Warfarin Management- Adult - Ambulatory Clinical Practice Guideline

Note: Active Table of Contents – Click each header below to jump to the section of interest

Table of Contents

Content Expert(s):
Name: Anne Rose, PharmD - Pharmacy
Phone Number: (608) 263-9738
Email Address: arose@uwhealth.org

Contact for Changes:
Name: Philip Trapskin, PharmD, BCPS – Drug Policy
Phone Number: (608) 265-0341
Email Address: ptrapskin@uwhealth.org

Guideline Author(s): (As Appropriate)
Anne Rose, PharmD – Anticoagulation Stewardship

Workgroup Members:
David Ciske, MD – Anticoagulation Clinic/Internal Medicine
Erin Robinson, PharmD, CACP – Anticoagulation Clinic

Reviewer(s): (As Appropriate)
David Yang, MD – Lab

Committee Approval(s): (Include the appropriate final approval body)
Inpatient Anticoagulation Committee: December 2019
Ambulatory Anticoagulation Committee: November 2010; June 2012; May 2013; September 2015; January 2020
UW Health Pharmacy and Therapeutics: December 2010; July 2012; June 2013; October 2015; April 2020

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.[1]

Warfarin works by inhibiting the reduction of vitamin K epoxide and limiting the activation of vitamin K dependent 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.[2]

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 ambulatory warfarin management.[1-7]

Scope

Intended User(s):
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 initiated and maintained on warfarin therapy in the clinic setting.

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 based on INR results and changing patient conditions?

Recommendations

1. INR goals and duration of therapy are listed in Table 1[1,3-8]
   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[1,3-9]

Indication	INR (Range)	Duration	Comments
Thrombophilia with Thromboembolic Event			
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			
$CHA_2DS_2VASc = 0$; 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			
Cardioembolic stroke or TIA			
-With cerebral venous sinus thrombosis	2.5 (2-3)	3-6 months	
Thromboembolism (DVT, PE) symptomatic or asymptomatic			
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			
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; TAVR - transcatheter aortic valve replacement; 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.[1,2] *(UW Health GRADE high quality evidence, S recommendation)*

3. There are various clinical tools available to help 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 warfarin therapy.[10] *(UW Health GRADE moderate quality evidence, S recommendation)*
   3.1
   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) *(UW Health GRADE moderate quality evidence, S recommendation)*
   3.3 Table 2 outlines the HAS-BLED score and bleeding classification[10]

Table 2: HAS-BLED Score[10]

Factors	**Points**	**Scoring**	
Hypertension (SBP >160 mmHg)	**1**		
Abnormal lab values - Creatinine >2.26 mg/dL - Bilirubin >2x the upper limit of normal (ULN) *and* AST/ALT/AP >3x ULN	**1**	**Score = 0-1:** Low risk **Score = 2:** Moderate risk **Score ≥3:** High risk **High bleed risk considerations:** - Optimize blood pressure control - Check INRs frequently - Utilize anticoagulation clinic - Focus on fall prevention - Utilize direct oral anticoagulants	
Stroke history	**1**		
Bleeding history or predisposition	**1**		
Labile INRs: Time in Therapeutic Range <60%	**1**		
Elderly: > 65 years	**1**		
Drugs - EtOH abuse - ASA or NSAID use	**1**		

4. 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.[1,2,10] *(UW Health GRADE high quality evidence, S recommendation)*
   4.1 Examples of these risk factors are included in Table 3

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

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

<u>Warfarin Dosing Considerations</u>

5. Initial dosing should be tailored based on baseline INR, patient bleed risk, potential sensitivity to warfarin, indication for anticoagulation, goal INR range and if potential drug interactions are present[2] *(UW Health GRADE high quality evidence, S recommendation)*
6. A dose larger than the anticipated maintenance dose (loading dose) should be avoided in most patients[2] *(UW Health GRADE low quality evidence, C recommendation)*
   6.1 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[1] *(UW Health GRADE moderate quality evidence, C recommendation)*
7. A baseline INR should be resulted prior to initiating warfarin therapy[2] *(UW Health GRADE low quality evidence, C recommendation)*
8. Warfarin should be adjusted based on current INR results 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[1,2] *(UW Health GRADE moderate quality evidence, S recommendation)*
   8.1 Table 4 should be utilized for warfarin dose adjustments within the first week of therapy[11] *(UW Health GRADE low quality evidence, C recommendation)*
   8.2 Tables 5-7 should be utilized for warfarin dose adjustments after at least 7 days of therapy[11] *(UW Health GRADE low quality evidence, C recommendation)*
   8.3 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 uses. *(UW Health GRADE low quality evidence, C recommendation)*

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[2,5] *(UW Health GRADE high quality evidence, S recommendation)*

Table 4. Warfarin Initiation (Week 1) with INR Goal 2-3[11]

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

Table 5. Warfarin Maintenance Dosing Protocol with INR Goal 1.5-2.0[11]

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%	**MD order required** 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[11]

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%	**MD order required** 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[11]

