### WARFARIN

**THERAPEUTICS**

**Brands**
- Coumadin, Jantoven, Carfin, Marevan, Panwarfin, Warx

**Generic?**
- Yes

**Class**
- Anticoagulant

**Commonly Prescribed for** *(FDA approved in bold)*
- Prophylaxis or treatment of thromboembolic complications associated with atrial fibrillation or cardiac valve replacement, and to prevent embolism after myocardial infarction (MI)
- Venous thrombosis/pulmonary embolism

**How the Drug Works**
- Interferes with the synthesis of vitamin K-dependent clotting factors II, VII, IX, and X and anticoagulant proteins C and S. This decreases risk of thromboembolism

**How Long Until It Works**
- Anticoagulant effect is delayed for up to 7 days. Heparin is preferred for rapid anticoagulation

**If It Works**
- Continue to use with appropriate monitoring

**If It Doesn’t Work**
- Patients can still have stroke despite treatment. Warfarin is only superior to antiplatelet agents for cardiogenic stroke, i.e., related to atrial fibrillation or ventricular thrombus
- Control all stroke risk factors, such as smoking, hyperlipidemia, and hypertension
- For acute events, admit patients for treatment and diagnostic testing. Check international normalized ratio (INR) to determine drug effectiveness

**Best Augmenting Combos for Partial Response or Treatment-Resistance**
- The combination of aspirin and warfarin in patients with mechanical heart valves appears beneficial despite increased risk of bleeding. Aspirin combined with warfarin did not appear to reduce risk of stroke, systemic embolism, or myocardial infarction in patients with atrial fibrillation in the SPORTIF trials

**Tests**
- Monitor prothrombin time (PT) and INR to determine effectiveness

**ADVERSE EFFECTS (AEs)**

**How Drug Causes AEs**
- Anticoagulation increases bleeding risk

**Notable AEs**
- Abdominal pain/cramping, elevated liver enzymes/jaundice, hypotension, weakness, paresthesias, diarrhea, nausea, pruritus and alopecia

**Life-Threatening or Dangerous AEs**
- Bleeding complications, especially with elevated INRs. Hemorrhage in organs or tissues can cause death
- Necrosis associated with local thrombosis can occur within days of starting treatment
- Patients with venous thrombosis and heparin-induced thrombocytopenia have a risk of limb ischemia, necrosis, and gangrene when stopping heparin and starting warfarin
- May increase risk of cholesterol plaque emboli, typically 3–10 weeks after starting therapy
- “Purple toes syndrome” is a dark, mottled, often purple discoloration on the sides and plantar surface of toes; may be reversible or may lead to necrosis or gangrene

**Weight Gain**
- Unusual

**Sedation**
- Unusual
WARFARIN (continued)

What to Do About AEs
• Stop or lower dose or give vitamin K based on INR and presence of bleeding. For systemic atheroemboli/microemboli, stop drug

Best Augmenting Agents for AEs
• Most AEs cannot be improved by an augmenting agent

DOSING AND USE

Usual Dosage Range
• 2–10 mg daily

Dosage Forms
• Tablets: 1, 2, 2.5, 3, 4, 5, 6, 7.5 and 10 mg
• Injection: 5.4 mg (2 mg/mL)

How to Dose
Give once daily, usually starting at 2 to 5 mg/day. Start at lower dose in patients with genetic variations in CYP2C9 or VKORC1 enzymes, the elderly or debilitated and those with potentially greater than expected PT/INR response to warfarin. Adjust dose based on PT/INR determinations. Loading doses of warfarin do not offer more protection against thrombi formation and may increase bleeding risk

Intravenous warfarin dosing is the same as oral. Use in patients without the ability to take oral drugs
• Goal INR is 2–3 for most conditions, including acute MI, atrial fibrillation, pulmonary embolism, venous thrombosis, valvular heart disease, and tissue heart valves
• Goal INR is 2.5–3.5 for patients with mechanical heart valves and for prevention of recurrent MI
• Continue heparin therapy for 4–5 days after starting warfarin until the desired therapeutic response has been reached based on INR. Then stop heparin. Patients with supratherapeutic INR:
  • < 5: lower or omit a dose
  • ≥ 5 but < 9: if no significant bleeding, omit next few doses, increase monitoring frequency and resume warfarin at a lower dose once INR is therapeutic. When there is significant bleeding, omit dose and give ≤ 5 mg of vitamin K. If there is still significant bleeding and INR has not normalized, give an additional 1–4 mg vitamin K
  • ≥ 9: If no significant bleeding, hold warfarin and give 5–10 mg vitamin K orally
    • For any serious or life-threatening bleeding, hold warfarin, give vitamin K 10 mg intravenously, and supplement with plasma or prothrombin complex concentrate

Dosing Tips
• Food decreases rate of absorption. If a dose is missed, do not double the next dose
• Asian patients may also require lower initiation and maintenance doses

Overdose
• Bleeding complications, such as blood in stools or urine, excessive menstrual bleeding, petechiae, or oozing from superficial injuries. Check INR and treat by holding warfarin therapy and giving vitamin K if indicated

Long-Term Use
• Safe for long-term use

Habit Forming
• No

How to Stop
• No need to taper, but patients will be at increased risk of thromboembolic complications soon after

