



# Warfarin Management - Adult - Ambulatory Clinical Practice Guideline

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## **Executive Summary**

### **Guideline Overview**

This guideline outlines the evidence for managing anticoagulation therapy with oral vitamin K antagonist (warfarin). Evidence is based on recommendations from the Antithrombotic Therapy and Prevention of Thrombosis, 9<sup>th</sup> edition: American College of Chest Physicians Clinical Practice Guidelines. It provides recommendations for how to initiate, dose adjust and monitor warfarin therapy in the ambulatory setting.

### **Key Practice Recommendations**

1. Initial warfarin dosing should be tailored based on patient bleed risk, potential sensitivity to warfarin, indication, goal INR range, and if potential drug interactions are present.
2. Maintenance warfarin dose adjustments should be based on current INR results and trends and patient assessment of any missed doses, drug interactions, dietary intake or supplements, documentation of bleeding, or other changes that may affect the INR.
3. Table 5, 6 and 7 provide recommendations for warfarin dosing for INR goals of 1.5-2.0, 2-3 and 2.5 -3.5.

### **Companion Documents**

1. Warfarin Management – Adult – Inpatient Clinical Practice Guideline
2. Atrial Fibrillation – Adult – Inpatient/Ambulatory Clinical Practice Guideline
3. Antithrombotics in Non-Valvular Atrial Fibrillation – Adult – Inpatient/Ambulatory Clinical Practice Guideline
4. HealthDecision<sub>TM</sub> Atrial Fibrillation Risk Stratification Tool
5. Indications for Blood Product Transfusion – Adult – Inpatient/[Ambulatory](#)

### **Pertinent UW Health Policies & Procedures**

1. UWHC Policy #2.3.1 Anticoagulation Monitoring by UW Anticoagulation Clinic Pharmacists
2. UW Health Policy #7.98 Entering Test Results into UW Health Link (EPIC)

### **Patient Resources**

1. Health Facts For You #6900: Warfarin (Coumadin, Jantoven)
2. Health Facts For You #322: Food-Drug Interactions: Coumadin & Warfarin Diet Interactions
3. Health Facts For You #6915: Heparin (Unfractionated and Low Molecular Weight)
4. Health Facts For You #6115: Stopping Anticoagulation and Antiplatelet Therapy

## **Scope**

### **Disease/Condition(s):**

This guideline will apply to any disease or condition requiring anticoagulation with oral vitamin K antagonist (warfarin) therapy

### **Clinical Specialty:**

Internal Medicine  
Family Practice  
Cardiology  
Hematology  
Pharmacy  
Nursing

### **Intended Users:**

Physicians  
Advanced Practice Providers  
Pharmacists  
Nurses

### **Objective(s):**

To provide a strategy for the management of warfarin therapy in ambulatory adult patients using a standardized process while offering an individualized assessment.

### **Target Population:**

Adult patients being initiated and maintained on warfarin therapy in the clinic setting.

### **Interventions and Practices Considered:**

This guideline provides strategies and recommendations designed to assist clinicians in developing warfarin management plans. It begins with providing recommendations for target INR ranges based on indication for use. It focuses on how to dose warfarin based on individual patient risk factors, INR response, drug interactions, and dietary interactions.

### **Major Outcomes Considered:**

Thromboembolic events while initiating and maintaining warfarin therapy  
Hemorrhagic events while initiating and maintaining warfarin therapy  
Need for reversal agents in the event of a bleeding event or emergent surgery/procedure.

### **Guideline Metrics:**

Metrics will include time within target INR range, sub and supratherapeutic INR values, critical INR values, appropriate dose adjustments based on drug and dietary interactions while receiving warfarin therapy.

## Methodology

### Methods Used to Collect/Select the Evidence:

(1) completing a comprehensive literature search of electronic databases; (2) conducting an in-depth review of relevant abstracts and articles; (3) conducting thoughtful discussion and interpretation of findings; (4) ranking strength of evidence underlying the current recommendations that are made.

### Methods Used to Assess the Quality and Strength of the Evidence:

A similar grading system for the recommendations from the American College of Chest Physicians was utilized.

