



**Principal Developer:** B. Bartle

**Secondary Developers:** M. Crowther, W. Geerts, M. Kovacs

Warfarin, an oral vitamin K antagonist (OVKA), is the commonest oral anticoagulant used in North America. It blocks the regeneration of the reduced form of vitamin K which is an essential cofactor in the carboxylation of glutamic residues on the procoagulant forms of factors II, VII, IX and X. This ultimately leads to a decreased formation of thrombin and fibrin.

Warfarin also blocks the formation of the endogenous anticoagulant proteins, C and S. The potential clinical significance of this will be discussed later.

Warfarin is a racemic mixture of S and R enantiomers. These enantiomers are metabolized by different cytochrome (CYP) P450 enzymes in the liver. The more potent S isomer of warfarin is broken down by CYP 2C9, which has been shown to have a number of **inherited variants** that make some patients much more sensitive to warfarin and potentially at **high risk for bleeding**, especially during initiation of therapy. Presently, there is no widely-accessible test to identify these patients in a timely fashion at the beginning of therapy.

Nicoumalone (Sintrom™), another OVKA available in Canada, is used much less frequently but will be discussed briefly later in this monograph.

### MONITORING OF OVKA

The prothrombin time (PT) is the most commonly used test to monitor oral anticoagulant therapy. The PT is reported using the **International Normalized Ratio (INR)** in order to improve the standardization of the PT results irrespective of the thromboplastin reagent and analyzer used. See the INR Guideline on this website for more detail.

For most indications for OVKAs, the optimal INR range is 2-3; the INR range for patients with a mechanical mitral valve is generally 2.5-3.5. Lower intensity warfarin (INR 1.5-2.0) has shown benefit over no anticoagulation in the prevention of venous thromboembolism in patients receiving chemotherapy for stage III-IV breast cancer, and, when compared with no treatment, for the prevention of recurrent venous thrombosis. However, when long-term anticoagulation with a target INR range of 1.5-2.0 was compared with the range of 2-3, the latter was more effective and as safe as the lower range.

### INDICATIONS FOR OVKA

OVKAs are indicated for the **prevention of thrombosis and systemic embolism** in prosthetic heart valves, atrial fibrillation, mitral-valve disease and myocardial infarction (MI). They have also been shown to **prevent recurrent thrombosis** in patients with venous thromboembolism.

See other monographs elsewhere on this website for additional, indication-specific, information.

### INITIATION OF THERAPY

Patients with atrial fibrillation and no recent TIA/stroke may be started with an estimated maintenance dose of warfarin. A patient's dosage requirement will be affected by many factors, including age, race, weight, nutritional status and concomitant medications. **Age** has been shown to have a significant inverse relationship on warfarin dosage requirements; patients less than 50 years of age may require 5.0-10.0 mg daily while patients 80 and older generally require 2.5-3.0 mg daily. There is a linear decline in the dosage requirements between these two extremes of age.

## Clinical Guide - Oral Vitamin K Antagonists (Warfarin)

Patients receiving amiodarone when warfarin is started require a dosage reduction of approximately 25% of the estimated maintenance dose based on the patient's age.

Variants of the CYP450 2C9, the patient's vitamin K intake, and different haplotypes of vitamin K epoxide reductase (VKORC1) are three other factors that can have a significant effect on the warfarin dosage requirements; however, none of these factors can be easily identified or quantitated for clinical purposes at present.

The benefit of starting a **loading dose** of warfarin is controversial, given the conflicting results of several recent studies evaluating this dosing strategy. A loading dose may be useful in patients whose initial anticoagulation therapy requires either intravenous heparin or therapeutic doses of a low molecular weight heparin (LMWH) in order to shorten the period of the parenteral anticoagulant.

Exact loading dose requirements have not been established but should reflect an increase over the patient's estimated daily maintenance dose. For example, if a patient's estimated daily maintenance dose is 5mg, then give 7.5-10 mg daily for the first 1-2 days. The heparin or LMWH should be given for at least 5 days, and can be discontinued when the INR is therapeutic for at least 2 consecutive readings. Alternatively, for outpatient initiation of warfarin in patients with acute venous thromboembolism, the accompanying nomogram of Kovacs et al that uses 10 mg doses on day 1 and 2 could be used, but should be **RESTRICTED TO PATIENTS WHO ARE 60 YEARS OF AGE OR YOUNGER**. However, even some of these patients will have an exaggerated initial response to these loading doses because of unknown inherited sensitivities to warfarin.

**There is generally no need to do daily INRs, especially in outpatients.** During the initial 1-2 weeks of warfarin therapy, the INRs should generally be done twice per week. As the desired INR target is maintained, the time between the tests can lengthen. A maximum time between tests should generally be no more than 4-5 weeks. Between tests, patients need to keep their dosing supervisor informed of any changes in their health status or medication regimen.

