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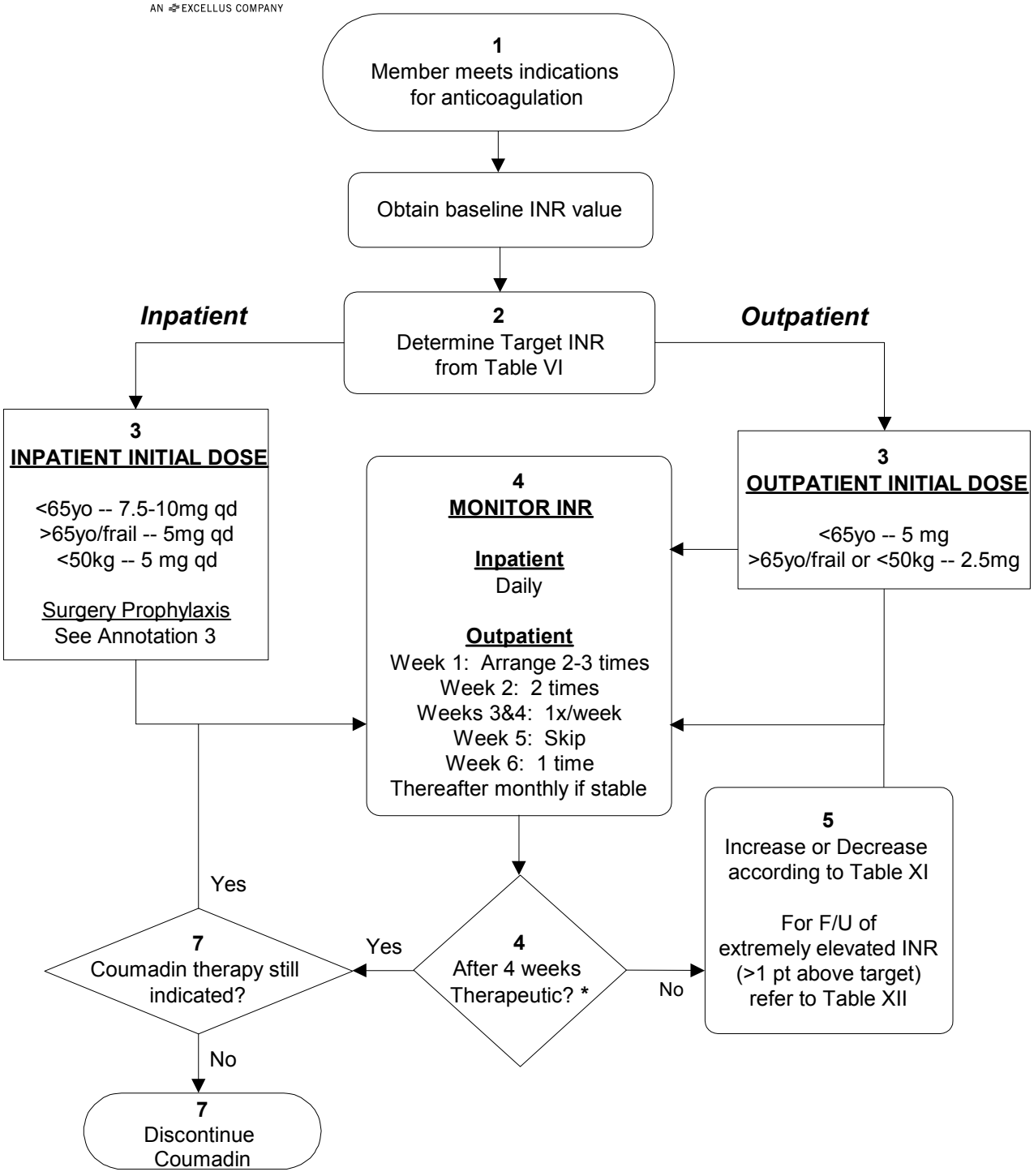
Clinical Guideline: ORAL ANTICOAGULATION THERAPY



*** For Week 1-3, individualize using clinical judgment**

This clinical guideline is designed to assist clinicians by providing an analytical framework for the evaluation and treatment of members and is not intended to either replace a clinician's judgement or to establish a protocol for all patients with a particular condition. A guideline will rarely establish the only approach to a problem.

INTRODUCTION

The use of oral anticoagulation is growing as scientific evidence mounts regarding the benefits in additional medical conditions. To minimize risks of bleeding and maximize therapeutic benefit, a systematic approach is essential. This guideline has been developed to assist practitioners in obtaining optimal therapy and avoiding adverse drug reactions.

ANNOTATIONS

1. INDICATIONS FOR ORAL ANTICOAGULATION

The Fifth Consensus Conference on Antithrombotic Therapy (October, 1999) revised guidelines for the safe and effective use of Antithrombotic agents. Major areas addressed in these recommendations include:

a. Mechanical Valves

Warfarin therapeutic range for prevention of thromboembolism associated with mechanical valve prostheses had been high intensity (INR 3.0 - 4.5). Evidence now suggests that an INR goal of 3 (Range 2.5-3.5) is as effective with significantly lower risk of bleeding. The one exception to this is listed below.

