WARFARIN DOSING GUIDELINE

PURPOSE: This document is intended as a guide to managing patients requiring warfarin therapy. It should be coupled with, and not supersede, clinical judgment. Evidence-based tools, such as dosing nomograms, should always be used in conjunction with clinical information pertaining to specific patient characteristics and conditions.

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Table of Contents

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I. Role in therapy

The use of warfarin is declining with preference now being given to direct oral anticoagulants (DOACs) as first-line therapy in common anticoagulation indications, such as VTE treatment and prevention of recurrence, and stroke prevention in non-valvular atrial fibrillation (NVAF). Despite this, not all patients are appropriate candidates for DOAC therapy. As such, warfarin occupies a niche in therapy for patients with contraindications to DOACs, including but not limited to mechanical heart valves, certain hypercoagulable states, or personal preferences

Please click **here** to jump to the "direct oral anticoagulant guideline" on the pharmacy webpage which provides detailed guidance on criteria for DOAC use.

II. Factors that may affect a patient's warfarin requirements[1,2,3]

Factor		Potential INR effect	Mechanism
Diet	Decreased PO intake	↑	Decreased dietary intake of or increased flushing of vitamin K from GI tract
	Increased PO intake	↓	Increased dietary intake of vitamin K
	Starting tube feeds	↓	May result in warfarin binding to protein in formula, warfarin binding to the tubing or may be due to vitamin K content of tube feed formulation.
	Stopping tube feeds	↑	May result in increased INR if the warfarin dose has been escalated to overcome binding
	TPN or PPN	↑↓	Varies depending on vitamin K content of TPN/PPN
	Low albumin*	↑	Warfarin is highly protein bound (Low albumin = more free warfarin)
Broad spectrum antibiotics		↑	Potentially reduces vitamin K-producing gut flora
GI	Constipation	↓	Decreased elimination of gut vitamin K
	Diarrhea	↑	Increased elimination of gut vitamin K
Disease	Decompensated CHF	↑	Concomitant congestive hepatopathy decreases warfarin metabolism
	Infection	↑	Disruption of hemostasis/increased catabolism; reduced levels of clotting factors
	Malignancy	↑	Potential interactions with chemotherapy agents

**** A baseline albumin level should be obtained for ALL new warfarin patients to guide therapy***

III. Drug-drug interactions (DDI)[1,2,3]

- Isoenzymes commonly involved in DDI with warfarin are CYP3A4, 2C9 and 2C19, though other mechanisms of interaction exist. The below list of drugs is not all-inclusive:

Inhibitors of warfarin metabolism (may require less warfarin)			Inducers of warfarin metabolism (may require more warfarin)	Increased bleeding risk
Amiodarone	Fibrates	Phenytoin	Azathioprine	Aspirin
Azole antifungals	H2RAs	PPIs	Barbiturates	Clopidogrel
Bactrim	Isoniazid	SSRIs	Carbamazepine	Fondaparinux
Cephalosporins	Macrolides	Statins	Nafcillin	NSAIDs
Chemotherapy	Metronidazole	Steroids	Phenytoin	Prasugrel
Diltiazem	Protease inhibitors	Thyroid meds	Primidone	Ticagrelor
Doxycycline	Quinolones		Rifamycins	UFH/LMWHs

- It is recommended to perform a drug interaction check using a tool such a LexiComp for all warfarin patients

IV. Warfarin dosing adjustment nomogram (for target INR 2-3) – INITIATION[4]

- Does patient have ≥ 1 of the following conditions that might make them warfarin **sensitive**?