### MAINTENANCE OF OVKA THERAPY

INRs will vary from time to time because of the many factors that affect warfarin therapy. Many INRs that fluctuate just outside the therapeutic range generally return to the desired range without a change in the weekly maintenance dose, and thus many experienced anticoagulation practitioners only change the maintenance dose when 2-3 consecutive results remain just outside the therapeutic range. A change in dose is usually not required unless, either the patient states there has been a change in their nutritional or medication status, or the INR is either dangerously prolonged or subtherapeutic.

Generally speaking, if the maintenance dose needs to be changed, a **10-15% increase or decrease** in the total weekly dose is all that is required to return to the therapeutic range. This can be accomplished by adding or subtracting the equivalent of one day's dose per week; there is no need to change the tablet strength. **For example, a patient taking 5mg warfarin daily has INRs of 1.8 and 1.9 over the last month. An appropriate dosing change would be to have the patient take 7.5 mg on Mondays and Fridays and 5mg all the other days of week, and check the INR in 1-2 weeks.**

Various tools to improve the control of warfarin therapy have been developed, evaluated and published. However, with sufficient training/education and experience, appropriate and safe anticoagulation control can probably be achieved in a variety of clinical practices without resorting to computer-based dosing systems.

Several studies have also shown that anticoagulation clinics can significantly improve both INR control and outcomes for patients on OVKA's. These anticoagulation services are increasing in number; **if available, we recommend that patients on OVKA's be monitored by such clinics.**

Patient self-directed oral anticoagulation following training for a point-of-care capillary INR monitor and dosing principles can also improve INR control and outcomes. The cost of these devices remains substantial **in Canada**, however, and the cost of the tests might also have to be borne by the patient.

Other **practical recommendations** for improving the management of patients on OVKA's include:

1. Use a single form to record all INRs and dosage changes in each patient to allow easy review of long-term dosage-INR trends

## Clinical Guide - Oral Vitamin K Antagonists (Warfarin)

2. Have the patient use a 'pocket size' calendar provided by most warfarin manufacturers to record all INR results and dosage instructions.
3. Use a single strength of warfarin tablet at any one time.
4. Obtain an additional INR 4-6 days after any new drug therapy is added to the patient's regimen. Almost any drug can be safely taken with warfarin as long as this additional INR(s) is utilized at the beginning of therapy; **exceptions to this rule are the 'older' NSAIDs, as most may increase the bleeding risk without affecting the INR.** Patients having amiodarone added to their warfarin regimen should have their INR monitored more frequently for several months given the very long half-life of this anti-dysrhythmic drug.
5. Daily INRs for an extended period are almost never required for outpatients. During warfarin initiation, the first INR should be obtained on the day of the third or fourth warfarin dose, the dose adjusted accordingly, with the next INR in another 2-3 days, if not far outside the desired range.

### REVERSAL OF ANTICOAGULATION AND 'BRIDGING THERAPY'

One of the most common therapeutic decisions that has to be made for a patient on warfarin is responding to an INR of >5.0 without any evidence of major bleeding. Several studies now show that giving a **1 mg oral dose of vitamin K** will lower the INR more quickly than just eliminating 1-2 doses of the anticoagulant; however, patients who receive vitamin K, though, are more likely to have a subtherapeutic INR 24-48 hours after the antidote. Vitamin K might be best reserved for patients at risk for bleeding, or for patients whose elevated INRs have been shown to decline more slowly because of, or characterized by, active cancer therapy, drug interaction, exacerbation of CHF, or small warfarin dose requirement, **and INRs above 8.0**

Most patients receive their warfarin dosing instructions by telephone. Some of these patients may be prescribed a dose of vitamin K to keep at home and use only on instructions from their INR supervisor; this may avoid unnecessary visits to an Emergency Department.

Patients on OVKA may require procedures that may necessitate temporary interruption of therapeutic anticoagulation. Certain procedures, such as dental extraction(s), skin biopsies or injections or aspirations of soft tissue or joints, can be carried out with no interruption in the level of anticoagulation.

Procedures that carry a higher risk of bleeding will require discontinuation of the warfarin for approximately 3-5 days before the procedure; re-institution of the OVKA can generally commence on the same day as the procedure since it will take several days to re-establish full anticoagulation again.

Patients requiring temporary discontinuation of warfarin, but who are judged to be at significant risk of a thrombotic event off the warfarin, can be taught to administer an appropriate dose of a LMWH for 1-2 days before, and several days after the procedure, until the INR is therapeutic. The dose of the LMWH should reflect an assessment of bleeding/thrombotic risk of the patient.

INRs generally do not need to be taken immediately before the procedure unless the patient's INR pattern tends to include frequent supra-therapeutic results or the procedure carries a high risk of bleeding.