TABLE I – MECHANICAL PROSTHETIC HEART VALVES

PATIENT CHARACTERISTICS	RECOMMENDATION
Bileaflet mechanical valve in the aortic position, left atrium of normal size, NSR, normal ejection fraction	Goal INR 2.5; range 2 to 3
Tilting disk valve or bileaflet mechanical valve in the mitral position	Goal INR 3, range 2.5 to 3.5*
Bileaflet mechanical aortic valve and AF	Goal INR 3; range 2.5 to 3.5*
Caged ball or caged disk valves	Goal INR 3; range 2.5 to 3.5; and aspirin therapy (80 to 100 mg/d)
Additional risk factors	Goal INR 3; range 2.5 to 3.5; and aspirin therapy (81 mg/d)
Systemic embolism, despite adequate therapy with oral anticoagulants	Goal INR 3; range 2.5 to 3.5; and aspirin therapy (81 mg/d)
** Alternative: goal INR 2.5; range 2 to 3; and aspirin therapy (80 to 100 mg/d)*	

b. Thromboembolism (DVT and PE)

Low intensity anticoagulation (Goal INR 2.5, range 2-3) is recommended in all situations. Initial treatment and prevention of recurrence should be for three to six months. Chronic therapy is recommended for recurrence and when there is continued presence of risk factors, [e.g., Antithrombin III or protein C or S deficiency, malignancy or hereditary resistance to Activated Protein C (APC)].

TABLE II - DURATION OF TREATMENT IN VENOUS THROMBOEMBOLIC DISEASE*	
PATIENT CHARACTERISTICS	LENGTH OF TREATMENT
Most patients	Heparin or LMWH and warfarin can be started together; heparin or LMWH can be discontinued on day 5 or 6, if the INR has been in therapeutic range for 2 consecutive days; continue warfarin for 3 to 6 months
Massive PE or severe iliofemoral thrombosis	Consider a longer period of heparin therapy
Reversible or time-limited risk factors† and a first event	Treat 3 to 6 months
Heterozygous APC resistance and a first event	Treat 3 to 6 months
First episode of idiopathic DVT	Treat at least 6 months
Recurrent venous thrombosis, or first event with a continuing risk factor (cancer, inhibitor deficiency states, antiphospholipid antibody syndrome)	Treat indefinitely
APC resistance (Factor V Leiden)	Probably treat indefinitely, if patients have recurrent disease, are homozygous for the gene, or have multiple thrombophilic conditions
Patients with symptomatic isolated calf vein thrombosis	Treat with anticoagulants for at least 3 months; if anticoagulation cannot be given, perform serial noninvasive studies of the lower extremity to assess for proximal extension of thrombus over the next 7 to 14 days.
* Subject to modification according to patient's age, comorbidity factors, likelihood of recurrence. † Transient immobilization, trauma, surgical procedure, estrogen use. APC = activated protein C	

c. Hereditary Thrombophilias

Hereditary and acquired thrombophilias are common causes of venous thromboembolism. Widely available laboratory assays demonstrate that up to 25% of patients with the first deep venous thrombosis and as many as 60% of patients with recurrent venous thrombosis have one or more coagulation defects. The identification of patients wit hypercoaguable states are important because such knowledge may alter the duration or intensity of treatment, encourage aggressive prophylaxis before high risk events such as surgery and may allow early identification of other family members with the disorder. Screening may include testing for protein C and S deficiencies, hereditary resistance to activated protein C (Leiden mutation), antithrombin III deficiency, antiphospholipid antibodies, and hyperhomocysteinemia. In general, these tests should be performed prior to the initiation of anticoagulant therapy with coumadin or several weeks after coumadin has been discontinued. Antithrombin III testing cannot be done if a patient is actively being treated with heparin. The latter information has important implications for anticoagulation initiated in the emergency room.

The table below summarizes the incidence of thromboembolism associated with various hypercoagulable states.

TABLE III FREQUENCY OF HEREDITARY THROMBOPHILIA IN PATIENTS WITH THROMBOEMBOLISM		
DEFICIENCY	1ST EVENT	RECURRENT EVENTS
Antithrombin III	0.7%	2-3%
Protein C	2.3%	7%
Protein S	2.0%	5-10%
Hereditary APC resistance	21%	52-64%

d. Nonvalvular Atrial Fibrillation

Low intensity goal 2.5 (INR 2-3) is recommended for patients with nonvalvular atrial fibrillation. All cases should be anticoagulated except patients <65 years of age without major risk factors. Low intensity is also recommended for three weeks before and four weeks after cardioversion of atrial fibrillation with onset of greater than 48 hours. Atrial fibrillation in patients <65 years of age without major risk factors (such as previous TIA, stroke, systemic embolization, poor LV function, recent CHF or HTN) should be treated with ASA. Patients 65-75 years of age with atrial fibrillation and no major risk factors, can be treated with ASA or warfarin, but there is no consensus on drug choice. The greater efficacy of oral anticoagulation, compared with ASA, must be balanced against greater risk of bleeding. Treat patients >75 years of age with warfarin. For patients with other risk factors such as diabetes, CAD or thyrotoxicosis, the greater efficacy of coumadin compared to ASA should be balanced against a greater risk of bleeding.