### Rating Scheme for the Strength of the Evidence:

For all other recommendations a modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) developed by the American Heart Association and American College of Cardiology (Figure 1.) has been used to assess the Quality and Strength of the Evidence in this Clinical Practice Guideline.<sup>1</sup>

## Definitions

1. Baseline INR – an INR resulted within the previous 30 days prior to initiating warfarin
2. Current INR – an INR reported on the same calendar date as the scheduled warfarin dose

## Introduction

This guideline outlines the evidence for managing anticoagulation therapy with oral vitamin K antagonist (warfarin). For dosing and monitoring of warfarin therapy it is recommended that standardized and validated decision support tools be used for most patients. Evidence has shown improved time in therapeutic INR range and clinical outcomes in patients managed by trained staff using standardized procedures and dosing decision support tools.<sup>2</sup>

Warfarin works by inhibiting the reduction of vitamin K epoxide and limiting the activation of vitamin K dependant clotting factors: II, VII, IX and X. It also inhibits the synthesis of anticoagulant proteins C, S and Z. When administered orally warfarin is rapidly and completely absorbed. It is highly protein bound and metabolized by the cytochrome P450 (CYP) enzyme 2C9, 1A2 and 3A4. The half-life of warfarin is 36-42 hours.<sup>3</sup>

This guideline provides recommendations that are based on the evidence outlined from the Antithrombotic Therapy and Prevention of Thrombosis 9<sup>th</sup> edition: American College of Chest Physicians Clinical Practice Guidelines (CHEST).<sup>2-8</sup>

## Recommendations

1. INR goals and duration of therapy listed in Table 1 are recommended by the CHEST guidelines.<sup>2-8</sup> (**Class I, Level B**)

- 1.1. Exceptions include orthopedic surgery INR goals which are recommendations provided by UW Health Orthopedic surgeon consensus and based on the American Association of Orthopedic Surgeons clinical guideline on Prevention of Symptomatic Pulmonary Embolism in Patients Undergoing Total Hip or Knee Arthroplasty<sup>9</sup> (**Class IIb, Level C**)
- 1.2. Alternative INR goals may be chosen for specific patients when bleeding risk outweighs clotting risk and will be determined by the individual's provider (**Class IIb, Level C**)

**Table 1.** Indications for Antithrombotics, INR Ranges, and Duration of Therapy<sup>2-10</sup>

Indication	INR (Range)	Duration	Comments
<b>Thrombophilia with Thromboembolic Event<sup>2</sup></b>			
Antiphospholipid Syndrome	2.5 (2-3)	Chronic	
Homozygous Factor V Leiden	2.5 (2-3)	Chronic	
Deficiency of Protein C, S or Anti-Thrombin	2.5 (2-3)	Chronic	
<b>Atrial Fibrillation (AF)/ Atrial Flutter<sup>4</sup></b>			
CHA <sub>2</sub> DS <sub>2</sub> VASc = 0; Low stroke risk	None		May choose aspirin 75-325 mg daily
CHA <sub>2</sub> DS <sub>2</sub> VASc ≥ 1; Intermediate/High stroke risk	2.5 (2-3)	Chronic	Anticoagulation CI: aspirin 75-325 mg and clopidogrel 75 mg daily
Pre-cardioversion (AF or flutter >48 hours)	2.5 (2-3)	3 weeks	
Post-cardioversion (in NSR)	2.5 (2-3)	4 weeks	
<b>Ischemic Stroke<sup>9</sup></b>			
Non-cardioembolic stroke or TIA	None	Chronic	Use antiplatelet therapy
<b>Cardioembolic stroke or TIA</b>			
-With warfarin CI	None	Chronic	Aspirin 81-325 mg daily
-With cerebral venous sinus thrombosis	2.5 (2-3)	3-6 months	
- With patent foramen ovale	None	Chronic	Use antiplatelet therapy
<b>Thromboembolism (DVT, PE) symptomatic or asymptomatic<sup>6</sup></b>			
Provoked VTE event	2.5 (2-3)	3 months	
<b>Unprovoked: 1<sup>st</sup> VTE event</b>			
- Proximal or Distal DVT	2.5 (2-3)	3 months	After 3 months evaluate risk-benefit for extended therapy
- PE	2.5 (2-3)	> 3 months	After 3 months evaluate risk-benefit for extended therapy
<b>Unprovoked: 2<sup>nd</sup> VTE event</b>			
- DVT or PE	2.5 (2-3)	> 3 months	Consider chronic
With malignancy	2.5 (2-3)	> 3 months	LMWH preferred over warfarin Consider chronic
<b>Acute Upper Extremity DVT</b>			
- Associated with central venous catheter that was removed	2.5 (2-3)	3 months	
- Associated with central venous catheter that was NOT removed	2.5 (2-3)	Extended	Continue anticoagulation until catheter removed
- Not associated with a central venous catheter	2.5 (2-3)	3 months	
Spontaneous superficial vein thrombosis	None	45 days	Prophylaxis LMWH or Fondaparinux

