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Disclaimers:

These practice parameters are designed to provide general information for training and as a resource for HFMG Ambulatory Anticoagulation Services. This document is not a substitute for the best professional judgment of physicians or other health professionals, taking into consideration the individual circumstances presented by the patient. Acceptable medical practice may include a variety of responses to a particular clinical problem and all rationale should be documented in the patient's chart.

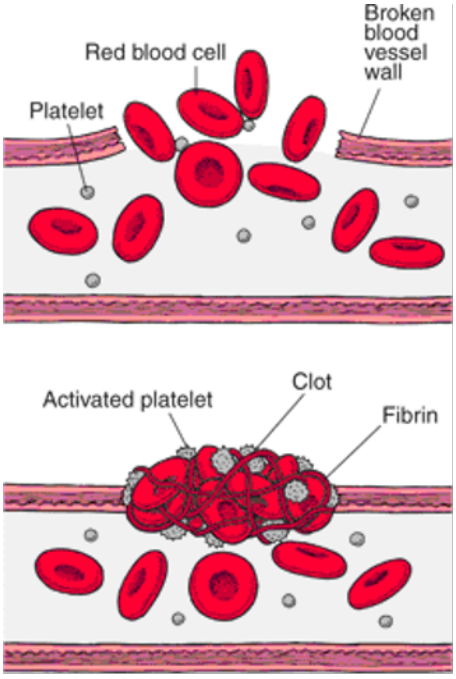
As practice guidelines and protocols frequently change, this document is periodically updated. Therefore, depending on when they are printed, hardcopies may not contain the most current information.

I. **Physiology of Coagulation**:

Hemostasis is the body's way of stopping injured blood vessels from bleeding. Hemostasis includes clotting of the blood. Too much clotting can block blood vessels that are not bleeding; consequently, the body has control mechanisms to limit clotting and dissolve clots that are no longer needed. An abnormality in any part of this system that controls bleeding can lead to excessive bleeding or excessive clotting, both of which can be dangerous. When clotting is poor, even a slight injury to a blood vessel may lead to major blood loss. When clotting is uncontrolled, small blood vessels in critical places can become clogged with clots. Clogged vessels in the brain can cause strokes; clogged vessels leading to the heart can cause heart attacks; and pieces of clots from veins in the legs, pelvis, or abdomen can travel through the bloodstream to the lungs and block major arteries there (pulmonary embolism).

Hemostasis involves three major processes: narrowing (constriction) of blood vessels, activity of platelets, and activity of blood clotting factors.

An injured blood vessel constricts so that blood flows out more slowly and clotting can start. At the same time, the accumulating pool of blood outside the blood vessel (a hematoma) presses against the vessel, helping prevent further bleeding. As soon as a blood vessel wall is damaged, a series of reactions activates platelets so that they stick to the injured area. The "glue" that holds platelets to the blood vessel wall is von Willebrand factor, a protein produced by the cells of the vessel wall. The proteins collagen and thrombin act at the site of the injury to induce platelets to stick together. As platelets accumulate at the site, they form a mesh that plugs the injury. The platelets change shape from round to spiny, and they release proteins and other substances that entrap more platelets and clotting proteins in the enlarging plug that becomes a blood clot.



Blood Clots: Plugging the Breaks

When an injury causes a blood vessel wall to break, platelets are activated. They change shape from round to spiny, stick to the broken vessel wall and each other, and begin to plug the break. They also interact with other blood proteins to form fibrin. Fibrin strands form a net that entraps more platelets and blood cells, producing a clot that plugs the break.

Formation of a clot also involves activation of a sequence of blood clotting factors that generate thrombin. Thrombin converts fibrinogen, a blood clotting factor that is normally dissolved in blood, into long strands of fibrin that radiate from the clumped platelets and form a net that entraps more platelets and blood cells. The fibrin strands add bulk to the developing clot and help hold it in place to keep the vessel wall plugged.

The reactions that result in the formation of a blood clot are balanced by other reactions that stop the clotting process and dissolve clots after the blood vessel has healed. Without this control system, minor blood vessel injuries could trigger widespread clotting throughout the body—which actually happens in some diseases.

II. **Hypercoagulable States**:

Hypercoagulable states (thrombophilia) are a group of inherited or acquired conditions associated with a predisposition to venous thrombosis (including upper and lower extremity deep venous thrombosis with or without pulmonary embolism, cerebral venous thrombosis, and intra-abdominal venous thrombosis), arterial thrombosis (including myocardial infarction, stroke, acute limb ischemia, and splanchnic ischemia), or both. These conditions can be categorized as either acquired or genetic (inherited). Examples of each type are listed in the table below:

Acquired **causes of thrombosis**	***Genetic*** **causes of thrombosis**
Trauma	Activated protein C resistance, e.g.,
Immobility or postoperative state	factor V Leiden
Cancer	Prothrombin 20210 mutation
Myeloproliferative disorder, e.g., polycythemia	Antithrombin deficiency
vera, essential thrombocytosis	Protein C deficiency
Estrogens, pregnancy	Protein S deficiency
Heparin-induced thrombocytopenia	Hyperhomocystinemia
Antiphospholipid syndrome	Dysfibrinogenemia
Anticardiolipin antibodies	Abnormal plasminogen
Disseminated intravascular coagulation	Increased factor VIII
Surgery	Sticky platelet syndrome

Activated protein C resistance and Prothrombin 20210 mutation account for approximately 50% of the genetic hypercoagulable states. More than 60% of patients with an unprovoked venous thromboembolism have an underlying inherited hypercoagulable abnormality. In patients with venous thromboembolism, presence or absence of hypercoagulable states, among other factors, may influence whether these patients will require bridge therapy with low molecular weight heparin.

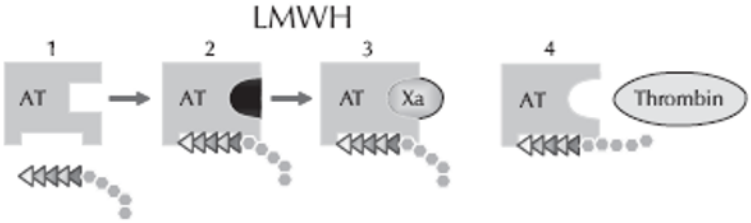
III. Low-Molecular-weight-Heparins (LMWH) Essential Skills:

LMWH are smaller molecular weight fragments derived from unfractionated heparin (UFH) by chemical or enzymatic depolymerization. Currently, the HFHS anticoagulation clinics utilize enoxaparin (Lovenox) as the formulary LMWH agent. LMWH have improved pharmacokinetic (what body does to the drug e.g., absorption, distribution, metabolism, and excretion) and Pharmacodynamic (what drug does to body e.g., receptor sensitivity, post-receptor effects) properties in comparison to UFH. Other advantages of using LMWH over UFH include: greater bioavailability; extensive clinical experience with subcutaneous administration, often facilitating outpatient treatment; longer duration of the anticoagulant effect, permitting administration only once or twice daily and administration in the outpatient setting; better correlation between dose and anticoagulant response, permitting administration of a fixed dose

without laboratory monitoring; lower risk of heparin-induced thrombocytopenia and lower incidence of osteoporosis.

