WARFARIN CLINICIAN SUMMARY

Mechanism of Action: Warfarin competitively inhibits a subunit of the Vitamin K epoxide reductase (VKOR) complex, thus depleting functional vitamin K reserves and reducing the synthesis of vitamin K-dependent active clotting factors II, VII, IX, and X, as well as proteins C and S.[1,2]

BACKGROUND

Warfarin is an oral anticoagulant agent with a long history of use.
It is indicated for the prophylaxis and treatment of various thromboembolic states, which include:

- Prevention and treatment of venous thrombosis
- Treatment of pulmonary embolism
- Prevention of systemic embolism in:
  - Tissue heart valves
  - Mechanical prosthetic heart valves
  - Myocardial infarction
  - Valvular heart disease
  - Atrial fibrillation
  - Recurrent systemic embolism
  - Cardiomyopathy

Administration

Administer with or without food. It is usually suggested patients take late in the day (i.e., dinner time) to allow INR to be checked and dosage adjusted for the day.

Pharmacologic Profile[1]

Onset	24-72 hours
Peak effect	5-7 days Clinical effect corresponds to the time required for inactive clotting factors to be produced and on the half-life of existing clotting factors
Bioavailability	100%
Half-life	40 hours (range 20-60 h, highly variable in patients)
Distribution	Highly protein bound (99%)
Metabolism	Hepatic, primarily via CYP 2C9; minor pathways include CYP 3A4, 2C19, 1A2, 2C8, 2C18 Reduced clearance of warfarin may be observed in patients with genomic variants of CYP 2C9
Elimination	Renal excretion (92% as inactive metabolites)

DOSAGE

Warfarin doses are highly individualized and are adjusted according to patient response using INR results.[1]

General Considerations

1. Consider contraindications (see below). All contraindications are relative to a patient's risk for thrombosis weighed against the risk for bleeding while on vitamin K antagonist anticoagulation therapy. For a complete list of contraindications, refer to the product monograph.
2. Obtain baseline PT/INR and investigate if abnormal.

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3. Consider effects of potential drug interactions (see below). For example, suggest reduction of the usual warfarin dose in patients on amiodarone, ciprofloxacin or sulfamethoxazole.[3,4]
4. Provide patient education on safety, monitoring, drug and food interactions.
5. For acute thrombosis, overlap with heparin/LMWH/fondaparinux until INR is therapeutic (5+ days)[2]

Dose Initiation

- Recommended initiation doses are 5-10 mg for 1-2 days, with subsequent dosing based on INR.[2,5,6]
- Choice of initial dose may be <5 mg for elderly patients, those with liver disease, taking medications that are likely to increase the effect of warfarin, are malnourished, debilitated, have heart failure, are acutely ill or had recent surgery. [2]
- Loading doses of 10 mg are generally reserved for healthy non-elderly patients[2,6,7] or those with previously identified maintenance dose requirements of ≥5 mg
- An example of a guide for initiating warfarin dosing for a target INR of 2-3, which includes suggested dosing for days 1 to 10, is available from the American Society of Hematology: see page 2 of the 2011 Clinical Practice Guide on Anticoagulant Dosing and Management of Anticoagulant Associated Bleeding complications in Adults, accessible at http://www.hematology.org/Practice/Guidelines/2934.aspx.[8]

Note: Guidelines should serve as a general framework for dosage adjustment and doses should be modified as individual needs dictate

Laboratory Monitoring

- Prothrombin time (PT) reported using the International Normalised Ratio (INR) is the most common test used to measure the anticoagulant effect of warfarin. Different INR targets exist for the different warfarin indications.

INR Targets at UHN[12]

Indication	Target INR (range)	Duration of therapy
Atrial fibrillation	2.5 (2.0-3.0)	Duration of AF
Deep vein thrombosis	2.5 (2.0-3.0)	Minimum 6 months
Pulmonary embolism	2.5 (2.0-3.0)	Minimum 6 months
Mechanical valves	Aortic position (2.5-3.0) Mitral position (3.0-3.5)	Permanent

Monitoring

- A framework for suggested frequency of INR monitoring is provided below[9.]
- For patients taking warfarin with previously stable INRs who present with a single out-of-range INR of ≤0.5 below or above therapeutic target, continue current dosing and test the INR within 1-2 weeks.[5,6]

