Warfarin Management – Adult – Inpatient Clinical Practice Guideline

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Introduction

Warfarin is a medication with a narrow therapeutic index that relies on a targeted range for efficacy and reduction of complications.[1] With this narrow therapeutic range, warfarin is associated with bleeding complications, longer lengths of stays, adverse drug reactions, and higher hospitalization costs.[1,2] It is recommended to use standardized and validated dosing and monitoring tools for most patients on warfarin therapy.[3]

Warfarin inhibits the reduction of vitamin K epoxide which limits the activation of vitamin K dependent clotting factors II, VII, IX and X. Warfarin is highly protein bound with a half-life of 36-42 hours. It is metabolized by the cytochrome P450 enzymes: 2C9, 1A2, and 3A4.[1]

This guideline provides recommendations that are based on the evidence outlined from the Antithrombotic Therapy and Prevention of Thrombosis 9th edition: American College of Chest Physicians Clinical Practice Guidelines (CHEST) and from more recent individual articles focusing on inpatient warfarin management.[1,3,4-7]

Scope

Intended User(s):
Physicians, Advanced Practice Providers, Pharmacists, Nurses

Objective(s):
To provide a strategy for the management of warfarin therapy in adult hospitalized patients using a standardized process while offering an individualized assessment.

Target Population:
Adult inpatients either being initiated on warfarin or continued on home warfarin therapy during hospitalization.

Clinical Questions Considered:

- How should warfarin therapy be initiated in patients with a new indication for anticoagulation?
- How should warfarin therapy be monitored and adjusted for patients previously on warfarin but with a new or worsening disease progression that could affect anticoagulation?

Definitions

1. Baseline INR: (for patients not previously on warfarin)
    - For scheduled surgical patients, the INR must be resulted within the electronic medical record within the past 30 days
    - For all other patients the INR must be within 72 hours of warfarin order and prior to verification of the warfarin dose.

2. Current INR: (for patients previously on warfarin)
    - An INR reported on the same calendar date as the scheduled warfarin dose

Recommendations

1. INR goals and duration of therapy are listed in Table 1[1,3,4-9]
   1.1. Alternative INR goals may be chosen for specific patients when bleeding risk outweighs clotting risk and will be determined by the individual's provider *(UW Health GRADE very low-quality evidence, C recommendation)*

Table 1. Indications for warfarin, INR Ranges, and Duration of Therapy[1,3,4-9]

Indication	INR (Range)	Duration	Comments
Thrombophilia with Thromboembolic Event[4]			
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	
Atrial Fibrillation (AF)/ Atrial Flutter[5]			
$CHA_2DS_2VASc = 0$; Low stroke risk	None		More information can be found: Atrial Fibrillation Guideline
CHA_2DS_2 VASc ≥ 1 for men or ≥ 2 for women; Intermediate/High stroke risk	2.5 (2-3)	Chronic	More information can be found: Atrial Fibrillation Guideline
Pre-cardioversion (AF or flutter >48 hours)	2.5 (2-3)	3 weeks	INR must be within target range for 3 consecutive weeks prior to cardioversion
Post-cardioversion (in NSR)	2.5 (2-3)	4 weeks	
Ischemic Stroke[6]			
Cardioembolic stroke or TIA			
-With cerebral venous sinus thrombosis	2.5 (2-3)	3-6 months	
Thromboembolism (DVT, PE) symptomatic or asymptomatic[7]			
Provoked VTE event	2.5 (2-3)	3 months	
Unprovoked: 1st VTE event			
- Proximal or Distal DVT - PE	2.5 (2-3)	3 months	After 3 months evaluate risk-benefit for extended therapy If low-moderate bleeding risk than consider extended therapy. If high bleeding risk than consider 3 months
Unprovoked: 2nd VTE event			
- DVT or PE (with or without malignancy)	2.5 (2-3)	3 months	After 3 months evaluate risk-benefit for extended therapy If low-moderate bleeding risk than consider extended therapy. If high bleeding risk than consider 3 months
Spontaneous superficial vein thrombosis	None	45 days	Prophylaxis LMWH or Fondaparinux
Valve Replacement – Bioprosthetic			
Aortic or TAVR*	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			

