

## Guideline for the Laboratory Monitoring of Oral Anticoagulation (Warfarin)

CLP014

Revised September, 2008

Warfarin is the most commonly prescribed vitamin K antagonist in Canada. This Guideline is intended to assist clinicians in the management of patients for whom warfarin has been prescribed. Guidelines, however, cannot apply to every clinical situation, nor can they serve as a substitute for sound clinical judgment.

### 1. Background

Therapeutic monitoring of the anticoagulant effect of Vitamin K antagonists is performed by measuring the prothrombin time (PT). PT is the time, in seconds, taken for blood to clot when mixed with a fixed amount of thromboplastin and calcium. Results are now reported as the International Normalized Ratio (INR), which helps minimize inter-laboratory variation.

Warfarin and the other Vitamin K antagonists increase the INR by selectively inhibiting the synthesis of several vitamin K-dependent clotting factors (II, VII, IX and X). Warfarin also inhibits the synthesis of coagulation inhibitors (Proteins C and S). After warfarin therapy is initiated, or the dosage increased, the plasma concentration of these clotting factors decreased at variable rates, depending on their half lives. (Half-lives range from 6 hours for Factor VII to 72 hours for Factor II). The INR stabilizes when the concentration of these clotting factors reach their functional steady-states. Note that reductions in dosage are subject to this same time frame for restabilization.

### 2. Procurement of PT/INR Specimens in the Clinician's Office

Blood specimens for coagulation testing must be collected into light blue-top vacutainer tubes containing 3.2% sodium citrate as the anticoagulant. Other anticoagulants are not acceptable and will result in specimen rejection.<sup>1</sup>

The proportion of blood to sodium citrate solution is critical. Incomplete filling of the collection tube will lead to inaccurate results and/or specimen rejection.

Studies have shown that a discard tube is not necessary, unless a winged blood collection set (butterfly) is used for venipuncture. If a butterfly is used, a discard tube is required to ensure the maintenance of proper anticoagulant to blood ratio.<sup>1</sup>

In general, when multiple tubes are being drawn, the coagulation tube should be drawn before any others except a blood culture tube.<sup>2</sup> This will avoid the possibility of contamination by anticoagulants or clot activators, which may interfere with the INR. Follow the order of draw prescribed in your laboratory's specimen collection manual.

### 3. Source of Pre-Analytical Error

- **Inadequate mixing**  
Inadequate mixing of the specimen may lead to partial clotting in the tube and an inaccurate INR. Conversely, vigorous mixing should be avoided.<sup>3</sup>
- **Incorrect draw volume**  
Incomplete filling of the collection tube will lead to inaccurate results and/or specimen rejection.<sup>3</sup>

- **Traumatic or difficult draws**  
Traumatic or difficult venipuncture may result in partial clotting and/or hemolysis. Either will cause an inaccurate result. Samples with obvious hemolysis or detectable clotting will be rejected. For these reasons, when the venipuncture is traumatic, discard the collected tube and repeat venipuncture at another site.<sup>3</sup>
- **Syringe**  
If a syringe must be used, a small volume syringe (less than 20ml) is recommended, so that clotting does not take place in the syringe.<sup>1</sup>
- **Needle size**  
In general, 21 gauge or larger needles should be used because smaller gauges tend to increase turbulence and the potential for clots. Winged collection sets (butterflies) are not recommended because the longer path length to the anticoagulant may cause platelet activation. When a butterfly must be used, a discard tube is mandatory.

#### Vascular Access Devices

- **Heparin Lines**  
Collection of blood from a line previously flushed with heparin should be avoided. If the blood must be drawn through such a line, heparin contamination and specimen dilution can be avoided by flushing the line with at least 5ml of saline and discarding the first 5ml of blood or dead space volume.<sup>1</sup>
- **Air leaks**  
Blood specimens for coagulation testing generally should not be drawn from a vascular access device. If this is unavoidable, all components of the blood collecting system (collecting device - syringe, needle) should be checked to ensure compatibility to avoid air leaks that may cause hemolysis and incorrect draw volume.<sup>1</sup>

#### 4. Sample Integrity, Storage and Transportation

The allowable time interval between collection of the specimen and testing of the sample is 24 hrs when stored in an unopened tube and kept at 18-24°C.<sup>1</sup>

Collected samples should not be refrigerated. Cold activation of Factor VII may alter the INR result.<sup>1</sup>

Different analytical systems will inevitably yield slightly different INR results on the same specimen. It is therefore recommended that individual patients consistently use the same laboratory for their INR testing.