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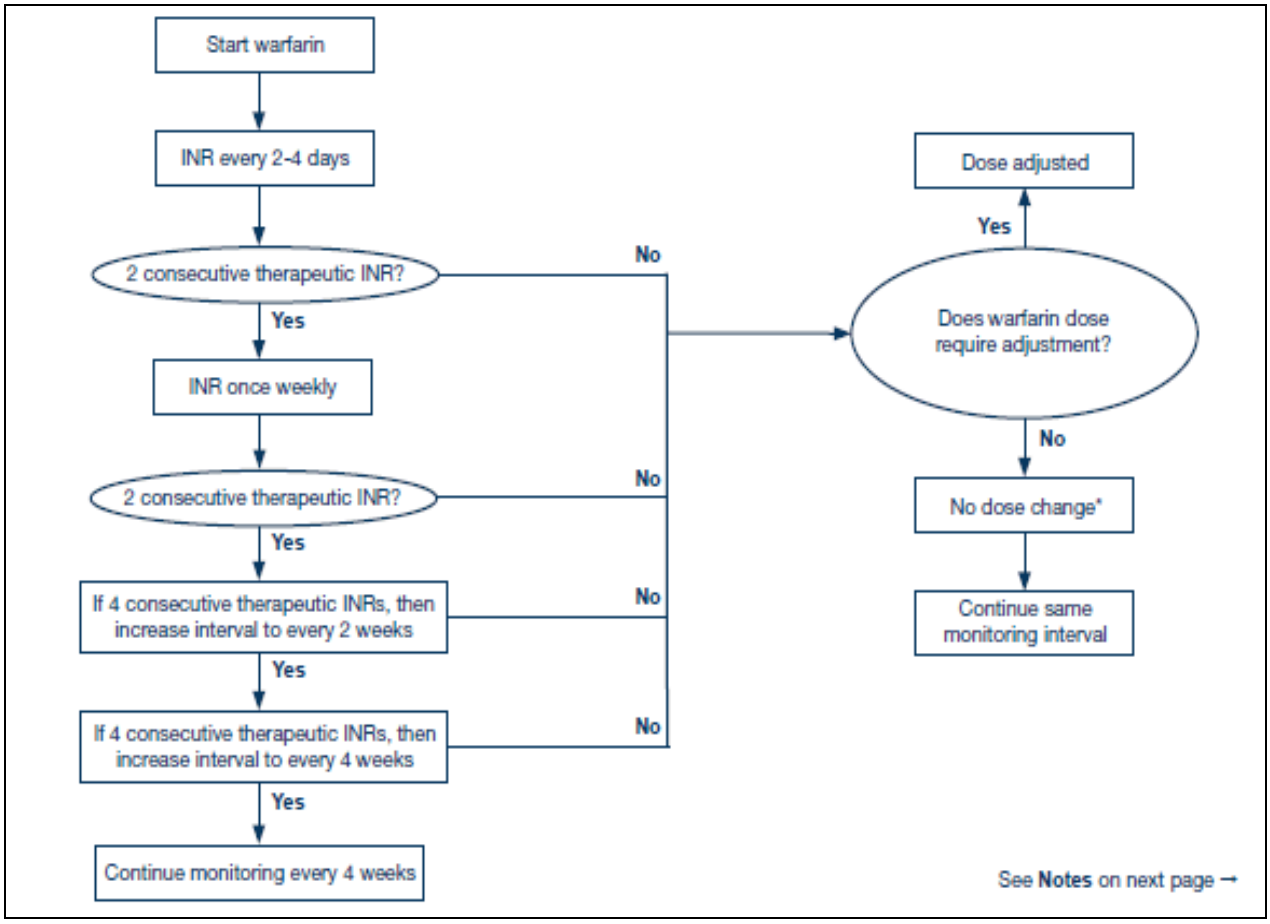
Recommended Frequency of INR Monitoring for Patients Started and Maintained on Warfarin[9]



*Monitoring every 12 weeks may be appropriate for patients with consistently stable INRs[3]

Maintenance Dose Adjustment

- Decision support tools to assist with warfarin dosing have been reported in the literature. (See Holbrook A, et al. Chest. 2012;141(suppl2):e163-164s for an excellent discussion.[6]) Multiple maintenance dose adjustment guidelines, utilizing a paper nomogram are available[4,8,9,10,11] – if the patient requires changes in their maintenance dose, a change of 10-15% in the total weekly dose is generally followed.
- An example of a guide for maintenance dose adjustment for a target INR of 2-3 from the Canadian Cardiovascular Pharmacist Network is provided below.[10]

Note: Guidelines should serve as a general framework for dosage adjustment and doses should be modified as individual needs dictate.