Age > 75 yoa **Decompensated CHF** **Suboptimal nutrition** **Thyrotoxicosis**
Liver disease **Drug interactions** **Malignancy** **High risk for bleed**

YES (warfarin sensitive)			NO (standard dosing)		
	INR	**Dosage**		**INR**	**Dosage**
Day 1	Obtain baseline INR	2.5 mg	Day 1	Obtain baseline INR	5-7.5 mg
Day 2	< 1.5	2.5 mg	Day 2	< 1.5	5 -7.5 mg
	1.5 -1.9	1-1.5 mg		1.5 -1.9	2.5-3.75 mg
	2 – 2.5	0.5-1.5 mg		2 – 2.5	1-2.5 mg
	>2.5	Hold		>2.5	Hold
Day 3	< 1.5	2.5-5 mg	Day 3	< 1.5	5-10 mg
	1.5 -1.9	1-2.5 mg		1.5 -1.9	2.5 - 5 mg
	2 – 3	0.5-1.5 mg		2 – 3	0- 2.5 mg
	>3	Hold		>3	Hold
Day 4	< 1.5	5 mg	Day 4	< 1.5	7.5-10 mg
	1.5 -1.9	2.5- 3.75 mg		1.5 -1.9	5-7.5 mg
	2 – 3	0.5-2.5 mg		2 – 3	1.25-5 mg
	>3	Hold		>3	Hold
Day 5	< 1.5	5 mg	Day 5	< 1.5	10 mg
	1.5 -1.9	3.75-5 mg		1.5 -1.9	7.5-10 mg
	2 – 3	0.5-2.5 mg		2 – 3	1.25-5 mg
	>3	Hold		>3	Hold
Day 6	< 1.5	5-7.5 mg	Day 6	< 1.5	7.5-12.5 mg
	1.5 -1.9	3.75-5mg		1.5 -1.9	5-10 mg
	2 – 3	0.5-5 mg		2 – 3	1.25-7.5 mg
	>3	Hold		>3	Hold

*Day 1= day warfarin starts
This nomogram is meant to serve as a guide. Initiation of warfarin should be individualized depending on the clinical scenario.

- **RULES OF THUMB for warfarin dose adjustments for hospitalized patients**
    - If INR increases > 0.5, consider decreasing the warfarin dose
    - If INR increases ≥ 1, consider holding warfarin for a one dose
    - Other clinical aspects may significantly influence warfarin requirements and adjustments beyond the above suggestions may be warranted
    - Dose changes are ***not*** limited to 2.5mg increments if individual patient and clinical factors favor an alternative increment
        - However, if a patient is on warfarin therapy outpatient, ensure that patient is discharged on a regimen that utilizes their home tablet strength whenever possibe, even if they required use of differing tablet strenth while hospitalized.
        - If a change in tablet strength is required for discharge (this should be rare):
            - Patient should be counseled on change and to bring old warfarin tablets in at next appointment for safe disposal
            - The prior warfarin strength should be removed from medication profile
            - Any pre-existing prescriptions should be cancelled at patient's outpatient pharmacy

V. Warfarin dosing nomogram for MAINTENANCE therapy (≥ 1 week of warfarin therapy) of non-bleeding patients[5]

- Primarily geared toward outpatient therapy. More conservative adjustments may be warranted.
- Confirm there is no bleeding.
- Consider non-adherence, illness, drug interaction, or dietary change as reason for out-of-range INR.

