UWHealth

Warfarin Management - Adult - Inpatient
Consensus Care Guideline

Population/Problem:

Warfarin is an anticoagulant used for the primary and secondary prevention of venous and arterial thromboembolic events.[1] The efficacy and safety of warfarin are dependent upon achieving and maintaining a patient's INR within a target range. The complex pharmacokinetics, pharmacodynamics, and pharmacogenomics of warfarin require regular monitoring and dosing adjustments.

The guideline provides consensus recommendations for the initiation or continuation of warfarin for hospitalized adults (e.g., target INR ranges, duration of therapy, dosing, monitoring).

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

Table 1. Indications for use, INR Ranges, and Duration of Therapy

Table 1. Target INR Ranges and Duration of Therapy			
Indication	INR Goal (Range)	Duration	
Thrombophilia with Thromboembolic Event[2-4]			
Antiphospholipid Syndrome	2.5 (2-3)	Indefinite	*ACCP Grade 2B*
Homozygous Factor V Leiden	2.5 (2-3)	Indefinite	
Protein C, S or Anti-Thrombin deficiency	2.5 (2-3)	Indefinite	
Atrial Fibrillation (AF)/Atrial Flutter[5,6]			
Note: additional management information is available UW Health Atrial Fibrillation Guidelines			
Prior stroke, transient ischemic attack (TIA)	2.5 (2-3)	Indefinite	*AHA/ACC/HRS Grade IA*
For AF: CHA$_2$DS$_2$-VASc score of 2 or greater in men or 3 or greater in women	2.5 (2-3)	Indefinite	*AHA/ACC/HRS Grade IA*
For AF: CHA$_2$DS$_2$-VASc score of 1 or greater in men or 2 or greater in women	2.5 (2-3)	Indefinite	*AHA/ACC/HRS Grade IIb, C-LD*
Pre-cardioversion (AF or atrial flutter $\geq$48 hours or unknown duration) regardless of CHA$_2$DS$_2$VASc score	2.5 (2-3)	At least 3-weeks unless the need for immediate cardioversion	*AHA/ACC/HRS Grade IB*
Post-cardioversion to normal sinus rhythm	2.5 (2-3)	At least 4-weeks	*AHA/ACC/HRS Grade IB*
Cerebral Venous Thrombosis (CVT)[7,8]			
Cerebral venous thrombosis (CVT)	2.5 (2-3)	3-6 months	*ACCP Grade 2B*
Provoked CVT associated with a transient risk factor (e.g., pregnancy, dehydration, infection)	2.5 (2-3)	3-6 months	*AHA/ASA Grade IIb, C*
Unprovoked CVT	2.5 (2-3)	6-12 months	*AHA/ASA Grade IIb, C*
Recurrent CVT, VTE after CVT, or first CVT with severe thrombophilia	2.5 (2-3)	Indefinite	*AHA/ASA Grade IIb, C*
Venous Thromboembolism (VTE)[9,10]			
Note: additional management information is available UW Health VTE Diagnosis and Treatment Guideline			
Deep Vein Thrombosis (DVT) or pulmonary embolism (PE)	2.5 (2-3)	At least 3 months	Individualize the duration based upon provoked events, risk factors for thrombosis and bleeding.

(Table continues on next page)

Table 1. Target INR Ranges and Duration of Therapy (cont)

