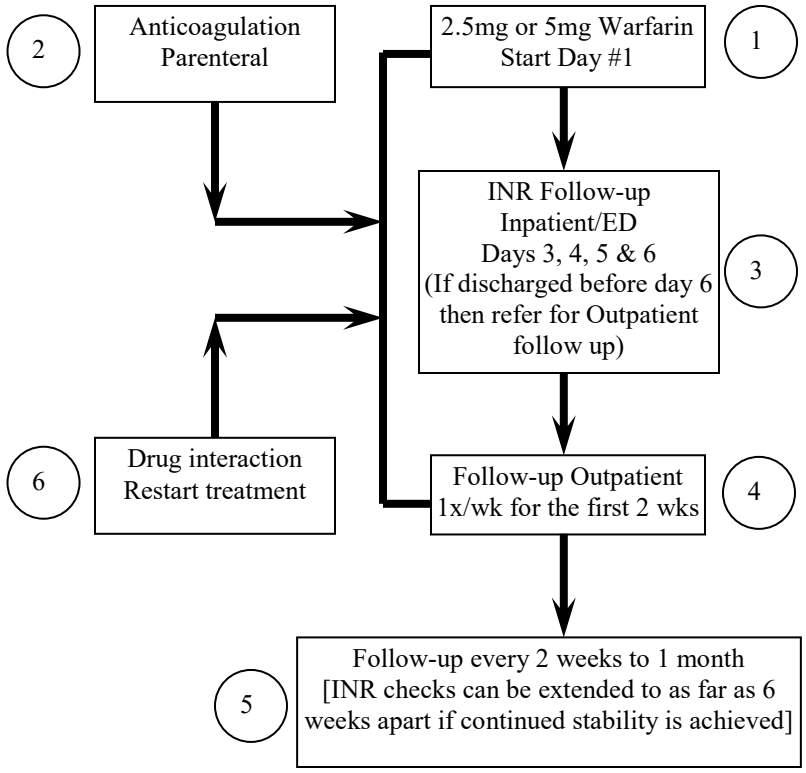
Warfarin Initiation and Management Guideline for Adults

Topic **Page Number**

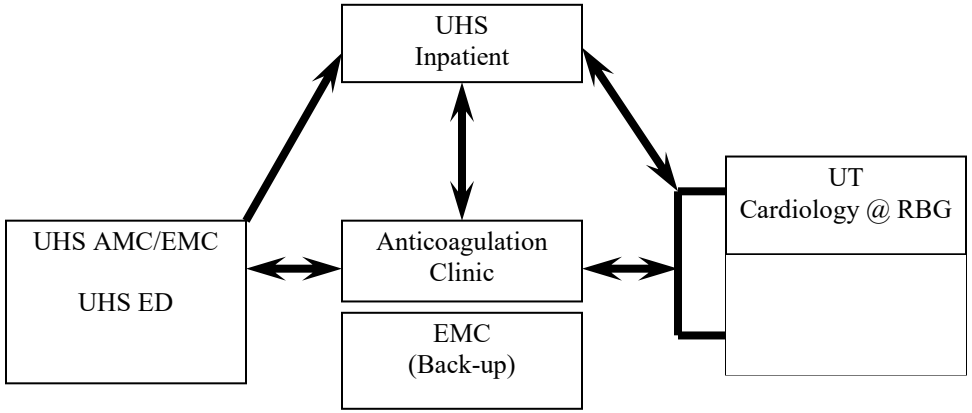
…

Hypercoagulable Disorders	Stroke Prevention in Atrial Fibrillation	Deep Vein Thrombosis (DVT)	Pulmonary Embolism (PE)	Heart Valve Replacements/Repair	Others*

MEDICATION FLOW



PATIENT FLOW



*Examples include: Left Ventricular Thrombus, Splenic Infarct, Portal/Mesenteric Vein Thrombus, etc.

UHS=University Health System, UMA=University Medicine Associates, AMC=Ambulatory Connections Clinic, ED=Emergency Department, EMC=Express Med Clinic, RBG=Robert B. Green Campus, UT=University of Texas

❖ **Patient Flow** (See page 2)
- Warfarin therapy can be initiated from any locations, i.e. Emergency Center, Inpatient Care, Express Med Clinic or other clinics.
- Adult patients started on warfarin therapy may be followed by the RBG Anticoagulation Clinic or other permanent medical homes (i.e. PCP, UMA clinics, specialty clinics, etc.).
- **Consults** for Anticoagulation follow up can be placed using the EMR consult order or by calling the clinic directly. Access Plus reviews consults for patients discharging from hospital and schedules appointments at the RBG Anticoagulation Clinic, AMC or the patient's PCP if followed outside of the health system.
- Contact numbers for available INR monitoring sites:
  - RBG Anticoagulation Clinic – 210-358-3296 or 210-358-6518
  - SE Clinic – 210-358-5538
  - SW Clinic – 210-358-5171 or 210-358-5107/5121
  - North Clinic – 210-358-0837
  - Access Plus – 210-358-5952

