WARFARIN DOSING GUIDELINE

This document is intended as a guideline only and should not replace sound clinical judgment

PURPOSE: This document is intended as a guide to managing warfarin therapy in hospitalized patients. 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.

I. Factors that may affect vitamin K levels or INR in hospitalized patients on warfarin

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 content of TPN/PPN
	Low albumin	↑	Warfarin is highly protein bound (Low albumin = more free warfarin)
Broad spectrum antibiotics		↑	Reduces vitamin K-producing gut flora
GI	Constipation	↓	Decreased elimination of vitamin K via bowel movements
	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	↑	Interactions with chemotherapy agents

II. Drug-drug interactions (DDI)

- Isoenzymes commonly involved in DDI with warfarin are 3A4, 2C9 and 2C19, though other mechanisms of interaction exist

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

- The above list of drugs is not all-inclusive, but it highlights some of the most common interactions
  - It is recommended to perform a drug interaction check using a tool such a LexiComp for all warfarin patients

III. Inpatient warfarin dosing adjustment nomogram (for target INR 2-3) – INITIATION

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

Age > 65 yoa **Decompensated CHF** **Suboptimal nutrition** **Thyrotoxicosis**
Liver disease **Drug interactions (e.g. Amiodarone, Triazoles, Bactrim)** **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.

IV. Warfarin dosing nomogram for MAINTENANCE therapy[5] (≥ 1 week of warfarin therapy)

- Primarily geared toward outpatient therapy, more conservative adjustments may be warranted

Goal INR 2-3	Dosing Adjustments	Goal INR 2.5-3.5
INR < 1.5	– Consider a booster dose of 1½ - 2 times daily maintenance dose – If dosage adjustment needed, increase maintenance dose by 10-20%*	INR < 2
INR 1.5 – 1.8	– Consider a booster dose of 1½ - 2 times daily maintenance dose – If dosage adjustment needed, increase maintenance dose by 5-15%*	INR 2 – 2.3
INR 1.8 – 1.9	– No dosage adjustment may be necessary if the last two INRs were in range** – Consider a booster dose of 1½ - 2 times daily maintenance dose – If dosage adjustment needed, increase maintenance dose by 5-15%*	INR 2.3 – 2.4
INR 2 – 3	– **Desired range**	INR 2.5 – 3.5
INR 3.1 – 3.2	– No dosage adjustment may be necessary if the last two INRs were in range** – If dosage adjustment needed, decrease maintenance dose by 5-10%*	INR 3.6– 3.7
INR 3.3 – 3.4	– Consider holding ½ to 1 dose – If dosage adjustment needed, decrease maintenance dose by 5-10%*	INR 3.8 – 3.9
INR 3.5 – 3.9	– Consider holding 1 dose – If dosage adjustment needed, decrease maintenance dose by 5-15%*	INR 4.0 – 4.4
INR ≥ 4.0	– Hold until INR < upper limit of therapeutic range – Consider use of low-dose vitamin K – If dosage adjustment needed, decrease maintenance dose by 5-15%*	INR ≤ 4.5

*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 of warfarin should be individualized depending on the clinical scenario.

V. Warfarin reversal

- Please refer to "Antithrombotic reversal guidelines" on the pharmacy webpage (https://hospitals.health.unm.edu/intranet/pharmacy/index.shtml) for additional guidance

VI. Perioperative management of warfarin

- Please refer to "UNMH guideline for perioperative management of antithrombotic therapy" on the pharmacy webpage (https://hospitals.health.unm.edu/intranet/pharmacy/index.shtml) for additional guidance

VII. OPTIMAL THERAPEUTIC RANGE AND DURATION OF ANTICOAGULATION

(Based on recommendations from ACCP Practice Guidelines 9th ed, ACC/AHA guidelines, and Canadian Cardiovascular Society)

