® Dosing
  - Administer with Vitamin K concurrently

Pre-treatment INR	2 – <4	4 – 6	>6
Dose* of Kcentra (Units of Factor IX) / kg body weight	25	35	50
Maximum dose (units of Factor IX)	Not to exceed 2500	Not to exceed 3500	Not to exceed 5000

* Dose based on actual potency as stated on the carton

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Pharmacy Resources

- American College of Chest Physicians (CHEST Journal)
- Pharmacy.uchc.edu
  - Inpatient collaborative practice protocol
- Warfarindosing.org
- Global RPh

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Conclusion

Initial dose selection

- Target INR
- New start versus continuing maintenance
- Drug, disease, dietary interactions
- Laboratory findings
  - Hepatic/renal function
  - Nutritional status
  - PT/INR
  - Hemoglobin/hematocrit

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Case 1

- A 75 year old female patient is being bridged to warfarin therapy following a pulmonary embolism. She has a past medical history of hypothyroidism, type 2 diabetes, and hypertension.
- Her baseline INR is 1.4.
- Her renal and hepatic function are normal.

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Case 1

- Home Medication list
  - Lisinopril 5 mg QD
  - Levothyroxine 50 mcg QD
  - Metformin 500mg BID
- Inpatient Medication List
  - Lisinopril 2.5mg QD
  - Insulin sliding scale

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Case 1

- What initial dose of warfarin would you recommend for this patient?
  A. 1 mg
  B. 2.5 mg
  C. 5 mg
  D. 7.5 mg
  E. 10 mg

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Case 1

- The medical team disagrees with your recommendation and gives the patient a 5 mg dose for 2 days. The INR is found to be 7.9 after the patient received the warfarin 5 mg. The patient has no evidence and is not expressing any symptoms of bleeding.

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Case 1

- The medical resident contacts you and asks what the next step should be regarding this patient's therapy. What would you suggest?
  A. Administer 5 mg vitamin K PO
  B. Administer 5 mg vitamin K IV
  C. Hold warfarin until INR is therapeutic

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