❖ **Medication Flow** (See page 2)
- Warfarin 2.5mg or 5mg will be initiated on day #1 along with a parenteral anticoagulant if bridging is indicated
  - For treatment of acute DVT or PE, and for patients with Afib and heart valve replacements deemed to be at high thromboembolic risk, overlap (bridge) with a parenteral agent for at least 5 days AND until 2 consecutive therapeutic INRs are achieved (24 hours apart).
  - For information on parenteral anticoagulant dosing, see Table 6
  - For more information on bridging, see the Perioperative Management of Patients on Oral Anticoagulants guideline posted to the UHS Clinical Pathways and Guidelines page under "Anticoagulation" (https://www.universityhealthsystem.com/services/pharmacy/clinical-pathways-guidelines)

❖ **INR Monitoring**
- INR target range will be determined based on indication(s) (see Table 1)
- Warfarin therapy will be adjusted according to Initiation and Maintenance Dose Nomograms (see Tables 2-4)
- INRs will be checked at baseline and:
  - Inpatient/EC: on days #3, #4, #5 and #6 and at least twice weekly thereafter while hospitalized
  - Outpatient: at least every 2-4 days until within target range, then once per week for 2 weeks
    - Duration between visits may then be prolonged by 1 additional week if INR is within target range.
    - If warfarin therapy is stable (multiple consecutive therapeutic INR levels), the duration between visits may be extended to a maximum of 6 weeks.
    - Note: Point-of-care INR cannot be used for patients with INR ≥ 4.5, Hematocrit < 30, patients on parenteral anticoagulation, patients with lupus anticoagulant or anti-phospholipid antibodies - venous blood draw is required.

❖ **Drug Interactions** (See Table 5)

- If a prescribed medication has a *known* interaction with warfarin, the patient should be followed up within 3-7 days, then weekly until after the interacting medication course is completed and/or INR level is stable in therapeutic range.
- If a prescribed medication has *minimal or no known* interaction with warfarin, the patient should be counseled to monitor for signs and symptoms of increased bleeding and follow-up as indicated above.

Table 1: Target INR and Duration of Therapy

Indication	Target INR	Therapy Duration	Evidence
DVT or PE			
First episode, provoked	2.0 – 3.0	3 months	B
[Oral contraceptive, pregnancy, surgery or hospitalization in past 3 months, trauma, central venous lines, prolonged travel]			
First episode, unprovoked	2.0 – 3.0	At least 3 months but extended therapy is preferred if no contraindications and low-moderate bleeding risk	B
Recurrent DVT	2.0 – 3.0	Indefinitely	B
Cancer associated DVT or PE			
(Consider LMWHs or DOACs over warfarin)		At least 6 months, may continue beyond 6 months in patients with active	
Warfarin	2.0 – 3.0	cancer and/or metastasis or on chemotherapy	
Atrial Fibrillation	2.0 – 3.0	Indefinitely	
Anticoagulation after cardioversion		At least 4 weeks after cardioversion (For subsequent therapy refer to CHA2DS2-VASc Score on Afib Treatment Algorithm)	
Valve Replacement			
Bio-prosthetic valves: Warfarin, ASA	2.0 – 3.0	First 3-6 months if low bleeding risk, followed by indefinite ASA 81mg daily	B
Mechanical valve: Aortic – Warfarin + ASA	2.0 – 3.0	Indefinitely + ASA 81mg daily	B
	2.5 – 3.5	Consider higher INR goal if high risk (Afib, previous thromboembolism, hypercoagulable state, LV dysfunction) or caged ball valve AND low bleed risk	B
On-X Aortic Valve – Warfarin + ASA	1.5 - 2.0	Reasonable to target lower goal (1.5-2.0) after first 3 months of higher goal (2.0-3.0)	B
Mechanical valve: Mitral (includes On-X valve) – Warfarin + ASA	2.5 – 3.5	Indefinitely + ASA 81mg daily	B
Transcatheter aortic valve replacement (TAVR)			
ASA 75 mg–100 mg daily		Indefinitely	
Clopidogrel 75 mg daily		First 3–6 months	
Consider warfarin if at risk of AF or VTE	2.0-3.0		
Valve Repair			
Aortic valve: ASA 81mg daily			
Mitral valve: Warfarin; then ASA	2.0 - 3.0	First 3 months, then ASA 81 mg daily	B