e. Post MI and Left Ventricular Dysfunction

Consider anticoagulation for all patients after acute MI. If indicated, patients should receive up to three months of warfarin. Aspirin should be withheld until warfarin is completed but begun promptly at end of warfarin therapy to avoid hypercoaguable state. For patients with high risk of thromboembolism and those with significant left ventricular dysfunction, long term warfarin therapy should be considered. INR Goal 3 (2.5–3.5). If ASA is contraindicated, consider clopidogrel or warfarin.

f. Embolism Occurring While Anticoagulated

It is recommended that if recurrent systemic embolizations occurs despite adequate warfarin therapy, the addition of aspirin (80 to 100mg/d) be considered. For those patients unable to take aspirin, alternative strategies may include the addition of dipyridamole, 400mg/d or ticlopidine, 250 mg bid or clopidogrel, 75mg/d.

g. Atherothrombotic Cerebral Ischemic Events

Every patient who has had an atherothrombotic (noncardioembolic) stroke or TIA should receive an antiplatelet agent regularly, unless contraindicated, to reduce the risk of recurrent stroke and other vascular events. Aspirin (50 to 325mg/d) is recommended for initial therapy. Other options include clopidogrel (75mg qd), ticlopidine (250mg bid), and aspirin with dipyridamole.
Inadequate data are available regarding the efficacy and safety of oral anticoagulant therapy for prevention of atherothrombotic cerebral ischemic events. At an INR of 3 or higher, the risk of brain hemorrhage outweighs any potential benefit for stroke prevention.

h. Antithrombotic Therapy Post-Angioplasty

- Coronary Angioplasty

Long term treatment with aspirin (160-325 mg/d) is recommended as secondary prevention against cardiovascular events. There is no convincing evidence that long-term aspirin influences the rate of restenosis after coronary angioplasty. For patients who cannot tolerate aspirin, treatment with ticlopidine, 250 mg bid, is reasonable.

TABLE IV – RECOMMENDATIONS FOR THERAPY IN CORONARY ANGIOPLASTY	
GOAL	RECOMMENDATION
Reduce incidence of early complications	Aspirin (80–325 mg), at least 2 h before angioplasty; or ticlopidine (250 mg bid), ideally at least 24 h before elective angioplasty; or clopidogrel (75 mg/d)
Reduce incidence of cardiovascular events (secondary prevention)	Long-term treatment with aspirin (160–325 mg/d)
Reduce incidence of ischemic complications (especially in patients with unstable angina or other factors associated with high risk)	Consider GP IIb-IIIa receptor inhibition using abciximab, eptifibatide, or tirofiban
Reduce incidence of ischemic complications in patients undergoing primary angioplasty for AMI	Consider use of abciximab
** Dipyridamole should not be used routinely.*	

- Stent Implantation

See recommendations below.

TABLE V – THERAPEUTIC GUIDELINES IN STENT IMPLANTATION	
DRUG	RECOMMENDATION
Aspirin	Administer (80–325 mg) at least 2 h before stent placement; continue therapy (160–325 mg/d) for secondary prevention of cardiovascular events
Dipyridamole	No longer recommended
Dextran-40	Should not be used
Heparin	Administer during stent deployment in doses similar to those used during conventional coronary angioplasty (see above)
Ticlopidine	Administer (250–500 mg/d) for at least 14 days; consider 30 days in patients at high risk for stent thrombosis
Warfarin	No longer recommended, unless there are other indication for its use
LMWH	May be a useful adjunct in patients at high risk for stent thrombosis
GP IIb-IIIa inhibitors	Should be considered

i. Angina/CAD

Unstable Angina:	Aspirin, 160-325 mg/d. If aspirin intolerant consider ticlopidine, clopidogrel. It should be continued indefinitely.
Stable Angina/CAD:	Aspirin 160-325 mg/d indefinitely.
Primary Prevention:	Individuals age <50 with no history of AMI, stroke, or transient ischemic attack (TIA): routine use of aspirin is not recommended. Persons age >50 with at least one major risk factor for CAD: consider aspirin therapy (80–325 mg/d) Men at high risk of cardiovascular events: low-intensity warfarin (INR 1.5) is an alternative to aspirin. Men at very high risk: consider low-dose aspirin (75–80 mg/d) with low-intensity warfarin (INR 1.5).
Status Post CABG:	Saphenous Vein Graft - Aspirin 325 mg/d. Consider ticlopidine or clopidogrel if ASA allergic. Internal Mammary Artery – ASA 160–325 long term

