



Warfarin Therapy Management

Effective Date: April 1, 2015

Scope

This guideline provides recommendations for the long-term management of warfarin therapy in patients aged ≥ 19 years in the primary care setting. The guideline describes: 1) warfarin initiation, 2) international normalized ratio (INR) monitoring with optimal ranges, and 3) warfarin dosage adjustment. This guideline assumes the physician has reviewed the indications for warfarin and the duration of therapy as these are not discussed in this guideline. Perioperative management of warfarin is covered in the [BCGuidelines.ca – Warfarin Therapy – Management During Invasive Procedures and Surgery](#).

This guideline is part of the [BCGuidelines.ca – Stroke and Atrial Fibrillation](#) series. The series includes three other guidelines: *Stroke and Transient Ischemic Attack – Acute and Long-Term Management*; *Atrial Fibrillation – Diagnosis and Management*; and *Use of Non-Vitamin K Antagonist Oral Anticoagulants (NOAC) in Non-Valvular Atrial Fibrillation*.

Key Recommendations

- Warfarin should be dosed to achieve the target therapeutic INR for the specific indication. Under- or over-anticoagulation is associated with high risks of thrombosis and bleeding.
- Consider using a standard dosing nomogram or computerized decision-support software to maximize the time in therapeutic range.
- Patients are advised to maintain a stable and consistent intake of vitamin K in their diet and **not** avoid vitamin K-containing foods.
- Patient and caregiver education is necessary to promote compliance and stability of warfarin anticoagulation.

Description

Warfarin therapy reduces the risk of thromboembolic events and has demonstrated effectiveness for the prevention of stroke in patients with atrial fibrillation (AF).¹⁻³ Approximately 44,000, or 6%, of British Columbians > 65 years live with AF.^{4,5} Studies have shown that warfarin therapy could reduce the risk of stroke in these patients by about 66%.³ 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^{1,6} because of the complex pharmacology and numerous drug, disease, dietary and herbal interactions.

Warfarin is given orally and is absorbed rapidly and completely.⁶⁻⁸ Absorption is not impacted by food. It is almost fully bound to albumin in blood; thus hypoalbuminemic patients (e.g., malnourished, liver disorders, post-operative, etc.) need lower doses. An effect on the INR generally occurs within 24 hours after drug administration. However, the full anticoagulant effect may be delayed for 5-7 days due to the long half-life of prothrombin.⁶

The major challenge in warfarin therapy is its narrow therapeutic range. Over-anticoagulation may lead to hemorrhage while under-anticoagulation can result in thrombosis. Bleeding is the most serious complication of warfarin therapy.⁹⁻¹² The average yearly bleeding rates vary widely depending on patient lifestyle, co-morbidities and the concomitant use of antiplatelet drugs. Estimated annual incidences are 0.6% for fatal bleeding, 3.0% for major bleeding, and 9.6% for minor bleeding.¹¹⁻¹²

A good warfarin management plan, including ongoing patient education, follow-up, dosing tools, and involved caregivers/ other health professionals, can maximize the benefit to harm ratio. The time in therapeutic range (TTR) is an accepted measure of the quality of warfarin dosing and INR control. It represents the proportion of treatment time that a patient’s INR is within the therapeutic range. Most experts agree that the optimal or acceptable TTR is 65% or higher.

Management

Warfarin management can be challenging. Dosing tools, ranging from paper-based nomograms to computerized decision-support software programs, are available and have been shown to improve the TTR (see *Resources* section). Patient and caregiver education is also essential to maximize compliance and maintain stability.

► Initiation of Warfarin Therapy

Prior to initiating warfarin treatment:

- 1) Consider the contraindications below in Table 1. All contraindications are relative to a patient’s risk for thrombosis weighed against the risk for bleeding (refer to Table 2 below) while on vitamin K antagonist anticoagulation therapy.¹³
- 2) Establish the baseline INR in every case and will guide further therapy.
- 3) Discuss with the patient potential drug and diet interactions, the need for monitoring and signs of over- and under anticoagulation. For more information, refer to the Patient Education and Resources section below.