Indication	INR Goal (Range)	Duration	
Valve Surgical Replacement – Bioprosthetic[11,12]			
Aortic or Mitral	*Aspirin 75 mg to 100 mg per day is reasonable in all patients with a bioprosthetic aortic or mitral valve. AHA/ACC IIa, B*		
Aortic or Mitral with low risk of bleeding	2.5 (2-3)	3 to 6 months	*AHA/ACC IIa, B-NR*
Valve Surgical Replacement – Mechanical[11-13]			
Aortic bileaflet or current-generation single-tilting disk and no risk factors for thromboembolism	2.5 (2-3)	Chronic	*AHA/ACC IB*
Aortic with additional risk factors for thromboembolic events (AF, previous thromboembolism, LV dysfunction, or hypercoagulable conditions) or an older-generation mechanical AVR (such as ball-in-cage)	3 (2.5-3.5)	Chronic	*AHA/ACC IB*
Mitral	3 (2.5-3.5)	Chronic	*AHA/ACC IB*
Dual Aortic and Mitral Valve	3 (2.5 -3.5)	Chronic	*AHA/ACC IB*
On-X Aortic	2.5 (2-3)	3 months	After 3 months consider decrease the INR goal to 1.5-2.0 (in conjunction with aspirin 81mg daily) *AHA/ACC IIb, B-R*
On-X Mitral	3 (2.5-3.5)	Chronic	*AHA/ACC IB*
Aspirin 75 mg to 100 mg daily is recommended in addition to anticoagulation with warfarin in patients with a mechanical valve prosthesis. AHA/ACC IA			
Anticoagulant therapy with oral direct thrombin inhibitors or anti-Xa agents should not be used in patients with mechanical valve prostheses. AHA/ACC III:Harm			
Transcatheter Aortic Valve Replacement (TAVR)[12,14]			
	Guideline		
	Pivotal Trials (Placement of Aortic Transcatheter Valve Trial [PARTNER] and US CoreValve[15-17]	American College of Cardiology/American Heart Association Guidelines 2017[12]	European Society of Cardiology/ European Association for Cardiothoracic Surgery Guidelines 2017[18]
First 3 to 6 months	Aspirin plus clopidogrel for first 3 or 6 months followed by monotherapy	Clopidogrel 75mg daily for the first 6 months in addition to lifelong aspirin 75-100mg *(AHA/ACC IIb, C)*	Low-dose aspirin plus P2Y12 inhibitor for 3 to 6 months followed by lifelong single antiplatelet therapy in patients without indication for oral anticoagulation *(ESC/EACTS IIb, C)*
Lifelong treatment	If vitamin K antagonist is indicated, aspirin plus warfarin (without clopidogrel)	Warfarin with an INR of 2.5 (2-3) for at least 3 months in patients with low bleeding risk *(AHA/ACC IIb,B)*	Lifelong oral anticoagulants for patients with indication *(ESC/EACTS IC)*

(Table continues on next page)

Table 1. Target INR Ranges and Duration of Therapy (cont)			
Indication	INR Goal (Range)	Duration	
Orthopedic Surgery[19]			
Total Knee or Hip Arthroplasty*	1.8-2.2	10-14 days	INR goal per surgeon
Hip Fracture Surgery*	1.8-2.2	10-14 days	INR goal per surgeon
Trauma Surgery*	1.8-2.2	35 days	INR goal per surgeon
* If other indication for anticoagulation exist - INR goal should be clarified			

Patient Assessment

2. Patients 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] *(UW Health GRADE high quality evidence, S recommendation)* (see Table 2)

Table 2. Warfarin sensitivity factors
Increases sensitivity (usually require lower doses)
• Baseline (pre-warfarin) PT/INR (e.g., greater than 1.4)
• Advanced age (e.g., 60 years of age or older)[20-29]
• Underweight (e.g., BMI less than 18kg/m^2)[28,30,31]
• Nutritional status (e.g., malnourished, low vitamin K intake/stores)
• Genetic factors (e.g., CYP2C9, VKORC1 phenotypes)
• Drug-drug interactions
• Hypoalbuminemia[32,33]
• Ethnicity (Asian)[29,34,35]
• Liver disease[29,36]
• Thyroid Disease (e.g., hyperthyroidism, Graves' disease)[37-40]
• Heart Failure[41,42]
• Febrile illness
• Prolonged vomiting and diarrhea
• Surgery and blood loss
• Cannabinoids
• Alcohol
• Drug interactions
Decrease warfarin sensitivity (may require higher doses)
• Enteral feedings
• High-vitamin K intake
• Estrogens
• Chewing tobacco