<b>Valvular Disease<sup>7</sup></b>			
Rheumatic mitral valve disease			
- Left atrial diameter < 55 mm	None		
- With AF, left atrial thrombus, or left atrial diameter > 55 mm	2.5 (2-3)	Chronic	
<b>Valve Repair</b>			
Aortic	None		Aspirin 81 mg daily
Mitral	None	3 months	Antiplatelet therapy
<b>Valve Replacement - Bioprosthetic</b>			
Aortic or TAVI*	None		Antiplatelet therapy
Mitral	2.5 (2-3)	3 months	Followed by aspirin 81 mg daily
* If other indication for anticoagulation exist – see specific indication for therapy recommendations			
<b>Valve Replacement - Mechanical</b>			
Aortic	2.5 (2-3)	Chronic	Low bleed risk: add aspirin 81 mg
Mitral	3 (2.5-3.5)	Chronic	Low bleed risk: add aspirin 81 mg
Dual Aortic and Mitral Valve	3 (2.5 -3.5)	Chronic	Low bleed risk: add aspirin 81 mg
<b>Orthopedic Surgery<sup>8,9</sup></b>			
Total Knee or Hip Arthroplasty*	1.8-2.2	10-14 days	INR goal per UWHC Orthopedics
Hip Fracture Surgery*	1.8-2.2	10-14 days	INR goal per UWHC Orthopedics
Trauma Surgery*	1.8-2.2	35 days	INR goal per UWHC Orthopedics
* If other indication for anticoagulation exist - INR goal should be clarified			

AF- atrial fibrillation; CAD – coronary artery disease; CI- contraindications; DVT- deep vein thrombosis; LMWH- low molecular weight heparin; NSR- normal sinus rhythm; PE- pulmonary embolism; TIA- transient ischemic attack; TAVI - transcatheter aortic valve transplantation; VTE – venous thromboembolism

## Patient Assessment

2. Before initiating warfarin therapy the patient should be assessed for risk factors that may increase their risk for bleeding, thromboembolic events and for risk factors that may impact the sensitivity of the response to warfarin.<sup>2,3</sup> (**Class I, Level C**)
3. There are various clinical tools available to assess a patient’s bleeding risk, however, the HAS-BLED score has been shown to accurately predict the risk of major bleeding in patients receiving antithrombotic therapy.<sup>10</sup> (**Class IIb, Level A**)
  - 3.1 It stratifies patients as low, moderate or high bleed risk
  - 3.2 This score should not automatically exclude patients from receiving anticoagulation if clinically indicated, but instead should be used to identify modifiable risk factors that can be corrected (ex. uncontrollable hypertension) (**Class IIb, Level C**)
  - 3.3 Table 2 outlines the HAS-BLED score and bleeding classification<sup>10</sup>

**Table 2: HAS-BLED Score<sup>10</sup> (Class IIb, Level A)**

Factors	Points	Scoring
Hypertension (SBP >160 mmHg)	1	<b>Score = 0-1:</b> Low risk <b>Score = 2:</b> Moderate risk <b>Score ≥3:</b> High risk  <b>High bleed risk considerations:</b> - Optimize blood pressure control
Abnormal lab values - Creatinine >2.26 mg/dL - Bilirubin >2x the upper limit of normal (ULN) <i>and</i> AST/ALT/AP >3x ULN	1	
Stroke history	1	

Bleeding history or predisposition	1	<ul style="list-style-type: none"> <li>- Check INRs frequently</li> <li>- Utilize anticoagulation clinic</li> <li>- Focus on fall prevention</li> <li>- Utilize direct oral anticoagulants</li> </ul>
Labile INRs: Time in Therapeutic Range <60%	1	
Elderly: > 65 years	1	
Drugs <ul style="list-style-type: none"> <li>- EtOH abuse</li> <li>- ASA or NSAID use</li> </ul>	1	

4. Patients with multiple high sensitivity risk factors may require a lower initiation dose and reduced maintenance doses<sup>2,3,10</sup> **(Class IIb, Level C)**

4.1 Examples of these risk factors are included in Table 3

**Table 3. Factors for Identifying Warfarin Sensitive Patients<sup>2,3,10</sup> (Class I, Level C)**

Increased Warfarin Sensitivity	
Increased INR Response	Increased Bleeding Risk
Baseline INR ≥ 1.5	Current antiplatelet therapy
Age > 65	Thrombocytopenia: platelet <75 K/uL
Actual body weight < 45 kg or actual < ideal	Significant hepatic disease: cirrhosis or total bilirubin.>2.4 mg/dL
Malnourished/ NPO >3 days	Alcohol abuse history
Hypoalbuminemia <2 g/dl	End stage renal disease
Chronic diarrhea	GI bleed within past 30 days
Significant drug interactions	Surgery within past 2 weeks
Decompensated heart failure	Intracranial bleed within past 30 days