Similar to UFH, effect of LMWH is mediated by binding to antithrombin (AT), a natural anticoagulant, and potentiates its activity. The result is inhibition of factor Xa and thrombin (factor II) activity.

LMWH Mechanism of Action



But unlike UFH, which inhibits factor Xa and thrombin activity to approximately the same extent, the inhibitory effect of LMWH is roughly 4 times greater on factor Xa than it is on thrombin. Because the partial thromboplastin time (PTT) is more sensitive to thrombin than it is to factor Xa, the PTT does not accurately measure the anticoagulant activity of LMWH. The elimination half-life of enoxaparin is about 4 hours which allows once or twice daily dosing. The primary route of elimination of LMWH is renal and dosage of enoxaparin is summarized below, based on creatinine clearance (renal function):

Creatinine clearance (CrCl)*	**Enoxaparin dose for therapeutic indications**
≥ 30 ml/min **	1 mg/kg SC q **12** hours
< 30 ml/min	1 mg/kg SC q **24** hours

* Calculation of creatinine clearance is discussed in this section.

** Collaboration with the anticoagulation physician may be necessary regarding patients with **moderate** (creatinine clearance 30–50 mL/min), particularly the elderly. Once daily dosing may be necessary in some of these patients based on case-by-case evaluation to minimize the risk of bleeding.

Dosing of enoxaparin (Lovenox) is based on actual (total) body weight. Dose rounding at the HFHS is summarized as follows, based on the available syringe size and concentration:

Dose required	Dose to be administered	Syringe to be dispensed
35 – 44 mg	40 mg once or twice a day	40 mg syringe
45 – 54 mg	50 mg once or twice a day	60 mg syringe
55 – 64 mg	60 mg once or twice a day	60 mg syringe
65 – 74 mg	70 mg once or twice a day	80 mg syringe
75 – 84 mg	80 mg once or twice a day	80 mg syringe
85 – 94 mg	90 mg once or twice a day	100 mg syringe
95 – 104 mg	100 mg once or twice a day	100 mg syringe
105 – 112 mg	105 mg once or twice a day	120 mg syringe*
113 – 127 mg	120 mg once or twice a day	120 mg syringe*
128 – 142 mg	135 mg once or twice a day	150 mg syringe*
143 – 154 mg	150 mg once or twice a day	150 mg syringe*

* Per Lovenox manufacturer package insert, maximum dose is 150 mg SC q 12 hours.

The 120mg and 150mg syringes are graduated in 15 mg per 0.1 ml increment. Enoxaparin 60mg, 80mg, and 100mg syringes are graduated in 10mg per 0.1 increments.

For dosing in patients who weigh more than 150 kg, Lovenox dosing and administration must be determined by an anticoagulation clinic pharmacist**.

****Considerations for Enoxaparin Dosing in Morbid Obesity:** Clinical practice guidelines do not offer consensus recommendations regarding enoxaparin dosing in morbidly obese patients. In patients with morbid obesity, differences in enoxaparin pharmacokinetics may lead to altered enoxaparin exposure. Observational studies have described therapeutic enoxaparin requirements in patients with body mass indices of > 40-50 kg/m2 and weights of > 140-200 kg. These studies demonstrated increased risk of enoxaparin over-exposure, based on supratherapeutic anti-Xa levels, when standard dosing (1 mg/kg Q12 hours) was used according to actual body weight. These studies also showed that lower weight-based doses (~0.7-0.85 mg/kg Q12 hours based on actual body weight) had a greater association with anti-Xa values within goal range.

(see page 51 and Appendix N regarding considerations for enoxaparin use in obesity)

Heparin-induced thrombocytopenia:

Heparin-induced thrombocytopenia (HIT) is serious complication associated with all types of heparins, including unfractionated heparin and low molecular weight heparin (LMWH). At the Henry Ford Health System, enoxaparin (Lovenox) is the formulary agent for LMWH. The incidence of HIT is about 1-2% at the most with unfractionated heparin. The incidence is even lower with LMWH and is probably less than 1%. Regardless of which heparin agent is used (unfractionated heparin or LMWH), the risk of HIT must be considered by the anticoagulation provider. At the anticoagulation clinic, monitoring for HIT mainly involves patients receiving enoxaparin (Lovenox).

By definition, HIT is a drop in platelet count of ≥ 50% from baseline even if platelet count nadir remains > 150,000/ul. With HIT, there is a 20-50% risk of developing thrombosis if the patient was not treated with a proper alternative anticoagulant in place of a heparin product. In general, there are three types of HIT presentations discussed in the literature. The most common presentation of HIT is when thrombocytopenia is detected at a minimum of 5 days after exposure to a heparin product. The estimated incidence for this presentation is about 65% of all HIT patients. Another possible presentation of HIT may be seen in the first 4 days of therapy and that is mostly seen in patients recently (< 100 days ago) exposed to a heparin product. For example, a patient that was hospitalized 1-2 weeks ago and treated with a heparin product during hospitalization would be a possible scenario where early onset HIT can be encountered. The estimated incidence for this presentation is about 35% of all HIT patients. The third possible presentation for HIT is that of a delayed onset. Typically, this type of a scenario can be encountered up to 40 days after exposure to a heparin product. Although we do not routinely monitor platelet counts after enoxaparin is discontinued, detection of thrombocytopenia after discontinuation of enoxaparin should prompt the anticoagulation provider to consider HIT as a possible cause and further evaluation may be necessary.

HIT is typically diagnosed by clinical presentation along with serology testing for heparin induced antibodies. If HIT is considered likely, enoxaparin must be discontinued immediately and consultation with the anticoagulation physician and/or physician champion is mandatory at that time. Further referral to a hematology service may be necessary afterwards. Warfarin is often discontinued if HIT diagnosis is confirmed and it may not be restarted until platelet count returns to normal (usually above 150,000). In such cases, warfarin doses should not exceed 5mg to avoid warfarin-induced drop in the natural anticoagulants such as protein C and S. Heparin induced thrombocytopenia with thrombosis (HITTS) refers to the above-mentioned decline in platelet count with ongoing venous or arterial thrombosis. HITTS is a more aggressive life-threatening condition than suspected HIT and requires therapy with a non-heparin anticoagulant (argatroban, fondaparinux or a direct oral anticoagulant [DOAC]). Please refer to the HFHS Tier1 guidelines: Heparin Induced Thrombocytopenia (HIT) for information regarding indication and dosage of these anticoagulants.

To summarize the role of the anticoagulation provider in the detection and management of HIT, the following should be considered:

- Order platelet counts according to protocol (baseline and every 2-3 days from day 4 to day 14 after starting enoxaparin)
- Consider closer monitoring of platelet count in patients recently exposed to IV heparin during a hospital stay.
- Evaluate recent use of heparin products whenever you encounter a patient with thrombocytopenia.
- Look for thrombosis (venous and arterial) regardless of presence of HIT and evaluate if patient was recently exposed to a heparin product.
- Patients with HIT cannot be challenged with any heparin product for at least 100 days, if not longer. Keep any information of development of HIT in EPIC Workflow.
- If HIT diagnosis is confirmed, warfarin is usually held temporarily until platelet count normalizes. Avoid aggressive warfarin dosing when warfarin is resumed.
- Remember to document the occurrence of HIT in the electronic medical record.