** see table next page **

2. OPTIMAL THERAPEUTIC RANGE FOR ORAL ANTICOAGULANTS

TABLE VI

INDICATION	DETAILS	TARGET INR 2.5 (RANGE 2–3)	TARGET INR 3 (RANGE 2.5–3.5)	DURATION OF THERAPY
Atrial Fib/Flutter	In valvular/nonvalvular heart disease	X		Chronic
	Atrial fibrillation if age >75	X		Chronic
	Atrial fibrillation with major risk factors <75	X		
	Pre-cardioversion (for AFib >48 hours)	X		3 weeks
	Post-cardioversion	X		4 weeks
Cardioembolic Ischemic Event		X		Chronic
Left Ventricular Dysfunction	Transient LV dysfunction following myocardial infarction	2.0–3.0 plus ASA 160 mg qd	OR 2.5–3.5 without daily ASA	3 months
Myocardial Infarction	Following acute MI		X	3 months then ASA 160-25 mg/d
	Following Acute MI with AFib	X		Chronic
	Following acute MI with thromboembolic risk(s) (CHF, LV dysfunction, mural thrombus, history of thromboembolism)		X	3 months then ASA 160-25 mg/d
Thrombo-embolism (DVT, PE)	Following MI with continued risk factor(s) (CHF, LV dysfunction, mural thrombus)	X		3 months
	Treatment/prevention of recurrence	X		Chronic
	Recurrence despite anticoagulation	X Inferior vena cava filter placement is recommended		Chronic
	Continued presence of risk factor(s) (AT-III, protein C, or protein S deficiency; malignancy)	X		Chronic

TABLE VII				
VALVULAR DISEASE				
INDICATION	DETAILS	TARGET INR 2.5 (RANGE 2–3)	TARGET INR 3 (RANGE 2.5–3.5)	DURATION OF THERAPY
Aortic Valve Disease	With concurrent mitral valve disease	X		Chronic
	With associated atrial fibrillation	X		Chronic
	Systemic embolization			
Mitral Annular Calcification	With history of systemic embolization	X		Chronic
	With associated AFib	X		Chronic
Mitral Valve Prolapse	With history of systemic embolization	X		Chronic
	With associated AFib	X		Chronic
	With history of TIA despite ASA treatment (initial Rx of TIA in pt with MVP is ASA)	X		Chronic
Rheumatic Mitral Valve Disease	Status post embolic event despite anticoagulation	X Plus ASA 80–100 mg qd or, if ASA contraindicated, dipyridamole 400 mg/qd or ticlopidine 250 mg bid or clopidogrel		Chronic
	Left atrial diameter >5.5cm; NSR	Consider long term anticoagulation Goal 1NR 2.5 (Range 2–3) Base decision on risk factors for thromboembolism		
	With associated AFib	X		Chronic
	With history of systemic embolization	X		Chronic
Artificial Valve Prosthesis	Mechanical valve prosthesis		X	Chronic
	Mechanical valve following systemic embolization		2.5–3.5 (chronic) plus consider ASA 80–100 mg qd	Chronic
	Tissue valve prosthesis	X		3 months
	Tissue valve with history of systemic embolization	X		3 – 12 months
	With atrial fibrillation	X		Chronic
	With enlarged left atrium	X		Chronic
	Permanent Pacemaker	X but optional		Chronic
	NSR	ASA 162 mg/d		Chronic

3. TREATMENT

SCREENING FOR RISKS

- Patients Requiring Anticoagulation Who Are NOT Candidates for warfarin Therapy

  In pregnancy, severe short bowel syndrome, warfarin should not be used. Therapy with adjusted dose subcutaneous heparin can be substituted.

- Age

  The average daily warfarin maintenance dose steadily decreases with age, when controlled for gender, weight, history of CHF, history of alcohol abuse, duration of therapy, total number of medical problems, drugs prescribed and drug interactions.

- Gender

  Older females with reduced body mass, require lower doses than males.

INITIAL WARFARIN DOSING

- Outpatient Setting

  When warfarin is being initiated without concomitant heparin therapy, the goal is to avoid over anticoagulation while achieving a therapeutic INR in 5 to 6 days. See Tables VIII & IX for recommendations on inpatient and outpatient warfarin initiation. Loading doses are not useful in that the full anticoagulant effect of a dose is not seen for 72-96 hours, and the patient is exposed to extra risk.

TABLE VIII – RECOMMENDED INITIAL WARFARIN DOSE FOR OUTPATIENT TITRATION

PATIENT CHARACTERISTIC	DOSE	COMMENT
<65 years of age	5 mg	Avoid initial 10 mg doses which tend to over-anticoagulate 20-50% of patients
>65 years of age	2.5 mg	
Frail patients	2.5 mg	
<50 kg patient weight	2.5 mg	

- Inpatient Setting

  Warfarin should be initiated within 24 hours of starting heparin to assure a 5 day overlap and having 1-2 therapeutic INR results before discontinuing heparin. When warfarin is initiated in the hospital setting with daily prothrombin times, more aggressive dosing is supportable.

  Surgery prophylaxis: There are many levels of surgical risk. Discuss with surgeon on the case as appropriate.

TABLE IX - RECOMMENDED INITIAL WARFARIN DOSE FOR INPATIENT TITRATION.		
PATIENT CHARACTERISTIC	DOSE	COMMENT
<65 years of age	7.5 mg–10 mg	Average maintenance daily doses still range from 2.5–5 mg/day to attain INR goal 2.5 (Range 2–3)
>65 years of age	5 mg	
Frail patients	5 mg	
<50 kg patient weight	5 mg	
Orthopedic surgery prophylaxis: male patients <65 years of age who weight >70 kg	10 mg	Patients are males, younger than 65 years of age, and are >70 kg
Orthopedic surgery prophylaxis: all females, and all patients >65 years of age, or less than 70 kg	5 mg	

4. MONITORING INR

INPATIENT

- Daily follow-up

OUTPATIENT

- Protocol for Initiation of Therapy

  During the first week of anticoagulation INR should be performed every 2-3 days. If it is stable and within therapeutic target range +/- 0.5, INR could be performed twice weekly. If INR is stable as defined above, INR could be monitored weekly for 2 weeks. If stable and within therapeutic range, INR should be repeated in 2 weeks. If within therapeutic range, INR should be monitored monthly.