Warfarin Dosing Considerations

3. Initial warfarin dosing should be tailored based on baseline INR, patient bleed risk, potential sensitivity to warfarin (see Table 2), indication, goal INR range and if potential drug interactions are present[1] *(UW Health GRADE high quality evidence, S recommendation)*
4. 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[1,9] *(UW Health GRADE high quality evidence, S recommendation)*

5. Prior to making a dose adjustment, assess for any missed doses, drug interactions, dietary intake or supplements, documentation of bleeding, change in medical condition or other changes that may affect INR[1,2]   *(UW Health GRADE moderate quality evidence, S recommendation)(See Table 3)*
   5.1. Pregnant patients should not take warfarin and should be transitioned to an alternative anticoagulant (e.g. low molecular weight heparin) *(UW Health GRADE high quality evidence, S 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)*

Table 3. Monitoring Considerations
• Signs and symptoms of thrombosis progression or bleeding
• PT/INR (daily during initiation or unstable, and at least weekly when stable)
• CBC without differential prior to warfarin initiation and then at least every 3 days
• Missed or held doses
• Drug-drug and drug-food interactions
• Nutrition
• Activity level

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	2.5 - 5 mg	< 1.5	5 - 7.5 mg
	≥ 1.5	0 - 2.5 mg	≥ 1.5	0 - 5 mg
Day 3	< 1.5	5 - 7.5 mg	< 1.5	7.5 - 10 mg
	1.5-1.9	5 mg	1.5-1.9	7.5 mg
	2.0-2.5	2.5 mg	2.0-2.5	5 mg
	≥ 2.5	0 (no dose)	≥ 2.5	0 (no dose)
Day 4	< 1.9	7.5 mg	< 1.9	10 mg
	2.0-2.4	5 mg	2.0-2.4	7.5 mg
	2.5-3.5	2.5 mg	2.5-3.5	5 mg
	≥ 3.6	0 - 1 mg	≥ 3.6	0-2.5 mg
Day 5	< 1.9	10 mg	< 1.9	12.5 mg
	2.0-2.4	yesterday's dose + 2.5 mg	2.0-2.4	yesterday's dose + 2.5 mg
	2.5-3.5	yesterday's dose	2.5-3.5	yesterday's dose
	3.6-4.0	yesterday's dose – 2.5 mg	3.6-4.0	yesterday's dose – 2.5 mg
	≥ 4.0	0 (no dose)	≥ 4.0	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[1,2] *(UW Health GRADE low quality evidence, C recommendation)*

Baseline		
Within the past 30 days	• Baseline INR • Pregnancy test* • CBC without diff	*Pregnancy test is not needed if: 1. Are postmenopausal (12 months of amenorrhea in a woman > 45 years old in the absence of other biological or physiological causes)
Within the past 90 days	• ALT • Creatinine	2. Had a hysterectomy or bilateral salpingo-oophorectomy 3. Have ovarian failure 4. Had a bilateral tubal ligation or other surgical sterilization procedure 5. Are known to be pregnant 6. Have had a miscarriage or abortion in the last 7 days 7. Have given birth within the past 4 weeks
During Admission		
Daily	• INR	If providing a daily warfarin dose
At least weekly	• CBC without diff • INR	If providing a weekly warfarin dose
After Discharge		
Within 3-4 days	• INR	

Drug Interactions

7. Most drug interactions with warfarin will start to have an effect within 3-5 days of concomitant therapy. In general, it is recommended to check an INR 3-4 days after starting a medication that has the potential to interact with warfarin. If the INR is affected at that time, then a dose adjustment can be made. There are some notable exceptions to this:

Medication	INR check after starting	Adjustment
Amiodarone	Every 7 days	Target a 50% weekly dose reduction over 2 weeks
Rifampin	Every 7 days	Target a 50% weekly dose increase over 2 weeks
Fluconazole	2 – 3 days	Target a 30% weekly dose decrease
Metronidazole	2 – 3 days	Target a 30% weekly dose decrease
Sulfamethoxazole/ Trimethoprim	2 days *Should reduce dose prior to starting medication to avoid critical INR elevation*	Target a 30% weekly dose decrease