Warfarin maintenance dose adjustment for patients with a target INR of 2-3[10]

INR	Action
<1.5	Reload* 0-2 doses; increase weekly dose by 5-15%
1.5-1.9	Reload* 0-1 dose; increase weekly dose by 0-10%
2.0-3.0	No change
3.1-3.5	Hold 0-1 dose; decrease weekly dose by 5-15%
3.6-4.9	Hold 0-2 doses; decrease weekly dose by 5-15%

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INR	Action
5.0-9.0**	Hold warfarin
> 9 **	Hold warfarin (vitamin K 2.5 to 5 mg orally)

* Reload refers to giving the patient up to twice the daily maintenance dose

**see reversal guidelines regarding use of vitamin K in the case of significant bleeding

Contraindications

- Clinically significant active bleeding or risk (i.e., cerebral infarct in the previous 6 months, active peptic ulcer disease with recent bleeding, impairment of hemostasis)
- Pregnant women
- Major regional lumbar block anesthesia or traumatic surgery resulting in large, open surfaces
- Recent/potential surgery of the eye or CNS
- Severe uncontrolled/malignant hypertension
- Pericarditis/pericardial effusion
- Bacterial endocarditis

Precautions

- Advanced age
- History of falls
- Genomic variants of CYP2C9 and/or VKORC1: CYP2C9*2 or *3 allele or VKORC1 polymorphism may increase risk of bleeding
- Purple toe syndrome
- Necrosis, caution in heparin-induced thrombocytopenia with DVT due to limb ischemia

Drug Interactions

Warfarin is highly susceptible to drug interactions. These include pharmacokinetic interactions and pharmacodynamic interactions. Selected nutritional supplements and natural health products may also interact.

For a comprehensive list of important warfarin drug interactions and how to manage them, please refer to the practice tool by Bungard T, et al. in the Canadian Pharmacists Journal, 2011; available at http://cph.sagepub.com/content/144/1/21.full.pdf+html.[3]

Useful summary tables of important warfarin interactions are also available in:

- Ageno W, et al. Chest. 2012;141(suppl2):e44s-88s; see table 1 on page c48S.[2]
- Warfarin therapy management, Oct 1, 2010 - Produced by the BC Guidelines and Protocol Advisory Committee, see Appendix A; available at http://www.bcguidelines.ca/pdf/warfarin_management.pdf.[9]

For patients on warfarin, concomitant use of drugs that may interact should be avoided, when feasible. If non-interacting alternatives are not available, the frequency of monitoring should be increased and adjustments made based on INR response. Prospective adjustments to warfarin should be avoided, due to the unpredictable nature of response to interactions.

Food Interactions

Foods high in vitamin K (i.e., beef liver, pork liver, green tea, and leafy green vegetables) inhibit anticoagulant effect.

- Patients should maintain a constant amount of green leafy vegetables if they enjoy them in their diet. They should consult a healthcare professional if drastic changes in their diet occur. A balanced diet with a consistent intake of vitamin K is essential.

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- Patients should avoid large amounts of alfalfa, asparagus, broccoli, cabbage, cauliflower, green teas, kale, lettuce, spinach, turnip greens, and watercress, as these may decrease the efficacy of warfarin.
- Case reports of increased INRs have been reported with ingestion of mango, cranberry juice, and grapefruit juice while on warfarin therapy

More detailed information on potential warfarin food interactions can be accessed at:

- Health Canada: http://www.hc-sc.gc.ca/hl-vs/alt_formats/pacrb-dgapcr/pdf/iyh-vsv/med/warfarin-eng.pdf
- National Institutes of Health: http://www.cc.nih.gov/ccc/patient_education/drug_nutrient/coumadin1.pdf

Renal Impairment

No adjustment is required, however, patients with renal failure have an increased risk of bleeding complications. End-stage renal disease is also associated with reduced activity of CYP2C9, potentially leading to lower warfarin dosing requirements in these patients.[2.]

Hepatic Impairment

Monitor effect at usual doses, response to may be markedly enhanced in obstructive jaundice, hepatitis, and cirrhosis.

Pregnancy/Lactation

- Contraindicated in women who are pregnant.
- Breastfeeding women may be treated with warfarin. Based on available data, warfarin does not pass into breast milk. Women who are breast-feeding should be carefully monitored to avoid excessive anticoagulation.