The **4Ts** is a pretest scoring system for HIT that was developed to improve and standardize clinical diagnosis. It incorporates 4 typical features of HIT: (1) magnitude of thrombocytopenia; (2) timing of thrombocytopenia with respect to heparin exposure; (3) thrombosis or other sequelae of HIT; and (4) likelihood of other causes of thrombocytopenia. The system yields an integer score between 0 and 8 with scores of 0-3, 4-5, and 6-8 classified as low, intermediate, and high pretest probability for HIT, respectively.

The 4Ts scoring system

4Ts category	2 points	1 point	0 points
Thrombocytopenia	PLT count fall > 50% and PLT nadir $\geq$ 20 AND no surgical procedure within the last 3 days	PLT count 30% - 50% or PLT nadir 10-19 OR PLT fall > 50% BUT surgical procedure within the last 3 days	PLT count fall < 30% or PLT nadir < 10
Timing of PLT count fall	Clear onset days 5-10 or PLT fall $\leq$ 1 day (prior heparin exposure within past 5-30 days)	Consistent with days 5-10 fall, but not clear (e.g. missing PLT counts); onset after day 10; or fall $\leq$ 1 day (prior heparin exposure 30 – 100 days ago)	PLT count $\leq$ 4 days without recent exposure to heparin in the past 100 days
Thrombosis or other sequelae	New thrombus (confirmed); skin necrosis; acute systemic reaction postintravenous UFH bolus	Progressive or recurrent thrombosis; non-necrotizing (erythematous) skin lesions; suspected thrombosis (not proven)	None
Other causes of thrombocytopenia	Nonapparent	Possible	Probable other cause present

Adapted from BLOOD, 15 NOVEMBER 2012 VOLUME 120, NUMBER 20

Creatinine Clearance (CrCl) Calculation:

CrCl = $\frac{(140 - age) \times IBW}{72 \times Scr}$ * (Multiply result by 0.85 for females)

FOR DOACs USE:

CrCl = $\frac{(140 - age) \times ABW}{72 \times Scr}$ * (Multiply result by 0.85 for females)

IBW: Ideal body weight in kilograms Scr: serum creatinine in mg/dl

ABW: Actual Body Weight (use for DOACs)

For patients with body height of less than 5 feet, use a height of 5 feet

* Body Weight to Use in Cockcroft-Gault Creatinine Clearance Calculation

Total Body Weight	Weight to use in CrCl calculation
Less than ideal body weight (IBW)	total body weight (TBW aka ABW [Actual Body Weight])
1 to 1.2 x IBW	ideal body weight (IBW) Male: 50 kg + [2.3 x (height in inches - 60)] Female: 45.5 kg + [2.3 x (height in inches - 60)]
1.2 x IBW	adjusted body weight (with factor of 0.4) AdjBW = IBW + [0.4 x (TBW - IBW)]

Example for calculation of CrCl:

68-year-old female with height of 5 ft., 3 inches and Scr of 1 mg/dl

IBW = 45.4 + (2.3 x 3) = 45.5 + 6.9 = 52.4 kg

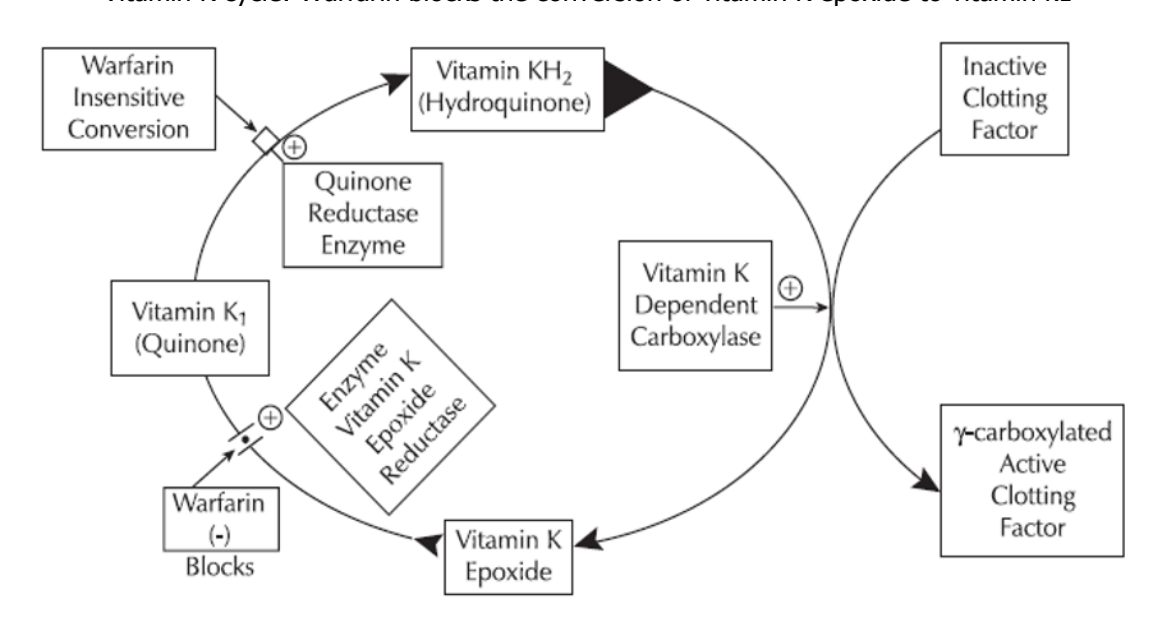
CrCl = $\frac{(140-68)\,x\,52.4}{72\,x\,1}$ x 0.85 = 44.5 ml/min

IV Warfarin Essential Skills:

Pharmacology:

Warfarin reduces clot formation by disrupting the liver's production of functional vitamin k dependent clotting factors II, VII, IX, and X. Warfarin prevents reductive metabolism of the inactive vitamin K epoxide back to its active hydroquinone (K_1) form.