Table 1. Warfarin contraindications*

Absolute Contraindications	Some Relative Contraindications
<ul style="list-style-type: none"> • The presence of a severe or active bleeding diathesis • Non-adherence to medication and INR monitoring • Pregnancy²⁸ (avoided at least during the first trimester and from about 2 to 4 weeks before delivery) • Allergy or intolerance to warfarin (consider warfarin alternative – Nicoumalone) 	<ul style="list-style-type: none"> • Uncontrolled hypertension (> 160/100 mm Hg) • Severe liver disease • Recent surgery and procedures involving the nervous system, spine or eye

Abbreviation: INR = international normalized ratio.

Footnote: *For a complete list of contraindications, refer to the product monograph.

Pregnancy: If possible, warfarin therapy should be avoided during pregnancy.²⁸ If warfarin therapy is essential, it should be avoided at least during the first trimester (because of teratogenicity) and from about 2 – 4 weeks before delivery to reduce risk of hemorrhagic complications. Unfractionated heparin or low molecular weight heparin could be substituted when appropriate because these agents do not cross the placenta and are considered the anticoagulant drugs of choice during pregnancy. Consider referral to hematologist and obstetrician.

Table 2. Risk factors for bleeding complications of anticoagulation therapy^{6,9,13}

Risk Factor Category	Specific Risk Factors
Age	> 70 years
Time Period	Within 3 months of warfarin treatment
Cardiac	Uncontrolled hypertension, heart failure
Gastrointestinal	History of gastrointestinal hemorrhage, active peptic ulcer, hepatic insufficiency
Hematologic/Oncologic	Thrombocytopenia, platelet dysfunction, coagulation defect, underlying malignancy
Neurologic	History of stroke, cognitive or psychological impairment
Renal	Renal insufficiency
Trauma	Recent trauma
Alcohol	Excessive alcohol intake
Medications	Use of aspirin or NSAIDs, discontinuing medications that reduce INR, See <i>Appendix A: Important Interactions with Warfarin</i>

Abbreviations: INR = international normalized ratio; NSAIDs = Nonsteroidal anti-inflammatory drugs.

Adapted from: Warfarin Reversal Position Statement, Australasian Society of Thrombosis & Hematosis.²⁷

► Initial Warfarin Dose

Initial dose of warfarin is typically 5 mg/day in most patients.^{14,15} A starting dose of < 5 mg may be considered for patients > 70 years of age, elevated baseline INR > 1.1, hypoalbuminemic patients (e.g., malnourished, liver disorders, post-operative), impaired nutrition (weight < 45 kg), heart failure, known to take medications that increase sensitivity of warfarin (*Appendix A: Important Interactions with Warfarin*), or previously documented increased sensitivity to warfarin.^{1,16}

Whenever feasible, a single strength warfarin tablet (highly recommend 1 mg only for safety and dose flexibility) should be prescribed such that doses are multiples of one tablet strength. Patients should take their warfarin once a day at the same time in the evening, 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.

Pharmacogenetics-based therapy has been suggested in the estimation of the therapeutic warfarin dose by genotyping patients for single nucleotide polymorphisms that affect warfarin metabolism or sensitivity. Although Health Canada has updated the label of warfarin to include information on pharmacogenetic testing, there is currently no evidence that genotyping will improve clinically relevant outcomes in **individual** patients.^{1,6,17,18}

► INR Target and Frequency of Monitoring

The optimal maintenance dose for warfarin varies from patient to patient and at different times in the same patient.^{6,19-21} There is no maximal or minimal dose to maintain a therapeutic range. The actual dose is not important and can range from 0.5 – 20 mg or higher daily. Asians tend to require lower doses while Blacks tend to use higher doses because of the differences in genetic polymorphisms in these populations.

