Warfarin Management - Adult - Inpatient Consensus Care Practice Guideline

Target Population: Adult inpatients receiving anticoagulation therapy with the oral vitamin K antagonist, warfarin

Full Guideline: Warfarin Management - Adult - Inpatient

Guideline Overview

- Target INR and duration of therapy are based on indication for warfarin use- see full guideline
- Risk factors which alter sensitivity to warfarin
- Monitoring considerations
- Warfarin dosing protocol with INR goal 2-3
- Warfarin dosing protocol with INR goal 2.5-3.5
- Laboratory monitoring
- Dose adjustments for drug interactions
- Factors that increase INR
- Factors that decrease INR
- Warfarin reversal
- Transitioning to outpatient management
- References- see full guideline for citations

Table 1: see full guideline for INR goals and recommended duration of therapy by indication (with link when ready)

Risk factors which alter sensitivity to warfarin

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)
- Underweight (e.g. BMI less than 18kg/m^2)
- Nutritional status (e.g. malnourished, low vitamin K intake/stores)
- Genetic factors (e.g. CYP2C9, VKORC1 phenotypes)
- Drug-drug interactions
- Hypoalbuminemia
- Ethnicity (Asian)
- Liver disease
- Thyroid Disease (e.g. hyperthyroidism, Graves' disease)
- Heart Failure
- 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

Table 3. Monitoring Considerations

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)

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 ≥ 2.5	5 - 7.5 mg 5 mg 2.5 mg 0 (no dose)	< 1.5 1.5-1.9 2.0-2.5 ≥ 2.5	7.5 - 10 mg 7.5 mg 5 mg 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)

Laboratory Monitoring

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) 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
Within the past 90 days	• ALT • Creatinine	
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	

Dose Adjustment Recommendations for Common/Significant Warfarin-Drug Interactions

Medication	INR check after starting	Adjustment
Amiodarone	Every 7 days	Target a 25-50% weekly dose reduction over 2-4 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	Target a 30% weekly dose decrease ***Should reduce dose prior to starting medication to avoid critical INR elevation***

Table 6. Medications, Dietary Supplements, and Foods that INCREASE INR or bleeding risk

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

*Indicates significant interaction

Table 7. Medications, Dietary Supplements, and Foods that DECREASE INR

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	

*Indicates significant interaction

Click here for information on Warfarin Reversal

Transitioning to outpatient management

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

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.