

Why We Hate Coumadin

Abstract

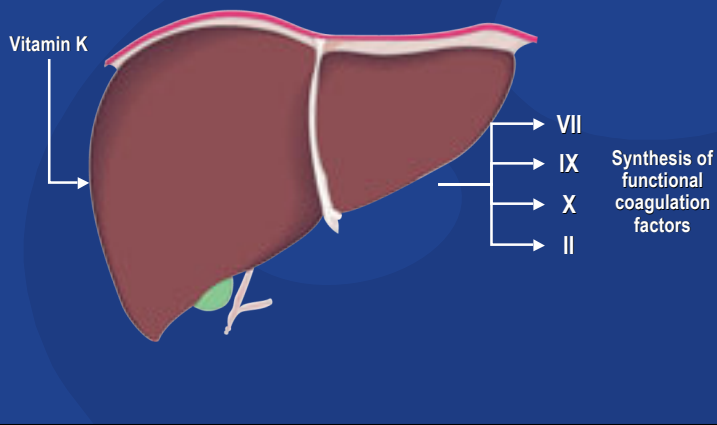
Warfarin has been used for over 50 years. First starting out as rat poison, and eventually ending up as the cornerstone for treating thrombotic conditions ranging from DVT's to the prevention of stroke in atrial fibrillation. Warfarin is a racemic mixture which means that there is a "left" and "right" hand version of the molecule. Each one behaves differently in the body. Warfarin also has multiple interactions in the cytochrome P450 system. It is also affected by the amount of vitamin K that our patients eat. All in all warfarin is one of the most difficult medications to manage in clinical practice. However, by understanding how warfarin works, we can avoid many of the potential pitfalls and thereby minimize the risk while reaping the benefits of this therapy.

Why We hate Coumadin.

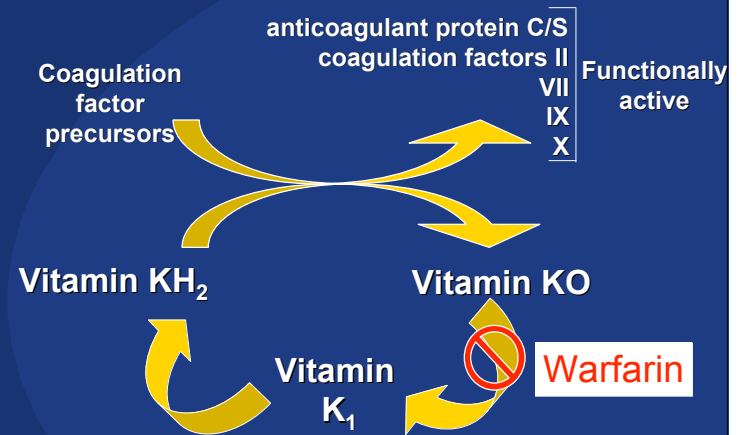
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Warfarin – mechanism of action



Vitamin K Cycle



Reviewing the Reality – Why We Need to Change

Food interactions Green leafy vegetables counteract effects of warfarin

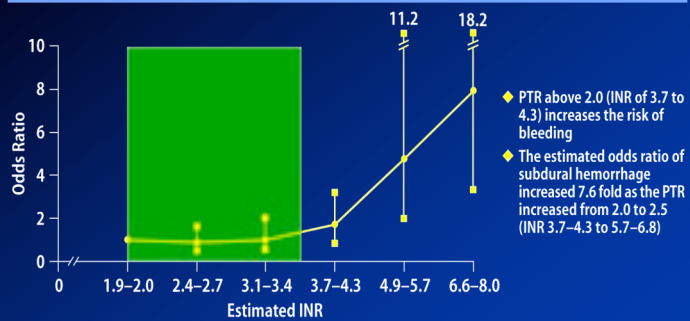


- **Foods with high amounts of vitamin K, e.g.:**
 - Cauliflower
 - Green cabbage
 - Seaweed
 - Broccoli
 - Green tea
 - Turnip greens
 - Soybean oil (often used to fry foods in restaurants)
 - Raw spinach