INR < 1.9ŧ	INR 1.9 - 2.4ŧ	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%	**MD order required** 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

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

Special Considerations for Warfarin Dosing

10. INRs minimally above or below therapeutic range by ≤ 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 continuing current dose and test INR in 1-2 weeks.[1] *(UW Health GRADE low quality evidence, C recommendation)*
11. If an extra dose or hold dose is recommended:
    11.1 A partial-full extra or partial–full held dose can be utilized based on INR and patient's sensitivity to warfarin. *(UW Health GRADE low quality evidence, C recommendation)*
    11.2 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. *(UW Health GRADE low quality evidence, C recommendation)*
12. If warfarin is dosed at > 50 mg per week then smaller weekly dose adjustments should be targeted (ex. 5%) *(UW Health GRADE low quality evidence, C recommendation)*
13. Daily low dose vitamin K supplement should not be used to improve INR control[1] *(UW Health GRADE low quality evidence, C recommendation)*

Laboratory Monitoring[1,2,12,13]

14. INR
    14.1 A baseline INR must be resulted prior to the first dose of warfarin *(UW Health GRADE high quality evidence, S recommendation)*
    14.2 Table 8 outlines recommendations for monitoring the INR when initiating warfarin therapy.[12,13] *(UW Health GRADE low quality evidence, C recommendation)*
    14.3 Table 9 outlines recommendations for monitoring the INR during maintenance warfarin therapy.[12,13] *(UW Health GRADE low quality evidence, C recommendation)*
    14.4 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). *(UW Health GRADE low quality evidence, C recommendation)*

15. Hematocrit, platelet, ALT, total bilirubin, and serum creatinine should be resulted within the preceding 3 months and periodically thereafter per physician discretion *(UW Health GRADE low quality evidence, C recommendation)*

16. 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)*

Table 8. Frequency of INR Monitoring After Initiation of Warfarin[12,13]

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	Until INR is within therapeutic range for at least 3 months
Then every 8 weeks	If INR remains within therapeutic range can extend interval
Then every 12 weeks	

Table 9. Frequency of INR Monitoring for Maintenance of Warfarin[12,13]

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 < 3 months
Every 8-12 weeks	If patient maintained on same stable dose for at least 3 months

Symptomatic Monitoring

17. 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[1,2] *(UW Health GRADE high quality evidence, S recommendation)*
    17.1 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[5,14]

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.[1,2,15,16] 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.

18. 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)*
    18.1 For amiodarone target a 50% *reduction* in weekly maintenance dose for warfarin after 7-14 days of dual therapy[15] or if initiating warfarin start at 2.5 mg dose *(UW Health GRADE moderate quality evidence, S recommendation)*
    18.2 For rifampin target a 50% *increase* in weekly maintenance dose for warfarin after 7-14 days of dual therapy.[15] *(UW Health GRADE moderate quality evidence, S recommendation)*

Table 11. Medications, Dietary Supplements and Food that **INCREASE** INR or Bleeding Risk.[1,2,15,16]

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 12. Medications, Dietary Supplements and Food that **DECREASE** INR.[1,2,15,16]

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	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.[2,15,17-19]

20. Promote consistent intake of dietary vitamin K and not avoidance[2] *(UW Health GRADE high quality evidence, S recommendation)*
21. For enteral nutrition hold the tube feed 1 hour before and 1 hour after warfarin administration[17,19] *(UW Health GRADE moderate quality evidence, S recommendation)*
    - 21.1 If unable to hold enteral nutrition, increase warfarin dose until a therapeutic INR is achieved[19] *(UW Health GRADE low quality evidence, C recommendation)*
    - 22.2 If on cycled tube feeding, administer warfarin at a time when tube feeds are off[19,20] *(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

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 to 2019

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:

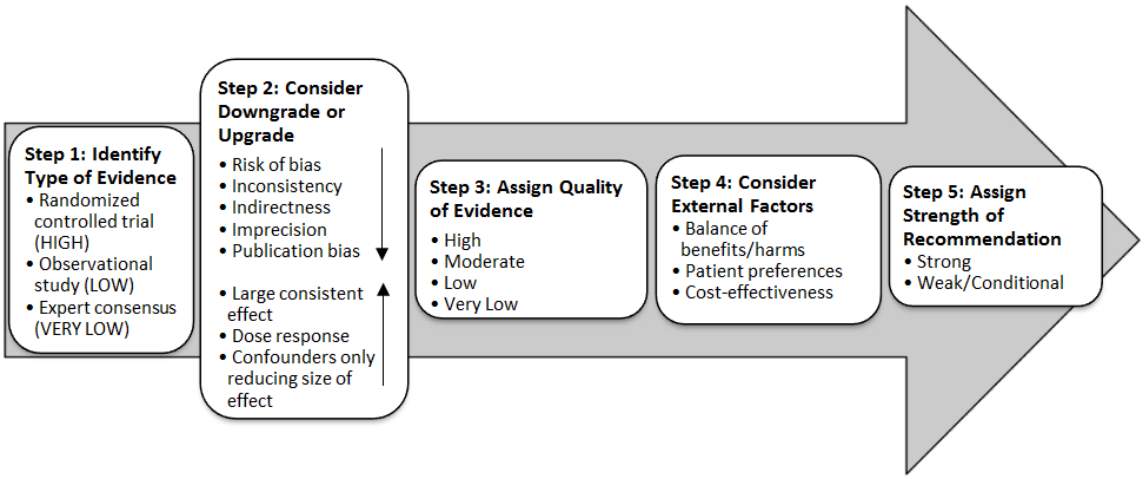
The workgroup members agreed to adopt recommendations developed by external organizations and/or created recommendations internally via a consensus process using discussion of the literature and expert experience/opinion. If issues or controversies arose where consensus could not be reached, the topic 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

