Novant Health Inpatient Warfarin Dosing Program Guidance

Program Outline	

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Introduction

Warfarin (Vitamin K antagonist) is a narrow therapeutic index medication that requires targeted INR range for efficacy and reduction of bleeding complications. Improper dosing of warfarin can lead to bleeding or thromboembolism which may prolong hospital stay, require frequent follow-ups, and contribute to increased healthcare costs. Standardized dosing and monitoring tools are recommended for most patients on warfarin.

Novant Health inpatient warfarin dosing program provides recommendations to manage anticoagulation therapy with warfarin. Its recommendations are based on the evidence outlined from the Antithrombotic Therapy and Prevention of Thrombosis 9th edition: American College of Chest Physicians Clinical Practice Guidelines (CHEST).[1-7]

Definitions

1. Medically stable	Patient is clinically stable for at least 7 days along with INR being stable for at least 7 days on warfarin regimen. In addition, there are no new drug and dietary interactions that may influence warfarin's effect on INR.
2. INR	International normalized ratio. Baseline INR will be required to dose warfarin. Daily INR will be monitored until it is stable for 7 days, and then every 3 days.
3. CBC	Complete blood count. Baseline CBC will be obtained within 48 hours prior to initiating warfarin and then a minimum of every 3 days.
4. POD	Postoperative day
5. EHR	Electronic Health Record

1. Purpose

a. To establish collaboration between Novant Health providers and pharmacists for management of warfarin therapy for all hospitalized adult patients through utilization of a standardized approach

b. To optimize warfarin therapy by increasing efficacy, minimizing adverse effects, and educating patients and healthcare professionals regarding the safe use of warfarin

2. Procedures for warfarin dosing program

a. Provider responsibilities:

i. The provider must order ***pharmacy consult to dose warfarin through warfarin order set***. Indication, target INR range, and intended duration of therapy is provided to pharmacy via documentation within the required warfarin order placeholder in the order set.

ii. The consulting provider is ultimately responsible for overseeing the care of the consulted patients. Provider collaboration with the pharmacist is essential for facilitating optimal quality and continuity of care for patients. The provider should notify the pharmacist if any of the listed situations occur:

- When the patient's dosage is changed by a provider other than the consulting pharmacist
- When a bleeding or thromboembolic event is diagnosed or suspected
- When anticoagulation should be held for any reason (e.g., scheduled procedure while admitted)
- When anticoagulation consult is cancelled for any reason

iii. The provider is responsible for notifying pharmacy if there are any known

complicated diseases that could impact warfarin dosing such as active liver disease, severe anemia, and acute heart failure.

iv. The provider must order any reversal agents or blood products if necessary.
v. The provider must work collaboratively with pharmacy and be available for communication and questions.
vi. Pharmacogenomic testing may be considered/ordered by the provider if desired. Note: Currently, there is a 5 - 7 days turnaround time for test completion, which limits utility of these tests during inpatient admissions.

b. Clinical pharmacist responsibilities:

i. It is an expectation that all clinical pharmacists complete required training prior to participating in the Warfarin Dosing Program **(section 3.l.).**
ii. Upon receiving the initial warfarin order and pharmacy consult order, pharmacist assumes the responsibility of dosing warfarin daily based on INR, CBC, and clinical status until pharmacy consult is discontinued or patient is discharged.
iii. If pharmacy consult to dose warfarin is not ordered by provider and only warfarin dose is ordered, pharmacist reaches to the provider to initiate warfarin order set and requests pharmacy consult to dose warfarin. If the provider chooses to not order pharmacy consult for warfarin, then pharmacist still monitors warfarin regimen daily according to warfarin dosing program guidance and suggests necessary recommendations to the provider.
iv. *Patient assessment for warfarin dosing:* Prior to dosing warfarin, pharmacist must perform a comprehensive patient assessment including:
    - Review of patient's past medical history, home dose (included recent missed doses), and current medications
    - Assessment of risk factors that may make patients more sensitive to the effects of warfarin **(section 3.d.)**
    - Review of baseline INR, daily INR, CBC, albumin, drug-interactions, drug-disease interactions, and dietary considerations
v. *Laboratory Monitoring:* Pharmacist has the ability to order lab work related to warfarin.
    - INR:
        - Baseline PT/INR and PTT must be assessed/available in the electronic health record (EHR) prior to verification of warfarin.
        - A current INR must be assessed in the EHR prior to adjusting the warfarin dose.
        - Obtain daily PT/INR until INR is stable for at least 7 days and patient is medically stable, then minimally every 3 days.
    - CBC:
        - A baseline CBC should be obtained within 48 hours prior to initiating warfarin and a minimum of every 3 days thereafter.
    - Urine HCG:
        - Urine HCG (pregnancy test) should be obtained for women of childbearing age before initiating warfarin.
vi. *Determination of warfarin dosing*:
    - Initiation and maintenance dosing nomograms **(sections 3.f. & 3.g.**) are

provided in this document that can be utilized by the pharmacist to assist in dosing warfarin; however, these nomograms are NOT a substitute for clinical judgment. Warfarin dosing should be tailored based upon patient's bleeding risk, potential sensitivity to warfarin, indication, goal INR range, drug interactions, dietary considerations, clinical status, and pharmacogenomic testing (if available).