Valve Replacement – Mechanical			
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
Valve Replacement – Newer Generation Mechanical			
On-X Aortic	2.5 (2-3)	3 months	After 3 months decrease the INR goal to 1.5-2.0
On-X Mitral	3 (2.5-3.5)	Chronic	Lower INR goals have not been studied in the mitral position
Orthopedic Surgery[9]			
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 replacement; VTE – venous thromboembolism

Patient Assessment

2. Patients newly started on warfarin should be assessed for risk factors that may make them more sensitive to the effects of warfarin. If multiple high sensitivity risk factors are present then a lower initiation dose or reduced maintenance dose may be needed.[1,3] *(UW Health GRADE high quality evidence, S recommendation)*

   2.1. Table 2 identifies risk factors that may increase either INR response or bleeding risks.[1,3,10]

Table 2. Factors for Identifying Warfarin Sensitive Patients[1,3,10]

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

Warfarin Dosing Considerations

3. Initial warfarin dosing should be tailored based on baseline INR, patient bleed risk, potential sensitivity to warfarin, indication, goal INR range and if potential drug interactions are present[1] *(UW Health GRADE high quality evidence, S recommendation)*
4. A dose larger than the anticipated maintenance dose (loading dose) should be avoided in most patients[3] *(UW Health GRADE low quality evidence, C recommendation)*

4.1 In healthy patients with acute VTE warfarin 10 mg for the first 2 days may be considered followed by dosing based on INR measurements[3,11,12] *(UW Health GRADE moderate quality evidence, C recommendation)*

5. For patients on warfarin prior to admission without changes to medications or medical condition that would affect the INR, may resume their home dose *(UW Health GRADE low quality evidence, C recommendation)*
6. Warfarin dosing should be based on current INR results and the dose should not be administered until an INR has been resulted within the medical record. *(UW Health GRADE low quality evidence, C recommendation)*
7. Prior to making a dose adjustment, assess for any missed doses, drug interactions, dietary intake or supplements, documentation of bleeding, or other changes that may affect INR[1,3] *(UW Health GRADE moderate quality evidence, S recommendation)*
   7.1 Tables 3 and 4 provide recommendations for warfarin dosing in the first 5 days of therapy for INR goals of 2-3 or 2.5-3.5.
8. 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[1,6] *(UW Health GRADE high quality evidence, S recommendation)*

Table 4. Warfarin Dosing Protocol with INR Goal 2-3

	High Sensitivity to Warfarin		**Low Sensitivity to Warfarin**	
	INR Value	**Dose**	**INR Value**	**Dose**
Day 1	<1.5	2.5 - 5 mg	<1.5	5 - 7.5 mg
Day 2	<1.5 ≥1.5	2.5 - 5 mg 0 - 2.5 mg	<1.5 ≥1.5	5 - 7.5 mg 0 - 5 mg
Day 3	<1.5 1.5-1.9 2-2.5 ≥2.6	5 mg 2.5 mg 1 mg 0 (no dose)	<1.5 1.5-1.9 2-2.5 ≥2.6	7.5 mg 5 mg 2.5 mg 0 (no dose)
Day 4	<1.5 1.5-1.9 2-3 > 3	7.5 mg 5 mg 2.5 mg 0 - 1 mg	<1.5 1.5-1.9 2-3 >3	10 mg 7.5 mg 5 mg 0-2.5 mg
Day 5	<1.5 1.5-1.9 2-3 3-3.5 >3.5	10 mg yesterday's dose + 1 mg yesterday's dose yesterday's dose – 1 mg 0 (no dose)	<1.5 1.5-1.9 2-3 3-3.5 >3.5	12.5 mg yesterday's dose + 2.5 mg yesterday's dose yesterday's dose – 2.5 mg 0 (no dose)