WEEK	FREQUENCY
1	Arrange 2 – 3 times
2	2 times
3–4	1 time per week
6	1 time (skip week 5)
Thereafter	1 time per month

5. DOSING ADJUSTMENTS

ADDRESS PATIENT FACTORS PRIOR TO CONSIDERING DOSE CHANGE

Before adjusting "out of range INR's" assure that patient factors affecting INR have been ruled out:

- Noncompliance (check patient's understanding of regimen and compliance)
- Dietary changes (change in vitamin K intake)
- Drug interactions
- Activity level (bed rest increases response)
- Illness (fever reduces response)

ADJUSTING THE DOSE

We are unaware of any strong scientific evidence for the recommendations below. They are based on consensus opinion.

General principles

Adjust dose based on weekly milligrams of warfarin using Appendix 1. Avoid skipping days when dosing, this tends to cause fluctuation in INR. Avoid measuring INR more frequently than every week (patients on therapy <30 days) or every two weeks (patients on therapy >30 days) unless INR >1 point out of range.

INR GOAL OF 2.5 (Range 2-3)

Tolerate a single low/high INR result (1.5-3.5), but recheck in 2 weeks, not 4. Adjust dose when 2 out of 2 INR values, or 2 out of 3 INR values are out of target range:

If INR <2	Increase weekly dose 10-15%, recheck 2 weeks
If INR 3.1-3.5	Reduce weekly dose 5-15%, recheck 2 weeks
If INR 3.5-4	Hold warfarin 1 day and decrease weekly dose 10-15%, recheck 1 week
If INR >4	Hold warfarin 2 days, decrease weekly dose 10-15%, recheck 1 week

INR GOAL OF 3 (Range 2.5 – 3.5)

Tolerate single low/high result (2-4), but recheck in 2 weeks, not 4. Adjust dose when 2 of 2 INR values, or 2 of 3 INR values are out of target range:

If INR <1.5	Increase weekly dose 10-15%, recheck in 1 week
If INR 1.5 - 2.5	Increase weekly dose 5-15%, recheck 2 weeks
If INR 3.5-3.8	Decrease weekly dose 5-15%, recheck 2 weeks
If INR 3.9-4.2	Hold warfarin 1 day and decrease weekly dose 5-15%, recheck 1 week
If INR >4.2	Hold warfarin 1-2 days and decrease weekly dose 10-15% and recheck prothrombin time in 1 week

**** see table next page ****

TABLE X - WARFARIN DOSING SCHEDULE IN MILLIGRAMS

SUN	MON	TUE	WED	THU	FRI	SAT	Weekly Total	PLUS 5%	PLUS 10%	PLUS 15%	MIN 5%	MIN 10%	MIN 15%
2	2	2	2	2	2	2	14	15	15	16	13	13	12
2	3	2	2	2	3	2	16	17	18	18	15	14	14
2.5	2.5	2.5	2.5	2.5	2.5	2.5	17.5	18	19	20	17	16	15
2.5	2.5	2.5	5	2.5	2.5	2.5	20	21	22	23	19	18	17
2.5	5	2.5	2.5	2.5	5	2.5	22.5	24	25	26	21	20	19
2.5	5	2.5	5	2.5	5	2.5	25	26	27.5	29	24	22.5	21
5	2.5	5	2.5	5	2.5	5	27.5	29	30	32	26	25	23
5	2.5	5	5	5	2.5	5	30	32	33	35	29	27	26
5	5	5	2.5	5	5	5	32.5	34	36	37	31	29	28
5	5	5	5	5	5	5	35	37	39	40	33	32	30
5	5	5	7.5	5	5	5	37.5	39	41	43	36	34	32
5	7.5	5	5	5	7.5	5	40	42	44	46	38	36	34
5	7.5	5	7.5	5	7.5	5	42.5	45	47	49	40	38	36
7.5	5	7.5	5	7.5	5	7.5	45	47	50	52	43	41	38
7.5	5	7.5	7.5	7.5	5	7.5	47.5	50	52	55	45	43	40
7.5	7.5	7.5	5	7.5	7.5	7.5	50	52.5	55	57.5	47.5	45	42.5
7.5	7.5	7.5	7.5	7.5	7.5	7.5	52.5	55	58	60	50	47	45
7.5	7.5	7.5	10	7.5	7.5	7.5	55	58	61	63	52	50	47
7.5	10	7.5	7.5	7.5	10	7.5	57.5	60	63	66	55	52	49
7.5	10	7.5	10	7.5	10	7.5	60	63	66	69	57	54	51
10	7.5	10	7.5	10	7.5	10	62.5	66	69	72	59	56	53
10	7.5	10	10	10	7.5	10	65	68	72	75	62	59	55
10	10	10	7.5	10	10	10	67.5	71	74	78	64	61	57
10	10	10	10	10	10	10	70	74	77	81	67	63	60
10	10	10	12.5	10	10	10	72.5	76	80	83	69	65	62
10	12.5	10	10	10	12.5	10	75	79	83	86	71	68	64
10	12.5	10	12.5	10	12.5	10	77.5	81	85	89	74	70	66
12.5	10	12.5	10	12.5	10	12.5	80	84	88	92	76	72	68
12.5	10	12.5	12.5	12.5	10	12.5	82.5	87	91	95	78	74	70
12.5	12.5	12.5	10	12.5	12.5	12.5	85	89	94	98	81	77	72
12.5	12.5	12.5	12.5	12.5	12.5	12.5	87.5	92	96	101	83	79	74
12.5	12.5	12.5	15	12.5	12.5	12.5	90	95	99	104	86	81	77
12.5	15	12.5	12.5	12.5	15	12.5	92.5	97	102	106	88	83	79
12.5	15	12.5	15	12.5	15	12.5	95	100	105	109	90	86	81
15	12.5	15	12.5	15	12.5	15	97.5	102	107	112	93	88	83
15	12.5	15	15	15	12.5	15	100	105	110	115	95	90	85
15	15	15	12.5	15	15	15	102.5	108	113	118	97	92	87
15	15	15	15	15	15	15	105	110	116	121	100	95	89