Goal INR 2-3	Dosing Adjustments	Goal INR 2.5-3.5
INR < 1.5	– Consider a one-time dose increase of 1½ - 2 times daily maintenance dose – If adjustment to maintenance dose needed, increase dose by 10-20%* – Repeat INR in 1 week	INR < 2.0
INR 1.5 – 1.7	– Consider a one-time dose increase of 1½ times daily maintenance dose – If adjustment to maintenance dose needed, increase dose by 5-15%* – Repeat INR in 2 weeks	INR 2.0-2.2
INR 1.8 – 1.9	– No dosage adjustment may be necessary if the last two INRs were in range** – Repeat INR within 8 weeks – Consider a one-time dose increase of 1½ times daily maintenance dose – If adjustment to maintenance dose needed, increase dose by 5-10%* – Repeat INR in 2 weeks	INR 2.3 – 2.4
INR 2 – 3	**Desired range** **Repeat INR within 8 weeks**	INR 2.5 – 3.5
INR 3.1 – 3.2	– No dosage adjustment may be necessary if the last two INRs were in range** – Repeat INR within 8 weeks – Consider a one-time dose decrease of ½ of daily maintenance dose – If adjustment to maintenance dose needed, decrease dose by 5-10%* – Repeat INR in 2 weeks	INR 3.6– 3.7
INR 3.3 – 4.0	– Consider holding ½ to 1 dose – If adjustment to maintenance dose needed, decrease dose by 5-10%* – Repeat INR in 2 weeks	INR 3.8 – 4.4
INR 4.0 – 6.0	– Hold 1-2 doses – If adjustment to maintenance dose needed, decrease dose by 5-15%* – Repeat INR within 1 week	INR 4.5 – 6.0
INR 6.1-8.9	– Hold 1-2 doses – If adjustment to maintenance dose needed, decrease dose by 10-20%* – Repeat INR within 5 days – If outpatient, consult clinic supervisor	INR 6.1 - 8.9
INR >9.0	– Hold until INR < upper limit of therapeutic range – Consider use of vitamin K PO 2.5mg – 5mg – Repeat INR in 1-2 days – If outpatient, consult clinic medical director – When safe, resume warfarin at lowered dose (10-20%)	INR > 9.0

*Consider resumption of prior maintenance dose if factor causing the change in INR is transient

**If there is no clear explanation for the INR to be out of range, and if in the judgment of the clinician, the INR does not represent an increased risk (hemorrhage or thromboembolism) for the patient

This nomogram is meant to serve as a guide. Initiation and maintenance of warfarin should be individualized depending on the clinical scenario.

VI. Warfarin reversal

- Please click **here** to access the "Antithrombotic reversal guidelines" on the pharmacy webpage for additional guidance. (When dialogue box opens, simply click OK to go directly to the PDF)

VII. Perioperative management of warfarin

- Please click **here** to access the "UNMH guideline for perioperative management of antithrombotic therapy" on the pharmacy webpage for additional guidance. (When dialogue box opens, simply click OK to go directly to the PDF)

VIII. Optimal therapeutic ranges and durations of anticoagulant therapy

INDICATION	INR (RANGE) If on warfarin	DURATION	COMMENT
VENOUS THROMBOEMBOLISM (VTE)			
▪ Please click **here** to access the "VTE treatment guidelines" on the pharmacy webpage for guidance. (When dialogue box opens, simply click OK to go directly to the PDF)			
Non-VALVULAR ATRIAL FIBRILLATION (NVAF)/ATRIAL FLUTTER (see Appendix A for CHA_2DS_2VASc scoring tool)[6,7,9,10, 11,18,21]			
CHA_2DS_2VASc =0	n/a	n/a	No antithrombotic therapy
CHA_2DS_2VASc =1	2.5 (2.0 - 3.0)	chronic	OAC* or ASA 81mg or no therapy
CHA_2DS_2VASc ≥2	2.5 (2.0 - 3.0)	chronic	*
With prior history of stroke/TIA/systemic embolism	2.5 (2.0 - 3.0)	chronic	*
Following open heart surgery (in NSR)	2.5 (2.0 - 3.0)	4 weeks	*
Pre-cardioversion (Afib or flutter > 48 hours)	2.5 (2.0 - 3.0)	3 weeks	*
Post-cardioversion (in NSR)	2.5 (2.0 - 3.0)	4 weeks	*
Patients with cardiac stents (+ AF)			
• CHA_2DS_2VASc = 0-1 + stent	none	12 months	DAPT
	none	> 12 months	ASA 81 mg daily
• CHA_2DS_2VASc ≥2 + DES†	2.5 (2.0-3.0)†	3-6 months	+ ASA 81 mg + clopidogrel + pantoprazole OR + clopidogrel w/o ASA[22] OR low dose rivaroxaban[9] + clopidogrel
	2.5 (2.0-3.0)†	6-12 months	+ ASA 81 mg OR low dose rivaroxaban[9]+ clopidogrel
	2.5 (2.0-3.0)†	> 12 months	DOAC* full dose+ ASA 81mg >VKA+ ASA 81mg >ASA + clopidogrel OR if stable CAD (no ACS w/in last 12 months), OAC alone
• CHA_2DS_2VASc ≥2 + BMS†	2.5 (2.0-3.0)†	1 month	+ASA 81 mg +clopidogrel+ pantoprazole OR + clopidogrel w/o ASA[22] OR low dose rivaroxaban[9] + clopidogrel
	2.5 (2.0-3.0)†	2-12 months	DOAC* + ASA 81mg >VKA + ASA 81mg OR low dose rivaroxaban[9] +clopidogrel
	2.5 (2.0-3.0)†	> 12 months	DOAC* + ASA 81mg >VKA + ASA 81mg> ASA 81 mg +clopidogrel OR if stable CAD (no ACS w/in last 12 months), OAC alone
Patients with ACS and no stenting (+AF)			
• $CHADS_2VASc$ 0 + ACS without stenting	none none	12 months ≥ 12 months	DAPT ASA 81 mg daily
• $CHADS_2VASc$ ≥ 1 + ACS without stenting	2.5 (2.0-3.0) 2.5 (2.0-3.0)	12 months ≥ 12 months	OAC*+ ASA 81 mg daily OAC*+ ASA 81 mg daily OR if stable CAD (no ACS w/in last 12 months), OAC alone[23]