### DURATION OF THERAPY

1. Generally, a patient taking warfarin for mechanical heart valves or atrial fibrillation require lifelong anticoagulation.
2. Patients undergoing cardioversion for atrial fibrillation should remain on warfarin during the procedure and for approximately one month following return to normal sinus rhythm.
3. The duration of OVKA therapy for patients with venous thrombosis(VTE) is evolving based on new information from clinical trials. Issues that influence the recommended duration of anticoagulation include: 1) the presence of on-going risk factors for VTE, 2) whether the VTE was provoked by a known reversible risk factor or was idiopathic, 3) resolution of the DVT, 4) risk of major bleeding, and 5) patient preferences.

**Consult the guideline on this <http://www.tigc.org> for the most current information on duration of anticoagulation treatment in VTE.**

### **PREGNANCY AND OVKA**

OVKAs cross the placenta and can produce a characteristic embryopathy as well as CNS abnormalities, fetal bleeding and increased rates of fetal death. **It appears that the risk of fetal complications is reduced if the coumarin derivative is stopped before the sixth week of gestation.** Women receiving OVKA should be counselled about the risks of warfarin therapy before pregnancy occurs.

In women already receiving an OVKA, the ACCP guidelines favour having the woman perform frequent pregnancy tests and substitute unfractionated heparin or a LMWH when the test is positive. LMWHs are known to be safe to the fetus during pregnancy but may require anti-Xa level monitoring from time to time to maintain an effective level of full anticoagulation.

OVKAs can be taken by breast-feeding mothers without harm to the fetus.

### **BLEEDING AND ADVERSE EVENTS**

Bleeding is the major side effect of oral anticoagulant therapy and its risk must be constantly assessed against the potential benefit of the drug in a given patient.

**For example, risk of falls in a patient with atrial fibrillation is rarely sufficient to justify withholding the initiation of the drug.**

The major determinants of OVKA-induced bleeding are:

1. intensity of the anticoagulant effect
2. length of therapy
3. concomitant use of other drugs that interfere with hemostasis
4. recent history of surgery or bleeding
5. renal failure

Bleeding is the major side effect of OVKAs and its risk must be constantly assessed against the potential benefit of the drug in a given patient.

Clinical trials have demonstrated a rate of major bleeding between 3-5% per year for patients with prosthetic heart valves. For patients with atrial fibrillation, an increased absolute risk of bleeding of 0.3% per year was found compared to patients not receiving an oral anticoagulant. For patients with venous thromboembolic disease, the major bleeding rate is approximately 1% per year.

**The rates of intracranial hemorrhage in these studies are between 0.1 and 0.3% per year.** This risk increases with age. Rates of major bleeding are likely to be higher in patients on OVKA in everyday practice since patients enrolled in studies are generally selected to have a relatively low risk of bleeding and control of the INR is probably less precise in real practice compared to clinical trials.

If a patient experiences a bleeding episode, the cause should be determined and treated and the warfarin effect must be reversed with 1-10 mg vitamin K, intravenously, and fresh frozen plasma or prothrombin-complex concentrates, if available. **See the most recent ACCP Consensus Conference on Antithrombotic Therapy for more detailed treatment guidelines for treating OVKA-associated bleeding.**

Other adverse events with OKVA are rare and include isolated case reports of alopecia, skin rash and hepatitis.

Skin necrosis is a rare complication of OVKA that usually begins within a few days of starting the drug, and is thought to be due to depletion of the vitamin K-dependent anticoagulant factors, protein C and S. This condition is rare with current anticoagulation practices of administering heparin or LMWH at the beginning of therapy and using smaller loading doses of warfarin; in addition, this condition is most likely to occur only in patents with an

inherited protein C or S deficiency, a rare hypercoaguable state.

Patients who are thought to be intolerant to warfarin may be tried on the OVKA, nicoumalone(Sintrom™). **Nicoumalone is twice as potent as warfarin and thus it should be started at 50% of the warfarin dose that the patient was taking and then adjusted according to the INR result.**

### References

1. Ansell J, Hirsh J, Dalen J et al. Managing oral anticoagulant therapy. Chest 2001;119(Suppl):22S-38S
2. Schulman S. Care of patients receiving long-term anticoagulant therapy. N Engl J Med 2003;349:675-83
3. Gage BF, Fihn SD, White RH. Management and dosing of warfarin therapy. Am J Med 2000;109:481-88
4. Wilson SE, Watson HG, Crowther MA. Low dose oral vitamin K for management of asymptomatic patients with an elevated INR: a brief review. CMAJ 2004;170:821-4
5. Dunn AS, Turpie AGG. Perioperative management of patients receiving oral anticoagulants. Arch Int Med 2003;163: 901-8