INDICATION	INR (RANGE) If on warfarin	DURATION	COMMENT
Non-VALVULAR ATRIAL FIBRILLATION (NVAF)/ATRIAL FLUTTER (see Appendices A and B for $CHADS_2$ and CHA_2DS_2VASc scoring tools)			
$CHADS_2$=0 → Go to CHA_2DS_2VASc:			
• No additional risk factors	none	N/A	No antithrombotic therapy
• Either female gender or vascular disease	none	chronic	ASA 81 mg daily
• Age > 65 or female gender AND vascular disease	2.5 (2.0 - 3.0)	chronic	ASA 81 mg daily is a reasonable alternative in some patients
$CHADS_2$=1	2.5 (2.0 - 3.0)	chronic	TSOAC>VKA>ASA 81 mg +clopidogrel
$CHADS_2$=2	2.5 (2.0 - 3.0)	chronic	TSOAC>VKA>ASA 81 mg +clopidogrel
With prior history of stroke/TIA/systemic embolism	2.5 (2.0 - 3.0)	chronic	TSOAC>VKA>ASA 81 mg +clopidogrel
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			
• $CHADS_2$= 0-1 + stent	none	12 weeks	DAPT
	none	After 12 weeks	ASA 81 mg daily
• $CHADS_2$≥2 + DES*	2.5 (2.0-3.0)	3-6 months	+ ASA 81 mg +clopidogrel
	2.5 (2.0-3.0)	6-12 months	+ ASA 81 mg daily
	2.5 (2.0-3.0)	≥ 12 months	TSOAC>VKA>ASA+clopidogrel
• $CHADS_2$≥2 + BMS*	2.5 (2.0-3.0)	1 month	+ ASA 81 mg +clopidogrel
	2.5 (2.0-3.0)	1-12 months	+ ASA 81 mg daily
	2.5 (2.0-3.0)	≥ 12 months	TSOAC>VKA>ASA 81 mg +clopidogrel
Patients with ACS and no stenting			
• $CHADS_2$ 0 + ACS without stenting	none	12 months	DAPT
	none	≥ 12 months	ASA 81 mg daily
• $CHADS_2$ ≥ 1 + ACS without stenting	2.5 (2.0-3.0)	12 months	+ ASA 81 mg daily
	2.5 (2.0-3.0)	≥ 12 months	TSOAC>VKA>ASA 81 mg +clopidogrel
AF and stable CAD (if choosing OAC)	2.5 (2.0 - 3.0)	chronic	TSOAC>VKA>ASA 81 mg +clopidogrel
VALVULAR AF/FLUTTER			
With mitral stenosis or prosthetic heart valve	2.5 (2.0 - 3.0)	chronic	-or higher valve-specific goal INR -VKA> ASA 81 mg +clopidogrel
ISCHEMIC STROKE			
Non-cardioembolic stroke or TIA	none	chronic	Clopidogrel>Aggrenox>ASA 81mg
Cardioembolic stroke or TIA	2.5 (2.0 - 3.0)	chronic	ASA 160-325 mg recommended rather than therapeutic anticoagulation in the immediate post-stroke period (first 1-2 weeks) Once risk for hemorrhagic conversion is minimal (~ 14 days out from index stroke), consider transition to warfarin using ASA as bridge until INR >2
• With contraindications to warfarin	none	chronic	ASA 81 mg +clopidogrel> ASA
• Associated with aortic atherosclerotic lesions	none	chronic	ASA 81 mg daily

• Associated with mobile aortic arch thrombi	2.5 (2.0 - 3.0)	chronic	or ASA 81 mg daily
• Associated with patent foramen ovale	none	chronic	ASA 81 mg daily
PRIMARY PREVENTION OF CARDIOVASCULAR DISEASE (CVD)	none	chronic	ASA 81 mg daily
SECONDARY PREVENTION OF CVD			
Established (a.k.a. STABLE) CAD (≥1 year post- ACS, with prior revascularization, coronary stenosis >50% and/or evidence of ischemia on testing)	none	chronic	ASA 81 mg daily
NSTEMI/UA			
• ACS without PCI	none	12 months	DAPT (ticagrelor+ASA>clopidogrel+ASA)
		≥12 months	ASA 81 mg daily
• ACS with PCI but no stent	none	1 month	DAPT
		≥ 1 month	ASA 81 mg daily
• ACS with PCI and stent placement			
BMS	none	12 months	DAPT (ticagrelor+ASA>clopidogrel+ASA)
		≥12 months	ASA 81 mg daily
DES	none	≥12 months	DAPT (ticagrelor+ASA>clopidogrel+ASA) or ASA 81 mg daily monotherapy depending on bleed risk
STEMI			
Following MI in high risk patients [anterior MI, significant heart failure, intracardiac thrombus, hx TE]			
• without stenting	2.5 (2.0 - 3.0)	3 months	+ ASA 81 mg daily
	None	3-12 months	DAPT
	none	≥ 12 months	ASA 81 mg daily
• with BMS*	2.5 (2.0 - 3.0)	1 month	+ ASA 81 mg +clopidogrel
	2.5 (2.0 - 3.0)	2-3 months	+ ASA 81 mg daily
	none	3-12 months	DAPT
		≥ 12 months	ASA 81 mg daily
• with DES*	2.5 (2.0 - 3.0)	3-6 months	+ASA 81 mg +clopidogrel
	none	6-12 months	DAPT
	none	≥ 12 months	DAPT or ASA 81 mg daily monotherapy depending on bleed risk
VENOUS THROMBOEMBOLISM {with concurrent UFH/LMWH/fonda for at least 5 days and until INR>2 for > 24 hrs} **(for DVT, add elastic compression stockings with 30-40mmHg at ankle for 2 years)*			
Provoked			
• Transient risk factors	2.5 (2.0 - 3.0)	3 months	May also consider rivaroxaban single drug therapy
• Persistent risk factors (e.g. obesity, hormone therapy)	2.5 (2.0 - 3.0)	≥ 3 months	
Unprovoked			
• First event	2.5 (2.0 - 3.0)	≥ 3 months	Consider use of *DASH* score (Appendix C) or *Men Continue HERDOO2* score (Appendix D) to determine duration of therapy May also consider rivaroxaban single drug therapy
• Second event	2.5 (2.0 - 3.0)	chronic	
With active malignancy	2.5 (2.0 - 3.0)	chronic	preceded by LMWH x 3-6 months
Chronic thromboembolic pulmonary hypertension	2.5 (2.0 - 3.0)	chronic	
Cerebral venous sinus thrombosis	2.5 (2.0 - 3.0)	up to 12 mo.	
Spontaneous superficial vein thrombosis	2.5 (2.0 - 3.0)	4 weeks	or prophylactic LMWH or fondaparinux x 4 weeks
VALVULAR DISEASE			
Mitral valve prolapse:			
• With TIAs or ischemic stroke	none	chronic	ASA 81mg 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 81mg daily or INR 2.5-3.5
VALVE REPLACEMENT – BIOPROSTHETIC			
Aortic	none	chronic	- ASA 81 mg daily - may also consider warfarin (INR 2-3) for 1st 3 months, then ASA 81 mg daily
• Transcatheter aortic valve insertion (TAVI)	none	3 months	ASA 81 mg +clopidogrel
	none	≥ 3 months	ASA 81 mg po daily
Mitral	2.5 (2.0 - 3.0)	3 months	followed by ASA 81mg daily
• With LA thrombus	2.5 (2.0 - 3.0)	until resolution	
• With prior history of systemic embolism	2.5 (2.0 - 3.0)	≥ 3 months	
• With additional risk factors for thromboembolism [AF, previous thromboembolism, hypercoagulable condition, low EF]	2.5 (2.0 - 3.0)	chronic	add aspirin 81mg daily if low bleed risk
VALVE REPLACEMENT - MECHANICAL♦			
Aortic			
• Bileaflet in NSR with normal LA size	2.5 (2.0 - 3.0)	chronic	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	May also consider INR of 2.5-3.5 for first 3 months
• Starr-Edwards or mechanical disk valve	3.0 (2.5 - 3.5)	chronic	
• Following prosthetic valve thrombosis	3.5 (3.0 - 4.0)	chronic	
Mitral			
• Bileaflet or tilting disk	3.0 (2.5 - 3.5)	chronic	
• Following prosthetic valve thrombosis	4.0 (3.5 - 4.5)	chronic	
Caged ball or caged disk (aortic or mitral)	3.0 (2.5 - 3.5)	chronic	
With additional risk factors for thromboembolism [AF, MI, LA enlargement, hypercoagulable condition, low EF]	3.0 (2.5 - 3.5)	chronic	
With systemic embolism despite adequate anticoagulation	increase INR goal	chronic	
Both aortic and mitral	3.0 (2.5 - 3.5)	chronic	