(UW Health GRADE moderate quality evidence, S recommendation)

Table 6. Medications, dietary supplements, and food that **INCREASE** INR or bleeding risk.[1,2,29,43]

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	Dandelion Danshen	Capsicum **Forskolin***	

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Table 6. Medications, dietary supplements, and food that **INCREASE** INR or bleeding risk.[,](cont)

Drug Class	Known Interaction	Probable Interaction	Possible Interaction	Unlikely Interaction
Herbal Supplement	Fish Oil Ginkgo Quilinggao	Don Quai Lycium PC-SPES Red or Sweet Clover	Garlic Ginger Turmeric	
Other	Anabolic Steroids Capecitabine Zileuton	Fluorouracil Gemcitabine Levamisole Paclitaxel Tamoxifen Tolterodine	Acarbose Cyclophosphamide Danazol Iphosphamide Trastuzumab	Etoposide Carboplatin Levonorgestrel

*Indicates significant interaction

Table 7. Medications, dietary supplements, and food that **DECREASE** INR.[1,2,29,43]

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	

*Indicates significant interaction

Dietary Interactions

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.[1,29,44-46]

8. Promote consistent intake of dietary vitamin K and not avoidance[1] *(UW Health GRADE high quality evidence, S recommendation)*

9. For enteral nutrition hold the tube feed 1 hour before and 1 hour after warfarin administration[44,46] *(UW Health GRADE moderate quality evidence, S recommendation)*
   9.1 If unable to hold enteral nutrition, increase warfarin dose until a therapeutic INR is achieved[46]*(UW Health GRADE low quality evidence, C recommendation)*
   9.2 If on cycled tube feeding, administer warfarin at a time when tube feeds are off[46,47] *(UW Health GRADE moderate quality evidence, S recommendation)*

10. A significant decrease ($\geq$ 50%) in total dietary intake for $\geq$3 days may cause an increase in INR.

Warfarin Reversal: see Antithrombotic Reversal- Adult- Inpatient guideline

Transitioning to Outpatient Management

Prior to discharge from the emergency department, urgent care, or hospital setting a follow up care plan that includes contact with the provider or clinic who will manage warfarin, plan for a follow up INR within 3-4 days of discharge, and education on compliance, dietary advice, follow up monitoring and drug interactions and adverse drug reactions must be provided to the patient and/or caregiver prior to ED discharge.[1,2] If outpatient INR monitoring cannot be established at the time of discharge then consider an alternative oral anticoagulant or parenteral anticoagulant.

Communication to the next provider of care	Indication
	Target INR range
	Warfarin dose
	Date for next INR check
	Name of the clinic or provider assuming warfarin management
	Length of therapy
	Potential drug, herbal, or supplement interactions
	Longitudinal record of inpatient INR values and warfarin doses
	Bridging therapy if needed
	Educational materials provided to the patient

Disclaimer
Consensus care models 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.

