Warfarin

Thrombosis Canada
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Objective:

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

Background:

Warfarin is an indirect anticoagulant producing its effect by decreasing the ability of the liver to produce fully functional coagulation factors II, VII, IX, and X, as well as the endogenous anticoagulants, protein C and protein S.

Current Clinical Practice Guidelines generally recommend direct oral anticoagulants (DOACs) over warfarin for most patients with venous thromboembolism (VTE) and atrial fibrillation (AF) as DOACs require less monitoring, are as effective, and cause similar or less bleeding. However, there are still clinical circumstances where warfarin is preferable or indicated. This guide will try to address these issues.

Indications:

Common uses of warfarin include:

- prevention of stroke or systemic embolism in patients with AF (especially those with rheumatic mitral stenosis, where DOACs should be avoided)
- treatment of acute VTE (overlapped with parenteral anticoagulation until INR therapeutic)
- long-term secondary prevention of VTE
- prevention of thrombosis or systemic embolization in patients with mechanical heart valves or with certain diseases of the native heart valves

Less common uses include:

- management of patients with acute anterior myocardial infarction
- prevention of systemic embolization from the heart, e.g. mural thrombus
- prevention of recurrent stroke in selected patients without AF
- to maintain hemodialysis access and arterial graft patency
- prevention of VTE in high risk patients, e.g. hip or knee arthroplasty
- prevention of recurrent venous and arterial embolism in those with antiphospholipid antibody syndrome

Dosing:

- The maintenance dose of warfarin varies widely among patients, from less than 1 mg/day to greater than 20 mg/day.
- In general, warfarin should be started at the dose estimated to be required for long-term therapy. For most adults, a reasonable starting dose is 5 mg daily. In those who are frail, underweight or of Asian descent, starting a lower dose at 1 – 2 mg daily may be more suitable.
- Factors affecting the maintenance dose of warfarin include:
    - Age
    - Body weight
    - Ancestry
    - Nutritional status, diet
    - Genetic variation in the enzyme that is the site of warfarin action (VKOR)
    - Genetic variation in the enzyme system that metabolizes warfarin (CYP_{450})
    - Concomitant drugs
    - Alcohol intake
    - Comorbidities (e.g. liver disease, heart failure)
    - Activity level

Monitoring:

- Routine laboratory monitoring is required for all patients taking warfarin.
- The target INR (international normalizing ratio) for most patients is 2.5 (range 2.0-3.0). For most patients with mechanical mitral valves the target INR is 3.0 (range 2.5-3.5). Patients with low-thrombogenicity mechanical aortic valves (e.g., On-X) after 3 months of standard warfarin therapy may be candidates for a lower INR target of 1.5-2.0 with concurrent ASA administration.
- The time it takes for warfarin to produce a change in the INR depends on the time for pre-existing vitamin K-dependent clotting factors to be metabolized. Depending on the dose of warfarin and individual factors, the timeframe for this process is approximately 3 to 7 days. Therefore, it is recommended that following a baseline INR measurement monitoring be performed no earlier than 2 to 3 days after the first dose and subsequent dose changes.
- Once a stable INR is achieved, frequency of monitoring can be reduced. Many patients are monitored once monthly. Some patients require more frequent monitoring, while very stable patients may be monitored as infrequently as every 12 weeks.
- Unstable INR control is often related to overly frequent monitoring (with dose changes occurring before the effect on INR from the prior dose change has equilibrated) or to excessively large dose adjustments. [See also the **Clinical Guide:** Warfarin: Management of Out-of-Range INR].
- There are a variety of tools to aid in the management of warfarin therapy, including:
    - Dosing aids:
        - Computerized monitoring
        - Paper-based dosing algorithms
    - Point-of-care INR testing (versus laboratory-based venipuncture)

A summary of advantages, disadvantages and examples of each of these approaches is provided in the **Table 1**. All approaches used to monitor the effectiveness and safety of warfarin therapy should incorporate clear patient education and a system of data management to record and track all INRs and warfarin doses.

Table 1: Advantages, Disadvantages, and Examples of Warfarin Management Tools

	Advantages	Disadvantages	Examples
Computerized dosing and monitoring	• At least as effective as dosing by an experienced clinician • Automatically calculates whether or not a dose adjustment is necessary • Determines the new dose and testing frequency	• Upfront software / subscription costs • May not manage patients with highly variable INRs well • Not optimal for warfarin initiation	DAWN-AC® INR Online®
Paper-based dosing algorithm	• Cost-effective • Minimizes subjective decisions on dosing and thereby reduces variation among multiple prescribers • Supported by long-term clinical experience • Standardizes dosing approach, yet allows for flexibility to over-ride the nomogram in patients not responding appropriately to recommendations	• Few algorithms and limited validation studies • Some algorithms primarily based on expert clinician's experience rather than evidence • May not manage patients with highly variable INRs well	See **Clinical Guide Warfarin: Management of Out-of-Range INR**
Point-of-Care INR testing	• Measures clotting time using a fingerprick sample of blood • INR result within 30 seconds allows immediate dosing recommendations • Highly convenient • Allows for patient self-testing and self-management in a select group of trained patients • May be combined with computerized monitoring or paper-based dosing algorithms	• High upfront costs for POC monitor and ongoing costs of test strips and lancet devices • Accuracy reduced in some patients with antiphospholipid antibodies • At supratherapeutic INRs, results may deviate from laboratory based venipuncture INRs	CoaguCheck®

Other practical recommendations for improving management of warfarin therapy include