Table 2

5mg Warfarin Initiation Nomogram *		
Day	**INR**	**Warfarin Dose (mg)**
Day 1		5mg
Day 2		5mg
Day 3	< 1.5	10mg
	1.5-1.9	5mg
	2.0-3.0	2.5mg
	>3.0	0
Day 4	< 1.5	10mg
	1.5-1.9	7.5mg
	2.0-3.0	5mg
	>3.0	0
Day 5	< 2.0	10mg
	2.0-3.0	5mg
	>3.0	0
Day 6	< 1.5	12.5mg
	1.5-1.9	10mg
	2.0-3.0	7.5mg
	>3.0	0
*Adapted from Crowther et al. (INR = international normalized ratio)		

Table 3

2.5mg Warfarin Initiation Nomogram		
Day of Therapy	**INR**	**Warfarin Dose (mg)**
Day 1	2.5mg (if elderly, malnourished, liver disease, high bleeding risk, CHF exacerbation or interacting drugs) 5mg (should result in INR within 4-5 days)	
Day 2	< 1.5	5mg
	1.5-1.9	2.5mg
	2.0-2.5	1-2.5mg
	>2.5	Omit dose
Day 3	< 1.5	5-7.5mg
	1.5-1.9	2.5-5mg
	2.0-3.0	0-2.5mg
	>3.0	Omit dose
Day 4	< 1.5	10mg
	1.5-1.9	5-7.5mg
	2.0-3.0	0-5mg
	>3.0	Omit dose
Day 5	< 1.5	10mg
	1.5-1.9	7.5-10mg
	2.0-3.0	0-5mg
	>3.0	Omit dose
Day 6	< 1.5	7.5mg-12.5mg
	1.5-1.9	5-10mg
	2.0-3.0	0-7.5mg
	>3.0	Omit dose

Table 4: Maintenance Dose Adjustment Algorithms (Based on Total Weekly Dose)

For Target INR = 2.0-3.0, no bleeding						
INR	**< 1.5**	**1.5-1.9**	**2.0-3.0**	**3.1-3.9**	**4.0-4.9**	**>5.0**
Adjustment	Increase dose 10-20%, consider extra dose	Increase dose 5-10% †	No change	Decrease dose 5-10% †	Hold 0-1 day Decrease dose 10%	**See table 7**
Next INR	4-8 days (within 1 week if inpatient)	7-14 days (within 1 week if inpatient)	No. of consecutive in-range INR x 1wk (max 6 wks) ‡	7-14 days (next day if inpatient)	4-8 days (next day if inpatient)	**See table 7**
For Target INR = 2.5-3.5, no bleeding						
INR	**< 1.5**	**1.5-2.4**	**2.5-3.5**	**3.6-4.5**	**4.5-6.0**	**>6.0**
Adjustment	Increase dose 10-20%, consider extra dose	Increase dose 5-10% §	No change	Decrease dose 5-10% §	Hold 0-1 day Decrease dose 10%	**See table 7**
Next INR	4-8 days (within 1 week if inpatient)	7-14 days (within 1 week if inpatient)	No. of consecutive in-range INR x 1wk (max 6 wks) ‡	7-14 days (next day if inpatient)	4-8 days (next day if inpatient)	**See table 7**

If INR increases by 0.8-1.0 within a 24-hour time period, consider holding dose or reducing dose by half that day, with a follow up INR the next day
† If INR is 1.7-1.9 or 3.1-3.3, consider no change with repeat INR next day if inpatient or in 7-14 days if outpatient
‡ For example, if a patient has had 4 consecutive in-range INR values, re-check in 4 weeks
§ If INR is 2.3-2.4 or 3.6-3.7, consider no change with repeat INR next day if inpatient or in 7-14 days if outpatient