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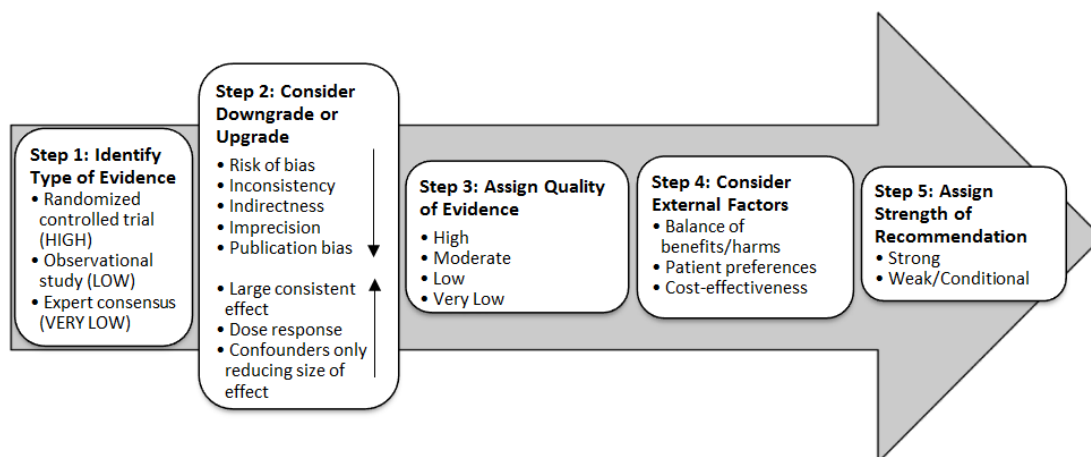Pharmacy & Therapeutics Committee: February 2013; July 2020; May 2021

Step 1: Identify Type of Evidence
- Randomized controlled trial (HIGH)
- Observational study (LOW)
- Expert consensus (VERY LOW)

Step 2: Consider Downgrade or Upgrade
- Risk of bias
- Inconsistency
- Indirectness
- Imprecision
- Publication bias

- Large consistent effect
- Dose response
- Confounders only reducing size of effect

Step 3: Assign Quality of Evidence
- High
- Moderate
- Low
- Very Low

Step 4: Consider External Factors
- Balance of benefits/harms
- Patient preferences
- Cost-effectiveness

Step 5: Assign Strength of Recommendation
- Strong
- Weak/Conditional

Table 1. 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.

Table 2. 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.)

TABLE 1 **Applying Class of Recommendation and Level of Evidence to Clinical Strategies, Interventions, Treatments, or Diagnostic Testing in Patient Care* (Updated August 2015)**

CLASS (STRENGTH) OF RECOMMENDATION

CLASS I (STRONG) — Benefit >>> Risk

Suggested phrases for writing recommendations:
- Is recommended
- Is indicated/useful/effective/beneficial
- Should be performed/administered/other
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is recommended/indicated in preference to treatment B
  - Treatment A should be chosen over treatment B

CLASS IIa (MODERATE) — Benefit >> Risk

Suggested phrases for writing recommendations:
- Is reasonable
- Can be useful/effective/beneficial
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is probably recommended/indicated in preference to treatment B
  - It is reasonable to choose treatment A over treatment B

CLASS IIb (WEAK) — Benefit ≥ Risk

Suggested phrases for writing recommendations:
- May/might be reasonable
- May/might be considered
- Usefulness/effectiveness is unknown/unclear/uncertain or not well established

CLASS III: No Benefit (MODERATE) — Benefit = Risk
(Generally, LOE A or B use only)

Suggested phrases for writing recommendations:
- Is not recommended
- Is not indicated/useful/effective/beneficial
- Should not be performed/administered/other

CLASS III: Harm (STRONG) — Risk > Benefit

Suggested phrases for writing recommendations:
- Potentially harmful
- Causes harm
- Associated with excess morbidity/mortality
- Should not be performed/administered/other

LEVEL (QUALITY) OF EVIDENCE‡

LEVEL A
- High-quality evidence‡ from more than 1 RCT
- Meta-analyses of high-quality RCTs
- One or more RCTs corroborated by high-quality registry studies

LEVEL B-R (Randomized)
- Moderate-quality evidence‡ from 1 or more RCTs
- Meta-analyses of moderate-quality RCTs

LEVEL B-NR (Nonrandomized)
- Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies
- Meta-analyses of such studies

LEVEL C-LD (Limited Data)
- Randomized or nonrandomized observational or registry studies with limitations of design or execution
- Meta-analyses of such studies
- Physiological or mechanistic studies in human subjects

LEVEL C-EO (Expert Opinion)
Consensus of expert opinion based on clinical experience

COR and LOE are determined independently (any COR may be paired with any LOE).