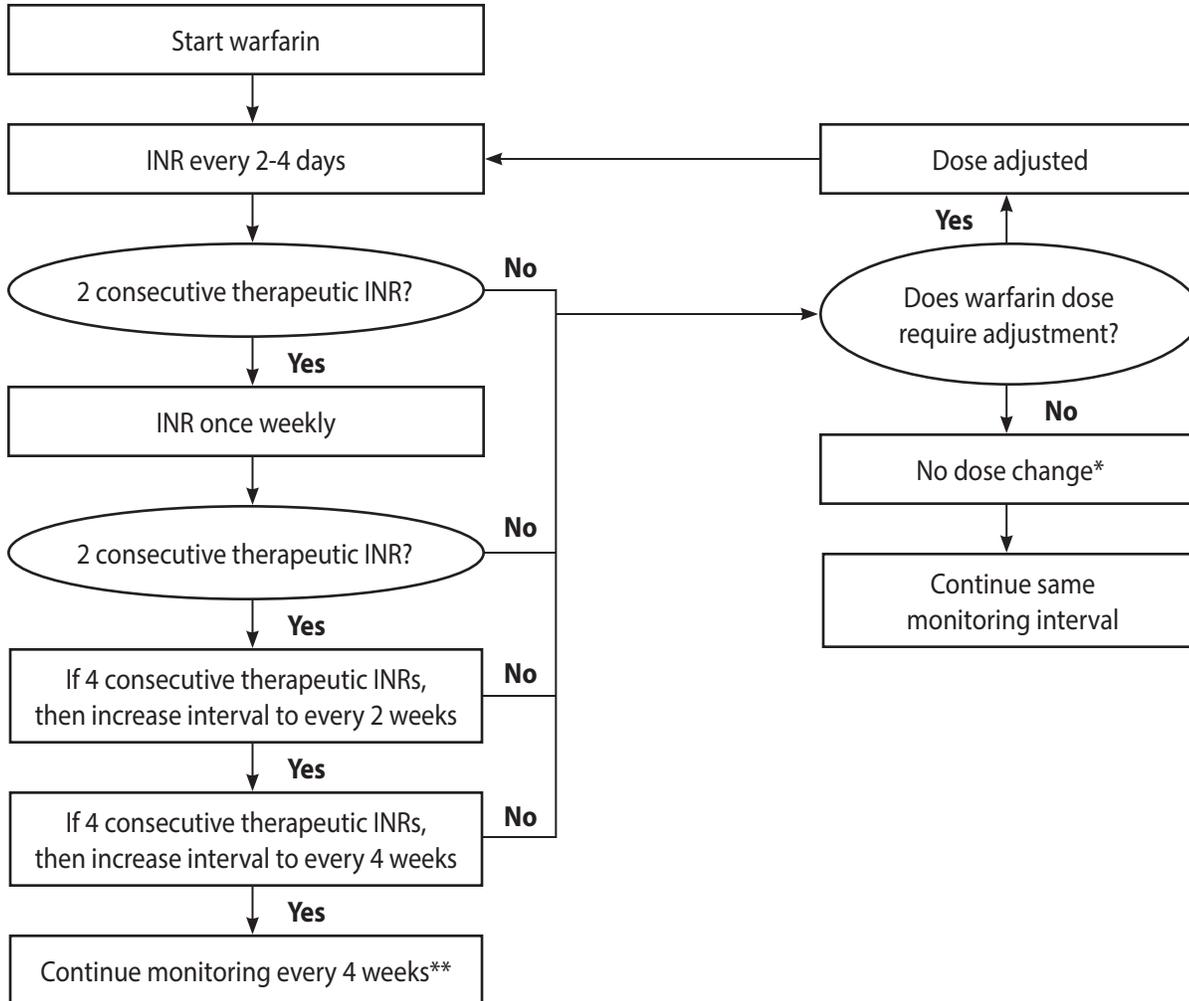
Two therapeutic ranges are recommended, depending on the indication for anticoagulation.

- Target INR is 2.5 with a range of 2.0 – 3.0 for most indications for warfarin therapy.^{6,19}
- Target INR is 3.0 with a range of 2.5 – 3.5 for the following indications:^{19,22}
 - Mechanical heart valves in mitral position
 - Non-bileaflet valve in aortic position (establish desired range with a specialist)

Under-anticoagulation can result in stroke, recurrent venous or arterial thrombosis, while 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. During the first few 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 are not recommended.**

During the induction or initiation phase, it is recommended that INR be monitored every 2 – 4 days (initially daily if on therapeutic heparin) until the INR is in the patient’s target range for two consecutive values. Once the INR is stabilized within the patient’s target range, it can be monitored weekly. The interval can be gradually increased up to every 4 weeks if the INR remains stable and within the therapeutic range. Monitoring frequency of up to 12 weeks can be considered in patients with stable and therapeutic INRs whose doses have been unchanged for at least 3 months.²³ For more information INR monitoring, refer to Figure 1 below.