- The pharmacist selects frequency of **once 1700** instead of daily 1700 (even if home regimen is being followed). This allows the pharmacist to review warfarin daily and prevent errors (e.g., duplicate warfarin doses, unintended doses).
- The pharmacist evaluates the need for anticoagulant bridge therapy and contacts the provider if bridging is recommended but not ordered. Pharmacist may discontinue concomitant unfractionated heparin or low molecular weight heparin (LMWH) when two consecutive therapeutic INRs have been obtained **(section 3.h.).**

vii. Documentation of warfarin consults and ancillary notes

- **Inpatient:** The pharmacist documents an ancillary note **(section 3.j.)** in the EHR on initiation of pharmacy consult, and then daily thereafter.
- **Skilled nursing facility/behavioral health:** The pharmacist documents an ancillary note **(section 3.j.)** in the EHR on initiation of pharmacy to dose order and then daily thereafter. Once INR is stable for 7 days and patient is medically stable, INR frequency may be changed to every 3 days, necessitating an ancillary note every 3 days at that point.
- Ancillary notes and i-vents will be documented and available within 24 hours of dosing warfarin
- When contacting providers, Novant Health's mobile communication system, including secure text messaging, phone call, and pages, versus communication note to providers are utilized depending on situation urgency.

viii. Notification to provider

- The ordering provider is contacted if INR > 4.5 (unless provider has already noted that they are aware of INR elevation and do not wish to use reversal agents at that time). The need for reversal agents or blood products is discussed with the provider and must be ordered by the provider if necessary.

ix. *Warfarin counseling:* Pharmacist is available for patient counseling about warfarin upon request **(section 3.k.)**.

c. Nursing responsibilities:

i. The nurse monitors for signs and symptoms of bleeding (e.g., bleeding from surgical site, blood in stools, emesis, bruising, pallor) for all warfarin patients.
ii. The nurse notifies pharmacy and provider regarding bleeding complications and falls.
iii. The nurse notifies pharmacy if there is a planned procedure requiring warfarin therapy to be interrupted
iv. The nurse provides education to patient regarding warfarin that includes but is not

limited to

- Goals of therapy
- Desired INR range
- Signs and symptoms of bleeding and thromboembolic events and the steps to take in those instances
- Potential drug-drug and drug-food interactions

v. The nurse should be able to request pharmacy education for complicated patient cases.

3. Warfarin overview

a. Mechanism of action: Vitamin K Antagonist – Inhibits vitamin K epoxide reductase complex 1 (VKORC1), responsible for cyclic interconversion of Vitamin K in the liver. Reduced Vitamin K is a cofactor required for carboxylation of the vitamin K- dependent coagulation factors II (prothrombin), VII, IX, and X and the endogenous anticoagulants, proteins C and S. By inhibiting the reduced vitamin K supply needed for production of these proteins, warfarin therapy produces coagulation proteins with less activity. By suppressing clotting factor production, warfarin prevents initial thrombus formation and propagation.[8]

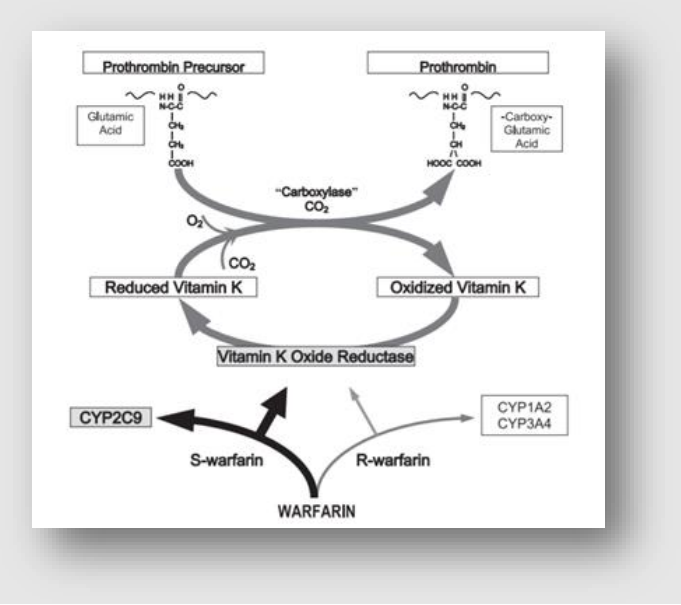

Figure 1. Vitamin K_1 is reduced to vitamin KH2. The major warfarin-sensitive enzyme in this reaction is the vitamin K oxide reductase mainly inhibited by the S-enantiomer of warfarin. S-warfarin is metabolized by CYP450 enzyme, CYP2C9.[3]

b. Pharmacokinetics / Pharmacodynamics[9]:

Administration Route	Oral
Drug Composition	Racemic mixture of R and S enantiomers; S- enantiomer is ~ 3 to 5 times more potent than the R-enantiomer
Absorption	Rapid and complete
Onset of Action	Typically, 24 to 72 hours. **NOTE:** A peak therapeutic effect is seen 5 to 7 days after initiation. However, patient's INR may increase within 24 to 36 hours after dose administration. Consider half-lives of inhibited clotting factors when dosing warfarin (factor VII = 6 hours, factor XI = 24 hours, factor X = 36 hours, factor II = 72 hours). Functional clotting factors already produced must "run their course" and cannot be inhibited with higher doses, regardless of the INR.
Duration of Action	2 to 5 days
Volume of distribution	0.14 L/kg, small
Protein binding	99%
Metabolism	Hepatic, primarily via CYP2C9; minor pathways include CYP2C8, 2C18, 2C19, 3A4
Half-life elimination	20 to 60 hours; mean: 40 hours

c. Warfarin indications, INR goals, and therapy duration

i. **Optimal INR target range in atrial fibrillation (AF):** For stroke prevention in patients with AF receiving warfarin, the optimal INR target range is 2 – 3. Numerous observational studies have demonstrated that the risk of thromboembolism/ ischemic stroke is greater when INR is < 2, whereas INR levels > 3 are associated with a greater incidence of major bleeding, especially intracranial hemorrhage when the INR rises above 3.5.[10]

ii. INR goals and duration of therapy listed in **table 1** are recommended by the CHEST guidelines.

Table 1: Warfarin indications, INR goals, and duration of therapy [1-7, 10]

Indications with target INR 2 – 3	**Duration of therapy**
Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE)	At least 3 months
Atrial Fibrillation/ Atrial Flutter (AF/AFL) • CHA_2DS_2 VASc ≥ 1 • Pre-cardioversion (AF or AFL > 48 hours) • Post-cardioversion	 Chronic 3 weeks 4 weeks
Cardioembolic stroke or transient ischemic attack (TIA) with cerebral venous sinus thrombosis	3-6 months
Rheumatic mitral valve disease (with left atrial diameter >55 mm, left atrial thrombus, AF or previous systemic embolism)	Chronic
Mitral bio-prosthetic valve replacement	3 months
Aortic mechanical valve replacement	Chronic
Prophylaxis of venous thromboembolism (VTE) after high-risk surgery • Total knee or hip arthroplasty • Hip fracture surgery	At least 10-14 days (up to 35 days postop)
Antiphospholipid syndrome	Chronic
Homozygous factor V Leiden	Chronic
Deficiency of protein C, S, or anti-thrombin	Chronic
Acute high-risk myocardial infarction (MI)- (includes large anterior MI, significant heart failure, intracardiac/LV thrombus and thromboembolism)	At least 3 months
WATCHMAN Left Atrial Appendage Closure Device	45 days
Aortic On-X mechanical valve **(can consider 1.5 – 2 after 3 months)*	3 months*
Indications with target INR 2.5 – 3.5	**Duration of therapy**
Mitral mechanical valve replacement	Chronic
Dual aortic and mitral valve	Chronic
First generation aortic mechanical prosthetic valve (i.e. caged ball or caged disk)	Chronic
Modern aortic valve with AF or other risk factors for thromboembolism • Cardiomedics bi-leaflet • Medtronic-Hall tilting disk	Chronic
Mechanical prosthetic valve with systemic embolism despite adequate anticoagulation	Chronic
Mechanical valve and risk factors (AF, MI, left atrial enlargement, low EF, endocardial damage)	Chronic
Embolism developed with therapeutic INR	Chronic
Mitral On-X mechanical valve	Chronic

d. Factors affecting warfarin sensitivity

i. Risk factors that can increase patient's sensitivity to the effects of warfarin should be assessed when dosing warfarin. A lower initiation dose or reduced maintenance dose is recommended when one or more risk factors exist. Clinical pharmacist should review patient's medical history prior to dosing warfarin.

ii. Pharmacogenomic testing for warfarin is not recommended for **inpatients** due to delayed turnaround time (~ 5 to 7 days). Greatest utility is anticipated to be in outpatient setting.

iii. Table 2 provides risk factors that may increase INR response or bleeding risks.

Table 2: Factors for identifying warfarin sensitive patients [1, 3, 11]

Increased INR Response	Increased Bleeding Risk
Acute infection	Alcohol abuse
Age > 65 years	Current anti-platelet therapy
Baseline INR ≥ 1.5	Fall risk
Chronic diarrhea (variable)	GI bleed within the past 30 days
Fever	History of stroke
Heart failure	Hyperthyroidism (variable)
Hypoalbuminemia < 2g/ dL	Liver disease (cirrhosis, elevated LFTs)
Low body weight (actual < ideal)	Renal disease
Malignancy (variable)	Select ethnic group (e.g., Asians)
Malnourished/ NPO	Surgery within the past 14 days
Significant drug interactions	Thrombocytopenia (platelets < 10,000/ microliter)

e. Drug, food, and dietary supplement interactions with warfarin[3, 12]

i. Warfarin has > 200 identified drug interactions; therefore, clinical pharmacist must run a drug interaction report in database (e.g Lexicomp, Micromedex, Epic) before determining a warfarin dose.