Warfarin – potential drug and food interactions

Increased anticoagulation		Reduced anticoagulation	
Specific drug	Drug class	Specific drug	Drug class
paracetamol	analgesic	barbiturates	anxiolytic
amiodarone	antiarrhythmic	carbamazepine	anticonvulsant
cimetidine	ulcer drug	dichloralphenazone	relaxant
clofibrate	cholesterol-lowering	glutethimide	sedative
disulfiram	antialcoholic	St John's wort	
erythromycin	antibiotic	ginseng	
fluconazole	antifungal	garlic	
fluoxetine	antidepressant	avocado	
metronidazole	antibiotic	spinach	
sulfinpyrazone	uricosuric	broccoli	
tamoxifen	antioestrogen		
trimethoprim	antibiotic		
thyroid hormone			

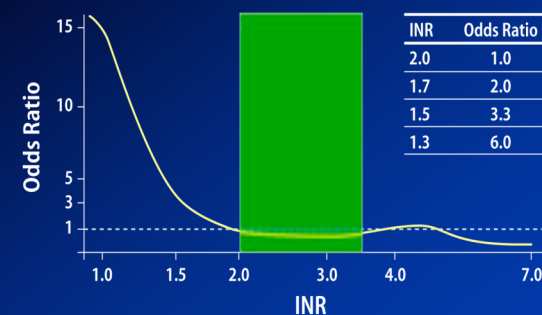
Risk of Intracranial Hemorrhage in Outpatients



Adapted from: Hylek EM, Singer DE, Ann Int Med 1994;120:897-902

Hylek, et al, studied the risk of intracranial hemorrhage in outpatients treated with warfarin. They determined that an intensity of anticoagulation expressed as a prothrombin time ratio (PTR) above 2.0 (roughly corresponding to an INR of 3.7 to 4.3) resulted in an increase in the risk of bleeding.

Lowest Effective Intensity for Warfarin Therapy for Stroke Prevention in Atrial Fibrillation



INR below 2.0 results in a higher risk of stroke

Hylek EM, et al. NEJM 1996;335:540-546.

Reviewing the Reality – Why We Need to Change

Managing Patients with High INR Values/ Minor or No Bleeding

Clinical Situation

INR >therapeutic range but <5.0, no clinically significant bleeding, rapid reversal not indicated for reasons of surgical intervention

INR >5.0 but <9.0, no clinically significant bleeding

Guidelines

Lower the dose or omit the next dose; resume warfarin therapy at a lower dose when the INR approaches desired range

If the INR is only minimally above therapeutic range, dose reduction may not be necessary

Patients with no additional risk factors for bleeding; omit the next dose or two of warfarin, monitor INR more frequently, and resume warfarin therapy at a lower dose when the INR is in therapeutic range

Patients at increased risk of bleeding; omit the next dose of warfarin, and give vitamin K₁ (1.0 to 2.5 mg orally)

Patients requiring more rapid reversal before urgent surgery or dental extraction: vitamin K₁ (2–4 mg orally); if the INR remains high at 24 h, an additional dose of 1–2 mg

American Heart Association

Managing Patients with High INR Values/ Serious Bleeding

Clinical Situation

INR >9.0, no clinically significant bleeding

Life-threatening bleeding or serious warfarin overdose

Continuing warfarin therapy indicated after high doses of vitamin K₁

Guidelines

Vitamin K₁ (3–5 mg orally); closely monitor the INR; if the INR is not substantially reduced by 24–24 h, the vitamin K₁ dose can be repeated

Serious bleeding, or major warfarin overdose (e.g., INR >20.0) requiring very rapid reversal of anticoagulant effect: Vitamin K₁ (10 mg by slow IV infusion), with fresh plasma transfusion or prothrombin complex concentrate, depending upon urgency; vitamin K₁ injections may be needed q12h

Prothrombin complex concentrate, with vitamin K₁ (10 mg by slow IV infusion); repeat if necessary, depending upon the INR

Heparin, until the effects of vitamin K₁ have been reversed, and patient is responsive to warfarin

American Heart Association

Dosage Adjustment Algorithm

INR	Warfarin Dose Adjustment*	Current Daily Dose (mg)			
		2.0	5.0	7.5	10.0
12.5					
1.0-2.0	Increase x 2 days	5.0	7.5	10.0	12.5
15.0					
2.0-3.0	No change	—	—	—	—
3.0-6.0	Decrease x 2 days	1.25	2.5	5.0	7.5
10.0					
6.0-10.0 [†]	Decrease x 2 days	0	1.25	2.5	5.0
7.5					
10.0-18.0 [§]	Decrease x 2 days	0	0	0	0
2.5					
>18.0 [§]	Discontinue warfarin and consider hospitalization/reversal of anticoagulation				

American Heart Association