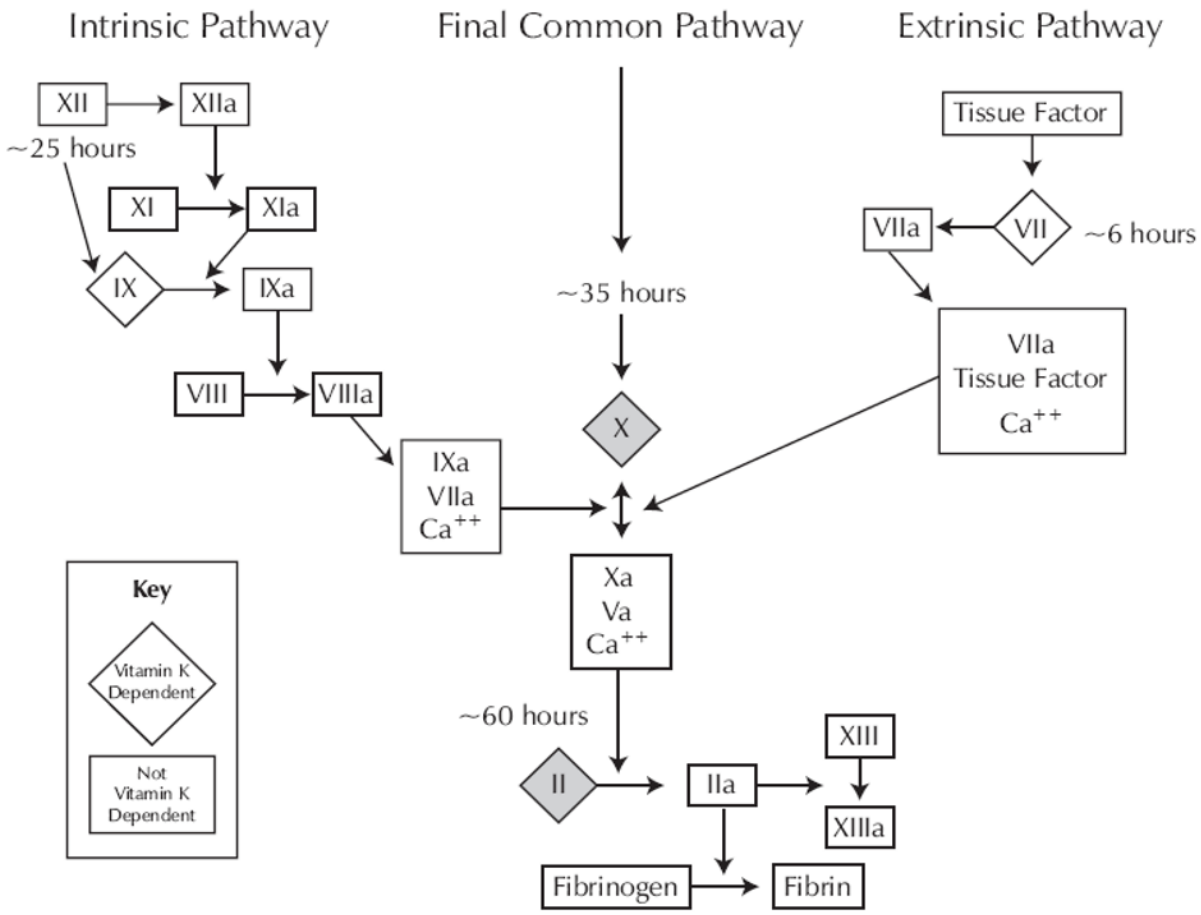
Vitamin K cycle: Warfarin blocks the conversion of vitamin K epoxide to vitamin k1



Vitamin k dependent clotting factors differ in their degradation half-lives. The following table summarizes this point:

Clotting factor	Half life
VII	5 hours
IX	25 hours
X	35 hours
II	60 hours

The coagulation cascade is arbitrarily divided into the intrinsic pathway, the extrinsic pathway, and the common pathway. The intrinsic and extrinsic pathways converge at the level of factor X activation. The intrinsic pathway is largely an in vitro pathway, while the extrinsic pathway accounts for the majority of in vivo coagulation.



Coagulation cascade and vitamin K–dependent clotting factor half-lives: Shaded clotting factors are critical warfarin targets.

Theoretically, it takes at least 5 days to achieve partial depletion of factors X and II. Full depletion of factor II may not be achieved until approximately 2 weeks (or five times the half-life). Warfarin also interferes with the synthesis of other vitamin k dependent proteins like endogenous natural anticoagulant proteins C and S as well as other proteins located in bone, cartilage, and other tissues unrelated to coagulation. Half-lives of the vitamin k dependent natural anticoagulants also differ (see table below).

vitamin k dependent natural anticoagulants	**Half life**
Protein C	8 hours
Protein S	30 hours

Because proteins C and S have shorter half lives, their concentrations deplete before seeing an adequate depletion in vitamin k dependent clotting factors concentration. In theory, this induces a hypercoagulable condition early in warfarin therapy. For this reason, "loading doses" of warfarin should be avoided to avoid a precipitous drop in proteins C and S early in therapy. The

anticoagulant effect of warfarin results from a balance between partially inhibited synthesis and unaltered degradation of the four vitamin K-dependent clotting factors. The resulting inhibition of coagulation is dependent on their degradation half-lives in the circulation.

Warfarin is an equal mixture of two optically active isomers, R- and S- warfarin. The warfarin S isomer is more potent and each isomer is metabolized differently by the liver enzyme system. Oral warfarin is completely absorbed within 90 minutes. Warfarin's half-life is approximately 40 hours and the drug is extensively bound to plasma proteins.

Warfarin is monitored using the international normalized ratio (INR) system. Because thromboplastins vary in responsiveness to a reduction of the vitamin K-dependent clotting factors, the INR system was created to calibrate thromboplastin sensitivity according to an international sensitivity index (ISI). The ISI reflects the responsiveness of a given thromboplastin to the reduction of the vitamin K-dependent clotting factors compared with the primary World Health Organization (WHO) international reference preparations so that the more responsive the reagent, the lower the ISI value. The mathematical relationship between prothrombin time (PT) and INR is as follows:

$$\text{INR} = \left[\frac{Patient\ PT}{Mean\ normal\ PT}\right]^{\text{ISI}}$$

<u>Indications for Oral Anticoagulation</u>:

Warfarin is indicated for a diverse list of indications. The rationale for using warfarin may be slightly different based on the condition. The following summarizes the indications along with rationale for use:

<u>Atrial Fibrillation (AF)</u>: AF is a supraventricular tachyarrhythmia characterized by uncoordinated atrial activation with consequent deterioration of atrial mechanical function. AF patients receiving warfarin can have either paroxysmal or chronic AF. Thrombotic material associated with AF arises most frequently in the left atrium possibly due to reduced left atrial flow velocities related to loss of organized mechanical contraction during AF. Typically, Warfarin is used indefinitely in patients with chronic or paroxysmal AF. Cardioversion can be achieved through electrical or pharmacological means. At times, cardioversion can occur spontaneously. During conversion of AF

to sinus rhythm, transient reduction of the mechanical activity of the left atrium seems responsible for an increased risk of thromboembolic events after successful cardioversion, regardless of whether the method is electrical, pharmacological, or spontaneous. In patients where a thrombus is seen on transesophageal echocardiogram (TEE), a target INR of 2.0 to 3.0 is needed for 3 weeks before elective cardioversion and for at least 4 weeks after sinus rhythm has been maintained. In patients where no thrombus is seen on TEE, cardioversion is successful, and sinus rhythm is maintained, a target INR of 2.0 to 3.0 is needed for at least 4 weeks after sinus rhythm has been maintained.