VALVULAR AF/FLUTTER			
With rheumatic mitral stenosis or mitral valve repair [10,11,18]	2.5 (2.0 - 3.0)	Chronic	VKA
OTHER VALVULAR DISEASE			
Mitral valve prolapse:			
• With TIAs or ischemic stroke	none	chronic	ASA 81 mg daily
• With recurrent TIA despite ASA therapy	2.5 (2.0 - 3.0)	chronic	
Mitral annular calcification with AF	2.5 (2.0 - 3.0)	chronic	
Rheumatic mitral valve disease:			
• With AF, hx systemic emb, LA thrombus, LA>55mm	2.5 (2.0 - 3.0)	chronic	
• s/p thromboembolic event despite anticoagulation	2.5 (2.0 - 3.0)	chronic	add ASA 81 mg daily or INR 2.5-3.5
VALVE REPLACEMENT – BIOPROSTHETIC			
Aortic	2.5 (2.0 - 3.0) ‡ none	3-6 months ≥ 3 months	+ ASA 81 mg daily ASA 81 mg daily
• Transcatheter aortic valve replacement (TAVR)	none none	3 months > 3 months	ASA 81 mg + clopidogrel ASA 81 mg daily
Mitral	2.5 (2.0 - 3.0) ‡ none	3-6 months ≥ 3 months	+ ASA 81 mg daily ASA 81 mg daily
• With LA thrombus	2.5 (2.0 - 3.0)	until resolution	+ ASA 81 mg daily
• With prior history of systemic embolism	2.5 (2.0 - 3.0)	> 3 months	+ ASA 81 mg daily
• With additional risk factors for thromboembolism [AF, previous thromboembolism, hypercoagulable condition, low EF]	2.5 (2.0 - 3.0)	chronic	+ ASA 81 mg daily
VALVE REPLACEMENT - MECHANICAL			
Aortic			
• Bileaflet in NSR with normal LA size	2.5 (2.0 - 3.0)	chronic	+ ASA 81 mg daily May also consider INR of 2.5-3.5 for first 3 months
• Medtronic Hall tilting disk in NSR w/ nl LA size	2.5 (2.0 - 3.0)	chronic	+ ASA 81 mg daily May also consider INR of 2.5-3.5 for first 3 months
• On-x	2.5 (2.0-3.0)	3 months	+ ASA 81 mg daily
	1.5-2.0	> 3 months	May consider 1.5-2.0 goal based on FDA labeling, when no other TE risks (+ ASA 81mg daily)[19,20]
• Starr-Edwards or mechanical disk valve	3.0 (2.5 - 3.5)	chronic	+ ASA 81 mg daily
• Following prosthetic valve thrombosis	3.5 (3.0 - 4.0)	chronic	+ ASA 81 mg daily
Mitral			
• Bileaflet or tilting disk	3.0 (2.5 - 3.5)	chronic	+ ASA 81 mg daily
• Following prosthetic valve thrombosis	4.0 (3.5 - 4.5)	chronic	+ ASA 81 mg daily w/ low bleed risk
Caged ball or caged disk (aortic or mitral)	3.0 (2.5 - 3.5)	chronic	+ ASA 81 mg daily
With additional risk factors for thromboembolism [AF, MI, LA enlargement, hypercoagulable condition, low EF]	3.0 (2.5 - 3.5)	chronic	+ ASA 81 mg daily
With systemic embolism despite adequate anticoagulation	increase INR goal	chronic	+ ASA 81 mg daily
Both aortic and mitral	3.0 (2.5 - 3.5)	chronic	+ ASA 81 mg daily