### Initial Warfarin Dosing

5. Initial dosing should be tailored based on patient bleed risk, potential sensitivity to warfarin, indication for anticoagulation, goal INR range and if potential drug interactions are present<sup>3</sup> **(Class I, Level C)**
6. A baseline INR should be resulted prior to initiating warfarin therapy<sup>3</sup> **(Class I, Level C)**
7. A dose larger than the anticipated maintenance dose (loading dose) of warfarin is inappropriate and should not be used in most patients<sup>2</sup> **(Class IIb, Level C)**
- 7.1 In healthy patients with a PE or DVT warfarin 10 mg for the first 2 days may be considered followed by dosing based on INR measurements<sup>2</sup> **(Class IIb, Level C)**
8. Prior to making a dose adjustment assess for any missed doses, drug interactions, diet, documentation of bleeding, or other changes that may affect INR<sup>2,3</sup> **(Class I, Level C)**
- 8.1 Table 4 should be utilized for warfarin dose adjustments within the first week of therapy **(Class IIb, Level C)**
- 8.2 Warfarin should be adjusted based on current INR measurements<sup>2,3</sup> **(Class I, Level C)**
9. If appropriate, patients should receive another form of anticoagulation such as LMWH for at least 5 days and until they are therapeutic on warfarin for 24-48 hours<sup>3,6</sup> **(Class I, Level B)**

**Table 4. Warfarin Initiation (Week 1) with INR Goal 2-3 (Class IIb, Level C)**



Day Therapy	INR Value	Dose Adjustment
Day 1		5 mg daily (2.5 mg daily if high sensitivity to warfarin identified)
In 2-3 days after initiation	< 1.5 1.5-1.9 2.0-2.5 > 2.5	5 – 7.5 mg daily 2.5 - 5 mg daily 2.5 mg daily Hold and recheck INR next day
In additional 2-3 days after last INR check	< 1.5 1.5-1.9 2.0-3.0 > 3.0	7.5 – 10 mg daily 5 – 10 mg daily 2.5 – 5 mg daily Hold warfarin, recheck in 1-2 days

### Maintenance Warfarin Dosing

10. Warfarin should be adjusted based on current INR measurements and assessment of any missed doses, recent INR trends, changes in diet and activity level, potential drug interactions, symptoms of bleeding or clotting and other changes that may affect INR level as described in Appendix A. Patient Assessment Tool<sup>2,3</sup> **(Class I, Level C)**
  - 10.1. INRs minimally above or below therapeutic range by  $\leq 0.5$  in patients previously stable or if there is a specific reason for the INR to be out of range (ex. missed dose), then no dosing change may be needed. Recommend to continue current dose and test INR in 1-2 weeks.<sup>2</sup> **(Class IIa, Level C)**
11. Tables 5-7 should be utilized for warfarin dose adjustments after at least 7 days of therapy
  - 11.1 For INR ranges that do not have a corresponding dosing table, the same principles of adjusting the weekly dose by approximately 10% for an out of range INR should be used. **(Class IIb, Level C)**
  - 11.2 Daily low dose vitamin K supplement should not be used to improve INR control<sup>2</sup> **(Class IIa, Level C)**
12. Prior to cardioversion procedure the INR must remain within goal for 30 days.<sup>4</sup> If an INR is trending downward consider increasing the warfarin dose to prevent a subtherapeutic INR **(Class IIb, Level C)**

**Table 5. Warfarin Maintenance Dosing Protocol with INR Goal 1.5-2.0 (Class IIb, Level C)**

INR ≤ 1.2	INR 1.3 -1.4	INR 1.5 - 2.0	INR 2.1 – 3.0	INR 3.1 - 4.0*	INR 4.1-5.0*	INR 5.1-9.0*	INR > 9.0
Increase weekly dose 10%	Increase weekly dose 5%	No change	Decrease weekly dose 5%	Consider half dose x 1 and Decrease weekly dose 10%	Hold 1 dose Decrease weekly dose by 10-20%	<b>MD order required</b> Consider: Hold 2 doses Decrease weekly dose 10-20% Check Hct	Contact MD for urgent patient evaluation

**Table 6. Warfarin Maintenance Dosing Protocol with INR Goal 2-3 (Class IIb, Level C)**

INR < 1.5	INR 1.5 - 1.9	INR 2.0 - 3.0	INR 3.1- 4.0*	INR 4.1-5.0*	INR 5.1- 9.0*	INR > 9.0
Extra Dose Increase weekly dose 10-20%	Increase weekly dose 5-10%	No change	Decrease weekly dose 5-10%	Hold 1 dose Decrease weekly dose 10%	<b>MD order required</b> Consider: Hold 2 doses Decrease weekly dose 10-20% Check Hct	Contact MD for urgent patient evaluation

**Table 7. Warfarin Maintenance Dosing Protocol with INR Goal 2.5-3.5 (Class IIb, Level C)**

INR < 1.9†	INR 1.9 - 2.4†	INR 2.5 - 3.5	INR 3.6 - 4.5*	INR 4.6-5.0*	INR 5.1- 9.0*	INR > 9.0
Extra Dose Increase weekly dose 10-20%	Increase weekly dose 5-10%	No change	Decrease weekly dose 5-10%	Hold 1 dose Decrease weekly dose 10%	<b>MD order required</b> Consider: Hold 2 doses Decrease weekly dose 10-20% Check Hct	Contact MD for urgent patient evaluation