Pharmacokinetics
• Extensive metabolism by CYP450 isoenzymes into inactive metabolites, which are excreted in urine and bile. Half-life ranges from 20–60 hours (mean 40). Drug 99% protein bound

Drug Interactions
• Increased anticoagulant effect due to inhibition of hepatic metabolism: proton pump inhibitors, statins, allopurinol, azole antifungals, quinidine, quinine, sulfonamides
• Increased anticoagulant effect due to reduced clearance: macrolide antibiotics (azithromycin, erythromycin)
• Increased anticoagulant effect due to displacement from binding sites: loop diuretics (furosemide), valproate, nalidixic acid
Increased anticoagulant effect due to interference with vitamin K: aminoglycosides, tetracyclines, vitamin E
Increased anticoagulant effect due to effects on platelet function or GI irritant effects: NSAIDs, penicillins, salicylates, difunisal
Increased anticoagulant effect due to unclear reasons: SSRIs, cox-2 inhibitors, cephalosporins, beta-blockers, heparin, isonazid, influenza vaccine, quinolines (ciprofloxacin), ropinirrole, tamoxifen, thyroid hormones, tramadol, zafirlukast, methylphenidate
Decreased anticoagulant effect due to hepatic induction: barbiturates, nafcillin, carbamazepine, rifamycins
Decreased anticoagulant effect due to decreased absorption or increased elimination: spironolactone, thiazide diuretics, azathioprine
Decreased anticoagulant effect due to unclear reasons: clozapine, haloperidol, estrogens, griseofulvin, protease inhibitors, trazodone, ribavirin, isoretinoin, cyclopentamine, chlordiazepoxide, oral contraceptives
May increase or decrease anticoagulant effect: alcohol, corticosteroids, phenytoin, pravastatin, chloral hydrate, ranitidine, propylthiouracil
Many herbal medications can reportedly increase (ginkgo, dong quai, garlic, among others) or decrease (coenzyme q10 and St. John’s wort) the effect of warfarin
Vitamin-K-rich vegetables such as broccoli, spinach, seaweed, and turnips decrease warfarin effects

Other Warnings/Precautions
Use warfarin with great caution in patients at risk for trauma, infections of intestinal flora, indwelling catheters, known or suspected protein C or S deficiency, moderate-severe renal insufficiency, exposed raw surfaces, or severe hypertension

Do Not Use
Hypersensitivity to the drug; pregnancy; recent or impending surgery or procedure such as lumbar puncture or lumbar anesthesia; bleeding tendencies with active ulceration or overt bleeding of GI, GU or respiratory tracts; malignant hypertension; eclampsia or preeclampsia; aortic dissection; cerebral aneurysm; bacterial endocarditis; CNS hemorrhage; and unsupervised patients with senility, substance abuse, or psychosis

SPECIAL POPULATIONS

Renal Impairment
Patients with renal dysfunction are more likely to experience bleeding complications, perhaps due to increase in the unbound fraction of the drug. Use with caution

Hepatic Impairment
Use with much caution. Patients with moderate-severe disease have an increased risk of bleeding complications due to decreased metabolism and decreased synthesis of clotting factors

Cardiac Impairment
No known effects

Elderly
Lower initiation and maintenance doses needed

Children and Adolescents
Not well-studied in children but appears effective for prevention of thromboembolic complications. May require more frequent monitoring

Pregnancy
Category X. Associated with multiple serious birth malformations, including CNS and spontaneous abortions. Do not use. Heparin is preferred in pregnant patients who require anticoagulation

Breast Feeding
Not detected in limited studies in breast milk, but may increase bleeding time. Monitor bleeding time closely and perform coagulation tests in infants at risk
Warfarin (continued)

**The Art of Neuropharmacology**

**Potential Advantages**
- Drug of choice for ischemic stroke in patients with mechanical heart valves, cardiac thrombus, or atrial fibrillation

**Potential Disadvantages**
- Not as useful for non-cardiac ischemic stroke. Serious bleeding risks and drug interactions require frequent monitoring

**Primary Target Symptoms**
- Prevention of the neurological complications that result from ischemic stroke

**Pearls**
- There is no evidence to suggest that warfarin is superior to antiplatelet medications for secondary stroke prevention unless there is a clear cardiac source (i.e., atrial fibrillation or cardiac thrombus). It is also not superior for preventing stroke due to patent foramen ovale

- The WARSS trial compared warfarin to aspirin for the prevention of ischemic stroke. Warfarin was not more effective than aspirin, but the use of lower goal INR (1.4–2.8) could have affected results
- The WASID trial compared warfarin to high-dose aspirin for the secondary prevention of stroke due to intracranial stenosis. Warfarin was associated with greater AEs but not improved efficacy
- Goal INR may be increased in patients with recurrent embolism (to 3 or 3.5) despite therapeutic INR, but INR of 4 or greater does not appear more effective and is associated with more bleeding AEs
- Multiple drug interactions due mostly to hepatic metabolism, often unpredictable, require frequent monitoring with the addition or change of any medication — even those only for short-term use (e.g., antibiotics)
- CYP2C9 and VKORC1 genotypes may help predict dose variability, but routine testing before starting warfarin is not recommended

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**Suggested Reading**


