

# GUIDELINES & PROTOCOLS

## ADVISORY COMMITTEE

### Initiation and Maintenance of Warfarin Therapy

#### Scope

This guideline applies to the initiation and maintenance of warfarin therapy. It applies only to adults 19 years of age and over. Patient self-monitoring and self-management are not addressed. This is one of four related documents to be published concurrently. See also:

- *Treatment of Patients Overanticoagulated with Warfarin*
- *Management of Warfarin Therapy during Invasive Procedures and Surgery*
- *Warfarin: A Guide for Patients*

#### RECOMMENDATION 1: Contraindications

The absolute contraindications to warfarin are:

- the presence of a severe or active bleeding diathesis
- non-compliance
- first trimester of pregnancy.

Some relative contraindications include:

- uncontrolled hypertension (i.e. systolic blood pressure > 180 mm Hg, diastolic > 100 mm Hg)
- severe liver disease
- recent surgery involving the nervous system, spine or eye.

#### RECOMMENDATION 2: Therapeutic INR range

The target INR range is 2.0 - 3.0 for most indications for warfarin therapy.

The target range is 2.5 - 3.5 or greater for the following indications:

- many prosthetic heart valves (always establish desired range with a specialist physician)
- thromboembolism when INR already 2.0 - 3.0
- some patients with antiphospholipid antibody syndrome.

#### RECOMMENDATION 3: Initiation of warfarin

Initiation of warfarin should be at 5 mg/day in most patients.

A starting dose of < 5 mg should be considered for patients > 70 years of age, those with impaired nutrition (wt < 45 kg), liver disorder, or previously documented increased sensitivity to warfarin.

Note: Whenever feasible, a single strength warfarin tablet (e.g. 1.0, 2.0 or 2.5 mg) should be prescribed such that doses are multiples of one tablet strength.

**RECOMMENDATION 4: Frequency of INR monitoring**

During the induction phase, INR should be monitored every 1-3 days (initially daily if on therapeutic heparin) until the INR is in the patient’s target range for two consecutive values.

Once stable, INR may be performed less frequently (every 1- 4 weeks), depending on the stability of the results.

INR should be performed frequently (2-3 times a week) to ensure that it remains in the patient’s target range if any of the following happens: intercurrent illness, medication change (including herbal), significant diet change (See Appendices 1 and 2).

Note: Patients should take their warfarin once a day, preferably at the same time, and have their INR test performed in the morning. This limits diurnal variations and provides the physician with a same day window for dosage adjustment in the event of an unanticipated INR change.

**RECOMMENDATION 5: Dosage adjustment - maintenance therapy**

Dosage adjustment is not required for minor fluctuations of INR as long as the results remain within the patient’s target range.

Fluctuations of INR beyond the patient’s target range should always be investigated and corrected where possible. Consider causes such as a change in dosage of warfarin, patient compliance, medication profile, diet, and intercurrent illness.

The patient should be followed using the Warfarin Record Sheet (attached) or a similar log sheet. The following scheme is recommended for dosage adjustment in patients with an INR target range between 2.0 – 3.0:

<b>Dosage Adjustments for Patients on Warfarin Maintenance Therapy Target INR 2.0 – 3.0</b>	
<b>INR</b>	<b>Dosage Adjustment</b>
< 1.5	Increase weekly dose by 20% and give one time top-up additional amount equal to 20% of weekly dose
1.5 - 1.9	Increase weekly dose by 10%
2.0 - 3.0	No change
3.1 - 3.9	No change - recheck in one week. If persistent, decrease weekly dose by 10-20%
4.0 - 5.0	Omit 1 dose; decrease weekly dose by 10-20% and recheck in 2-5 days
> 5.0	See guideline for <i>Treatment of Patients Overanticoagulated with Warfarin</i>

- Notes:
- Changes in warfarin dosage may take several days to affect INR. Hence, frequent dosage adjustment is not recommended.
  - Adjustments may need to be modified in the presence of intercurrent illness.

