

Mechanisms of Action

1. Heparin:

- Binds to and causes conformational change in anti-thrombin III thereby accelerating inactivation of activated clotting factors IIa (thrombin), IXa, Xa, and XIIa, subsequently halting coagulation.
- Low-dose predominantly affects factor Xa (prophylaxis)
- Full-dose predominantly affects thrombin (established clot)

2. Warfarin:

- Inhibits reduction of vitamin K epoxide, thereby limiting activation of vitamin K dependent clotting factors: II (prothrombin), VII, IX, X. *Antithrombotic effect primarily due to reduction in prothrombin.*
- Inhibits synthesis of anticoagulant proteins C and S (potential pro-coagulant effects).

Pharmacokinetics

1. Heparin: (IV or SQ)

Absorption (SQ): completely absorbed; peak concentrations 2-4 hours after administration.

Distribution: primarily intravascular

Half-life: 90 minutes (range 0.5-2 hours)

- Mean time to steady state = 6 hrs (5 half-lives)
- Increases with larger doses (nonlinear)
- Decreases with PE, massive thrombosis, or new clot (increased clearance)

Metabolism: degraded by reticuloendothelial system

- No dosage adjustment necessary for renal or hepatic dysfunction.
- Not significantly affected by dialysis.

2. Warfarin: (PO)

Absorption: rapidly and completely absorbed

Distribution: primarily intravascular*

Half-life: 36-42 hours

- Time to steady state = approximately 10 days

Half-lives of Clotting Factors

Factor II	= 60 hrs
Factor VII	= 6 hrs
Factor IX	= 24 hrs
Factor X	= 40 hrs

Anticoagulant effects may be seen within 24 hrs due to inhibition of Factor VII, but **peak** anticoagulant activity is delayed for 72-96 hrs due to Factor II inhibition (2-3 days after 1st **therapeutic** INR)

Metabolism: Hepatic microsomal enzymes to inactive metabolites

- Reduce dose with hepatic dysfunction and with hypermetabolic states (increased catabolism of vitamin K-dependent factors)
- Not significantly affected by dialysis

* Extensively protein bound with numerous drug interactions (see Table 4)

Adverse Reactions

1. Heparin:

- Over Anticoagulation: - not symptomatic: see nomogram

- Significant bleeding: (GI, intracerebral)

Treatment: protamine sulfate

- 1 mg neutralizes approximately 100 u heparin
- Slow IV push protamine not to exceed 50 mg/10 minutes
- Check APTT 5-15 minutes after protamine given and again at 8 hrs as heparin rebound can occur
- Excessive doses can act as an anticoagulant

- Other:

- Thrombocytopenia and/or thrombosis - dc if platelets < 100,000/mm³ or >50% decrease from baseline
- Osteoporosis (risk with 15-20,000 units/day for > 6 mos.)
- Less frequent - increased transaminase, local urticaria, skin necrosis, hypoadosteronism with hyperkalemia

- Antithrombin-3 resistance: Consider if heparin requirements exceed 50,000 units/24 hrs

2. Warfarin:

- Over Anticoagulation:

Reversal:

- INR > 3.5 but < 5.0, pt not bleeding, rapid reversal not necessary: the warfarin can be lowered or omitted. Restart at a lower dose when INR within therapeutic range.
- INR > 5.0 but < 9.0, pt not bleeding, rapid reversal not necessary: the warfarin dose should be omitted until INR falls into the therapeutic range. If patient is at increased risk of bleeding and/or rapid reversal is required, give Vitamin K 1.25-5 mg orally. Reduction in INR will usually occur by 24 hours. If INR remains high at 24 hours, an additional dose of Vitamin K 1.25-2.5 mg orally can be given. Restart warfarin at a lower dose when INR is therapeutic.
- INR > 9.0 and not clinically significant bleeding: give Vitamin K 2.5-5.0 mg orally. INR usually reduced in 24 hours. Recheck INR and repeat with Vitamin K prn.
- If rapid reversal is required due to serious bleeding or INR > 20.0: give Vitamin K 10 mg slow IV over 60 minutes to prevent anaphylaxis. Check INR and repeat Vitamin K Q12H prn. May supplement with:
 - 1) Fresh frozen plasma - OR-
 - 2) Prothrombin complex concentrate

Warfarin resistance occurs for at least 1 week after high-dose (10-15 mg) Vitamin K. Warfarin resistance less likely with low-dose therapy (1.25-2.5 mg)

Adverse Reactions (continued)

Risk of Major Bleeds

- | | | |
|---------------------------------|---------------------------|--------------------------------|
| • Age over 65 years | • Renal insufficiency | • Alcoholism |
| • Concomitant use of aspirin | • Anemia | • Serious underlying condition |
| • History of stroke or GI bleed | • Surgery in last 14 days | |

Warfarin (cont.):

- Other:

- Skin necrosis syndrome (at 3-8 days) - occurs with loading dose of 15 mg or > or if heterozygous for Protein C or S deficiency

- Contraindication:

- Pregnancy - teratogenic, especially 1st trimester

Table 4.
Selected Factors Altering Warfarin Pharmacokinetics and Pharmacodynamics

Increased Warfarin Effect

Drugs
Acetaminophen
Amiodarone
Aspirin
Cimetidine
Ciprofloxacin
Clarithromycin
Dexamethasone (≥ 20 mg)
Disulfiram
Erythromycin
Flu vaccine
Fluconazole
Itraconazole
Levothyroxine
Metronidazole
Omeprazole
Phenytoin (long term)
Quinidine
Sulfonylureas
Tamoxifen
Tetracycline
TMP/SMX
Liver disease
Hypermetabolic states
Pyrexia
Thyrototoxicosis

