TARGET AUDIENCE: All Canadian health care professionals.

OBJECTIVE:
To provide an overview of the mechanism of action, dosing regimens, and side-effects of warfarin and other vitamin K antagonists.

ABBREVIATIONS:

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ASA</td>
<td>acetyl salicylic acid</td>
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<td>DVT</td>
<td>deep vein thrombosis</td>
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<tr>
<td>GI</td>
<td>gastrointestinal</td>
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<td>INR</td>
<td>international normalized ratio</td>
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<tr>
<td>NSAID</td>
<td>non-steroidal anti-inflammatory drug</td>
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<tr>
<td>VTE</td>
<td>venous thromboembolism</td>
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MECHANISM OF ACTION:
Warfarin is an indirect anticoagulant producing its anticoagulant effect by reducing the ability of coagulation factors II, VII, IX, X, protein S and protein C to participate in the coagulation cascade. Warfarin produces this effect by interfering with post-translational modification of these coagulation factors.

INDICATION:
Warfarin is widely used for the prevention and treatment of many thromboembolic disorders. Frequent uses include primary prevention of stroke in patients with atrial fibrillation, secondary prevention of venous thromboembolism (see DVT diagnosis, PE guides), primary and secondary prevention of thrombosis or systemic embolization in patients with native valvular diseases or those with mechanical heart valves. Less common uses include secondary prevention of unstable coronary syndromes, systemic embolization from unknown sources, and primary prevention of both arterial and thromboembolism in patients with hypercoagulable states, including some patients undergoing surgery with a high risk of thrombosis.

DOsing:
In general, warfarin doses should be started at those likely to be required for long-term therapy; on average, this dose is 5 mg per day, and decreases with increasing age. Healthy outpatients with acute thromboembolic disorders can be started on higher doses (e.g. 10 mg/day for 2-3 days), while hospitalized ill or post-operative patients should be started on a lower dose (as low as 1-3
mg/day). The dose should be individualized, based on the international normalized ratio (INR) response (see below).

**MONITORING:**

Routine monitoring is required for all patients taking warfarin. The target INR for all patients (with the exception of a small proportion of patients with mechanical heart valves at particularly high risk of thrombosis for whom the target INR is 2.5-3.5) is 2.0-3.0. Initial monitoring is performed as often as daily with initial doses, then weekly; once a stable INR is achieved, monitoring frequency should be reduced. Most patients are monitored once monthly; however, a small group of very stable patients may be monitored as infrequently as every 12 weeks.

Unstable INR control is often due to either overly frequent monitoring (with dose changes before the INR effect of the prior dose change has equilibrated) or due to excessively large dose adjustments.

A variety of point-of-care INR monitors are available. These devices may improve the quality of anticoagulant control for selected patients (see Point-Of-Care INR monitoring guide).

Various tools to improve the dosing and monitoring of warfarin therapy have been developed, evaluated and published. However, with a modest amount of training and diligence, appropriate and safe warfarin dosing 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 over standard practices. Selected patients can also be taught to monitor their own warfarin therapy with clinician ‘backup’ if necessary; this is usually accomplished with patients purchasing and being trained on a point-of-care device.

Other practical recommendations for improving management of warfarin therapy include:

a) using a log to record all INRs and dosage changes in each patient to allow easy review of long-term dosage/INR trends,

b) having the patient use a ‘pocket size’ calendar provided by most warfarin manufacturers and anticoagulant clinics to record all INR results and daily dosages,

c) using a single warfarin tablet of the appropriate dose, if possible,

d) giving the patient accurate, up-to-date, sensible printed information about warfarin. Many warfarin patient information sheets are suboptimal; we recommend that the warfarin patient information material on this website be given to the patient. It is produced by anticoagulation specialists and is reviewed and updated yearly.
**ADVERSE EFFECTS:**

The major adverse effect of warfarin is bleeding; concomitant use of antiplatelet drugs (see clopidogrel, ticagrelor, prasugrel, ASA guides) or other anticoagulants increases the bleeding risk. As a long-acting anticoagulant, warfarin should be used with care in patients at high risk of bleeding, after considering the relative risks of thrombosis and bleeding. Other reported side-effects include skin rash and alopecia, although evidence supporting the relationship with warfarin is lacking.

**PERI-PROCEDURAL MANAGEMENT:**

See the Peri-Operative Management of Warfarin guide.

**SPECIAL CONSIDERATIONS:**

The anticoagulant effect of warfarin can be reversed using vitamin K. For emergent reversal, vitamin K should be administered with a four factor prothrombin complex concentrate. Acenocoumarol (Sintrom®) is an alternate vitamin K antagonist used infrequently in Canada. Warfarin and acenocoumarol cross the placenta, are potentially teratogenetic, can cause fetal bleeding and are associated with increased rates of spontaneous abortion.

**DRUG INTERACTIONS:**

Most drug interactions with warfarin occur because of concurrent antiplatelet therapy or drugs that compete for cytochrome P450 2C9. The risk-benefit of using warfarin with an antiplatelet agent must be constantly assessed; many patients are receiving warfarin and ASA without proven benefit of the combination. This risk-benefit assessment also applies to using traditional non-steroidal anti-inflammatory drugs (NSAIDs) with warfarin; in addition, many of these NSAIDs are metabolized by 2C9. From an upper gastrointestinal (GI) bleeding perspective, celecoxib or a traditional NSAID plus a proton pump inhibitor may be the safest inflammatory therapy to use in patients on warfarin. The simplest approach to avoiding dangerous elevations or subtherapeutic INR in patients taking warfarin is to obtain an INR 4-5 days into the addition of any new drug and adjusting the dose if necessary. Generally speaking, almost no drug has to be avoided when using this approach. Also, it prevents any dangerous INR perturbation that the new medical condition may have on warfarin’s effect.

**PEDIATRICS:**

Warfarin can be used for the prevention of thrombosis in children. Therapy is complicated by the need for regular blood work which may be difficult to obtain in small children. Point-of-care devices may be of assistance in this setting. Pediatricians with expertise in thromboembolism should manage, where possible, pediatric patients with thromboembolism. When this is not
possible, a combination of a neonatologist/pediatrician and an adult hematologist, supported by consultation with an experienced pediatric hematologist, is recommended.

REFERENCES:


Please note that the information contained herein is not to be interpreted as an alternative to medical advice from your doctor or other professional healthcare provider. If you have any specific questions about any medical matter, you should consult your doctor or other professional healthcare providers, and as such you should never delay seeking medical advice, disregard medical advice or discontinue medical treatment because of the information contained herein.