To use this table, refer to dosing adjustment section above. Obtain patient's current INR and compare with goal. Use the dosing adjustment tables to determine percent increase or decrease in weekly dose required. Referring back to this table, select OLD weekly total dose from the center column. Move to the right of this column to the column corresponding to desired percent change and read new total weekly dose. Then return to the center column and select the line corresponding to the new total weekly dose.

To the left of this column, read individual daily doses for each day of the week and transcribe them to the prescription order.

INR GREATER THAN 1 POINT ABOVE TARGET - FOLLOW UP AND REVERSAL

TABLE XI

INR OUT OF RANGE	BLEED OR RISK FOR BLEED	WARFARIN HOLD (DAYS)	NEXT INR (PT)	REVERSAL
INR >1 above target and ≤5	None	1–2 (decrease weekly dose 10-15% per Table	1 week	Resume Coumadin when INR approaches desired range.
INR >5 but <9	None	2–3	2-3 days	Resume Coumadin when INR approaches desired range.
	Increase Bleed Risk	1	1 day	Vitamin K 1–2.5 mg orally.
INR >9	None		12–24	Vitamin K 3–5 mg orally. Repeat INR 12–24 hours. May be repeated if necessary.
	Some Bleeding			Serious bleeding, or major warfarin overdose (e.g., INR >20) requiring very rapid reversal of anticoagulant effect. Vitamin K (10 mg by slow IV infusion) may be used with fresh plasma transfusion or prothrombin complex concentrate, depending upon urgency. Vitamin K injections may be needed q12h
Life-threatening bleeding or serious warfarin overdose				Prothrombin complex concentrate, with vitamin K (10 mg by slow IV infusion); repeat if necessary, depending upon the INR
Continuing warfarin therapy indicated after high doses of vitamin K				Heparin, until the effects of vitamin K have been reversed, and patient is responsive to warfarin.

INR IS >1 POINT ABOVE INR GOAL RANGE, BUT INR <5

The patient should be contacted to assure that no clinical bleeding has occurred and to review patient factors; compliance with regimen, changes in diet, drug interactions, changes in activity level. Consider repeating INR. Have the patient abstain from warfarin for 1-2 days and then repeat prothrombin time in one week. If interaction detected and drug cannot be changed, reduce weekly dose by 10-15%. If rapid reversal needed for elective surgery, Vitamin K at 2–4 mg orally may be given. If INR elevated at 24 hours, repeat 1-2 mg. Do not use Vitamin K in high risk patients (artificial valves or prior embolism while on warfarin), but rather use fresh frozen plasma.

INR >5 or ≤ 9

- If elevated INR and no bleed, hold warfarin dose for 2 or 3 days and repeat INR. If patient is at increased risk of bleeding, omit next dose of warfarin and give Vitamin K 1–2.5 mg orally.
- If rapid reversal needed for surgery, use 2–4 mg vitamin K orally unless high risk. For high risk use FFP.

INR >9 OR IF BLEEDING HAS OCCURRED

Patient should be contacted promptly by the managing physician. Prothrombin time should be repeated. The patient should be treated based on risk of bleeding versus risk of embolism on reversing anticoagulation:

- If no clinically significant bleed, give 3–5 mg vitamin K orally. If INR not substantially reduced by 24-48 hours, repeat Vitamin K.

- If significant bleed and elevated INR, give full dose vitamin K 10 mg slow I.V. into FFP or prothrombin complex, depending on urgency. Vitamin K injection may be repeated every 12 hours if needed. Give plasma or RBCs as necessary, and be aware that reinitiation of warfarin may be ineffective for 7 to 14 days. Do not use Vitamin K in high risk patients (artificial valves or prior embolism while on warfarin), but rather use fresh frozen plasma.

- Life threatening bleeding or serious warfarin overdose: Prothrombin complex concentrate, with vitamin K (10 mg by slow IV infusion); repeat if necessary, depending upon the INR.