A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).

† For comparative-effectiveness recommendations (COR I and IIa; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

‡ The method of assessing quality is evolving, including the application of standardized, widely used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.

COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

Strength of Recommendations Grading System (American College of Chest Physicians 2012)

Grade of Recommendation/ Description	Benefit vs Risk and Burdens	Methodological Quality of Supporting Evidence	Implications
1A/strong recommendation, high-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1B/strong recommendation, moderate quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1C/strong recommendation, low-quality or very low-quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Observational studies or case series	Strong recommendation but may change when higher quality evidence becomes available
2A/weak recommendation, high-quality evidence	Benefits closely balanced with risks and burden	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2B/weak recommendation, moderate-quality evidence	Benefits closely balanced with risks and burden	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patients' or societal values
2C/weak recommendation, low-quality or very low-quality evidence	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced	Observational studies or case series	Very weak recommendations; other alternatives may be equally reasonable

Collateral Tools & Resources

The following collateral tools and resources support staff execution and performance of the evidence-based model 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)

Order Sets
1. IP – Warfarin Therapy – Adult – Supplemental [2441]

Protocols
Pharmacist Management of Warfarin – Adult - Inpatient [12]

References:

1. 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.

2. 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.

3. Garcia D, Erkan D. Diagnosis and Management of the Antiphospholipid Syndrome. *N Engl J Med.* 2018;379(13):1290.

4. Guyatt GH, Norris SL, Schulman S, et al. Methodology for the development of antithrombotic therapy and prevention of thrombosis guidelines: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012;141(2 Suppl):53S-70S.

5. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *Circulation.* 2014;130(23):e199-267.

6. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol.* 2019;74(1):104-132.

7. 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.

8. Saposnik G, Barinagarrementeria F, Brown RD, et al. Diagnosis and management of cerebral venous thrombosis: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* 2011;42(4):1158-1192.

9. 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.

10. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. *Chest.* 2016;149(2):315-352.

11. 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.

12. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation.* 2017;135(25):CIR.000000000000.

13. 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.

14. Saito Y, Nazif T, Baumbach A, et al. Adjunctive Antithrombotic Therapy for Patients With Aortic Stenosis Undergoing Transcatheter Aortic Valve Replacement. *JAMA Cardiol.* 2019.

15. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med.* 2011;364(23):2187-2198.
16. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med.* 2010;363(17):1597-1607.
17. Adams DH, Popma JJ, Reardon MJ, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med.* 2014;370(19):1790-1798.
18. Falk V, Baumgartner H, Bax JJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur J Cardiothorac Surg.* 2017;52(4):616-664.
19. 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.
20. Britt RP, James AH, Raskino CL, Thompson SG. Factors affecting the precision of warfarin treatment. *J Clin Pathol.* 1992;45(11):1003-1006.
21. Gurwitz JH, Avorn J, Ross-Degnan D, Choodnovskiy I, Ansell J. Aging and the anticoagulant response to warfarin therapy. *Ann Intern Med.* 1992;116(11):901-904.
22. Shendre A, Parmar GM, Dillon C, Beasley TM, Limdi NA. Influence of Age on Warfarin Dose, Anticoagulation Control, and Risk of Hemorrhage. *Pharmacotherapy.* 2018;38(6):588-596.
23. Shepherd AM, Hewick DS, Moreland TA, Stevenson IH. Age as a determinant of sensitivity to warfarin. *Br J Clin Pharmacol.* 1977;4(3):315-320.
24. Kamali F, Khan TI, King BP, et al. Contribution of age, body size, and CYP2C9 genotype to anticoagulant response to warfarin. *Clin Pharmacol Ther.* 2004;75(3):204-212.
25. Gladman JR, Dolan G. Effect of age upon the induction and maintenance of anticoagulation with warfarin. *Postgrad Med J.* 1995;71(833):153-155.
26. Dobrzanski S, Duncan SE, Harkiss A, Wardlaw A. Age and weight as determinants of warfarin requirements. *J Clin Hosp Pharm.* 1983;8(1):75-77.
27. Redwood M, Taylor C, Bain BJ, Matthews JH. The association of age with dosage requirement for warfarin. *Age Ageing.* 1991;20(3):217-220.
28. Wilke RA, Berg RL, Vidaillet HJ, Caldwell MD, Burmester JK, Hillman MA. Impact of age, CYP2C9 genotype and concomitant medication on the rate of rise for prothrombin time during the first 30 days of warfarin therapy. *Clin Med Res.* 2005;3(4):207-213.
29. Warfarin (Coumadin®) [prescribing information]. Brisol-Meyers Squibb, Inc.; Princeton, NJ. 2010.
30. Wallace JL, Reaves AB, Tolley EA, et al. Comparison of initial warfarin response in obese patients versus non-obese patients. *J Thromb Thrombolysis.* 2013;36(1):96-101.
31. Mueller JA, Patel T, Halawa A, Dumitrascu A, Dawson NL. Warfarin dosing and body mass index. *Ann Pharmacother.* 2014;48(5):584-588.
32. Abdelhafiz AH, Myint MP, Tayek JA, Wheeldon NM. Anemia, hypoalbuminemia, and renal impairment as predictors of bleeding complications in patients receiving anticoagulation therapy for nonvalvular atrial fibrillation: a secondary analysis. *Clin Ther.* 2009;31(7):1534-1539.
33. Yoshizawa M, Hayashi H, Tashiro Y, et al. Effect of VKORC1-1639 G>A polymorphism, body weight, age, and serum albumin alterations on warfarin response in Japanese patients. *Thromb Res.* 2009;124(2):161-166.
34. Dang MT, Hambleton J, Kayser SR. The influence of ethnicity on warfarin dosage requirement. *Ann Pharmacother.* 2005;39(6):1008-1012.
35. Zhang H, De T, Zhong Y, Perera MA. The advantages and challenges of diversity in Pharmacogenomics: Can minority populations bring us closer to implementation? *Clinical Pharmacology & Therapeutics.* 2019.

36. Qamar A, Vaduganathan M, Greenberger NJ, Giugliano RP. Oral Anticoagulation in Patients With Liver Disease. *J Am Coll Cardiol.* 2018;71(19):2162-2175.

37. Howard-Thompson A, Luckey A, George C, Choby BA, Self TH. Graves' Disease and Treatment Effects on Warfarin Anticoagulation. *Case Reports in Medicine.* 2014;2014:1-6.

38. Busenbark LA, Cushnie SA. Effect of Graves' disease and methimazole on warfarin anticoagulation. *Ann Pharmacother.* 2006;40(6):1200-1203.

39. Kellett HA, Sawers JS, Boulton FE, Cholerton S, Park BK, Toft AD. Problems of anticoagulation with warfarin in hyperthyroidism. *Q J Med.* 1986;58(225):43-51.

40. Self TH, Straughn AB, Weisburst MR. Effect of hyperthyroidism on hypoprothrombinemic response to warfarin. *Am J Hosp Pharm.* 1976;33(4):387-389.

41. Self TH, Reaves AB, Oliphant CS, Sands C. Does heart failure exacerbation increase response to warfarin? A critical review of the literature. *Curr Med Res Opin.* 2006;22(11):2089-2094.

42. del Campo M, Roberts G. Changes in Warfarin Sensitivity During Decompensated Heart Failure and Chronic Obstructive Pulmonary Disease. *Ann Pharmacother.* 2015;49(9):962-968.

43. 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.

44. 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.

45. Klang M, Graham D, McLymont V. Warfarin bioavailability with feeding tubes and enteral formula. *JPEN J Parenter Enteral Nutr.* 2010;34(3):300-304.

46. 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.

47. Petretich DA. Reversal of osmolite-warfarin interaction by changing warfarin administration time. *Clin Pharm.* 1990;9(2):93.