ii. As warfarin is metabolized via Cytochrome P450 (CYP) enzymes, it is important to be aware of interactions with certain CYP inducers and inhibitors

iii. Clinical pharmacist should also be aware of dietary interactions and patient's dietary status. Warfarin is a highly protein bound drug with 99% of the drug bound to plasma proteins. Patients who are malnourished with low albumin levels or NPO for a long period of time can have higher concentrations of unbound warfarin and may experience faster INR response. On the contrary, patients receiving enteral nutrition may have decreased INR response due to high protein concentrations.

iv. Warfarin drug, food, and dietary supplement interactions provided by the CHEST Guidelines are listed in **tables 3 and 4.**

Table 3: Warfarin major drug interactions[12]

Drug	Onset of Interaction	Adjustment
CYP Inhibitors – Increase risk of bleeding		
Amiodarone	7 to 21 days (may occur within 48 h with IV amiodarone or oral loading doses)	20% - 40% warfarin dose reduction*
Sulfamethoxazole/ Trimethoprim	Expect INR increase on day 3 to 5	25% - 40% warfarin dose reduction*
Fluconazole	Expect INR increase on day 3 to 5	20% - 50% warfarin dose reduction*
Metronidazole	Expect INR increase on day 3 to 5	25% - 40% warfarin dose reduction*
CYP Inducers – Decrease risk of bleeding		
Rifampin	As early as few days to weeks	50% dose increase
Carbamazepine	Weeks	50% dose increase

**Pharmacist must use clinical judgement when making dose adjustments*

Table 4: Common drugs, food, and dietary supplement interactions with warfarin[3] (NOTE: this is not a comprehensive list)

Potentiation			
Drug class	**Highly probable**	**Probable**	**Possible**
Anti-infectives	Ciprofloxacin Erythromycin Fluconazole Isoniazid Metronidazole Miconazole oral gel/vaginal suppository Voriconazole	Amoxicillin/clavulanate Azithromycin Clarithromycin Itraconazole Levofloxacin Ritonavir Tetracycline	Amoxicillin Amoxicillin/tranexamic rinse Chloramphenicol Gatifloxacin Miconazole topical gel Nalidixic gel Norfloxacin Ofloxacin Saquinavir Terbinafine
Analgesics, anti-inflammatories, and immunologics	Phenylbutazone Piroxicam	Acetaminophen Aspirin Celecoxib Interferon Tramadol	Celecoxib Indomethacin Leflunomide Sulindac Tolmetin Topical salicylates
Cardiovascular	Amiodarone Clofibrate Diltiazem Fenofibrate Propafenone Propranolol Sulfipyrazone (biphasic with later inhibition)	Aspirin Fluvastatin Quinidine Ropinirole Simvastatin	Amiodarone-induced toxicosis Disopyramide Gemfibrozil Metolazone Dronedarone
CNS drugs	Alcohol (also if concomitant liver disease) Citalopram Entacapone Sertraline	Disulfiram Chloral hydrate Fluvoxamine Phenytoin (biphasic with later inhibition)	Felbamate
GI drugs and food	Cimetidine Fish oil Mango Omeprazole	Grapefruit	Orlistat
Herbal supplements	Boldo-fenugreek Quilinggao	Danshen Don quai Lycium barbarum (Goji berry) PC-SPES Red rice yeast	Danshen/methylsalicylates
Other drugs	Anabolic steroids Zileuton	Fluorouracil Gemcitabine Levamisole/fluorouracil Paclitaxel Tamoxifen Tolterodine	Acarbose Cyclophosphamide/ methotrexate/fluorouracil Daptomycin Danazol Ifosfamide Trastuzumab
Inhibition			
Anti-infectives	Griseofulvin Nafcillin Ribavirin Rifampin	Dicloxacillin Ritonavir	Terbinafine
Analgesics, anti-inflammatories, and immunologics	Mesalamine	Azathioprine	Sulfasalazine
Cardiovascular	Cholestyramine	Bosentan	Telmisartan
CNS Drugs	Barbiturates Carbamazepine	Chlordiazepoxide	
GI drugs and food	High vitamin K content foods/ enteral feeds Large amount of avocado	Soy milk Sucralfate	Sushi containing seaweed

f. Initial dosing

i. Clinical pharmacist can utilize nomogram provided in this document to determine initial warfarin dose; however, clinical judgment is required to determine appropriate dose.

ii. As a reminder, clinical pharmacist should assess patient's bleeding risk, factors that increase warfarin sensitivity, indication, goal INR range, potential drug and dietary interactions, home warfarin dose (if applicable), and any missed doses (if applicable), when determining initial warfarin dose or adjusting the dose.

iii. Baseline INR and CBC **must** be available in EHR prior to the verification of the first warfarin dose. All warfarin dose adjustments **must** be based on current INR measurement.

iv. **Initial dose is typically 5 mg daily for most hospitalized patients. However, a lower starting dose of 2.5 mg should be considered in patients who have factors that can increase warfarin sensitivity (table 2). The 7.5 mg initiation nomogram should only be used in relatively young and healthy patients who are likely insensitive to warfarin, or who are taking concurrent medications that induce warfarin metabolism. For patients receiving warfarin prior to admission, their home dose should be taken into consideration.**

v. If INR is previously therapeutic, and a single out-of-range INR is 0.5 or less above or below the therapeutic range, then current dosing may be continued.

vi. No dose adjustment is needed if INR is within 0.1 of goal, but close monitoring is required (especially if below goal).

vii. Clinical pharmacist should allow 2 days (48 hours) after a dose adjustment before making any additional adjustments.

viii. Warfarin must be reviewed and dosed daily even if home regimen is being followed. Clinical pharmacist should avoid scheduled dosing of warfarin and must use **"once 1700" frequency** when dosing warfarin. Once the patient is medically stable for 7 days, the pharmacist may enter a scheduled regimen but should monitor daily for any changes to patient's medication therapy or clinical status that may impact warfarin's effect (INR and CBC to be obtained minimally every 3 days in stable patients).