Figure 1. Recommended Frequency of INR Monitoring



Abbreviation: INR = international normalized ratio.

Footnotes: Increase frequency of INR (every 2 – 4 days) if any of the following happens: non-therapeutic INR, intercurrent illness, any medication change (including herbal), significant diet change. * Some reasons for **not** changing the dose when the INR is not therapeutic:²⁵ 1) Patient noncompliant (forgot doses or took too many doses); 2) Inadequate number of days before previous dose change to take full effect; 3) Binge alcohol use (will transiently elevate INR).

**In a small group of very stable patients (stable INRs and no dosage change for 3 months), INR values can be monitored every 12 weeks.

► Dosage Adjustment and 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 prompt a direct communication with patient to determine cause. Consider causes such as a change in dosage of warfarin, patient adherence, medications including over-the-counter (OTCs), dietary changes, unusual alcohol consumption and intercurrent illness. For further dosage adjustment information, refer to Table 3 below.

The recent trend is to change the total weekly warfarin dose (TWD).¹⁵ For example, if the patient is taking 5 mg/day, the weekly dose is 35 mg. If the dose must be decreased by 10%, then the weekly dose should be 35 mg – 3.5 mg = 31.5 mg and the daily dose becomes 31.5 mg/7 = 4.5 mg.

Table 3. Dosage adjustments for patients on warfarin maintenance therapy (Target INR 2.0 – 3.0 or 2.5 or 3.5, No significant bleeding)

INR	Intervention – Refer to Figure 1 for timing of next INR
< 1.5	Give one time top-up equal to 20% of weekly dose and increase weekly dose by 10 – 20%.
1.5 < INR < therapeutic range	No change in dose. If two consecutive INRs are low, increase weekly dose by 10 – 20%.
INR in therapeutic range	No change.
INR > therapeutic range but < 5.0	Lower weekly dose (10 – 20%) or consider omitting one single dose. Increase the frequency of INR monitoring and resume therapy at 10 – 20% lower weekly dose when INR therapeutic. Note: If the INR is only minimally elevated (0.1 – 0.4 above upper limit of the therapeutic range), dose reduction may not be necessary. ²⁵
INR 5.0 – 9.0*	Omit 1-2 doses then recheck INR. Increase the frequency of INR monitoring and resume therapy at 10 – 20% lower weekly dose when INR therapeutic. If the patient is at high risk of serious bleeding, consider administering vitamin K** 1 – 2 mg orally.
> 9.0 no bleeding	Discontinue warfarin temporarily, consider administering vitamin K 2 – 5 mg orally then recheck INR.*** Increase the frequency of INR monitoring and resume therapy at 20% lower weekly dose when INR therapeutic. Give additional vitamin K if INR is not substantially reduced by 24 hours.***

Abbreviation: INR = international normalized ratio.

Footnotes: * Bleeding risk increases exponentially from INR 5 to 9²⁶ and should be monitored closely. ** If vitamin K is not available in your local pharmacy, it can be obtained from your local emergency department. Avoid intramuscular injections of vitamin K to prevent local injection site bleeding which also reduces bioavailability. *** The effect of a single dose of vitamin K on the INR can be expected between 8-24 hours.

► Bleeding Complications

The most common sites of serious bleeding are gastrointestinal tract, genitourinary tract, and soft tissues including wounds.¹⁰

An underlying cause should always be sought, especially if the INR is within the therapeutic range or lower.

If patient's clinical status is compromised due to bleeding, admit to an acute care facility for assessment and management.

Bleeding with a high potential for complications (e.g., elderly, propensity to fall) requires clinical judgement to determine whether to manage within the office setting or to send to an acute care facility. The patient should be followed using the *Associated Document: Warfarin Patient Record Sheet* (or a similar log sheet) and encouraged to keep their own record.

If patient is to undergo an invasive procedure or surgery, refer to BCGuidelines.ca – *Warfarin Therapy – Management During Invasive Procedures and Surgery*.

► Use of Vitamin K

If required, oral vitamin K therapy is a safe, effective and convenient treatment for over-anticoagulation.^{29,30} Subcutaneous vitamin K should be avoided as it may be absorbed unpredictably. Likewise, intramuscular vitamin K should be avoided as it promotes intramuscular haemorrhage. Intravenous vitamin K is the most predictable³⁰ but can cause facial flushing, diaphoresis, chest pain, hypotension, dyspnea, and, rarely, anaphylaxis, and should be given only in emergency situations and by slow infusion.