#### 5. Communication of Results by Laboratories

In order to facilitate appropriate clinical management, laboratories have the responsibility to communicate significantly elevated INR results to ordering clinicians in a timely manner. Clinicians have the responsibility to make arrangements to receive these results by providing laboratories with effective contact information that will allow the laboratory to deliver these results 24 hours a day when required. Two levels of elevation of the INR are defined in OAML Communique 020.

Level I (Critical) >6.0	Called by laboratories 24 hours per day, 7 days per week.
Level II (Alert) >4.5-6.0	Called by laboratories 08.00-20.00 hours, 7 days per week.

When clinically required, clinicians may request that INR results be treated as urgent by the laboratory, in which case the result will be called 24 hours per day independent of the INR value.

Delivery of results including elevated INRs during normal office hours is more likely if patients are encouraged to visit patient service centres early in the day. It is the experience of laboratories that communication of abnormal results is more difficult for laboratories as well as for clinicians when patients present for testing on Friday or on the weekend.

## 6. Initiation of Warfarin Therapy

In the treatment of venous thromboembolism and for patients with prosthetic cardiac valves, prompt anticoagulation is indicated and is generally initiated in hospital. Warfarin therapy is usually administered concurrently with or shortly after heparin (unfractionated or low molecular weight) in these conditions.

In outpatient situations where anticoagulation is not urgent, for example in the presence of chronic atrial fibrillation, warfarin is usually started as monotherapy, at the anticipated maintenance dose. Clinicians often prescribe initial doses in the range of 5 mg for most adult patients.<sup>4</sup> However, individuals who are rapid warfarin metabolizers or who are relatively resistant to warfarin, may require higher doses, often exceeding 10 mg. Conversely for patients who are elderly or malnourished, who are at high risk of bleeding, or who are taking multiple medications, initial doses in the range of 2 to 5 mg per day are usually prescribed.<sup>4</sup> The use of large loading doses of warfarin to achieve rapid anticoagulation is generally contraindicated because it increases the risk of bleeding or paradoxically, thrombosis (in the presence of protein C deficiency or heparin-induced thrombocytopenia) without reducing the time necessary to achieve a stable anticoagulant effect.

### Monitoring

Prior to initiation of therapy, samples should be drawn for INR, Activated Partial Thromboplastin Time (APTT) and a platelet count, to screen for underlying coagulation disorders and to establish baseline values. A second sample for INR should then be taken 2-3 days after the initiation of therapy. At this point a small change in INR is expected (0.1-0.3 units above baseline). Keep in mind that because of warfarin's long half life, there is a delay before the full effect of the ingested dose is seen. A rapidly rising INR, at initiation of therapy, indicates an overdose and dose reduction is mandatory. For most patients the anti-thrombotic effect is achieved over the next several days. Subsequent INRs should be performed two or three times a week and then weekly until stable.

## 7. Intensity of Therapy

For most indications, a therapeutic range for INR of 2.0-3.0 is recommended but there are exceptions.<sup>4</sup> Patients with metallic heart valves require a higher intensity of therapy, INR 2.5-3.5. However, patients with bileaflet or tilting disc-type valves in the aortic position can be managed with an INR of 2.0-3.0 as long as the patient is in normal sinus rhythm and has a normal left atrial size.<sup>5</sup> The optimal therapeutic range for patients with lupus anticoagulants is uncertain; higher intensity therapy has been recommended in the past, but more recent evidence suggests that this may not be necessary.<sup>6</sup>

## 8. Achieving the Therapeutic Range

Patients should be instructed to take warfarin at more or less the same time every day.<sup>4</sup> No specific time of day is optimal from a therapeutic standpoint; however, when warfarin is taken late in the evening or in the early morning, it is generally possible to prevent additional medication, if a value above the therapeutic range is reported by the laboratory.

## 9. Risk Factors for Major Bleeding in Patients on Warfarin

Certain patients receiving warfarin are at increased risk of bleeding, irrespective of their INR value and therefore require increased vigilance. The most consistently demonstrated predictor of major bleeding

while on warfarin is a previous history of clinically significant bleeding. Other risk factors include a history of stroke or the presence of a serious comorbid condition such as renal insufficiency, anaemia, or hypertension. For these patients, the risk/benefit of anticoagulation should be carefully considered. Age is not a contraindication to anticoagulation for patients who are otherwise suitable candidates.<sup>6</sup>

## 10. Factors which Influence PT/INR

Significant variations in INR results occur for a variety of reasons including drug interaction, diet, and disease state.