OTHER COMORBIDITIES

Risk of bleeding increases with renal insufficiency, hypertension, cancer, severe anemia, alcohol abuse and signs of GI lesions (fecal occult blood loss). *Anticoagulation should be used with caution or avoided in patients with recent peptic ulcer, esophageal, intraocular or intracranial bleeding, or pericarditis. Patients who are at risk of trauma or falls or who are unable to comply should also be approached cautiously.* Patients with fluctuating risks due to changes in alcohol intake or diet may be managed by keeping the INR at low end of therapeutic range.

FOLLOW-UP

Major bleeding is associated with a history of GI or GU bleeding. Most major bleeding that occurs when INR is <3, is due to an occult GI or GU lesion. **Patients with hematuria and guaiac positive stools** should not be ignored, but need to be worked up to rule out lesions. The risk

versus benefit of using anticoagulation in patients with a history of GI/GU bleed is unclear. Measures to minimize the risk of a flare of the lesions during anticoagulant therapy are prudent, e.g., maintenance doses H2 antagonists for reflux esophagitis and gastric/duodenal ulcer patients.

INITIAL AND FOLLOW-UP LAB MONITORING

A baseline prothrombin time, CBC, Chem Profile, and urinalysis are recommended to screen for potential risk factors. A more extensive work-up may be appropriate in patients with known risks, e.g., history of GI/GU bleed. Repeat CBC yearly unless otherwise indicated.

PATIENT EDUCATION

Tools include the "Coumadin today" materials (Dupont). Instruct patients on how warfarin acts, its side effects, drug and dietary interactions, adhering to the dosing schedule, and laboratory monitoring to reduce the risk of bleeding. Encourage the patient to carry a wallet card and wear a Medic-Alert type bracelet while on continuous anticoagulation therapy. Also, if the patient is of child-bearing age, discuss potential for fetal harm if pregnancy occurs.

DRUG INTERACTIONS WITH WARFARIN

In general, try to change or eliminate drugs, which have known interactions with warfarin. If no alternatives exist, consider reducing warfarin dose and monitoring every 2 to 3 days for the first week of concomitant therapy. Similar monitoring is recommended upon discontinuation of therapy.

TABLE XII – CLINICALLY SIGNIFICANT WARFARIN DRUG INTERACTIONS NOTE		
Other warfarin drug interactions not listed below may be clinically significant. Consult an up to date drug information reference for details.		
INTERACTING DRUG	EFFECT ON ANTICOAGULATION	DESCRIPTION OF INTERACTION
Acetaminophen	Increased	
Amiodarone	Increased	No alternative; monitor carefully for 2-4 weeks during initiation and discontinuation
Anabolic Steroids	Increased	Find alternative
Antibiotics	Variable	Systemic antibiotics may alter GI flora and Vitamin K absorption. Careful INR monitoring is advised.
Aspirin	Increased (also direct GI toxicity)	Avoid unless medically indicated, e.g., with low intensity warfarin patients who had thromboembolic events on warfarin therapy. Doses >325 mg/day are not recommended.
Azathioprine	Decreased	
Barbiturates	Decreased	Use alternative hypnotic. Monitor stable dose Phenobarbital anticonvulsant treatment carefully. (May bleed when Phenobarbital discontinued.)
Carbamazepine, Phenobarbital	Decreased	Monitor INR carefully when anticonvulsant dose is decreased or stopped.
Cefamandole	Increased	
Cefazolin	Increased	
Chloral Hydrate	Increased	
Chlorodiazepoxide	Decreased	
Cholestyramine	Decreased	Use alternative lipid lowering agent.
Cimetidine	Increased	
Ciproflaxcin	Increased	
Colibrate, Gemfibrozil	Increased	Use alternative lipid lowering agent.
Cyclosporine	Decreased	
Danazol	Increased	Use alternative if possible. Monitor carefully.
Dextrothyroxine	Increased	Avoid if possible. Monitor patients carefully when used.
Dicloxacillin	Decreased	
Disopyramide	Increased	
Disulfiram	Increased	Avoid in anticoagulated patients if possible.
Erythromycin	Increased	
Etretinate	Decreased	
Flu Vaccine	Increased	

TABLE XII (continued)
CLINICALLY SIGNIFICANT WARFARIN DRUG INTERACTIONS

INTERACTING DRUG	EFFECT ON ANTICOAGULATION	DESCRIPTION OF INTERACTION
Fluconazole, Ketoconazole	Increased	Monitor carefully when adding or removing these drugs from anticoagulated patient's regimen.
Fluorouracil	Increased	
Griseofulvin	Decreased	
H2 Antagonists	Increased	Avoid Cimetidine. Use Ranitidine (no interaction)
Heparin	Increased	
Ifosfamide	Increased	
Isoniazid	Increased	
Levothyroxine	Increased	No problem starting warfarin in a patient stabilized on thyroxine. Monitor carefully when starting thyroxine in anticoagulated patients.
Lovastatin	Increased	
Methimazole	Decreased	No alternative. Monitor INR carefully when adding or removing.
Metolazone	Increased	
Metronidazole, Trimethoprim/sulfa	Increased	Monitor carefully. Use alternative antibiotic if possible.
Moricizine	Increased	
Nafcillin	Decreased	
Naldixic Acid	Increased	
Norfloxicin	Increased	
NSAIDs	Increased (also direct GI toxicity)	NSAIDs which can significantly affect INR include: • phenylbutazone • fenoprofen • flurbiprofen • indomethacin • ketoprofen • meclofenamate • piroxicam • sulindac *Most NSAIDs affect platelet aggregation.* Ibuprofen, naproxen and tolmetin do not affect INR, **but** their effects on GI mucosa and platelet aggregation may predispose to GI bleeding. Trilisate (no platelet effects) or acetaminophen are preferred when risk of bleeding is significant, e.g., osteoarthritis requiring continuous treatment in the elderly. *If NSAIDs must be used, patient and physician need to be particularly aware of increased risk for GI bleeding.* **Monitor patients for GI bleeding and follow INR closely** to ensure it is not above the therapeutic range.