\* If the INR is above the specified range for accuracy per point of care (POC) device, a repeat venipuncture is required to verify INR

† If the INR < 2.0 and the patient has a mechanical valve then bridge therapy with a low molecular weight heparin should be considered

13. If an extra dose or hold dose is recommended:
  - 13.1 A partial-full extra or partial–full held dose can be utilized based on INR and patient’s sensitivity to warfarin. **(Class IIb, Level C)**
  - 13.2 The extra or held dose should not be included in the weekly dose adjustment unless the total weekly dose is ≥ 50 mg per week as a small percentage change can greatly impact the INR. **(Class IIb, level C)**
  
14. If warfarin is dosed at > 50 mg per week then smaller weekly dose adjustments should be targeted (ex. 5%) **(Class IIb, level C)**

## Laboratory Monitoring<sup>2,3</sup>

### 15. INR

15.1 A baseline INR must be resulted prior to the first dose of warfarin (**Class I, Level A**)

15.2 Upon discharge from the hospital an INR should be obtained within 2-4 days for newly initiated warfarin or if there were changes that could affect the INR. (**Class I, Level C**)

15.3 If bridging warfarin with low molecular weight heparin may consider checking the INR within 1-2 days if the INR is close to the therapeutic range (i.e. 1.7-1.9). (**Class I, Level C**)

15.4 If there were no changes then the INR may be checked at the next scheduled INR visit. (**Class I, Level C**)

15.5 Table 8 outlines recommendations for monitoring the INR when initiating warfarin therapy

15.6 Table 9 outlines recommendations for monitoring the INR during maintenance warfarin therapy.

16. Hematocrit, platelet, ALT, total bilirubin, and serum creatinine should be resulted within the preceding 3 months and periodically thereafter per physician discretion (**Class IIb, Level C**)

17. For women of child bearing age a pregnancy test is recommended before initiating warfarin (**Class IIb, Level C**)

**Table 8. Frequency of INR Monitoring After Initiation of Warfarin (Class IIb, Level C)**

INR Check	
Every 2 – 3 days	Until INR within therapeutic range on 2 consecutive INR checks
Then every week	Until INR within therapeutic range on 2 consecutive INR checks
Then every 2 weeks	Until INR within therapeutic range on 2 consecutive INR checks
Then every 4 weeks	When dose is stable check monthly

**Table 9. Frequency of INR Monitoring for Maintenance of Warfarin (Class IIb, Level C)**

INR Check	
After 1 week	If start/stop interacting medication, change in diet, change in activity level or other change that could affect INR
Every 1-2 weeks	If dose needed adjustment by 5-10%
Every 4 weeks	If patient maintained on same stable dose < 6 months
Every 6-8 weeks	If patient maintained on same stable dose for at least 6 months

## Symptomatic Monitoring

18. At each encounter for INR monitoring patients should be assessed for signs and symptoms of bleeding and clotting as well as any change that could affect the INR result<sup>2,3</sup>. (**Class I, Level C**)

- 18.1 Any significant signs or symptoms of major bleeding or clotting should be referred to a primary care provider or urgent care/emergency department for evaluation. Common signs and symptoms are listed in Table 10.

**Table 10. Common Signs and Symptoms of Major Bleeding and Clotting<sup>6,11</sup> (Class I, Level C)**

Signs and Symptoms of Bleeding	Signs and Symptoms of Clotting
Blood in urine or stool (enough to color toilet water)	Chest or unilateral leg pain
Blood in sputum	Shortness of breath
Bloody emesis (bright red or coffee ground-like)	Elevated heart rate (HR > 100 bpm)
Bleeding that has not resolved or slowed within 10 minutes	Unilateral lower extremity swelling

### Drug Interactions

Most drug interactions with warfarin will start to have an effect within 3-5 days of concomitant therapy. There are some notable exceptions which include amiodarone, carbamazepine, and rifampin which have a delayed effect after 7-14 days of dual therapy.<sup>2,3,12,13</sup> Tables 11 and 12 outline potential drug-drug, drug-food, and drug-herb interactions. Bolded medications are considered significant interactions. This table is not all inclusive.