Table 5: Warfarin Dosing Protocol with INR Goal 2 -3 [13]

Initiation nomogram for INR goal: 2 – 3		2.5 mg initiation	5 mg initiation	7.5 mg initiation
Day	**INR**	**Dose**	**Dose**	**Dose**
1	-	2.5 mg	5 mg	7.5 mg
2	< 1.5	2.5 mg	5 mg	7.5 mg
	1.5 – 1.9	1.25 mg	2.5 mg	5 mg
	2 – 2.5	0.5 – 1.25 mg	1 – 2.5 mg	1.5 – 3.5 mg
	> 2.5	0 mg	0 mg	0 mg
3	< 1.5	2.5 – 5 mg	5 – 10 mg	6.5 – 12mg
	1.5 – 1.9	1.25 – 2.5 mg	2.5 – 5 mg	3.5 – 6.5 mg
	2 – 2.5	0 – 1.25 mg	0 – 2.5 mg	0 – 3.5 mg
	2.5 – 3	0 – 1.25 mg	0 – 2.5 mg	0 – 3.5 mg
	> 3	0 mg	0 mg	0 mg
4	< 1.5	5 mg	10 mg	12 mg
	1.5 – 1.9	2.5 – 3.5 mg	5 – 7.5 mg	6.5 – 10 mg
	2 – 3	0 – 2.5 mg	0 – 5 mg	0 – 6.5 mg
	> 3	0 mg	0 mg	0 mg
5	< 1.5	5 mg	10 mg	12 mg
	1.5 – 1.9	3.5 mg – 5 mg	7.5 – 10 mg	10 – 12 mg
	2 – 3	0 – 2.5 mg	0 – 5 mg	0 – 6.5 mg
	> 3	0 mg	0 mg	0 mg
6	< 1.5	3.5 – 6.5 mg	7.5 – 12 mg	10 – 15 mg
	1.5 – 1.9	2.5 – 5 mg	5 – 10 mg	6.5 – 12.5 mg
	2 – 3	0 – 3.5 mg	0 – 7.5 mg	0 – 10 mg
	> 3	0 mg	0 mg	0 mg

The nomogram by Crowther et al.[13] was modified to create 2.5 mg and 7.5 mg nomograms since there are no published nomograms for 2.5 mg and 7.5 mg. NOTE: if goal INR 2.5 -3.5, slightly higher doses may be considered

g. Maintenance dosing nomogram for patients already on warfarin

i. Maintenance dosing nomogram can be utilized for patients already on warfarin

ii. Warfarin must be reviewed and dosed daily even if home regimen is being followed. Clinical pharmacist should avoid scheduled dosing of warfarin and must use **"once 1700" frequency** when dosing warfarin. Once the patient is medically stable for 7 days, the pharmacist can enter a scheduled regimen but should monitor daily for any changes to patient's medication therapy or clinical status that may impact warfarin effect (INR and CBC to be obtained minimally every 3 days in stable patients).

Table 6: Adjustment for maintenance therapy (patients already on warfarin*

Measured INR	Goal INR 2 – 3	Goal INR 2.5 – 3.5
< 1.5	Additional 50 – 100% of the daily dose x 1 day **AND** Increase weekly regimen by up to 20%	Additional 50 – 100% of the daily dose x 2 days **AND** Increase weekly regimen by up to 20%
1.5 – 2	Additional 0 – 50% of the daily dose x 1 day AND/OR Increase weekly regimen by up to 15%	Additional 50 – 100% of the daily dose x 1 day AND/OR Increase weekly regimen by up to 15%
2 – 2.5	No change	Increase weekly regimen by up to 10%
2.6 – 3	No change	No change
3.1 – 3.5	Decrease weekly regimen by up to 15% **AND/OR** Decrease by 50 – 100% of the daily dose x 1 day	No change
3.6 – 4	Hold 1 dose **AND/OR** Decrease weekly regimen by up to 20%	Decrease weekly regimen by up to 15% **AND/OR** Decrease by 50% of the daily dose x 1 day
Above 4	See section on Managing Elevated INRs	

*adapted from Johns Hopkins Warfarin Dosing Program (2017, 2020)

h. Bridging anticoagulation therapy [4, 14]

i. Patients receiving long-term treatment with warfarin may need warfarin therapy interruption due to upcoming surgery/procedure. Bridging anticoagulation therapy may be required, depending on their risk factors for thromboembolism.