Some effect of oral vitamin K therapy on INR is usually observed within 24 hours and with intravenous vitamin K in 6-8 hours.^{29,30} Patients who have received vitamin K, particularly parenteral doses above 5-10 mg, may be difficult to reanticoagulate. Accordingly, doses of vitamin K should be kept as low as feasible. An oral formulation of vitamin K is no longer available in Canada; most pharmacies administer oral doses of the parenteral preparation in juice or water. Oral vitamin K therapy may not be appropriate for patients with disorders that may affect the absorption of vitamin K such as biliary obstruction, liver insufficiency or other malabsorptive syndromes.

If emergency reversal of warfarin is required for life and limb threatening haemorrhage, plasma or prothrombin complex concentrate (Octaplex[®]) may be used in consultation with a specialist. For further information on the use of vitamin K in the perioperative period, see [BCGuidelines.ca – Warfarin Therapy – Management During Invasive Procedures and Surgery](#).

► Alternatives to Warfarin

Nicoumalone (Sintrom[®]) is a vitamin K antagonist available for patients allergic to warfarin. Several new orally administered alternatives to warfarin are approved for use in Canada for thromboprophylaxis during joint replacement or for stroke prevention in atrial fibrillation or treatment of thrombosis. The use of non-Vitamin K antagonist oral anticoagulants (NOAC; formally known as novel oral anticoagulant) in the prevention of stroke and systemic embolism in patients, aged ≥ 19 years, with non-valvular atrial fibrillation is discussed within the [BCGuidelines.ca – Use of Non-Vitamin K Antagonist Oral Anticoagulants \(NOAC\) in Non-Valvular Atrial Fibrillation](#).

► 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. For patient resources, refer to the Resources section below.

The effect of warfarin may be inhibited by very high dietary or supplemental vitamin K intake. However, it is **not** necessary to advise patients to avoid or limit vitamin K intake. It is generally recommended that patients on warfarin try to consume the adequate intake for vitamin K (90-120 mg),³¹ while avoiding large fluctuations in vitamin K intake that might interfere with the adjustment of their anticoagulant dose.

At the initiation of warfarin therapy, it is recommended to discuss the following with the patient and/or other care providers:

- The reason for prescribing warfarin and duration of treatment.
- The need to adhere with recommended warfarin dosage.
- The importance of monitoring and the patient's target INR.
- The need to take warfarin once a day → Recommend a routine of taking warfarin at the same time in the evening, and test INR in the morning, along with the use of a daily pill box to assist with improving compliance with warfarin therapy.
- Side effects, signs of bleeding and potential need for blood products → Set-up an agreed upon system of communication when side effects or changes occur.
- When to call the doctor or seek urgent attention at an emergency facility → Encourage wearing a MedicAlert[®] bracelet or necklace to assist with care in an emergency.
- The need for caution when initiating or stopping other medications (including ASA), herbs or supplements → Review of current medications (prescription and non-prescription), herbal supplements and diet for potential interactions.
- The importance of consistent vitamin K content in the diet.
- The need to avoid heavy or variable alcohol consumption.
- Influence of intercurrent illness.
- The importance of avoiding pregnancy while taking warfarin (if applicable).
- The importance of not changing brands of warfarin.
- The need to avoid intramuscular injections → For flu shots, recommend that a firm, prolonged pressure is applied for several minutes after a deltoid injection.

► References

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► Resources

- Thrombosis Canada, thrombosiscanada.ca, for patient information and dosing tools (paper-based nomograms and computerized decision-support software programs).
- Coumadin, www.coumadin.com, for patient information.
- HealthLink BC, www.healthlinkbc.ca, for more information on warfarin and vitamin K.

► Appendices

- Appendix A: Important Interactions with Warfarin

► Associated Documents

The following documents accompany this guideline:

- BCGuidelines.ca – *Warfarin Therapy – Management During Invasive Procedures and Surgery*
- BCGuidelines.ca – *Stroke and Transient Ischemic Attack – Acute and Long-Term Management*
- BCGuidelines.ca – *Atrial Fibrillation – Diagnosis and Management*
- BCGuidelines.ca – *Use of Non-Vitamin K Antagonist Oral Anticoagulants (NOAC) in Non-Valvular Atrial Fibrillation*
- Warfarin Patient Record Sheet

This guideline is based on scientific evidence current as of the Effective Date.