### Drugs and Herbal Preparation

- Prior to prescribing any new drug, interaction with warfarin should be considered. This includes over the counter drugs. Warfarin circulates bound to albumin in plasma, and other drugs which bind to albumin can displace warfarin increasing its therapeutic effect.<sup>7</sup> Conversely, removal of drugs which bind to albumin can decrease warfarin's therapeutic effect.
- Drugs which induce or are metabolized by the hepatic microsomal cytochrome P450 system will also alter the effect of warfarin, as the potent S-isomer of the drug is metabolized by this enzyme.<sup>7</sup>
- For patients taking warfarin or other vitamin K antagonists, the formulary should be consulted before starting the patient on a new drug or before changing the dose of any other drug

### Diet

- Since warfarin functions as a vitamin K antagonist, its clinical effect varies with the vitamin K content of the diet. Dietary vitamin K is largely derived from plant phyloquinones, and fluctuations in intake of green vegetables can alter the INR.
- Physicians should educate their patients about the impact of drugs, herbal preparation and diet on the therapeutic effect of warfarin, and to recognize the signs and symptoms of excessive anticoagulation. See the OAML's A Patient's Guide to Anticoagulant Therapy

When these pharmacodynamic or pharmacokinetic variables are considered together with warfarin's narrow therapeutic window, the need to increase the frequency of monitoring in anticipation of dose adjustment is clear.

## 11. Management of Patients with High INR Values and Minor or no Bleeding<sup>4,7</sup>

*The following is meant to serve as a general guideline only. Clinicians may choose to refer the patient to a specialist or consider referral of the patient to an acute care facility.*

The cause of all out of range INRs should be determined (e.g. change in diet, drugs, liver disorder or other illness).

Management Options for Over Anticoagulation: Therapy and Dose Adjustment		
Clinical Situation	Management Guideline	Recommended Frequency of INR Monitoring
No bleeding, INR <5.0	<ul style="list-style-type: none"> <li>• Lower or omit one dose</li> <li>• Resume therapy at 10-20% lower dose when INR reaches the patient's therapeutic range</li> </ul>	Increase frequency of INR monitoring to 2 to 3 times a week
No bleeding, INR 5.0-9.0	<ul style="list-style-type: none"> <li>• Omit one to two doses</li> <li>• Resume therapy at 10-20% lower dose when INR reaches the patient's therapeutic range</li> <li>• If the patient is at high risk of serious bleeding, consider administering 1 mg vitamin K<sub>1</sub> orally*</li> </ul>	Increase frequency of INR monitoring to daily

	<ul style="list-style-type: none"> <li>• A dose as low as 1 mg of vitamin K<sub>1</sub>* will avoid excessive shortening of the INR and subsequent prolonged warfarin resistance.</li> </ul>	
No bleeding, INR >9.0	<ul style="list-style-type: none"> <li>• Discontinue warfarin temporarily</li> <li>• Consider administering 3 to 5 mg vitamin K<sub>1</sub> orally *</li> <li>• Give additional vitamin K<sub>1</sub>* if INR is not substantially reduced by 24-48 hrs</li> <li>• Resume therapy at 20% lower dose when INR reaches the patient's therapeutic range</li> </ul> <p>or</p> <ul style="list-style-type: none"> <li>• Refer patient to an acute care facility</li> </ul>	Increase frequency of INR monitoring to daily and once the INR has stabilized consider more frequent routine INR monitoring.
Non trivial bleeding at any INR	<ul style="list-style-type: none"> <li>• Refer the patient to an acute care facility for assessment and management</li> </ul>	

*\*Please note that there is no oral vitamin K<sub>1</sub> formulation available in Canada, however; the appropriate dose can be given by using an intravenous solution, which is available in 10 mg ampoules. This solution can be given orally in lieu. Clinicians should consider keeping a supply of vitamin K<sub>1</sub> in their offices or refer patients to pharmacies that carry it.*

#### Cited References:

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## Acknowledgements

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### Warning & Disclaimer

This Guideline was prepared to assist clinicians who order tests from community laboratories. Users must ensure that their own practices comply with all specific legislative, government policies or accreditation requirements that apply to their organizations. The Guideline is not meant to be construed as legal advice or be all inclusive on this topic. Given the complexity of legal requirements, users are reminded that whenever there is uncertainty regarding whether some aspect of a Guideline is appropriate for their practice or organization further direction should be obtained from the Laboratory Director, their own professional association, college and/or legal counsel or appropriate government ministry.