TABLE XII (continued) **CLINICALLY SIGNIFICANT WARFARIN DRUG INTERACTIONS**		
INTERACTING DRUG	**EFFECT ON ANTICOAGULATION**	**DESCRIPTION OF INTERACTION**
Ofloxacin	Increased	
Omeprozole	Increased	
Phenytoin	Increased	
Propanolol	Increased	
Propoxyphene	Increased	
Quinidine	Increased	
Rifampin	Decreased	Avoid if alternative available. Monitor carefully if used.
Sucralfate	Decreased	
Tamoxifen	Increased	
Tetracycline	Increased	
Trazadone	Decreased	
Patients with CHF, or significant liver disease with bilirubin >4 mg/dL require lower doses.		

6. BENEFIT VS RISK

BENEFITS OF THERAPY

The principal benefit of therapy is reduction in risk of embolism. This must be weighed against the increased risk of hemorrhage secondary to anticoagulation.

TABLE XIII - EMBOLISM RISK (IF UNTREATED) FOR COMMON CONDITIONS FOR WHICH ORAL ANTICOAGULATION IS CURRENTLY INDICATED.	
INDICATION FOR ANTICOAGULATION	EMBOLISMS (% PER YEAR)
Nonvalvular AF with organic heart disease or hypertension, age >60	3–7.4%
Before elective cardioversion with NVAF present for >48 hours	5.3%/episode
Valvular heart disease: • with history of embolism, chronic AF, PAF • with NSF with LA >55 mm	 17% 7–9%
Mitral valve prolapse documented system embolism, chronic AF	4–5%
Bioprosthetic mitral valves in AF	5–8%
Bioprosthetic mitral or aortic valves in NSR	2–3%
Mechanical valve prostheses with embolism on warfarin	20–70%
After anterior MI with apical aneurysm	2–6%
Class IV CHF	2–6%
Dilated cardiomyopathy with: • CHF, AF or NSR • PAF	 2.4–11% 2–5%

RISKS OF THERAPY

The major risk is bleeding. The incidence of major(requiring transfusion) and minor bleeding varies with the population being studied and the time period.

TABLE XIV
INCIDENCE OF HEMORRHAGE IN PATIENTS ON ORAL ANTICOAGULATION

PATIENT POPULATION	TOTAL BLEED (%)	MAJOR BLEED (%)	FATAL BLEEDS (%)
Ischemic Cerebrovascular Disease	11.8–39.3	2.1–12.8	2.1–5.1
Prosthetic Heart Valves • Overall • Annual	 1.2–42.4 1.8–5.7	 0–10.3 0.8–4.1	 0–4.1 6–2.3
Atrial Fibrillation (INR goal 2–3) • Overall • Annual	 6.3–26.9 4–4.2	 1.7–5.8 1.7–4.2	 0–1.3 0–8
Ischemic Heart Disease	3.8–36.5	0–19.3	0–2.9
Venous Thromboembolism	17–37.5	4.1–16.7	0

7. DISCONTINUING ANTICOAGULATION

TEMPORARY DISCONTINUATION OF WARFARIN THERAPY FOR PROCEDURES

The evidence for the risks/benefits of temporarily discontinuing warfarin therapy for procedures is not conclusive. The following is a prudent approach:

- Many minor dental and surgical procedures may be carried out with low intensity anticoagulation (INR 2-3) at the surgeon's discretion. Local procedures for hemostasis (e.g., absorbable hemostatic agents, sutures, pressure dressings) should be available at the operating site. Alternatively, low intensity anticoagulation can be held for 2-4 days prior to surgery and for 1-2 days after surgery to minimize risk.

- The risk of bleeding versus the risk of embolism should be carefully weighed if warfarin therapy is interrupted, especially in cases, which have had systemic embolization. When patients require maximal anticoagulation, e.g., mechanical prosthetic heart valves, recurrent systemic embolization, the patient should be switched to IV unfractionated heparin, or low molecular weight heparin (LMWH).

- If temporary reversal is necessary for emergent minor procedure fresh frozen plasma 200-400 ml will reverse effects for 4-6 hours. If major surgery is required, restore coagulation to normal using fresh frozen plasma/prothrombin complex concentrate blood. Use heparin to cover anticoagulation needs.

- Perioperative anticoagulation is beyond the scope of this guideline.

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Initial Review: March 1996

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Review Dates: 2000, 2001 or 2002

Approved by:

Regional Healthcare Quality and Benefit Management Committee	April 3, 2002
Quality Council	November 10, 1999

Next Review: April 2004