Adverse Effects

- Bleeding
  The following are risk factors for higher INRs, and increased bleeding risk:
  - Elderly (>65 years)
  - Hepatic impairment
  - Excessive alcohol intake
  - History of bleeding disorders or tendencies
  - Hyperthyroidism
  - Renal failure
- Other rare side effects include necrosis of skin and other tissues, alopecia and hepatitis.

Switching between warfarin and other oral anticoagulants and vice versa

	Switching *to* Warfarin	**Switching *from* Warfarin**
Dabigatran	*Based on CrCl*: ***>50 mL/min*** Start warfarin 3 days before stopping dabigatran ***31-50 mL/min*** Start warfarin 2 days before stopping dabigatran ***15-30 mL/min*** Start warfarin 1 day before stopping dabigatran **Note:** INR is best measured at least 48 hours after last dabigatran dose.	Discontinue warfarin and start dabigatran once INR less than 2.0

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	Switching *to* Warfarin	Switching *from* Warfarin
Rivaroxaban	Continue rivaroxaban concurrently with warfarin until the INR >2.0 (best measured 24 hours after last Rivaroxaban dose)	Stop warfarin and start rivaroxaban at usual dose when INR is less than 2.5
Apixiban	Continue apixaban concurrently with warfarin until INR $\geq$ 2.0 (initiate testing on day 3 just prior to each dose of apixaban) OR Discontinue apixaban and start parenteral anticoagulants (bridging therapy) and warfarin at the time of the next apixaban dose. Discontinue the parenteral anticoagulant when the INR is therapeutic	Discontinue warfarin and start apixaban when INR <2.0

Neuraxial Anesthesia and Warfarin

When neuraxial (epidural/spinal) anesthesia or spinal puncture is performed, patients treated with anticoagulants are at risk for developing epidural or spinal hematoma that may result in long-term neurological injury or permanent paralysis. Traumatic or repeated epidural or spinal puncture also increases the risk of these events.

- We recommend discontinuation of warfarin 5 days prior to neuraxial intervention. The first dose of warfarin may be administered not earlier than 6 hours following spinal anesthesia, lumbar plexus block, or epidural catheter removal.
- Patients who have undergone epidural puncture and who are receiving warfarin should be monitored frequently for signs and symptoms of neurological impairment (e.g., numbness or weakness of legs, bowel or bladder dysfunction).

Periprocedural/Perioperative Management

Hold warfarin 5 days prior to the start of the procedure and restart once post-procedure hemostasis has been achieved. Use the patient pre-operative dose rather than reloading to minimize risk of bleeding.[13]

Consult Hematology for discussion of bridging anticoagulation in patients with:

- mechanical heart valves
- atrial fibrillation with prior neurologic event
- recent (less than 3 months' ago) venous thromboembolism
- intracardiac thrombus
- acute coronary syndromes

If a more urgent procedure is required and patient is taking warfarin, administer vitamin K_1 (phytonadione):[14]

- Administer 2 mg if re-anticoagulation is planned early post-procedure; 10 mg if prolonged reversal is required.
- Administer orally if is equal to or greater than 24 hours prior to the procedure; administer intravenously if it is 6-24 hours prior to the procedure.
- If it is **less** than 6 hours until the procedure, consider transfusion of either prothrombin complex concentrate or plasma (see Ordering & Administration of Blood Products policy 3.130.001).

Note: It is acceptable also to prepare blood products prior to the procedure but only transfuse in the event of bleeding.

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Acute Management of Acute Coronary Syndromes (ACS)

- For patients who arrive in the Emergency Department on warfarin and who need treatment for ACS:
  - Treatment should follow usual clinical practice.
  - Consideration should be given to temporarily suspend warfarin in the setting of ACS, due to need for invasive procedures, such as PCI or CABG, or if thrombolytic therapies are to be initiated.
  - Timing, choice, and dose of parenteral anticoagulation should be balanced against last intake of warfarin and risk of bleeding.