To determine a patient's risk for ischemic stroke with nonvalvular AF, there are two validated stratification schemes, $CHADS_2$ and $CHAD_2DS_2$-VASc, which are widely used. While the CHEST 2012 guidelines recommend the use of the $CHADS_2$ scoring system, the ACC/AHA Atrial Fibrillation Guidelines published in 2014 recommend the use of $CHAD_2DS_2$-VASc to determine a patient's risk for ischemic stroke in nonvalvular AF. In 2019, the ACC/AHA AF guidelines recommended that patients be started on anticoagulation therapy when the CHA2DS2-VASc score is $\geq$ 2 for males and $\geq$ 3 for females. Each scoring system, as well as patient stroke risk, are listed below:

Definition and Scores for $CHADS_2$ and CHA2DS2-VASc

$CHADS_2$ **SCORE**		**CHA2DS2-VASc**	**SCORE**
Congestive HF	1	Congestive HF	1
Hypertension	1	Hypertension	1
Age $\geq$ 75 y	1	Age $\geq$ 75 y	2
Diabetes Mellitus	1	Diabetes Mellitus	1
Stroke/TIA/TE	2	Stroke/TIA/TE	2
		Vascular disease (prior MI, PAD, Or aortic plaque)	1
		Age 65 – 74 y	1
		Sex category (i.e. female sex)	1
Maximum score	**6**	**Maximum score**	**9**

Adapted from 2014 AHA/ACC/HRS Atrial Fibrillation Guideline

Stroke Risk Stratification with the $CHADS_2$ and CHA2DS2-VASc Scores

$CHADS_2$	**Adjusted stroke rate (%/y)**	**CHA2DS2-VASc**	**Adjusted stroke rate (%/y)**
0	1.9%	0	0%
1	2.8%	1	1.3%
2	4.0%	2	2.2%
3	5.9%	3	3.2%
4	8.5%	4	4.0%
5	12.5%	5	6.7%
6	18.2%	6	9.8%
		7	9.6%
		8	6.7%
		9	15.2%

Adapted from 2014 AHA/ACC/HRS Atrial Fibrillation Guideline

Venous thromboembolism (VTE): Venous thromboembolism refers to deep venous thrombosis (DVT) and pulmonary embolism (PE). Warfarin is used initially along with an immediate-acting anticoagulant such as heparin or low molecular weight heparin. Once a therapeutic INR is achieved, the immediate-acting anticoagulant is discontinued, and warfarin is continued alone. At the HFHS, two consecutive therapeutic INRs must be achieved before the immediate-acting anticoagulant can be discontinued. It is important to understand that warfarin does not dissolve the clot, but rather halts the extension or growth of the clot while normal physiologic processes (fibrinolysis) break down the clot. The target INR in patients with VTE is usually at 2-3.

VTE prophylaxis in orthopedics: Patients with major joint orthopedic procedures such as total hip replacement, total knee replacement, or hip fracture surgery have a very high risk for thrombosis if not given thromboprophylaxis. Current guidelines support the use of low molecular weight heparin, Fondaparinux, or warfarin for these indications. If warfarin is used, the target INR should be 2-3.

Cardiomyopathy: Anticoagulation therapy in patients with heart failure and normal sinus rhythm is not supported by the current literature and current guidelines do not address this indication. The benefits of anticoagulation in such patients may not compensate for the relatively high risk of major bleeding caused by the treatment. Nevertheless, when warfarin is used for this indication, a target INR of 2-3 is typically used.

Mechanical heart valves: Patients with mechanical valves require antithrombotic prophylaxis. Lack of prophylaxis in such patients is associated with an unacceptable rate of major thrombotic complications. Patients with a mitral mechanical valve tend to have higher rates of these thrombotic complications than those with a mechanical aortic valve. Patients with bio prosthetic heart valves may require antithrombotic prophylaxis. Target INR for patients with mechanical or bio prosthetic heart valves are summarized below:

Valve Type	ACCP Guidelines 2021 (CHEST)
Aortic bio prosthetic (in sinus rhythm)	ASA 81 mg daily
Mitral bio prosthetic	Warfarin (INR 2-3) x 3 months then ASA indefinitely*
Mechanical aortic	Warfarin (2-3) + ASA 81mg if low risk of bleeding
Mechanical mitral	Warfarin (INR 2.5-3.5) + ASA 81mg if low risk of bleeding
Transcatheter aortic bio prosthetic (TAVR) (without indication for anticoagulation)	ASA 81 mg daily + Clopidogrel x 3 months then ASA indefinitely

Valve Type	AHA-ACC Guidelines 2020
Aortic bio prosthetic	Warfarin (INR 2-3) 3-6 months (if low bleed risk) followed by ASA
Mitral bio prosthetic	Warfarin (INR 2-3) 3-6 months (if low bleed risk) followed by ASA
Mechanical aortic **without** risk factors for thromboembolism (see risk factors below)	Warfarin (INR 2-3) (ASA added only if there is a separate indication for ATP and low bleed risk)
Mechanical mitral or Mechanical aortic **with** risk factors (see risk factors below)	Warfarin (INR 2.5-3.5) (ASA added only if there is a separate indication for ATP and low bleed risk)
Transcatheter aortic bio prosthetic (TAVR) (No baseline indication for OAC)	Warfarin (INR 2-3) for at least 3 months Clopidogrel 75 mg daily for first 6 months in addition to life-long ASA (75mg -100mg) daily
Transcatheter mitral bio prosthetic valve repair (TMVR) (No baseline indication for OAC)	ASA (75 mg-100 mg) daily and/or clopidogrel 75 mg daily x 3 – 6 months, then ASA or clopidogrel indefinitely
On-X® mechanical aortic valve replacement	Warfarin INR 2-3 first 3 months (with ASA 75-100mg ASA), then 1.5 – 2.0 after 3 months (with 75-100mg ASA) in patients with no thromboembolic risk factors

Risk factors for thromboembolism: (AF, previous thromboembolism, LV dysfunction, or hypercoagulable conditions) or an older-generation mechanical AVR (such as ball-in-cage)

*Not practiced at HFHS

2020 ACC/AHA Guideline for the Management of Patients with Valvular Heart Disease

For patients with left ventricular assist device (LVAD), clinic guidelines are summarized below:

INR goal by Device type			
Device	**INR Range**	**Enoxaparin Bridging Issues**	**Aspirin dose (mg)**
HeartMate II	2.0 to 3.0	Contact HFT if INR <1.8	81 mg
HeartMate 3	2.0 to 3.0	Contact HFT if INR <1.8	81 mg
HVAD	2.0 to 3.0	Contact HFT if INR <1.8	325 mg
TAH (Total Artificial Heart)	2.0 to 3.0	Contact HFT if INR <1.8	81 mg
Special Cases			
High Risk Bleeding	1.5 to 2.5	Contact HFT if INR <1.3 on two occasions	None or 81 mg per HFT
VAD + Mechanical Mitral Valve	2.5 to 3.5	Bridge when INR <1.8	325 mg
History of device thrombosis	2.5 to 3.5	Bridge when INR <1.8	325 mg
RVAD-HVAD + LVAD	2.5 to 3.5	Bridge when INR <1.8	325 mg
Subclavian or axillary outflow	2.5 to 3.5	Bridge when INR <1.8	81 mg