19. For most drug interactions with warfarin it is recommended to either increase or decrease (based on expected INR response) the weekly dose by 30% (**Class IIb, Level C**)
- 19.1 For amiodarone target a 50% *reduction* in weekly maintenance dose for warfarin after 7-14 days of dual therapy<sup>12</sup> or if initiating warfarin start at 2.5 mg dose (**Class IIb, Level C**)
- 19.2 For rifampin target a 50% *increase* in weekly maintenance dose for warfarin after 7-14 days of dual therapy.<sup>12</sup> (**Class IIb, Level C**)

**Table 11. Medications, Dietary Supplements and Food that INCREASE INR or Bleeding Risk.<sup>2,3,12,13</sup> (Class I, Level C)**

Drug Class	Known Interaction	Probable Interaction	Possible Interaction	Unlikely Interaction
Anti-Infective	Ciprofloxacin Erythromycin <b>Fluconazole</b> Isoniazid <b>Metronidazole</b> Miconazole Miconazole Vaginal Suppository Moxifloxacin <b>Sulfamethoxazole</b> Voriconazole	Amoxicillin/clavulanate Azithromycin Clarithromycin Itraconazole Ketoconazole Levofloxacin Ritonavir Tetracycline	Amoxicillin Chloramphenicol Darunavir Daptomycin Etravirine Ivermectin Nitrofurantoin Norfloxacin Ofloxacin Saquinavir Telithromycin Terbinafine	Cefotetan Cefazolin Tigecycline
Cardiovascular	<b>Amiodarone*</b> Clofibrate Diltiazem Fenofibrate Propafenone Propranolol	Aspirin Fluvastatin Quinidine Ropinirole Simvastatin	Disopyramide Gemfibrozil Metolazone	

Analgesics, Anti-Inflammatory	Piroxicam	Acetaminophen Aspirin Celecoxib Tramadol	Indomethacin Propoxyphene Sulindac Tolmentin Topical Salicylates	Methylprednisolone Nabumetone
CNS Drugs	Alcohol Citalopram Entacapone Sertraline	Disulfiram Chloral hydrate Fluvoxamine Phenytoin	Felbamate	Diazepam Fluoxetine Quetiapine
GI Drugs and Food	Cimetidine Mango Omeprazole	Grapefruit	Orlistat	
Herbal Supplement	Fenugreek Feverfew Fish Oil Ginkgo Quiltinggao	Dandelion Danshen Don Quai Lycium PC-SPES Red or Sweet Clover	Capsicum <b>Forskolin</b> Garlic Ginger Turmeric	
Other	Anabolic Steroids Capecitabine Zileuton	Fluorouracil Gemcitabine Levamisole Paclitaxel Tamoxifen Tolterodine	Acarbose Cyclophosphamide Danazol Iphosphamide Trastuzumab	Etoposide Carboplatin Levonorgestrel

**Table 12.** Medications, Dietary Supplements and Food that **DECREASE** INR.<sup>2,3,12,13</sup> (**Class I, Level C**)

Drug Class	Known Interaction	Probable Interaction	Possible Interaction	Unlikely Interaction
Anti-Infective	Griseofulvin Nafcillin Ribavirin <b>Rifampin*</b>	Dicloxacillin Ritonovir Rifapentine	Terbinafine Nelfinavir Nevirapine	Cloxacillin Rifaximin Teicoplanin
Cardiovascular	Cholestyramine	Bosentan	Telmisartan	Furosemide
Analgesics, Anti-Inflammatory	Mesalamine	Azathioprine	Sulfasalazine	
CNS Drugs	Barbiturates Carbamazepine	Chlordiazepoxide		Propofol
GI Drugs and Food	High content vitamin K food Avocado	Soy milk Sucralfate	Sushi containing seaweed	
Herbal Supplement	Alfalfa	Ginseng Multivitamin St. John's Wort Parsley Chewing Tobacco	Co-Enzyme Q10 Yarrow Licorice	Green Tea
Other	Mercaptopurine	Chelation Therapy Influenza vaccine Raloxifene	Cyclosporine Etretinate Ubidecarenone	

## Dietary Interactions

Patients on long term warfarin therapy can be sensitive to the fluctuating levels of vitamin K from both external dietary sources and internal gastrointestinal sources. Increased dietary intake of vitamin K from either food sources or nutritional supplement sources can reduce the effectiveness of warfarin and decrease the INR. Since warfarin is a high protein bound drug with up to 99% of the drug bound to plasma proteins, patients who are malnourished with low albumin levels will have higher concentrations of unbound drug and may experience faster INR response. Conversely, patients receiving enteral nutrition will have more bound drug due to the high protein concentration in these products.<sup>3,12,14-16</sup>

20. Promote consistent intake of dietary vitamin K and not avoidance<sup>3</sup> (**Class I, Level C**)
21. For enteral nutrition hold the tube feed 1 hour before and 1 hour after warfarin administration<sup>14,16</sup> (**Class IIa, Level B**)
  - 21.1 If unable to hold enteral nutrition, increase warfarin dose until a therapeutic INR is achieved<sup>16</sup> (**Class IIb, Level B**)
  - 22.2 If on cycled tube feeding, administer warfarin at a time when tube feeds are off<sup>16,17</sup> (**Class IIa, Level B**)