## **RECOMMENDATION 6: Patient education**

When warfarin therapy is initiated, the physician should discuss the following with the patient:

- The reason for prescribing warfarin and the duration of treatment
- The need to comply with recommended warfarin dosage
- The importance of monitoring and the target INR
- The need to take their warfarin once a day, preferably at the same time, and to have their INR test performed in the morning
- The importance of consistent Vitamin K content in the diet
- The need for caution when initiating other medications (including ASA), herbs or supplements
- The need to avoid heavy or variable alcohol consumption
- The importance of avoiding pregnancy while taking warfarin
- Side effects, signs of bleeding and potential need for blood products
- Influence of intercurrent illness
- Review of current medications
- When to call the doctor.

See also: *Warfarin: A Guide for Patients*

## **Rationale**

### **Introduction**

Warfarin therapy reduces the risk of thromboembolic events. There has been an extraordinary increase in the use of warfarin over the past decade, mainly because of aging of the population, and the demonstration of its benefit in atrial fibrillation.<sup>1-2</sup> Unfortunately, approximately a third of the patients who would benefit from warfarin never receive it, and over half of those who do receive warfarin are managed suboptimally,<sup>3</sup> because of the complex pharmacodynamics and numerous drug, diet and herb interactions. A consensus for optimal warfarin therapy is emerging from several recent publications.<sup>2-11</sup>

### **Pharmacodynamics**

Warfarin is given orally and is absorbed rapidly and completely.<sup>5,7,9</sup> It is almost fully bound to albumin in blood; thus hypoalbuminemic patients, e.g. malnourished, liver disorders, post-operative etc., need lower doses. The beginning and the peak of clinical anticoagulant activity of warfarin occur at 24 and 72-96 hours, respectively.

### **Dosing and monitoring**

The optimum induction and maintenance dose for warfarin vary from patient to patient and at different times in the same patient.<sup>3-5,12</sup> Two therapeutic ranges are recommended, depending on the indication for anticoagulation. Under-anticoagulation can result in recurrent venous or arterial thrombosis, while even a minor degree of over-anticoagulation can produce minor or major hemorrhagic complications. The narrow therapeutic index and a high risk:benefit ratio necessitate close and long-term monitoring. Prothrombin time testing in Canada is now reported as “International Normalized Ratio” (INR) which corrects for interlaboratory variations and allows the patient to be monitored at any laboratory. During the first two days of treatment, the INR rises without concomitant clinical anticoagulant effect. Moreover, during the maintenance phase, dose changes may not be reflected in INR for 4-5 days. For these reasons, frequent dose changes should be avoided. The recent trend is to change the total weekly warfarin dose (TWD),<sup>13</sup> rather than a daily dose.

## Factors affecting warfarin anticoagulation

Certain factors, either alone or in combination, can affect warfarin anticoagulation. These include: warfarin dose, compliance, liver disorders, age,<sup>5</sup> intercurrent illness,<sup>3,6</sup> other medications (including high doses of acetaminophen)<sup>3,6</sup> (Appendix 2), diet<sup>14-16</sup> (Appendix 1), herbs,<sup>17</sup> or supplements (Appendix 2) and alcohol intake. Heavy or highly variable alcohol intake results in liver dysfunction and may potentiate the effect of warfarin. Moderate, regular alcohol consumption has little effect on warfarin action. Vitamin K<sub>1</sub> rich foods should not be eliminated, but patients should eat a diet with consistent vitamin K<sub>1</sub> content. One in three Canadians consumes some form of herbs, vitamins or alternative medications. Many of these (e.g. coenzyme Q, ginseng, Gingko biloba, and Vitamin E) may influence the warfarin effect. While such supplements are not contraindicated in patients on warfarin, excessive intake may result in fluctuating INR values. Any medication that affects platelet function, including ASA and NSAIDs, increases the risk of hemorrhage. See Appendix 2.

## Patient education

Warfarin is more likely to be used safely by a patient who is aware of the potential for drug and diet interactions, understands the need for monitoring, and can recognize the signs of over- and under-anticoagulation. Consequently, patient education is critical to the success of warfarin therapy. A separate patient information sheet is available with these guidelines and should be discussed with the patient.

## References

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### Sponsors

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This guideline is based on scientific evidence current as of the effective date.