Decreased Warfarin Effect

Drugs
Barbiturates
Carbamazepine
Cholestyramine
Dicloxacillin
Griseofulvin
Nafcillin
Phenytoin
Rifampin
Sucralfate
Vitamin K

Increased Bleeding

Drugs
Aspirin
NSAIDs
Ticlopidine
Thrombocytopenia

References

- Sixth ACCP Consensus Conference on Antithrombotic Therapy. Chest 2001; 119:[Suppl 1]
 - Hirsh J. NEJM 1991; 324:1565-74
 - Harrison L, Johnson M, Massicote MP, et al. Comparison of 5 mg and 10 mg loading doses of warfarin therapy. Ann Intern Med 1997; 126:133-6
- ** Additional references available upon request **
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Table 1.
Rapid Anticoagulation and Predicted Maintenance Dose Regimen (adapted from: Harrison et al.³)

Day	INR	Warfarin Sensitive*	Warfarin Moderate Sensitive**	Warfarin Insensitive***
1		5.0 mg	7.5 mg	10.0 mg
2	<1.5	5.0 mg	7.5 mg	7.5-10.0 mg
	1.5-1.9	2.5 mg	2.5 mg	2.5 mg
	2.0-2.5	1.0-2.5 mg	1.0-2.5 mg	1.0-2.5 mg
	>2.5	0.0	0.0	0.0
Day	INR	Dosage		
3	<1.5	5.0-10.0 mg		
	1.5-1.9	2.5-5.0 mg		
	2.0-2.5	0.0-2.5 mg		
	2.6-3.0	0.0-2.5 mg		
	>3.0	0.0		
4	<1.5	10.0 mg		
	1.5-1.9	5.0-7.5 mg		
	2.0-3.0	0.0-5.0 mg		
	>3.0	0.0		
5	<1.5	10.0 mg		
	1.5-1.9	7.5-10.0 mg		
	2.0-3.0	0.0-5.0 mg		
	>3.0	0.0		
6	<1.5	7.5-12.5 mg		
	1.5-1.9	5.0-10.0 mg		
	2.0-3.0	0.0-7.5 mg		
	>3.0	0.0		

* > 65 years of age
 Significant hepatic disease
 Asian descent
 Decompensated CHF
 Malnourished
 Malabsorption syndrome/ chronic diarrhea

** 50-65 years of age
 Concurrent P-450 hepatic inhibitor

*** < 50 years of age with no risk factors
 If patient remains subtherapeutic after 3 days of a 10 mg load, may consider increasing dose to 15 mg

* Use actual body weight when dosing heparin, except for morbidly obese patients (>30% IBW) use adjusted body weight = IBW + 0.4 (TBW-IBW)

** Overlap is necessary to prevent thrombosis from early inhibition of anticoagulant proteins C & S and to achieve reduction in prothrombin ($t_{1/2}$ = 60 hrs)

*** If not on heparin and rapid anticoagulation not required (e.g., chronic atrial fibrillation), then begin warfarin with an average maintenance dose (2.5-5 mg) which achieves steady state anticoagulation in approximately 14 days.

**** For massive PE or severe iliofemoral thrombosis, a longer period of heparin therapy is recommended (approximately 10 days)

Table 2.
Optimal Therapeutic Range for Oral Anticoagulants

Indication	Target INR
Atrial Fibrillation	
Atrial fibrillation with high risk factors*	2.0-3.0 (chronic)
Atrial fibrillation with ≥ 2 moderate risk factors**	2.0-3.0 (chronic)
Pre-cardioversion (for Afib > 48 hours)	2.0-3.0 (3 weeks)
Post-cardioversion	2.0-3.0 (4 weeks)
Cardioembolic Stroke	
	2.0-3.0 (chronic)
Left Ventricular Dysfunction	
Ejection fraction < 30%	2.0-3.0 (chronic)
Following embolic event despite anticoagulation	2.0-3.0 (chronic) plus ASA 81 mg qd
Myocardial Infarction	
Following anterior MI	2.0-3.0 (1-3 months)
Following MI with continued risk factor(s) (Afib, LV dysfunction, CHF, mural thrombus, history of embolism)	2.0-3.0 (chronic)
Thromboembolism (DVT, PE)	
Treatment/prevention of recurrence (reversible or time-limited risk factors)	2.0-3.0 (3 months)
Treatment/prevention of recurrence (first episode of idiopathic thrombus)	2.0-3.0 (6 months)
Continued presence of risk factors (AT-III, protein C or protein S deficiency, malignancy)	2.0-3.0 (12 months-chronic)
Symptomatic calf vein thrombosis	2.0-3.0 (6-12 weeks)
* Age > 75 years, history of TIA or stroke, hypertension, hx of systemic embolus, mitral stenosis, bioprosthetic cardiac valve, thyrotoxicosis, left ventricular dysfunction, CHF, rheumatic mitral valve disease.	
** Age 65-75 years, DM, CAD	

Recommendations on Monitoring INR***

- Once daily until therapeutic for 2 consecutive days
 - 2-3 times/week for 1-2 weeks
 - Once weekly for 1-2 months
 - Every 2 weeks until stable, then every 4-6 weeks
- ***Depending on stability of results