If at any time INR increases > 0.5 consider reducing dose or if > 1 point consider holding dose
If holding for a high INR, restart warfarin at a reduced dose when INR is trending downward

Table 5. Warfarin Dosing Protocol with INR Goal 2.5-3.5

	High Sensitivity to Warfarin		**Low Sensitivity to Warfarin**	
	INR Value	**Dose**	**INR Value**	**Dose**
Day 1	< 1.5	2.5 - 5 mg	< 1.5	5 - 7.5 mg
Day 2	< 1.5 ≥ 1.5	2.5 - 5 mg 0 - 2.5 mg	< 1.5 ≥ 1.5	5 - 7.5 mg 0 - 5 mg
Day 3	< 1.5 1.5-1.9 2.0-2.5	5 - 7.5 mg 5 mg 2.5 mg	< 1.5 1.5-1.9 2.0-2.5	7.5 - 10 mg 7.5 mg 5 mg

	≥ 2.5	0 (no dose)	≥ 2.5	0 (no dose)
Day 4	< 1.9 2.0-2.4 2.5-3.5 ≥ 3.6	7.5 mg 5 mg 2.5 mg 0 - 1 mg	< 1.9 2.0-2.4 2.5-3.5 ≥ 3.6	10 mg 7.5 mg 5 mg 0-2.5 mg
Day 5	< 1.9 2.0-2.4 2.5-3.5 3.6-4.0 ≥ 4.0	10 mg yesterday's dose + 2.5 mg yesterday's dose yesterday's dose – 2.5 mg 0 (no dose)	< 1.9 2.0-2.4 2.5-3.5 3.6-4.0 ≥ 4.0	12.5 mg yesterday's dose + 2.5 mg yesterday's dose yesterday's dose – 2.5 mg 0 (no dose)

If at any time INR increases > 0.5 consider reducing dose or if > 1 point consider holding dose
If holding for a high INR, restart warfarin at a reduced dose when INR is trending downward

Laboratory Monitoring

9. INR
   - 9.1 A baseline INR must be resulted prior to verification of the first dose of warfarin *(UW Health GRADE high quality evidence, S recommendation)*
   - 9.2 A current INR must be resulted prior to verification of a warfarin dose adjustment *(UW Health GRADE low quality evidence, C recommendation)*
   - 12.3 Obtain a daily INR for patients without a stable warfarin dose *(UW Health GRADE low quality evidence, C recommendation)*
   - 12.4 Obtain a weekly INR (at minimum) for patients with a stable maintenance dose with no changes in medications or medical condition that could affect the INR. *(UW Health GRADE low quality evidence, C recommendation)*
   - 12.5 Upon discharge from the hospital an INR should be obtained within 3-4 days for patients newly started on warfarin or at the next scheduled INR visit if there are no changes in medications or medical conditions that would affect the INR *(UW Health GRADE low quality evidence, C recommendation)*

10. CBC should be obtained prior to initiating warfarin (baseline) and a minimum of every 3 days thereafter *(UW Health GRADE low quality evidence, C recommendation)*
11. Urine HCG (pregnancy test) should be obtained for women of child bearing age before initiating warfarin.[1,3] *(UW Health GRADE moderate quality evidence, C recommendation)*

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.[1,3,13,14] Tables 6 and 7 outlines potential drug-drug, drug-food, and drug-herb interactions. Bolded medications are considered significant interactions. This table is **not** all inclusive.