PRIMARY AND SECONDARY PREVENTION OF CORONARY ARTERY DISEASE & PERIPHERAL ARTERY DISEASE (CAD/PAD)			
• No routine OAC - antiplatelet therapies are the mainstay of therapy • See external references until internal resources developed (for references regarding CAD, see [13-15], and for references regarding PAD, see [16, 17])			
ACS: STEMI[7]			
Following MI in high risk patients [anterior MI, significant heart failure, intracardiac thrombus, hx TE]			
• without stenting	2.5 (2.0 - 3.0) none none	3 months 3-12 months > 12 months	+ ASA 81 mg daily ASA 81mg daily + clopidogrel ASA 81 mg daily
• with BMS*	2.5 (2.0 - 3.0) 2.5 (2.0 - 3.0) none	1 month 2-3 months 3-12 months > 12 months	+ ASA 81 mg +clopidogrel + pantoprazole + ASA 81 mg daily ASA 81mg daily or DAPT if low bleed risk ASA 81 mg daily
• with DES*	2.5 (2.0 - 3.0) none none	3-6 months 6-12 months > 12 months	+ASA 81 mg +clopidogrel + pantoprazole DAPT DAPT or ASA 81 mg daily monotherapy depending on bleed risk

* DOAC preferred for this indication unless contraindications exist

† For patients on triple therapy (e.g. warfarin, aspirin, clopidogrel), it might be reasonable to target a lower INR of 2-2.5 and use a PPI for duration of triple therapy

‡ Aspirin may be used as monotherapy. If the patient is high risk (e.g., LA thrombus, hx of thromboembolism, known thrombophilia, low LVEF, complicated procedure, etc) then a finite period of anticoagulation for 3-6 months with warfarin may be reasonable if the patient is at low bleed risk. If requiring long-term anticoagulation for atrial fibrillation and using ESC/CHEST definition of valvular atrial fibrillation (mechanical valve or moderate-severe mitral stenosis), then using a DOAC after the first 3 months is an option. [24,25]

ASA= aspirin; BMS= bare metal stent; CAD= coronary artery disease; DAPT= dual antiplatelet therapy; DES= drug eluting stent; LA= left atria; NSR= normal sinus rhythm; OAC=oral anticoagulant; PCI=percutaneous coronary intervention; DOAC= direct oral anticoagulant; VKA=vitamin K antagonist (warfarin)

Appendix A: CHA_2DS_2VASc to estimate annual risk of stroke in atrial fibrillation[8]

Risk factor	Score
Congestive heart failure/ LV dysfunction	1
Hypertension	1
Age ≥ 75 years	2
Diabetes mellitus	1
Stroke/TIA/thromboembolism	2
Vascular disease (prior MI, peripheral artery disease, aortic plaque)	1
Age 65-74 years	1
Sex **c**ategory (female gender)	1
Maximum possible score (since age may contribute 0,1 or 2 points	9

CHA_2DS_2VASc Score	Annual stroke risk (%) without anticoagulant therapy
0	0
1	1.3
2	2.2
3	3.2
4	4
5	6.7
6	9.8
7	9.6
8	6.7
9	15.2

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