ii. Bridging anticoagulation refers to administration of short-acting anticoagulant (e.g., low molecular weight heparin or unfractionated heparin) when warfarin therapy is interrupted, and its anticoagulant effect is below the target therapeutic range. Bridging anticoagulation aims to reduce patients' risk of developing blood clots, such as stroke, but may also increase patients' risk of developing potentially serious peri- and post-operative bleeding complications.

iii. Warfarin patients with the following indications may need bridge therapy based on risk factors for thrombosis outlined in **table 7**:

- Mechanical heart valve
- Atrial fibrillation
- Venous thromboembolism or other active thrombosis
- Hypercoagulable state

iv. Guidelines suggest that patients at high risk of thromboembolism should receive bridging anticoagulation, whereas no bridging is suggested for low-risk patients.

v. Clinical pharmacist should assess patients for bridging anticoagulation therapy when warfarin is interrupted and should contact provider when it is recommended but

not ordered. Agents that may be used as bridging anticoagulation are listed in **table 8.** Recommendations for interruption of warfarin therapy pre- and post-surgery are listed in **table 9.**

vi. When initiating patients on warfarin, and bridging anticoagulation therapy is warranted, then low molecular weight heparin or unfractionated heparin infusion will be continued until two consecutive INRs are in therapeutic range.

vii. At least 5 days of parenteral anticoagulation is required for VTE treatment when transitioning to warfarin.

viii. Patients with documented protein C and S deficiency should never receive warfarin alone. Concomitant administration of parenteral anticoagulation for 5 days is recommended.

ix. If patient is allergic to heparin or has a history of heparin induced thrombocytopenia (HIT), then argatroban may be utilized for bridging therapy anticoagulation. Clinical pharmacist should refer to **NH Clinical Guidelines: Heparin Induced Thrombocytopenia** for more information on argatroban as bridge anticoagulation therapy for warfarin.

Table 7: Risk stratification for thromboembolism

Thromboembolic Risk Category	**Mechanical heart valve**	**Atrial fibrillation**	**Venous thromboembolism**
High	Any mitral valve prosthesis Caged ball or tilting disc aortic valve prosthesis History of recent stroke, TIA, or cardioembolic event (within 6 months)	CHA_2DS_2 – VASc score ≥ 6 or $CHADS_2$ score of 5 – 6 Stroke or TIA within previous 3 months Rheumatic valvular disease	VTE within 3 months Severe thrombophilia (e.g., deficiency of protein C, protein S, or antithrombin; antiphospholipid antibodies; multiple abnormalities)
Moderate	Bi-leaflet aortic valve prosthesis and at least one of the following risk factors: - AF - previous stroke or TIA - hypertension - diabetes - congestive heart failure - age >75 yr	CHA_2DS_2 – VASc Score ≥ 4 to 5 or $CHADS_2$ score of 5 – 6 Previous stroke or TIA more than 3 months before	VTE within 3 to 12 months Non-severe thrombophilia (e.g., heterozygous factor V Leiden or prothrombin gene mutation) Recurrent VTE Active cancer (treated within 6 months or palliative)
Low	Bi-leaflet aortic valve prosthesis without AF or risk factors for stroke	CHA_2DS_2 – VASc score of 2 – 3 or $CHADS_2$ score of 0 – 2 (assuming no prior stroke or TIA)	VTE > 12 months prior or no other risk factors

Table 8: Agents used of bridge anticoagulation therapy

Unfractionated heparin IV infusion	Low therapeutic dose (ACS, AF, mechanical valve w/o active thrombus)	60 units/kg initial bolus, followed by 12 units/kg/h maintenance infusion
	High therapeutic dose (VTE/PE, mechanical valve with active thrombosis)	80 units/kg initial bolus, followed by 18 units/kg/h maintenance infusion
Low molecular weight heparin	Enoxaparin	• 1 mg/kg SC q12h or 1.5 mg/kg SC q24h • If CrCl < 30 ml/min: 1 mg/kg SC q24h or consider heparin IV continuous infusion • If CrCl <15 ml/min or dialysis, avoid low molecular weight heparin; recommend heparin IV continuous infusion
	Fondaparinux	• Weight < 50 kg: 5 mg SC q24h • Weight 50 – 100 kg: 7.5 mg SC q24h • Weight > 100 kg: 10 mg q24h • CrCl < 30 ml/min - Contraindicated

Table 9: Recommendations for interruption in warfarin therapy prior to procedure and initiation of warfarin therapy after procedure

Interruption of warfarin therapy pre-procedure						
***Only initiate bridge therapy when INR is below therapeutic goal**						
Schedule prior to surgery	**Day 5**	**Day 4**	**Day 3**	**Day 2**	**Day prior to surgery**	**Day of surgery**
Warfarin	Stop (last dose to be taken prior to procedure)	No warfarin	No warfarin	No warfarin	No warfarin	No warfarin
LMWH		Start in evening	Continue	Continue	Give morning dose only	No LMWH
UFH IV infusion		Start in evening	Continue	Continue	Continue	Stop 4 to 6h prior to surgery