Table 5: Warfarin Interactions: Drug, Herb and Food

Warfarin (Coumadin) Interactions: Drug, Herbs and Food		
Increase warfarin potency and/or bleeding risk		**Decrease warfarin potency**
Acetaminophen Alcohol (if concomitant liver disease Amiodarone Amoxicillin Anabolic steroids Antiplatelet agents such as: • Aspirin • Clopidogrel (Plavix) • Prasugrel (Effient) • Ticagrelor (Brillinta) Cephalosporins Cimetadine (Tagamet) Ciprofloxacin (Cipro) Disulfiram Doxycycline Erythromycin Fluconazole (Diflucan) Influenza vaccine Isoniazid (Nydrazid) Itraconazole (Sporanox) LevofloxacinLovastatin (Mevacor) Metronidazole (Flagyl) Miconazole (Monistat) Nonsteroidal anti-inflammatory drugs Norfloxacin (Noroxin)	Ofloxacin (Floxin) Omeprazole (Prilosec) Phenytoin (Dilantin) Propafenone Propranolol (Inderal) Quinidine Salicylates SSRIs Tamoxifen Tetracycline Thyroxine Tramadol Trimethoprim/sulfamethoxazole (Bactrim, Septra) **Herbal Products** Danshen Devil's claw Dong quai Garlic Ginkgo Papain Vitamin E	Azathioprine (Imuran) Barbiturates Carbamazepine (Tegretol) Cholestyramine (Questran) Cyclosporine (Sandimmune) Dicloxacillin Griseofulvin Nafcillin Rifampin Sucralfate Trazodone **Foods** -Enteral feeds with high vitamin K content -Foods with high vitamin K content such as avocados, broccoli, brussel sprouts, cabbage, collard greens, raw endive, kale, bib leaf and red leaf lettuce, mayonnaise, mustard greens, parsley, spinach, raw swiss chard, raw turnip greens, watercress -Green tea **Herbal Products** Coenzyme Q10 Ginseng St. John's wort
This table is not comprehensive, please see a drug reference such as Micromedex for a complete list		

Table 6: Parenteral Anticoagulant Dosing

	Parenteral Anticoagualtion	
	Lovenox (Enoxaparin)	**Arixtra (Fondaparinux)**
Prophylactic	30mg SQ BID 40mg SQ QD CrCl < 30mL/min – 30mg SQ QD	2.5mg SQ QD CrCl < 30mL/min – contraindicated
Treatment	1mg/kg SQ BID 1.5mg/kg SQ QD CrCl < 30mL/min – 1mg/kg SQ QD	<50kg – 5mg SQ QD 50-100kg – 7.5mg SQ QD >100kg – 10mg SQ QD CrCl < 30mL/min – contraindicated

Table 7: Management of Significantly Elevated INR with or without Bleeding
(See "Reversal of Anticoagulants and Management of Bleeding Guideline" for more information)

INR 4.5-9.0, no significant bleeding – omit 1-2 doses, reduce dose 10-20%, monitor frequently
INR > 9.0, no significant bleeding – hold warfarin therapy, give vitamin K 2.5-10mg orally, monitor daily until INR therapeutic, resume at lower dose
Serious bleeding, any INR – hold warfarin therapy, give vitamin K 10mg slow IV plus PCC, repeat vitamin K every 12-24 hours as needed
Life threatening bleeding, any INR – hold warfarin, give PCC plus vitamin K 10mg slow IV, repeat vitamin K every 12-24 hours as needed

*PCC = Prothrombin Complex Concentration (Kcentra®)

References:

1) Guyatt GH, Akl EA, Crowther M, et al. Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141(2):48S-119S.
2) Harrison L, Johnston M, Massicotee MP, et al. Comparison of 5 mg and 10 mg Loading Doses on Initiation of Warfarin Therapy. Ann Intern Med. 1997;126:133-136.
3) Crowther MA, Harrison L, Hirsh. Reply:Warfarin: Less May be Better. Ann Intern Med. 1997:127:333.
4) Ebell MH. Evidence-based adjustment of warfarin (Coumadin) doses. Am Fam Physician. 2005;71:1979-8.
5) Kearon C, Akl EA, Ornelas J, et al. Antithrombotic Therapy for VTE Disease: CHEST guideline and Expert Panel Report. CHEST 2016;149(2):315-352.
6) Streiff MB, Agnelli G, Connors JM, et al. Guidance for the treatment of deep vein thrombosis and pulmonary embolism. J Thromb Thrombolysis,2016;41:32-67.
7) Lip GYH, Banerjee A, Boriani G, et al. Antithrombotic Therapy for Atrial Fibrillation: CHEST Guideline and Expert Panel Report. CHEST. 2018;154(5):1121-1201.
8) January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation: A report of the American College of Cardiology/American Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Circulation. 2019;140:e125-e151.
9) Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease.
10) Khorana AA, Noble S, Lee AYY, et al. Role of direct oral anticoagulants in the treatment of cancer-associated venous thromboembolism: guidance from the SCC of the ISTH. J Thromb Haemost 2018;16:1891-4.
11) Key NS, Khorana AA, Kuderer NM, et al. Venous thromboembolism prophylaxis and treatment in patients with cancer: ASCO Clinical Practice Guideline Update. J Clin Oncol 2019;38:496-520.

Developed by: Dr. Liem Du, 10/2007
Revised by: Crystal Franco-Martinez, Pharm.D., and Kevin Zhao, PharmD 01/2020
Approved by: Anticoagulation Safety Committee, 2008, 2009, 2011, 2012, 2015, 2016, 2020
Approved by P&T: 10/2007, 08/2008, 11/2009, 04/2011, 05/2012, 01/2015, 10/2016, 06/2020