15. For most drug interactions with warfarin it is recommended to either increase or decrease (based on expected INR response) the weekly dose by 30% *(UW Health GRADE moderate quality evidence, C recommendation)*

15.1 For amiodarone target a 50% *reduction* in weekly maintenance dose for warfarin after 7-14 days of dual therapy[13] or if initiating warfarin start at 2.5 mg dose. *(UW Health GRADE moderate quality evidence, S recommendation)*

15.2 For rifampin target a 50% *increase* in weekly maintenance dose for warfarin after 7-14 days of dual therapy.[13] *(UW Health GRADE moderate quality evidence, S recommendation)*

Table 6. Medications, dietary supplements and food that **INCREASE** INR or bleeding risk.[1,3,13,14]

Drug Class	Known Interaction	Probable Interaction	Possible Interaction	Unlikely Interaction
Anti-Infective	Ciprofloxacin Erythromycin **Fluconazole** Isoniazid **Metronidazole** Miconazole Miconazole Vaginal Suppository Moxifloxacin **Sulfamethoxazole** 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	**Amiodarone*** Clofibrate Diltiazem Fenofibrate Propafenone Propranolol	Aspirin Fluvastatin Quinidine Ropinirole Simvastatin	Disopyramide Gemfibrozil Metolazone	
Analgesics, Anti-Inflammatory	Piroxicam	Acetaminophen Aspririn 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 Quilinggao	Dandelion Danshen Don Quai Lycium PC-SPES Red or Sweet Clover	Capsicum **Forskolin** Garlic Ginger Turmeric	
Other	Anabolic Steroids Capecitabine Zileuton	Fluorouracil Gemcitabine Levamisole Paclitaxel Tamoxifen Tolterodine	Acarbose Cyclophosphamide Danazol Iphosphamide Trastuzumab	Etoposide Carboplatin Levonorgestrel

Table 7. Medications, dietary supplements and food that **DECREASE** INR.[1,3,13,14]

Drug Class	Known Interaction	Probable Interaction	Possible Interaction	Unlikely Interaction
Anti-Infective	Griseofulvin Nafcillin Ribavirin **Rifampin***	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 Chewing Tobacco	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.[1,13,15-17]

16. Promote consistent intake of dietary vitamin K and not avoidance[1] *(UW Health GRADE high quality evidence, S recommendation)*
17. For enteral nutrition hold the tube feed 1 hour before and 1 hour after warfarin administration[15,17] *(UW Health GRADE moderate quality evidence, S recommendation)*
    - 17.1 If unable to hold enteral nutrition, increase warfarin dose until a therapeutic INR is achieved[17] *(UW Health GRADE low quality evidence, C recommendation)*
    - 17.2 If on cycled tube feeding, administer warfarin at a time when tube feeds are off[17,18] *(UW Health GRADE moderate quality evidence, S recommendation)*

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-Hemophiliac Bleeding Clinical Practice Guideline.[1,3]
http://www.uwhealth.org/files/uwhealth/docs/anticoagulation/Procoagulant_Guideline.pdf

Transitioning to Outpatient Management

18. Communication describing either warfarin initiation and/or management during the inpatient stay, along with the expected next INR check, should be communicated to the next provider of care. *(UW Health GRADE very low quality evidence, S recommendation)*
    18.1 Communication may occur electronically for patients who are managed in a UW Health clinic or by phone/fax for a patient who is managed in a non-UW Health clinic.

Disclaimer
Clinical practice guidelines assist clinicians by providing a framework for the evaluation and treatment of patients. This 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.

Methodology
Development Process
Each guideline is reviewed and updated a minimum of every 3 years. All guidelines are developed using the guiding principles, standard processes, and styling outlined in the UW Health Clinical Practice Guideline Resource Guide. This includes expectations for workgroup composition and recruitment strategies, disclosure and management of conflict of interest for participating workgroup members, literature review techniques, evidence grading resources, required approval bodies, and suggestions for communication and implementation.

Methods Used to Collect the Evidence:
The following criteria were used by the guideline author(s) and workgroup members to conduct electronic database searches in the collection of evidence for review.

Literature Sources:
- Electronic database search (e.g., PubMed)
- Databases of systematic reviews (e.g., Cochrane Library)
- Hand-searching journals, external guidelines, and conference publications

Time Period: 1990-2019

Search Terms:
- Inpatient warfarin
- Warfarin protocol
- Warfarin management

Methods to Select the Evidence:
Describe the inclusion/exclusion criteria used for selecting the literature; consider describing chosen variables such as language, study design, outcomes, and comparisons as appropriate.