Re-initiation of warfarin therapy post-procedure			
***Only initiate bridge therapy when INR is below therapeutic goal**			
Schedule after surgery	**POD 1 (day of surgery)**	**POD 2 – 3**	**POD 4 – 5**
Warfarin	Start 12 – 24 h post-surgery	Continue	Continue and dose adjust based on INR
LMWH or UFH IV infusion	Start 24 h post-surgery for non- high bleeding risk surgery	Start 48 – 72 h post-surgery for high bleeding risk surgery	Continue until INR in therapeutic range for 24 h and a minimum of 5 days overlap with warfarin

LMWH = low molecular weight heparin (e.g., enoxaparin and fondaparinux), UFH = unfractionated heparin

i. Warfarin reversal and management of elevated INRs [16]

i. No reversal agent can be initiated without a direct order from the provider

ii. As mentioned above, ordering provider will be notified by pharmacy when INR > 4.5. The need for reversal will be discussed with the provider and must be ordered by the provider. Guidelines for the management of elevated INR or bleeding warfarin patients are summarized in **table 10.**

iii. Vitamin K (phytonadione or vitamin K_1) is one of the agents utilized to reverse the anticoagulant effect of warfarin. Vitamin K reversal onset is delayed because several new clotting factors must be created to neutralize the effect of warfarin therapy. The following information should be considered when administering Vitamin K:

Vitamin K Formulation	Comments
Oral	Takes 24 – 48 h to normalize the INR Preferred route for managing INRs above the therapeutic range that are not associated with bleeding.
IV	Takes 8 – 12 h to normalize the INR with full effects not seen until 24 h. It should always be given as slow infusion instead of IV "push" because of concerns for allergic reactions.
SC	It should be avoided because of delayed and erratic absorption.

- Vitamin K should not be overdosed because this can lead to overaggressive reversal and difficulty in reinitiating warfarin therapy (warfarin resistance)
- If 4PCC (Kcentra) is required, vitamin K should always be given after 4PCC

iv. 4PCC is the agent used for warfarin reversal in patients requiring urgent surgery or with significant bleeding. When 4PCC is required for reversal of warfarin therapy, provider will use **NH Reversal of Vitamin K Antagonist: warfarin (Coumadin) – Adult order set** to order it. Clinical pharmacist should be aware of following information regarding 4PCC

- For warfarin therapy reversal, the dose of 4PCC will be 1000 units IV x 1 (doses ≤ 1000 units can be given as IV push over 5 minutes, but doses greater > 1000 units will be given as an IVPB over 20 minutes)
- An initial INR will not be required prior to ordering 4PCC, as long as it is known that patient has a life-threatening bleed and is on warfarin. However, **a 30-minute post Kcentra INR** is needed to evaluate if additional therapy is required. **If re-dosing is needed, it will need to be ordered from the "Reversal Re-Dosing for Vitamin K Antagonists: warfarin (Coumadin)" order set. There are recommendations for re-dosing if INR remains >1.4 on the order set for the 30-minute post infusion INR.**

Table 10: Management of elevated INR and warfarin reversal

INR	Bleeding	Intervention
Above goal but < 4.5	No significant bleeding	Omit doses of warfarin. Check INR daily. Restart warfarin at reduced dose once back in therapeutic range.
≥ 4.5 to ≤ 10	No significant bleeding	
≥ 4.5 to ≤ 10	Patient has risk factors for bleeding: (age > 65 years, concurrent anti-platelet therapy, concurrent NSAID use, history of GI bleed, recent surgery or trauma, high risk of fall or trauma, excessive alcohol use, renal failure, malignancy cerebrovascular disease)	Omit next 1 – 3 doses of warfarin AND administer vitamin K 5 mg PO or 1- 3 mg by slow IV infusion. Check INR in 12 – 24 h. If INR still >9, repeat administration of vitamin K. Check INR q 24h. Restart warfarin at reduced dose once therapeutic
> 10	No significant bleeding	
Elevated INR	Patient experiencing overt signs or symptoms of bleeding OR rapid reversal of excessive anticoagulation required and not at high risk of thrombosis*	Administer vitamin K 5 to 10 mg by slow IV infusion, together with 4PCC as needed. Check INR in 12 h and repeat vitamin K infusion as needed until INR normalized or within therapeutic range.

**History of hypercoagulability disorders, arterial or venous thrombosis within previous month, thromboembolism associated with malignancy, and high-risk mitral valve (with AF, poor ventricular function, or coexisting aortic valve*

Table 12: Warfarin conversion to and from other direct acting oral anticoagulants (DOAC)[17]