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The principles of the Guidelines and Protocols Advisory Committee are:

- to encourage appropriate responses to common medical situations
- to recommend actions that are sufficient and efficient, neither excessive nor deficient
- to permit exceptions when justified by clinical circumstances.



**Appendix 1. Vitamin K Content of Foods and Beverages\***  
**Daily requirement 65 - 80 micrograms (µg)**

Food Group	Vitamin K content (µg/100g)
<b>Greens/vegetables</b>	
Coriander or cilantro, cooked .....	1,510
Coriander, raw .....	310
Parsley, cooked .....	900
Parsley, raw .....	540
Brussel sprouts.....	438
Spinach, raw .....	400
Mint, raw .....	230
Broccoli, cooked .....	270
Cabbage, raw .....	145
Lettuce.....	120-210
Green beans .....	47
Peas, cooked.....	23
Celery, raw .....	12
Cauliflower,cooked .....	10
Other: Kidney beans, lima beans, corn, cucumber, .....	<10
egg plant, mushrooms, onion, pepper, potato, sweet potato, radish, tofu, tomato	
<b>Fruits</b>	
Apple with peel (green) .....	60
Apple without peel (raw) .....	0.4
Kiwifruit, raw .....	25
Other fruits .....	<20
<b>Dairy products</b> .....	<5
<b>Eggs</b> .....	2
<b>Nuts</b>	
Pistachio .....	70
All other nuts.....	<10
<b>Meat, poultry, fish (without oil)</b> .....	<5
<b>Grain products (without oil)</b> .....	<10
<b>Desserts (most)</b> .....	<15
<b>Fats/dressings</b>	
Soybean oil .....	193
Canola.....	141
Mayonnaise .....	81
Margarine, hard.....	51
Olive oil .....	49
Limit salad oil, canola oil, soybean oil to 2 tablespoons per day.	
Butter, gravy, sour cream, almond oil, corn oil, peanut oil, sesame seed oil, .....	<15
sunflower oil, salad dressing (Italian)	

\*Based on Provisional Table on the Vitamin K Content of Foods, United States Department of Agriculture, 1994.

## Appendix 2. Drugs, Herbs and Supplements: Potential Interactions with Warfarin\*

Warfarin Effect Increased	Warfarin Effect Decreased	Little or No Effect
<b>Medications</b>		
<p><b><u>Antibiotic/Antifungal</u></b>            azoles (fluconazole, itraconazole, miconazole, cotrimoxazole)            carbenicillin            cephalosporins            clarithromycin            erythromycin            isoniazid            metronidazole            quinolones            tetracycline            trimethoprim-sulfa combination</p>	<p><b><u>Antibiotic</u></b>            dicloxacillin            naphcillin            rifampin</p>	<p><b><u>Antibiotic/Antifungal</u></b>            Ketoconazole            vancomycin</p>
<p><b><u>Analgesic/anti-inflammatory</u></b>            acetaminophen (high doses)            aspirin &amp; some NSAIDs (including COX-2 inhibitors)            allopurinol            propoxyphene            sulfinpyrazone            Zafirlukast</p>		
<p>Antiarrhythmic            amiodarone            propaphenone            quinidine</p>		
<p><b><u>Miscellaneous</u></b>            anabolic steroids            chloral hydrate            cimetidine            clofibrate            disulfiram            heparins            omeprazole            phenytoin (transient effect)            simvastatin            tamoxifen            thyroxine</p>	<p><b><u>Miscellaneous</u></b>            barbiturates            carbamazepine            chlordiazepoxide            azathioprine            cyclosporine            etretinate            trazodone</p>	<p><b><u>Miscellaneous</u></b>            alcohol            antacids            atenolol            bumetadine            enoxacin            famotidine            fluoxetine            ketorolac            metoprolol            naproxen            nizatidine            psyllium            ranitidine</p>
<b>Herbs</b>		
<p>gingko            danshen</p>	<p>ginseng            vitamin K-containing herbs            (eg, alfalfa, green tea)</p>	<p>echinacea</p>

\*This list is not meant to be all-inclusive. For a detailed listing, please see References 17 and 18.