This guideline was developed by the Guidelines and Protocols Advisory Committee, approved by the British Columbia Medical Association, and adopted by the Medical Services Commission.

THE GUIDELINES AND PROTOCOLS ADVISORY COMMITTEE

The principles of the Guidelines and Protocols Advisory Committee are to:

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

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Appendix A: Important Interactions with Warfarin (Medications, Foods, Herbs and Supplements)

- Starting, changing or stopping any drug, herbal product, or supplement can potentially affect the activity of warfarin. Monitoring frequency should be increased.
- The following list includes only commonly used agents and only those with more than two case reports of clinically significant interaction and/or serious adverse effect. For a complete listing refer to the drug monograph.
- For further information on food interactions with warfarin, refer to HealthLink BC (website: www.healthlinkbc.ca).

Examples of Medications		
Increased bleeding risk due to increased effect of warfarin: ↑ INR		Decreased effect warfarin: ↓ INR
Analgesics <ul style="list-style-type: none"> Acetaminophen¹ aspirin (high dose) salicylates, topical tramadol Antiarrhythmics <ul style="list-style-type: none"> amiodarone propafenone Antibiotics <ul style="list-style-type: none"> amoxicillin cephalosporins (some) isoniazid fluoroquinolones² macrolides³ metronidazole sulfonamides telithromycin tetracyclines⁴ 	Anticonvulsants <ul style="list-style-type: none"> phenytoin (early on) sodium valproate Antidepressants <ul style="list-style-type: none"> duloxetine venlafaxine SSRI <ul style="list-style-type: none"> fluoxetine fluvoxamine paroxetine sertraline citalopram Antifungals <ul style="list-style-type: none"> fluconazole itraconazole ketoconazole miconazole (oral, vaginal) voriconazole 	Antihyperlipidemics <ul style="list-style-type: none"> ezetimibe fenofibrate fluvastatin gemfibrozil rosuvastatin Other <ul style="list-style-type: none"> allopurinol cimetidine corticosteroids (oral) proton pump inhibitors (PPI) – isolated case reports with all PPIs thyroid supplements
Antibiotics <ul style="list-style-type: none"> rifampin Antidepressants <ul style="list-style-type: none"> trazodone Antiepileptics <ul style="list-style-type: none"> carbamazepine phenobarbitone primidone phenytoin (later on) Other <ul style="list-style-type: none"> antithyroid agents cholestyramine 		
Increased bleeding risk due to non-warfarin mechanisms		
Analgesics <ul style="list-style-type: none"> aspirin Cox II Inhibitors Nonsteroidal anti-inflammatory drugs 	Anticoagulants/Antiplatelet agents Antidepressants <ul style="list-style-type: none"> selective serotonin reuptake inhibitors 	
Foods, Herbs and Supplements		
Increased bleeding risk due to increased effect of warfarin: ↑ INR		Decreased effect warfarin: ↓ INR
Alcohol (binges) ⁵ Birch Chitosan Cranberry juice/extract (dose dependent)	Danshen Dong Quai Fish oil Garlic supplements ⁶	Glucosamine±chondroitin Grapefruit Mango Papaya extract
Increased bleeding risk due to non-warfarin mechanisms Alcohol (heavy drinkers) Garlic supplements ⁶		Alcohol (chronic) ⁵ Coenzyme Q10 Ginseng (American, Asian) Smoking St. John's Wort Vitamin C (high dose) Vitamin K

Footnotes:

- Randomized controlled trials suggest 2-4 g acetaminophen daily has a clinically significant effect on INR [Parra, 2007; Mahe, 2006]
- Fluoroquinolones e.g., ciprofloxacin, Levofloxacin, moxifloxacin.
- Macrolides include azithromycin, erythromycin, and clarithromycin.
- Tetracyclines including tetracycline and doxycycline.
- Consuming small or moderate amounts of alcohol in patients with normal liver function is unlikely to have an effect.
- Consuming foods with small amounts of garlic is unlikely to have an effect.