WARFARIN DOSING GUIDELINE

SUMMARY
Warfarin (Coumadin®) is a Vitamin K antagonist used to treat a number of hypercoagulable disease states. Since each patient responds differently to the same dose, frequent monitoring and individual dose adjustment is required. The American College of Chest Physicians (ACCP), American Heart Association (AHA), and the American College of Cardiology (ACC) have developed evidence-based medicine guidelines for the dosing and monitoring of warfarin.

RECOMMENDATIONS

- **Level 1**
  - **Warfarin doses should be adjusted to achieve the target INR based on indication (Tables 1 & 2)**
  - **Loading doses of warfarin (i.e. 10 mg) should not be used**
- **Level 2**
  - **All patients should have a baseline INR**
  - **Newly initiated warfarin (or re-initiation) should have daily PT/INR checks, beginning 2-3 days into therapy, until stable**
- **Level 3**
  - **Patients with significant drug interactions or risk factors (Tables 2 & 3) should be initiated on a lower dose of warfarin**
  - **Patients with significant drug interactions (e.g. amiodarone, fluconazole, antimicrobial agents, etc) should have daily PT/INR checks until stable (Tables 3 & 4)**

INTRODUCTION

The use of Vitamin K antagonists (e.g. warfarin) has been well described in the literature for the treatment of a number of different hypercoagulable states (Table 1). The ACCP, AHA, and the ACC all collaborated on the development of detailed recommendations for dosing warfarin and target international normalized ratio (INR). These recommendations are summarized in the tables below.

Warfarin Dosing

Warfarin should be dosed to achieve the desired target INR based on indication (1,2). Patients with significant drug interactions should be initiated at a lower dose (1). There is no evidence to support "loading doses" of warfarin as this has been demonstrated to lead to supratherapeutic INRs and an increased risk of bleeding (4).

EVIDENCE DEFINITIONS

- **Class I:** Prospective randomized controlled trial.
- **Class II:** Prospective clinical study or retrospective analysis of reliable data. Includes observational, cohort, prevalence, or case control studies.
- **Class III:** Retrospective study. Includes database or registry reviews, large series of case reports, expert opinion.
- **Technology assessment:** A technology study which does not lend itself to classification in the above-mentioned format. Devices are evaluated in terms of their accuracy, reliability, therapeutic potential, or cost effectiveness.

LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

Approved 10/17/2006
Revised 08/31/2009

Monitoring
Patients should have a baseline PT/INR checked prior to initiating warfarin therapy (1,2). For patients with no risk factors (liver disease, poor nutritional status, renal failure, significant drug-drug interactions, etc…), a PT/INR should be re-checked 2-3 days after initiating therapy and then every 2-3 days until stable (1). For patient with significant drug interactions (see Tables 3 & 4) or risk factors, INR should be checked daily until stable (1,2,4). The full effect of a dose of warfarin may not be seen until 72 hours after the dose (4).

TABLE 1: Goal Therapeutic INR Ranges

Indication	Target INR	Range	Duration of Therapy
DVT Prophylaxis after hip or knee arthroplasty or hip fracture surgery	2.5	2-3	10 days Up to 35 days post-surgery for hip arthroplasty/fracture
Treatment of VTE (DVT/PE)	2.5	2-3	3 months – lifetime
Atrial Fibrillation	2.5	2-3	Variable
Myocardial Infarction • Low and high risk (with aspirin) • Low and high risk (without aspirin) • High risk, large anterior MI (with aspirin<100mg/day)	 2.5 3.5 2.5	 2-3 3-4 2-3	 4 years 4 years 3 months
Antiphospholipid Syndrome • No other risk factors, no lack of response (i.e. patient is not experiencing recurrent VTE) • Recurrent thromboembolic events with therapeutic INR or additional risk factors[1]	 2.5 3	 2-3 2.5-3.5	 Lifetime
Valvular Heart Disease	2.5	2-3	Lifetime
Aortic Valve Replacement (AVR) and/or Mitral Valve Replacement (MVR)			
Bioprosthetic (tissue) Valve • Aortic Valve (AVR) • Mitral Valve (MVR)	2.5	2-3	3 months
Mechanical Prosthetic Valve • **Mitral Valve (MVR)** – all mitral valves with or without risk factors for thromboembolism[1] • **Aortic Valve (AVR)** o First generation aortic valve (i.e. caged ball or caged disk) o Modern aortic valve in a patient with normal left atrium and in sinus rhythm o Modern aortic valve with atrial fibrillation or other risk factor(s) for thromboembolism[1] ▪ St. Jude medical bileaflet ▪ Carbomedics bileaflet ▪ Medtronic Hall tilting disk	 3 3 2.5 3	 2.5-3.5 2.5-3.5 2-3 2.5-3.5	 Lifetime