## Warfarin Reversal

The treatment for warfarin reversal should be based on the indication for use, location of bleed, severity of bleed and the extent of INR elevation. Guidelines for reversal of warfarin are available within the UW Health Adult Procoagulant Therapy for Treatment of Non-Hemophilic Bleeding Clinical Practice Guideline.<sup>2,3</sup>

[http://www.uwhealth.org/files/uwhealth/docs/anticoagulation/Procoagulant\\_Guideline.pdf](http://www.uwhealth.org/files/uwhealth/docs/anticoagulation/Procoagulant_Guideline.pdf)

## **UW Health Implementation**

### **Potential Benefits:**

This guideline will provide a resource for standardizing the approach to warfarin management for an individual patient. Individualization of a warfarin management plan should result in lower incidence of supra-therapeutic and critical INR results, minimize the risk for bleeding events and provide guidance for managing drug and dietary interactions.

### **Potential Harms:**

Warfarin is a complex medication that requires close monitoring to prevent adverse events. While significant bleeding more commonly occurs when the INR is above the therapeutic range, it, may also occur when the INR is within or slightly below target INR range. Bleeding is the most common adverse event of warfarin for which to monitor. Additionally, if the INR remains sub-therapeutic for an extended time there is the risk for thromboembolic events.

### **Qualifying Statements**

Despite providing recommendations to manage many common scenarios, there may be external factors that can influence the INR and dosing of warfarin that are not provided in this guideline. Since standardization of warfarin management is unrealistic, clinical judgement should be used when indicated to prevent unwanted adverse events

## **Implementation Plan/Tools**

Recommendations provided in this guideline will be disseminated to staff through a variety of venues including newsletters, clinic inservices and additional tools as described below:

1. Guideline will be housed on U-Connect in a dedicated folder for CPGs.
2. Guideline will also be posted on UW Health Anticoagulation Website:  
[www.uwhealth.org/anticoagulation](http://www.uwhealth.org/anticoagulation)
3. Online class and quarterly live training program on use of the Warfarin Management Guideline and Protocol will contain updates
4. Links to this guideline will be included in the Warfarin Management Protocol

## **Disclaimer**

CPGs are described to assist clinicians by providing a framework for the evaluation and treatment of patients. This Clinical Practice Guideline outlines the preferred approach for most patients. It is not intended to replace a clinician's judgment or to establish a protocol for all patients. It is understood that some patients will not fit the clinical condition contemplated by a guideline and that a guideline will rarely establish the only appropriate approach to a problem.

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## Appendix A. Ambulatory Warfarin Management – Adults – CPG

### Warfarin Management Dosing Tool

#### Warfarin Initiation Dosing Protocol (Week 1) with INR Goal 2-3

Day Therapy	INR Value	Total Daily Dose
Day 1		5 mg daily (2.5 mg daily for high sensitivity)
In 2-3 days after initiation	< 1.5	5 – 7.5 mg daily
	1.5-1.9	2.5 - 5 mg daily
	2.0-2.5	2.5 mg daily
	> 2.5	Hold and recheck INR next day
In additional 2-3 days after last INR check	< 1.5	7.5 – 10 mg daily
	1.5-1.9	5 – 10 mg daily
	2.0-3.0	2.5 – 5 mg daily
	> 3.0	Hold warfarin, recheck in 1-2 days

#### Frequency of INR Monitoring After Initiation of Warfarin

Check INR	
Every 2 – 3 days	Until INR within therapeutic range on 2 consecutive INR checks
Then every week	Until INR within therapeutic range on 2 consecutive INR checks
Then every 2 weeks	Until INR within therapeutic range on 2 consecutive INR checks
Then every 4 weeks	When dose is stable check monthly

#### Frequency of INR Monitoring for Maintenance of Warfarin

Check INR	
After 3-5 days	If start/stop interacting medication, change in diet, change in activity level or other change that could affect INR
Every 1-2 weeks	If dose needed adjustment by 5-10%
Every 4 weeks	If maintained on same stable dose < 6 months
Every 6-8 weeks	If maintained on same stable dose for at least 6 months

#### Warfarin Maintenance Dosing Protocol with INR Goal 1.5 – 2.0

INR ≤ 1.2	INR 1.3 -1.4	INR 1.5 -2.0	INR 2.1 – 3.0	INR 3.1 - 4.0*	INR 4.1-5.0*	INR 5.1-9.0*	INR > 9.0
Increase weekly dose 10%	Increase weekly dose 5%	No change	Decrease weekly dose 5%	Consider half dose x 1 Decrease weekly dose 10%	Hold 1 dose Decrease weekly dose by 10-20%	<b>MD order required:</b> Hold 2 doses Decrease weekly dose 10-20%	Contact MD for urgent patient evaluation