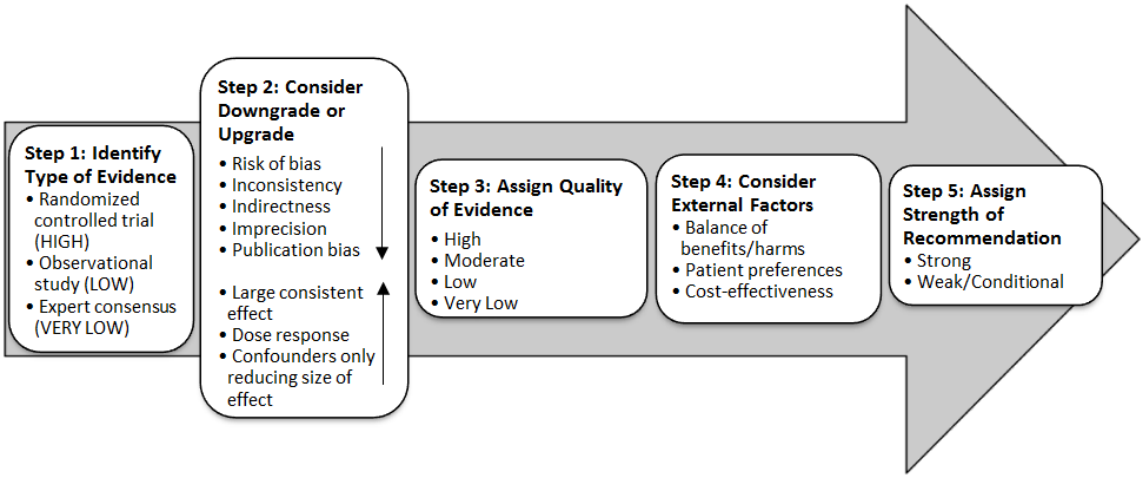
Methods Used to Formulate the Recommendations:
The workgroup members agreed to adopt recommendations developed by external organizations and/or created recommendations internally via a consensus process using

discussion of the literature and expert experience/opinion. If issues or controversies arose where consensus could not be reached, the topic was escalated appropriately per the guiding principles outlined in the UW Health Clinical Practice Guideline Resource Guide.

Methods Used to Assess the Quality of the Evidence/Strength of the Recommendations: Recommendations developed by external organizations maintained the evidence grade assigned within the original source document and were adopted for use at UW Health.

Internally developed recommendations, or those adopted from external sources without an assigned evidence grade, were evaluated by the guideline workgroup using an algorithm adapted from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (see **Figure 1**).

Figure 1. GRADE Methodology adapted by UW Health



Rating Scheme for the Strength of the Evidence/Recommendations:

GRADE Ranking of Evidence

High	We are confident that the effect in the study reflects the actual effect.
Moderate	We are quite confident that the effect in the study is close to the true effect, but it is also possible it is substantially different.
Low	The true effect may differ significantly from the estimate.
Very Low	The true effect is likely to be substantially different from the estimated effect.

GRADE Ratings for Recommendations For or Against Practice

S	Generally should be performed (i.e., the net benefit of the treatment is clear, patient values and circumstances are unlikely to affect the decision.)
C	May be reasonable to perform (i.e., may be conditional upon patient values and preferences, the resources available, or the setting in which the intervention will be implemented.)

Recognition of Potential Health Care Disparities: For all guidelines, review the literature and/or describe published or suspected health care disparities (e.g., racial, ethnic, socioeconomic, etc.).

- While warfarin is often a low-cost medication option compared to the direct oral anticoagulation class, the cost of INR lab testing and patient transportation to laboratory services must also be considered. These can be barriers to patients with mobility, transportation or socioeconomic challenges.
- Warfarin also requires a stable diet and level of overall patient compliance to reach and maintain INR goals. This can be a barrier to patients with food insecurity.

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