* For patients on triple therapy (e.g. warfarin, aspirin, clopidogrel), it might be reasonable to target a lower INR of 2-2.5

♦ For all patients with mechanical valve(s) at low risk of bleeding, consider adding ASA 81 mg po daily

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; PCI=percutaneous coronary intervention; SAPT=single antiplatelet therapy; TSOAC= target specific oral anticoagulant; VKA=vitamin K antagonist (warfarin)

Appendix A: $CHADS_2$ to estimate annual risk of stroke in atrial fibrillation

Risk factor	Score
Congestive heart failure (any history)	1
Hypertension (prior history)	1
Age ≥ 75 years	1
Diabetes mellitus	1
Stroke/TIA/ systemic embolism (prior history)	2
Maximum possible score	6

$CHADS_2$ Score	Annual stroke risk (%)		NNT
	With warfarin	No warfarin	
0	0.25	0.49	417
1	0.72	1.52	125
2	1.27	2.5	81
3	2.2	5.27	33
4	2.35	6.02	27
5 or 6	4.6	6.88	44

Appendix B: CHA_2DS_2VASc to estimate annual risk of stroke in atrial fibrillation

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

Appendix C: DASH score for idiopathic VTE treatment duration

Prognostic Recurrence Score $D_2A_1S_1H_2$
+2 points for positive post-anticoagulation (30 days) **D**-dimer
+1 for **A**ge < 50
+1 for male **S**ex
- 2 for **H**ormone use at the time of initial VTE

DASH score ≤1: consider discontinuing anticoagulation
DASH score >1: consider indefinite anticoagulation (if no contraindications exist)

Appendix D: Men Continue and $HERDOO_2$ score for idiopathic VTE treatment duration

- **MEN continue and HER DOO2 (Gender, HER, D-dimer, Obesity, Older age)**

Women with ≥ 2 of the following features should continue therapy (HERDOO2)
▪ Post-thrombotic signs **H**yperpigmentation **E**dema **R**edness in either leg
▪ **D**-dimer level> 250mcg/L at end of initial treatment period
▪ **O**besity (BMI >30 kg/m^2)
▪ **O**lder age (≥65 years)

- Men with an idiopathic VTE have a mean annual risk of >3% for a recurrent VTE event
  - Men should consider continued use of anticoagulation.
- Women with 0-1 risk factors have <3% mean annual risk of recurrence of VTE
  - Women may be stratified into low (≤1) and high risk (≥2)
    - Low risk women may not warrant indefinite anticoagulation
    - High risk women should consider continued use of anticoagulation

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