WARFARIN

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I. Introduction
1. Most frequently prescribed oral anticoagulant
2. 4th most prescribed CV agent
3. 11th most prescribed drug in US
4. Reluctance to prescribe despite evidence based benefits

II. Indication and INR Goals

Indication	**INR Goal**
DVT prophylaxis	2.0-3.0
Treatment of DVT	2.0-3.0
Treatment of PE	2.0-3.0
Prevention of systemic embolism Tissue heart valves Acute MI Valvular heart disease Atrial fibrillation	2.0-3.0
Mechanical prosthetic valves	2.5-3.5
Bileaflet mechanical valve in aortic position	2.0-3.0

III. Warfarin
1. MOA: antagonizes Vit K which is needed for synthesis of clotting factors II, VII, IX, X as well as Protein C and S

2. Pharmacokinetics:
   a. 99% protein bound to albumin
   b. t1/2plasma = 40 hrs t1/2racemic=20-60 hrs
   c. Duration: 2-5 days, therefore maximal effect occurs up to 48 hrs after administration

3. Pharmacodynamics
   a. Anticoagulant Effect
      -Depends on clearance of functional clotting factors
      -This is determined by t1/2
      -Earliest change in INR is 24-36 hrs after initial dose
      -Primarily due to **Factor VII (t1/2 6hrs)**
      -This is deceptive bc they don't affect the body's physiologic ability to halt clot expansion or form new thromboses

   b. Antithrombotic Effect
      -Depends on clearance of **Factor II (prothrombin, t1/2 50 hrs)**
      -So this can take up to 5 days to reach therapeutic INR

4. Why we don't load warfarin (ie. > 10mg)
   a. ↑ risk of bleed by ↓ production of Factor VII
   b. Source of prolonged hospital stay
   c. May ↑ risk of hypercoaguable state bc of Protein C and S depletion

5. Dosing
   a. Begin with 5mg PO QD for 3 days, then evaluate INR
   b. Dose adjustment (see algorithm)- in general may ↑ or ↓ **weekly** dose by 10-20%

6. Drug Interactions: MANY! Please carefully assess the medications. Especially antibiotics including Bactrim, Flagyl

7. Overdose Situations

OVERDOSE/TOXICITY GUIDELINES			
INR		**PATIENT SITUATION**	**ACTION**
>3 AND ≤5.0	And	No bleeding, no need for rapid reversal (ie. Surgery)	Omit next dose and restart at lower dose when INR approaches 3.0
> 5.0 and ≤ 9.0	And	No bleeding	If no risk factors for bleeding: a. Omit next 1 or 2 doses b. Monitor INR frequently c. Reinstitute at lower dose **Or** If increased risk for bleeding: Vit K 1-2.5 mg PO
> 5.0 and ≤ 9.0	And	Need rapid reversal for urgent surgery or dental extraction	Vit K PO 2-4mg (expected ↓ INR w/in 24hrs) If still high at 24hrs, may give additional 1-2mg Vit K
> 9.0 and ≤ 20	And	No bleeding	Vit K PO 3-5mg (expected ↓ INR w/in 24-48hrs)
> 20.0		Serious bleeding or major warfarin overdose	Vit K 10mg slow IV infusion with supplemental fresh plasma transfusion or prothrombin complex concentrate depending on urgency

*Hirsch J, Dalen, JE, Deykin D, et al. Oral anticoagulants: mechanism of action, clinical effectiveness, and optimal therapeutic range. *Chest* 1998:114 (5); 445S-469S.

7. Monitoring
   a. QD until 2 therapeutic INRs
   b. Then 2-3 x/week for 1-2 weeks
   c. Once stable, can widen to once every 4-6 weeks

8. Questions to ask when assessing an abnormal INR
   a. Did the patient miss or take an extra dose?
   b. Has their diet changed?
   c. Undisclosed drug use?
   d. Alcohol use?
   e. Self medication?
   f. Lab error?

9. Other considerations
   a. Generic vs Brand

10. Patient Education

References:

Horton J and Bushwick BM. Warfarin Therapy: Evolving strategies in anticoagulation. Am Fam Physician 1999; 59 (3):635-646.

Hirsch J, Dalen, JE, Deykin D, et al. Oral anticoagulants: mechanism of action, clinical effectiveness, and optimal therapeutic range. *Chest* 1998:114 (5); 445S-469S.