When bridging LVAD patients, please refer to the following policy on PolicyStat:

Tier 1: Anticoagulation Management of Patients on Durable Mechanical Circulatory Support at Henry Ford Health

Duration of Anticoagulation Therapy: CHEST 2021

Patients with mechanical heart valves require life-long anticoagulation therapy. Patients with bio prosthetic heart valves may require a short course of warfarin therapy (see table above). Patients with atrial fibrillation (AF) may require a variable duration of anticoagulation therapy depending on whether cardioversion (restoration of normal sinus rhythm) is successful. Patients with chronic or paroxysmal AF often require life-long anticoagulation therapy. Patients with venous thromboembolism (VTE) may require a variable duration of therapy as shown in the summary of the CHEST 2021 guidelines below:

Type of VTE*	Recommended Anticoagulation Duration
VTE that is **provoked**	3 months
Unprovoked VTE and low to moderate risk of bleeding	Indefinite
Unprovoked VTE and high risk of bleeding	3 months then evaluate for the risk-benefit ratio of extended therapy
VTE unprovoked or provoked by a persistent risk factor**	Extended anticoagulant therapy

*For acute symptomatic DVT of the leg, use of compression stockings is not recommended.
** persistent risk factor examples include cancer and antiphospholipid syndrome

VTE = venous thromboembolism DVT = deep venous thrombosis

Warfarin-Drug Interactions (Pharmacodynamic and Pharmacokinetic):

Warfarin, with its complex pharmacology, has a variable dose-response relationship. It is challenging to prescribe the right dose that takes into account drug interactions, avoids hemorrhagic complications and achieves sufficient suppression of thrombosis. Warfarin interacts with a number of medications resulting in either a potentiation or suppression of its effects. Mechanisms of these interactions are thought to be due to 1) enzyme induction (which increases warfarin metabolism and causes a decrease in INR), 2) enzyme inhibition (which decreases warfarin metabolism and causes an increase INR), 3) alteration in protein binding, and 4) alteration in absorption.

Pharmacokinetic Interactions: In general, warfarin is well absorbed and is approximately 99% protein bound. Therefore, it is suggested that other highly protein-bound drugs may displace warfarin from its binding sites, resulting in an enhanced warfarin response. However, this effect appears to be only transient and self-limiting. Being that warfarin is extensively metabolized by the Cytochrome (CYP) P450 enzyme system in the liver, there are several isoenzymes responsible

for metabolizing both the (R) – and (S)-isomer. The CYP2C9, which metabolizes (S)-warfarin, is considered to be most important, primarily because the (S)-isomer is approximately five times more potent than the (R)-isomer. The less active (R)-isomer is metabolized by both the CYP1A2 and CYP3A4 isoenzymes system. In managing warfarin drug interactions it is important to understand the magnitude of the interaction. Knowing which isoenzyme system is affected by other drugs will aid in predicting the severity of the interaction.

Enzyme inducers can reduce the response to warfarin by increasing the metabolism of warfarin, therefore requiring larger doses of warfarin. Typically, the effect on warfarin by the addition of an enzyme inducer is gradual because synthesis of new drug-metabolizing enzymes is required. There is usually a 1 to 2 week delay before the full effect of the interaction is observed. Likewise, the effects of discontinuing an enzyme inducer are gradual and length is variable.

The effect of enzyme inhibition is seen shortly after the drug is initiated, usually within the first 24 hours of therapy. It may take up to a week before the maximal effect is achieved. If the inhibition is subsequently discontinued, the offset of its effect is also rapid.

Pharmacodynamic Interactions: These interactions do not affect warfarin (or INR) levels but may either augment or diminish the antithrombotic effects of warfarin. For example, adding an antiplatelet drug may not affect the INR, but still increase the risk of bleeding in a patient receiving warfarin. Similarly, many herbal products may increase the risk of bleeding via their effects on platelet aggregation, but that may not be reflected in the INR.

Summary by Drug Class: The table below lists the most clinically relevant warfarin drug interactions. Please note that every drug should be considered a possible interaction. Some drugs listed as interacting with warfarin have only 1 or 2 case reports indicating the problem, and most do not have reports of re-challenge. When adjusting the warfarin dose, the INR should be repeated within 7-10 days, unless other specified for that particular drug. To find more information regarding drug interactions, there are three websites available via Sladen Library to reference for drug interactions: **Clinical Pharmacology Online**, **Micromedex and UpToDate.** It is recommended that these sites be the first references when investigating a drug query, as drug information may change over time. Recently updated recommendations for drug-drug interaction management can be found in **Appendix L**.

Most Clinically Relevant Warfarin-Drug Interactions	
Potentiation of Drug Effect (Increased INR or increased bleed risk)	**Inhibition of Drug Effect (Decreased INR)**
Acetaminophen	Barbiturates
Allopurinol	Bosentan
Amiodarone	Carbamazepine
Amoxicillin	Cigarette Smoking
Aspirin	Chlordiazepoxide
Azithromycin	Ginseng
Bactrim(TMP-SMX)	Griseofulvin
Cimetadine	Mercaptopurine
Ciprofloxacin	Multivitamin Supplement
Citalopram	Nafcillin
Clarithromycin	Phenobarbital
Clopidogrel	Ribavarin
Cotrimoxazole	Rifampin
Diltiazem	Secobarbital
Entacapone	St. John's wort
Erythromycin	Phenytoin
Fenofibrate	
Fish Oil	
Fluconazole	
Fluvastatin	
Gemcitabine	
Gemfibrozil	
Levofloxacin	
Lovastatin	
Metronidazole	
Miconazole (Suppository and Gel)	
Omeprazole	
Propafenone	
Propanolol	
Simvastatin	
SSRI's	
Tamoxifen	
Tetracycline	
Tramadol	

For a more comprehensive list of potential drug, food, and dietary supplement interactions see Ageno et al. Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines
http://journal.publications.chestnet.org/article.aspx?articleid=1159432

Warfarin-Chemotherapy Interactions:

CHEST 2016 recommendations: **In patients with DVT of the leg or PE and active cancer ("cancer-associated thrombosis") and who (i) do not have a high bleeding risk, we recommend extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy** (Grade 1B), **and (ii) have a high bleeding risk, we suggest extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy** (Grade 2B).

Patients with cancer are at an increased risk for thrombosis. Factors that may be responsible for this include stasis, alteration of blood components, lowered Protein C, disruption of blood vessel walls, age and higher incidence of recurrent thrombosis.

Physiologic changes in patients with cancer can also alter warfarin pharmacokinetics. Gastrointestinal toxicities caused by certain chemotherapy may impair the absorption of warfarin, resulting in a sub therapeutic effect. Adverse reactions to chemotherapy, such as vomiting, may lead to a supratherapeutic INR. Thrombocytopenia caused by chemotherapy or the disease state itself may put cancer patients at a higher risk for bleeding complications. As with other medications with potential to interact with warfarin, drug information for chemotherapeutic agents may be found on **Clinical Pharmacology Online, Lexicomp through UpToDate** or **Micromedex** via Sladen Library.