- Both the patient and the prescriber should keep a log to record all INRs and doses to allow easy review of long-term dosage/INR trends. Pocket size calendars are provided by some warfarin manufacturers and anticoagulant clinics.
- When possible, use of a single warfarin tablet strength to reduce dosing errors.
- Patients should be provided with accurate and clear printed information about warfarin. Many warfarin patient information sheets are suboptimal; we recommend that the warfarin patient information material on the Thrombosis Canada website be given to the patient (See **Warfarin: Patient Information Sheet**). It is produced by anticoagulation experts and is reviewed and updated regularly.
- **Patients should be informed there are no dietary restrictions while taking warfarin. Patients should not reduce the intake of foods high in vitamin K, but should be encouraged to maintain a regular and consistent diet. Vitamin K restricted diets may result in more labile INR control.**
- Acute infection or other changes in health status (e.g. diarrhea, vomiting, heart failure) can also alter warfarin response and should prompt more frequent INR monitoring.

Drug Interactions:

- Drug interaction with warfarin may result in increased risk of bleeding, or less frequently the reduced effectiveness of warfarin. Mechanisms for the drug interactions are varied, and include: interfering with warfarin metabolism through inhibition or induction of the cytochrome P450, the enzyme system that metabolizes warfarin (many drugs); interference with platelet function (e.g. antiplatelet agents, selective serotonin reuptake inhibitors); injury to gastrointestinal mucosa (e.g., NSAIDS); reduced Vitamin K synthesis (e.g., many antibiotics); or interference with the Vitamin K cycle (e.g., acetaminophen).

- There is a wide variation in the severity of drug interactions with warfarin, as well as the reliability of the information available. Use of a computerized drug interaction program may be helpful, however do not include other patient specific factors such age or comorbidities that may contribute to the overall effect.
- **Antiplatelet agents:** Most patients who take warfarin should not also use an antiplatelet agent, since the risk of bleeding is more than doubled and many patients do not derive additional thrombotic protection with the combination. Reasons for use of an antiplatelet agent in patients who also have an indication for anticoagulation include, but are not limited to: patients with acute coronary syndrome and/or those with new coronary artery stents, some patients with high-risk mechanical heart valves, and patients with a proven stroke or transient ischemic attack (TIA) while therapeutically anticoagulated with warfarin. For each patient, the risk-benefit of using warfarin with an antiplatelet agent must be carefully and repeatedly assessed and documented.
- **Non-steroidal anti-inflammatory drugs (NSAIDs):** The risk-benefit assessment also applies to using traditional NSAIDs with warfarin. In addition, many of these NSAIDs are metabolized in the liver by CYP 2C9 which also metabolizes warfarin. For patients who require both anticoagulation and an NSAID, strategies to reduce the risk of gastrointestinal bleeding include a COX2 inhibitor such as celecoxib or a traditional NSAID plus a proton pump inhibitor.
- Alterations in concomitant medications and new concurrent illness should result in more frequent INR testing.
- Antibiotics typically increase INR through multiple mechanisms (see above).
- For drugs that may affect warfarin metabolism or clearance, the simplest approach is to obtain an INR 3-4 days after the addition of the new drug and then adjust the dose, if necessary. In general, **very few drugs will need to be avoided when using this approach.**
- Alcohol and a number of health supplements (e.g. St. John's Wort) can also change the INR.

Adverse Effects:

- The major adverse effect of warfarin is bleeding. On average, the annual rate of major bleeding is 1-2% in patients on chronic warfarin, while minor bleeding events occur in 10-20% of warfarin users per year.
- Other, uncommon, side effects include hair loss and skin rash.

Initial Treatment of Acute VTE

Initial treatment of acute VTE with warfarin should be combined with an immediate-acting parenteral anticoagulant such as low molecular weight heparin (LMWH) **for at least 5 days and until the INR reaches at least 2.0 for 2 consecutive days**. Initial dosing is best guided by using standardized nomograms. Frequent monitoring is required until a stable, in-range INR is reached, after which time reduced frequency of testing is appropriate.

Special Considerations:

- The anticoagulant effect of warfarin can be reversed using vitamin K. For emergency reversal, intravenous vitamin K should be administered along with a four-factor prothrombin complex concentrate (Octaplex®, Beriplex®). In patients who do not require emergency reversal but have very

elevated INR results, oral vitamin K can be used [see Clinical Guide **Warfarin: Management of Out-of-Range INR**]. There is no role for subcutaneous vitamin K.

- Acenocoumarol (Sintrom©)is an alternate vitamin K antagonist that was used infrequently in Canada, for example in patients who had non-bleeding adverse effects on warfarin. Acenocoumarol is currently no longer available in Canada as it has been discontinued by the manufacturer but may be available in other countries.
- Warfarin and acenocoumarol cross the placenta, are potentially teratogenic, can cause fetal bleeding, and are associated with increased rates of spontaneous abortion. Their use is generally avoided in pregnancy, except in some women with high risk mechanical heart valves who are under the care of a thrombosis specialist and high risk obstetrical service.
- Warfarin is safe to use when breastfeeding.

Pediatrics:

- Warfarin can be used for the treatment and 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.

Other Relevant Thrombosis Canada Clinical Guides:

- Deep Vein Thrombosis (DVT): Treatment
- Mechanical and Bioprosthetic Heart Valves: Anticoagulant Therapy
- Pulmonary Embolism (PE): Treatment
- Stroke Prevention in Atrial Fibrillation
- Warfarin: Management of Out-of-Range INRs
- Warfarin: Peri-Operative Management
- Warfarin: Point-of-Care INR Monitoring

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