[1]**Thromboembolism Risk Factors:**
- Atrial fibrillation
- Left atrium enlargement
- Low left-ventricular ejection fraction
- Age < 70
- Prior thromboembolism
- Hypercoagulable state

Approved 10/17/2006
Revised 08/31/2009

TABLE 2: Recommendations for the Initiation and Maintenance of Warfarin (Coumadin) Therapy

Initiation of Warfarin (Coumadin®) 5mg Nomogram		
Day	**INR**	**Dosage**
1		5 mg**
2 or 3	< 1.5 1.5-1.9 2-2.5 > 2.5	5 mg 2.5 mg 1-2.5 mg 0 mg
4	< 1.5 1.5-1.9 2-2.5 2.5-3 > 3	5-10 mg 2.5-5 mg 0-2.5 mg 0-2.5 mg 0 mg
5	< 1.5 1.5-1.9 2-3 > 3	10 mg 5-7.5 mg 0-5 mg 0 mg
6	< 1.5 1.5-1.9 2-3 > 3	7.5-12.5 mg 5-10 mg 0-7.5 mg 0 mg

Maintenance of Warfarin (Coumadin®) Based on a therapeutic INR 2-3	
INR	**Weekly dose change**
< 1.1	Consider reinitiation
1.1-2	Consider increasing weekly dose by 10-20%
2-3	Maintain same dose
3-3.9	Consider decreasing weekly dose by 10-20%
> 4	Consider holding a dose and decreasing weekly dose by 20%

****Points to Remember in Initiating Therapy**

- Check INR at least 4 times during the first week of therapy
- User lower initial dose (2.5-5 mg) if Age > 75, Weight < 60 kg, interacting medication known to potentiate warfarin, hepatic dysfunction, severe heart failure, renal dysfunction, hypoproteinemia, impaired nutritional intake, and increase in baseline INR (INR > 1.4)
- Use higher initial dose (5-10mg) if: younger patients, interacting medications known to diminish warfarin effects, enteral nutrition, and a diet rich in Vitamin K.

Points to Remember in Maintenance Therapy

- If patient is on outpatient warfarin therapy, use the home dosage as a guide when continuing warfarin therapy in the hospital.
- Monitor INR for medication administration changes in interacting drugs, liver function changes, cardiac function changes, and changes in diet.
- Once on therapy for > 1 week, dose modifications between 5 to 20% are recommended. Larger changes, such as changing the weekly dose by one third can overcorrect an abnormally high or low INR. Recheck an INR within 4-6 days after adjustment for abnormal INR.

TABLE 3: Drugs that Lead to a *SIGNIFICANT INCREASE* in INR

- Amiodarone
- Antineoplastics:
  - Capecitabine
  - Fluorouracil
  - Imatinib
- Azole antifungals:
  - Fluconazole
  - Itraconazole
  - Ketoconazole
  - Voriconazole
- Metronidazole
- Trimethoprim/Sulfamethoxazole (Bactrim®, Septra®)

TABLE 4: Drugs That May *INCREASE/DECREASE* the INR

Drugs that may *INCREASE* the INR	Drugs that may *DECREASE* the INR

• Antineoplastics:
  o Etoposide
  o Gemcitabine
  o Ifofamide
• Celecoxib
• Disulfram
• Doxycycline
• Fibric acid:
  o Fenofibrate (Tricor®, Lofibra®)
  o Gemfibrozil (Lopid®)
• Fluoroquinolones:
  o Ciprofloxacin
  o Levofloxacin (non-formulary)
  o Moxifloxacin
• Isoniazid (≥ 600 mg/day)
• Macrolides:
  o Azithromycin
  o Clarithromycin
  o Erythromycin
• Phenytoin – biphasic effect, may initially ↑ INR
• Propafenone
• Saquinavir
• Simvastatin
• Tetracycline
	• Aprepitant
	• Carbamazepine
	• Cholestyramine
	• Cyclosporine
	• Nafcillin
	• Nevirapine
	• Phenobarbital
	• Phenytoin – biphasic, chronic use may ↓ INR
	• Rifamycin derivatives:
	  o Rifabutin
	  o Rifampin
	  o Rifaximin (non-formulary)
	• Ritonovir (Norvir®, Kaletra®)
	• Sucralafate

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