When dosing warfarin for a cancer patient, there are some issues to keep in mind. It's important to know the type and stage of cancer, the age of the patient, the primary reason for anticoagulation (DVT, PE, etc.), the name of the chemotherapy agents used, the cycle regimen (daily, weekly, etc.) and the duration of treatment for both chemotherapy and warfarin.

Keep in mind that the patient will most likely be taking medications other than chemotherapy agents for cancer treatment, such as corticosteroids or antiemetics, which may also have drug-drug interactions with warfarin. Frequent INR draws, at least weekly, are required during active chemotherapy treatment. Due to the risk of thrombocytopenia with cancer and/or chemotherapeutic agents, platelets should be considered prior to adjusting warfarin doses.

Warfarin-Disease State Interactions:

Disease State	Effect on INR	Possible Mechanism(s)
Decompensated heart failure	↑ in INR	Acute episodes of heart failure compromise blood flow to vital organs including the liver. Compromised hepatic blood flow and hepatic congestion may affect the liver's metabolizing capacity of warfarin.
Thyrotoxicosis	↑ in INR	Thyrotoxicosis creates a hypermetabolic state where the clotting factor consumption is increased and lead to exaggerated response to warfarin. Once the patient becomes euthyroid, the effects on warfarin metabolism and INR are removed.
Diarrhea	↑ in INR	Diarrhea causes expulsion of the vitamin-k producing bacteria in the lower intestinal tract. This leads to depletion of vitamin k stores and an exaggerated response to warfarin.
Liver dysfunction, including significant liver metastases	↑ in INR	Any condition associated with reduced hepatic metabolizing capacity can lead to increased levels of free drug and an exaggerated response to warfarin. Liver patients have defective hemostasis and the baseline INR may be elevated as a result.
Cancer	↑ in INR	Metastatic liver disease, malnutrition, and use of many chemotherapeutic agents can cause an increase in the INR.
Febrile illness	↑ in INR	Episodes of viral illness, pneumonia or other infections may induce a hypermetabolic condition where there is increased clearance of vitamin k-dependent clotting factors. This will cause an increase in the INR.
Renal Failure	↑ or ↓ in INR	In severe renal dysfunction, warfarin pharmacokinetics may change even though the drug is not renally eliminated. Changes in protein binding, acid-base disturbances, and changes in volume of distribution are among a few causes for these changes. Both increased and decreased response to warfarin may be expected.
Short bowel syndrome	↑ or ↓ in INR	Removal of a significant portion of the bowel may partially interfere with the absorption of warfarin, nutrients and vitamins, and may also induce watery stools. All of these factors can affect the warfarin pharmacokinetics and Pharmacodynamics. Impact on the INR may be variable.
Advanced gastroparesis	Delayed absorption or delayed ↑ in INR	Diabetic gastroparesis may often cause an initial lack of rise in INR. This may prompt a clinician to raise warfarin dose and cause an eventual delayed rise in the INR.

Disease State	Effect on INR	Possible Mechanism(s)
Hypothyroidism	↓ in INR (patient may require a higher warfarin dosage)	Hypothyroidism causes slowing down of the body's metabolic rate. Decreased catabolism of vitamin-k-dependent clotting factors is noted. This may lead to lack of response to warfarin and may require a dosage increase. Once the patient becomes euthyroid with treatment, the effects on warfarin metabolism and INR are removed. Close monitoring of INR is required until euthyroid status is achieved.
Gastric Bypass	↑ in INR in the immediate postoperative period after bariatric surgery (may require ~20% decrease in warfarin dose) but return to their preoperative doses after approximately 6 months.	• Disruption of drug dissolution and solubility: less HCl production causes increased gastric pH • Reduced mucosal exposure • Decreased gastric emptying • Decreased food and vit K intake post-surgery
S/P Heart Valve Replacement	↑ in INR in the immediate postoperative period (require lower warfarin dose during the initial phase), then are likely to need an increase in warfarin dose during early follow-up period	• Mechanism not identified, may be initial decrease in blood perfusion s/p procedure • Close monitoring required during the first 6-8 weeks

Warfarin-Herbal Interactions: For the most updated and comprehensive list of warfarin-herbal interactions, go to **Sladen Library/Subject Guides/A-Z databases**. You may also refer to EPIC as follows: Click on **Library** menu**/Natural medicines database/**Under "Search Natural Medicines Comprehensive Database" section**,** Click on **Natural product-drug interaction checker/Enter a Drug or Natural Medicine name then click on "Add" box**. Otherwise, for a quick reference on interactions between warfarin and the mostly commonly used herbal products, see **appendix-A** at the end of this manual.

Drug-induced diarrhea:

Diarrhea is one of the causes for elevated INRs. The anticoagulation provider needs to anticipate and monitor drug-induced diarrhea by evaluating the patient's medication list. Theoretically, all drugs can cause diarrhea. Below, are major drug classes that cause diarrhea in more than 10% of the patients. Please keep these in mind when managing our patients:

Drug class	Examples	Comments
Anticancer drugs	Irinotecan, cetuximab, 5-FU, Erlotinib, ipilimumab, and many others	Generally, drugs used for colon cancer tend to have the greatest chance of causing diarrhea (up to 80% chance for diarrhea)
Antibiotics	Beta-lactams, clindamycin, macrolides	Duration of therapy increases the risk for diarrhea. Drugs with anti-anaerobic coverage cause more diarrhea.
Intestinal anti-inflammatory agents	Mesalamine, balsalazide	10-20% chance for diarrhea
Antidiabetic	Metformin, incretin mimetics (e.g., Victoza, Trulicity, Byetta, Bydureon), Acarbose, Miglitol	10-20-% chance for diarrhea
Cholinesterase inhibitors (for dementia)	Aricept, Exelon, Razadyne, Reminyl	10-20-% chance for diarrhea
Peripherally-acting antiobesity drugs	Orlistat (Xenical, Alli)	Up to 20-% chance for diarrhea
Miscellaneous	SSRI, Brintellix, Magnesium, anagrelide, colchicine, misoprostol, PPIs, levothyroxine, leflunomide	

Keep in mind, diarrhea may be dose-related for some of these drugs and you may encounter it when dose is increased. Also, diarrhea may be delayed so watching the patient and anticipating for weeks may be necessary. Careful and continuous evaluation of medication changes helps anticipate drug-induced diarrhea and adjust frequency of INR monitoring accordingly.