Recommendations from CHEST guidelines regarding patients with AF receiving warfarin and having coronary artery disease.[5]

1. For patients with AF and stable coronary artery disease and who choose oral anticoagulation, warfarin alone (target INR 2.0-3.0) is recommended over warfarin and aspirin.
2. For patients with AF at high risk of stroke (e.g., $CHADS_2$ score ≥2) during the 1st month after placement of a bare-metal stent or the first 3 to 6 months after placement of a drug-eluting stent, triple therapy (e.g., warfarin, aspirin, and clopidogrel) is recommended. After this initial period of triple therapy, warfarin (INR 2.0-3.0) plus a single antiplatelet drug is suggested until after 12 months, at which time warfarin alone is recommended.
3. For patients with AF at intermediate to high risk of stroke ($CHADS_2$ score ≥ 1) who experience an ACS and do not undergo intracoronary stent placement, during the first 12 months, adjusted- dose warfarin therapy (INR 2.0-3.0) plus single antiplatelet therapy (e.g., aspirin or clopidogrel) or triple therapy (e.g., warfarin, aspirin, and clopidogrel) is recommended. After the first 12 months, antithrombotic therapy is recommended as for patients with AF and stable coronary artery disease.

Management of Bleeding Complications or Reversal of Warfarin

Warfarin-induced anticoagulation may need to be reversed if the INR is outside the therapeutic range. Both the INR value and the risk for bleeding are taken into consideration when deciding the agent to be used for anticoagulation reversal.[15]

Reversal of anticoagulation is also required perioperatively, and this depends on the urgency of the **procedure** (see below).

Warfarin Patient Counseling

Please refer to the UHN warfarin inpatient booklet for a list of counseling points available from UHN Pharmacy.

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Reversal of warfarin-induced anticoagulation from CHEST guidelines (2012)[6,15,16]

Clinical Situations Requiring Reversal of Anticoagulation	Options for Warfarin-Anticoagulation Reversal				
	Hold Warfarin	***Oral vitamin K***	***IV Vitamin K***	***Plasma transfusion/ Fresh frozen plasma (FFP)****	***Prothrombin complex concentrate (4 factor PCC)****
General Comments	Safest, most controlled method. Hold for 4-5 days +/- bridging anticoagulation with heparin Requires advanced planning	Very well tolerated **24-48** hours for peak effect May prolong time to re-establish therapeutic warfarin dose	Well tolerated, small risk of infusion reaction. **4-6** hours for peak effect May prolong time to re-establish therapeutic warfarin dose	Requires patient consent Risk of transfusion related acute lung injury and volume overload (especially if CHF) Peak effect **immediate** Requires 30 minutes to thaw Rebound anticoagulant effect seen after 6-8 hours.	Requires patient consent Risk of thrombosis Peak effect **immediate** Requires bedside reconstitution Rebound anticoagulant effect seen after 6-8 hours.
INR 4.5- 10 (NO bleeding)	YES	No advantage to routine use of vitamin K		NO	NO
INR >10 (NO bleeding)	YES	YES, **2.5-5** mg	NO	NO	NO
Any INR AND bleeding	YES	NO	**YES** 5-10 mg (slow)	In cases of major bleeding 4-factor PCC is preferred[6]	In cases of major bleeding ***PLUS*** IV vitamin K 5-10 mg (slow)
Any INR AND Bleeding/ Need for emergency surgery	**YES**		**YES** 5-10 mg (slow) ***PLUS*** 4 factor-PCC[6]	**YES** ***PLUS*** IV vitamin K 5-10 mg (slow)	**YES** ***PLUS*** IV vitamin K 5-10 mg (slow)

PCC - Prothrombin complex concentrates: mixtures of factors X, XI, VII and II (Octaplex or Beriplex, used for rapid reversal of anticoagulation induced by warfarin)
IV - intravenous, **PO -** *per os* (orally), **CHF-** congestive heart failure
***at UHN - PCC is the recommended product, if the patient has a history of heparin induced thrombocytopenia FFP can be used**

WARFARIN CLINICIAN SUMMARY

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Notice to Healthcare Providers:

The Pharmacotherapy Handbook is intended to be used as a tool to aid in the appropriate prescribing and administration of cardiovascular formulary agents.

This information in this Handbook is intended for use by and with experienced physicians and pharmacists. The information is not intended to replace sound professional judgment in individual situations, and should be used in conjunction with other reliable sources of information. Decisions about particular medical treatments should always be made in consultation with a qualified medical practitioner knowledgeable about Cardiovascular illness and the treatments in question.

Due to the rapidly changing nature of cardiovascular treatments and therapies, users are advised to recheck the information contained herein with the original source before applying it to patient care.

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Your comments on the usefulness of the resources contained in the Handbook are welcomed and may be forwarded to Amita Woods, Department of Pharmacy Services (amita.woods@uhn.ca).