Strong (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.)
Conditional (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.)

Cost Analysis: (As Appropriate) Describes any formal cost analysis performed and any published cost analyses reviewed.

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.

Collateral Tools & Resources (As Appropriate)

The following collateral tools and resources support staff execution and performance of the evidence-based guideline recommendations in everyday clinical practice.

Metrics

- Time within therapeutic INR range (%): goal > 70%
- % of patients with critical INR results

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)

Policies

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)

Protocols

Initiation and Management of Warfarin – Adult -Ambulatory [7]

Reporting Workbench Reports

Anticoagulation Responsible Pool [7364099]
AC Clinic Outreach Report [7594473]

References:

1. Holbrook A, Schulman S, Witt DM, et al. Evidence-based management of anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141(2 Suppl):e152S-e184S.
2. Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G. Oral anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141(2 Suppl):e44S-e88S.
3. You JJ, Singer DE, Howard PA, et al. Antithrombotic therapy for atrial fibrillation: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141(2 Suppl):e531S-e575S.
4. Lansberg MG, O'Donnell MJ, Khatri P, et al. Antithrombotic and thrombolytic therapy for ischemic stroke: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141(2 Suppl):e601S-e636S.
5. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141(2 Suppl):e419S-e496S.
6. Whitlock RP, Sun JC, Fremes SE, Rubens FD, Teoh KH. Antithrombotic and thrombolytic therapy for valvular disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141(2 Suppl):e576S-e600S.
7. Falck-Ytter Y, Francis CW, Johanson NA, et al. Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141(2 Suppl):e278S-e325S.
8. Johanson NA, Lachiewicz PF, Lieberman JR, et al. American academy of orthopaedic surgeons clinical practice guideline on. Prevention of symptomatic pulmonary embolism in patients undergoing total hip or knee arthroplasty. *J Bone Joint Surg Am.* 2009;91(7):1756-1757.
9. Puskas JD, Gerdisch M, Nichols D, et al. Anticoagulation and Antiplatelet Strategies After On-X Mechanical Aortic Valve Replacement. *J Am Coll Cardiol.* 2018;71(24):2717-2726.
10. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest.* 2010;138(5):1093-1100.
11. Rose AE, Robinson EN, Premo JA, Hauschild LJ, Trapskin PJ, McBride AM. Improving Warfarin Management Within the Medical Home: A Health-System Approach. *Am J Med.* 2017;130(3):365 e367-365 e312.
12. Margolis AR, Porter AL, Staresinic CE, Ray CA. Impact of an extended International Normalized Ratio follow-up interval on healthcare use among veteran patients on stable warfarin doses. *Am J Health Syst Pharm.* 2019;76(22):1848-1852.
13. Barnes GD, Kong X, Cole D, et al. Extended International Normalized Ratio testing intervals for warfarin-treated patients. *J Thromb Haemost.* 2018;16(7):1307-1312.
14. Dupras D, Bluhm J, Felty C, et al. Venous Tthromboembolism Diagnosis and Treatment. 2013; http://bit.ly/VTE0113. Accessed 03/10, 2015.

15. Warfarin (Coumadin®) [prescribing information]. Brisol-Meyers Squibb, Inc.; Princeton, NJ. 2010.
16. Nutescu EA, Shapiro NL, Ibrahim S, West P. Warfarin and its interactions with foods, herbs and other dietary supplements. *Expert Opin Drug Saf.* 2006;5(3):433-451.
17. Dickerson RN, Garmon WM, Kuhl DA, Minard G, Brown RO. Vitamin K-independent warfarin resistance after concurrent administration of warfarin and continuous enteral nutrition. *Pharmacotherapy.* 2008;28(3):308-313.
18. Klang M, Graham D, McLymont V. Warfarin bioavailability with feeding tubes and enteral formula. *JPEN J Parenter Enteral Nutr.* 2010;34(3):300-304.
19. Dickerson RN. Warfarin Resistance and Enteral Tube Feeding: An Old Problem With a New Solution. 2008;43(6):520-524. https://doi.org/10.1310/hpj4306-520.
20. Petretich DA. Reversal of osmolite-warfarin interaction by changing warfarin administration time. *Clin Pharm.* 1990;9(2):93.