\* If the INR is above the specified range for accuracy per POC device, a repeat venipuncture is required to verify INR

#### Warfarin Maintenance Dosing Protocol with INR Goal 2-3

INR < 1.5	INR 1.5 - 1.9	INR 2.0 - 3.0	INR 3.1 - 4.0*	INR 4.1-5.0*	INR 5.1-9.0*	INR > 9.0
Extra Dose Increase weekly dose 10-20%	Increase weekly dose 5-10%	No change	Decrease weekly dose 5-10%	Hold 1 dose Decrease weekly dose 10%	<b>MD order required</b> Hold 2 doses Decrease weekly dose 10-20%	Contact MD for urgent patient evaluation

\* If the INR is above the specified range for accuracy per POC device, a repeat venipuncture is required to verify INR

#### Warfarin Maintenance Dosing Protocol with INR Goal 2.5-3.5

INR < 1.9‡	INR 1.9 - 2.4‡	INR 2.5 - 3.5	INR 3.6 - 4.5*	INR 4.6-5.0*	INR 5.1-9.0*	INR > 9.0
Extra Dose Increase weekly dose 10-20%	Increase weekly dose 5-10%	No change	Decrease weekly dose 5-10%	Hold 1 dose Decrease weekly dose 10%	<b>MD order required</b> Hold 2 doses Decrease weekly dose 10-20%	Contact MD for urgent patient evaluation

\* If the INR is above the specified range for accuracy per POC device, a repeat venipuncture is required to verify INR

‡ If the INR < 2.0 and the patient has a mechanical valve then bridge therapy with a low molecular weight heparin should be considered

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## Warfarin Management CPG – Ambulatory Appendix A: Warfarin Management Dosing Tool – Adult – Ambulatory

### Dosing Tips:

- If INR is above or below therapeutic range  $\leq 0.5$  and previously stable or there is a specific temporary reason for INR to be out of range (ex. missed dose): then continue current dose and test INR in 1-2 weeks
- If indicated a partial to full extra dose or partial to full held dose can be utilized based on INR and patient’s sensitivity to warfarin
- Do not include extra or hold doses as part of a weekly dose adjustment
- Weekly warfarin doses  $\geq 50$  mg per week:
  - Smaller weekly dose adjustments should be targeted
  - *Include* extra or hold doses into the weekly dose adjustments
  - If an extra dose is indicated, avoid a full extra dose. Instead consider an extra half dose.

**Drug Interactions:** most drug interactions affect the INR within 3-5 days of concomitant therapy

Drug Interaction	Weekly Warfarin Dose Adjustment	Recheck INR
Fluconazole Metronidazole Sulfamethoxazole/trimethoprim	Day 1 of interaction: Decrease weekly warfarin dose by 30%	3 - 5 days
Amiodarone	Day 7 of amiodarone: Decrease weekly warfarin dose by 25% Day 14 of amiodarone: Decrease weekly warfarin dose by another 25%  <i>Target a 50% reduction in weekly warfarin dose after 2 weeks of dual therapy.</i>	After 7 days of dual therapy After 14 days of dual therapy After 21 days of dual therapy (if INR within goal then follow maintenance INR monitoring table)
Rifampin	Day 7 of rifampin: Increase weekly warfarin dose by 25% Day 14 of rifampin: Increase weekly warfarin dose by another 25%  <i>Target a 50% increase in weekly warfarin dose after 2 weeks of dual therapy.</i>	After 7 days of dual therapy After 14 days of dual therapy After 21 days of dual therapy (if INR within goal then follow maintenance INR monitoring table)
All other drug interactions	Adjust weekly warfarin dose if INR outside of therapeutic range after INR recheck	3 – 5 days

### Progress Note Documentation:

- “.Anticoagplan” – use for documenting warfarin management plan
- “.Anticoagassess” – use for documenting patient findings (positive/negative) table
- “.Anticoagmessage” – use for documenting when unable to reach a patient

### Anticoagulation Episode of Care Workflows

- To create a new episode use the “Enroll in Anticoagulation” order (found in order entry)
- Resolve the episode using the “discontinue therapy” button in the tracking section when a patient discontinues warfarin therapy, transfers care outside of UW Health or is deceased.
- If a patient transfers care within UW Health, the receiving clinic must resolve the current episode and re-enter a new Enroll in Anticoagulation order to reactivate the episode with their clinic specific information.

### Discontinuing Warfarin

When warfarin therapy is discontinued completed the following check list:

- ✓ Resolve the episode using the “discontinue therapy” button in the tracking section
- ✓ Check for open orders related to monitoring warfarin (ex – INR) and discontinue
- ✓ Medication list – remove warfarin from the patient’s medication list
- ✓ Problem list – remove any problems related to managing warfarin (ex. long-term monitoring of anticoagulants)