From dabigatran to warfarin	**From warfarin to dabigatran**
• CrCl ≥ 50: Start warfarin 3 days before discontinuing dabigatran • CrCl 31 – 50: Start warfarin 2 days before discontinuing dabigatran • CrCl 15 – 30: Start warfarin 1 day before discontinuing dabigatran • CrCl < 15: No dosing recommendations are available	Discontinue warfarin and start dabigatran when the INR < 2 (because dabigatran can contribute to an increased INR, the INR will better reflect warfarin's effect after dabigatran has been discontinued for at least 2 days)
From rivaroxaban to warfarin	**From warfarin to rivaroxaban**
Discontinue rivaroxaban and begin both a parenteral anticoagulant and warfarin when the next dose of rivaroxaban would have been taken. Discontinue the parenteral anticoagulant when the INR reaches an acceptable range	Discontinue warfarin and initiate rivaroxaban once INR < 3
From apixaban to warfarin	**From warfarin to apixaban**
Discontinue apixaban and begin both a parenteral anticoagulant and warfarin when the next dose of rivaroxaban would have been taken. Discontinue the parenteral anticoagulant when the INR reaches an acceptable range	Discontinue warfarin and initiate rivaroxaban once INR < 2
From edoxaban to warfarin	**From warfarin to edoxaban**
Oral option: For patients taking 60 mg of edoxaban, reduce the dose to 30 mg and begin warfarin concomitantly. For patients receiving 30 mg of edoxaban, reduce the dose to 15 mg and begin warfarin concomitantly. The INR must be measured at least weekly and just before the daily dose of edoxaban to minimize the influence of edoxaban on INR measurements. Once a stable INR ≥ 2 is achieved, edoxaban should be discontinued and warfarin continued. **Parenteral option:** Discontinue edoxaban, and administer a parenteral anticoagulant and warfarin at the time of the next scheduled edoxaban dose. Once a stable INR ≥ 2 is achieved, the parenteral anticoagulant should be discontinued and warfarin continued	Discontinue warfarin and start edoxaban when the INR is ≤ 2.5

j. Warfarin ancillary note and I-vent documentation

i. Clinical pharmacists are responsible for entering an I-vent and an ancillary note **daily** upon receipt of pharmacy consult to dose warfarin.

ii. Dose appropriateness is evaluated depending on patient condition after daily INR results. **After patient evaluation, ordering of 1700 warfarin once dose, ordering of appropriate follow up labs, i-vent documentation, and ancillary note documentation occurs. i-vent scratch notes are postdated for review the next day.**

iii. Clinical pharmacists will utilize the **.WARFARINNOTE** smart phrase built in EHR for warfarin consult i-vents and ancillary note documentation shown below:

Pharmacy Consult – Warfarin Dosing
Indication: ***
Relevant PMH/HPI/Risk Factors for increased warfarin sensitivity: ***
(e.g. heart failure, hepatic failure, shock, low body weight, malnutrition, diarrhea, advanced age, hyperthyroidism, ESRD, alcohol abuse)
Goal INR: ***
Home Dose: *** (missed doses? ***)

Relevant Labs: LFTs ***, Alb ***, SCr ***

Date	INR	Hgb	Plt	Dose
***	***	***	***	***
***	***	***	***	***

Drug-drug Interactions: ***
Diet (NPO/enteral feeds/PO percentage intake): ***
Additional anti-thrombotics/bridge therapy: ***
Bleeding Assessment: *** **Reversal agents given?** ***

Assessment/Plan: ***
**Initial or subsequent loading doses are not recommended. May take 3-5 days to see effect of dose change on INR.*
**For dose recommendation at discharge, please contact pharmacy.*

k. Patient education (Discharge warfarin counseling template addition)

i. Clinical pharmacists provide patient counseling about warfarin that should include:

- Education on purpose of anticoagulation, dose, route, and frequency
- Importance of medication compliance
- Rationale for evening dose administration
- Recommendations for missed doses
- Monitoring for signs and symptoms of bleed: easy bruising, blood in urine or stools, excessive menstrual bleeding, excessive nose bleeds, gum bleeds, and persistent bleeding from superficial wounds (minor cuts/ scrapes)
- Consistency with vitamin K intake
- Low alcohol consumption
- Minimization of fall risk with home safety
- Notification to provider if pregnant
- Discussion of over-the-counter medications and vitamins/herbal products

with provider or pharmacist
- Importance of INR checks

ii. Pharmacist opens and closes a "Document Patient Counseling" i-vent after providing counseling patient. Following template is utilized for documentation:

Pharmacist Discharge Attestation: Warfarin

Time spent counseling: *** min

Assessed patient's understanding of the disease state.

Educated (patient/family/caregiver) on:
- Changes to the medication regimen
- Mechanism of action
- Indication
- Adherence (e.g., missed doses)
- Side effects
- Monitoring (any serious fall or trauma to the head, bleeding that does not stop, bruises that do not heal, nosebleeds, vomiting blood, blood in the urine or stool, health status changes such as persistent diarrhea, vomiting or fever, etc)
- Drug interactions (aspirin, NSAID, etc)
- Food interactions (vitamin K)
- Stop prior to surgery/procedure

Understanding was assessed using teach back and ask me three.

l. Pharmacist Training:

i. Clinical pharmacists must complete the following to be able to participate in the Warfarin Dosing Program:
- Completion of an online competency module; will be required annually.
- Pass an anticoagulation assessment with a score of 90% or better.
- Train on site with another anticoagulation trained pharmacist.
- Complete 10 patient cases according to the warfarin dosing program and meet the criteria on the competency checklist; recommendations are approved by a trained program pharmacist.
- Pharmacists must keep up to date with ongoing changes in anticoagulation management; this will be accomplished through annual competency assessment.
- Education documentation will be maintained in the employees' files.

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