Warfarin-Nutrient and Lifestyle Interactions:

Warfarin-nutrient interactions can be sorted into the following categories:

a) Nutrient interactions related to vitamin k content of foods
b) Nutrient interactions related to changes in warfarin metabolism
c) Nutrient interactions related to changes in warfarin absorption
d) Miscellaneous Warfarin-Nutrient and Lifestyle Interactions

Nutrient interactions related to vitamin k content of foods

As discussed in an earlier section in this manual, Warfarin prevents reductive metabolism of the inactive vitamin K epoxide back to its active hydroquinone (K_1) form. The conversion of vitamin K_1 (Quinone) to vitamin KH_2 (hydroquinone) is vitamin k insensitive and addition of exogenous vitamin K_1 will promote the activation of the vitamin-k dependent clotting factors and antagonize the actions of warfarin (lower the INR). Conversely, a decrease in dietary vitamin k intake may lead to decreased activation of vitamin-k dependent clotting factors and exaggerate the actions of warfarin (raise the INR).

The US Food and Drug Administration recommends a daily intake of 80 micrograms of vitamin K, based on a 2000-calorie diet. This is called the Daily Value (DV). The more drastic the change in dietary vitamin k, the more significant the fluctuation in the INR. A more practical and feasible approach to maintaining consistency with dietary vitamin k is to assure patients consume a consistent amount of vitamin k from week to week. Patients should be reminded not to avoid dietary vitamin k necessarily, but rather avoid drastic changes in their dietary habits. For instance, eating large amounts of green leafy vegetables, when they normally do not, can increase the amount of vitamin K in their system.

In the following table, we will try to highlight the foods that contain more vitamin k than others in their categories. Serving size is also indicated to further quantify their potential impact on warfarin therapy:

Vitamin K Content of Selected Foods

Patients should count the number of servings of "High" Vitamin K foods you like to have in your diet. Keep this number of servings the same from one week to the next.						
Beverages				**Fats and Dressings**		
Coffee	brewed, decaf instant	Low		Margarine	7 tbsp	Medium
Cola	regular, diet	Low		Mayonnaise	7 tbsp	**HIGH**
Fruit juices	assorted types	Low		Canola oil	7 tbsp	**HIGH**
Milk	any	Low		Salad oil	7 tbsp	**HIGH**
Tea	black, brewed	Low		Soybean oil	7 tbsp	**HIGH**
Tea	green	**HIGH**		Olive oil	7 tbsp	Medium
Water	tap	Low		Corn oil	7 tbsp	Low
Vegetables				Peanut oil	7 tbsp	Low
Asparagus	7 spears	Medium		Safflower oil	7 tbsp	Low
Avacado	1 small	Medium		Sesame oil	7 tbsp	Low
Broccoli	1/2 cup, raw or cooked	**HIGH**		Sunflower oil	7 tbsp	Low
Brussel Sprouts	5 sprouts	**HIGH**		**Cereals and grain products**		
Cabbage	1 1/2 cups	**HIGH**		Bagel	plain	Low
Cabbage	1 1/2 cup, red	Medium		Bread	assorted	Low
Carrot	2/3 cup	Low		Cereal	assorted	Low
Cauliflower	1 cup	Low		Flour	assorted	Low
Celery	2 1/2 stalks	Low		Oatmeal	instant dry	Low
Collard greens	1/2 cup	**HIGH**		Rice	white	Low
Corn	2/3 cup	Low		Pasta	Dry	Low
Cucumber	1 cup, no peel	Low		**Meat**		
Eggplant	1 1/4 cup	Low		Beef		Low
Endive	2 cups, raw	**HIGH**		Chicken		Low
Green scallion	2/3 cups, raw	**HIGH**		Ham		Low
Kale	3/4 cup, raw	**HIGH**		Mackerel		Low
Lettuce	head, bib	**HIGH**		Pork		Low

Lettuce	1 3/4 cups red leaf	**HIGH**		Shrimp		Low
Mushroom	1 1/2 cups	Low		Tuna		Low
Mustard greens	1 1/2 cups raw	**HIGH**		Turkey		Low
Onion		Low		**Fruits**		
Parsley	1 1/2 cups	**HIGH**		Apple		Low
Peas	2/3 cup, green	Medium		Banana		Low
Pepper	green, raw	Low		Blueberries		Low
Potato		Low		Cantaloupe		Low
Pumpkin		Low		Grapes		Low
Sauerkraut	1/2 cup, canned	Low		Grapefruit		Low
Spinach	1 1/2 cup, raw	**HIGH**		Lemon		Low
Tomato		Low		Orange		Low
Turnip greens	1 1/2 cups, raw chopped	**HIGH**		Peach		Low
Watercress	3 cups, raw chopped	**HIGH**		**Condiments and Sweeteners**		
Dairy Products				Honey		Low
Butter		Low		Jell-O Gelatin		Low
Cheddar cheese		Low		Peanut Butter		Low
Sour cream		Low		Pickle	medium dill	Medium
Yogurt		Low		Sugar	white, granulated	Low
Eggs		Low				

Nutrient interactions related to changes in warfarin metabolism

Cranberry Juice:

A few mechanisms have been postulated as a cause for a warfarin-cranberry juice interaction:

a) Some natural component of cranberry juice (flavonoids) could inhibit the activity of Cytochrome P450-2C9 (CYP2C9), the enzyme responsible for metabolism of S-warfarin.
b) Salicylic acid, a constituent of many fruits and vegetables, including cranberries, is highly protein bound and can displace warfarin from its protein binding sites and cause an increase in free warfarin levels and can increase the INR.

Available case reports substantiate the likelihood that a clinically significant interaction can occur when patients taking warfarin drink large amounts (> 8 ounces) of cranberry juice. Long-term consumption (probably longer than 1-2 weeks) of large daily volumes (> 8 ounces) of the juice can potentially amplify destabilization of warfarin therapy. Therefore, patients receiving anticoagulation with warfarin should be informed to reduce or eliminate concomitant ingestion of cranberry juice until additional data become available.

Pomegranate Juice:

In vitro studies have demonstrated inhibition of CYP2C9 by pomegranate juice. Therefore, an interaction between pomegranate juice and warfarin is theoretically possible. Two case reports have been published so far showing an increase in the INR after consumption of pomegranate juice. Duration of pomegranate juice was at least 1 week and the magnitude of rise in the INR can be very significant. The anticoagulation provider should educate the patient about this interaction and inquire about such use if the INR is supratherapeutic. Patients receiving warfarin should be informed to reduce or eliminate concomitant ingestion of pomegranate juice.

Nutrient interactions related to changes in warfarin absorption

Enteral feedings:

Warfarin-enteral feeding interaction was first reported in the early 1980s and warfarin resistance was observed. Warfarin is highly protein bound and it may bind to the soy proteins in the enteral formulas. This causes a decrease in its intestinal absorption of warfarin and a reduction in its bioavailability and anticoagulant effect. Warfarin-enteral feeding interaction is independent of the vitamin k content of the enteral formula. Regardless of the various methods of enteral feeding administration (e.g., continuous, cyclic, bolus, or intermittent), the enteral formula must be separated from warfarin by at least 2 hours. Longer separation periods (e.g., 4 hours) are probably more reliable in avoiding this interaction. The anticoagulation provider should question the patient about the use of such products such as Ensure, Ensure Plus, Boost, Osmolite, Promote, etc.). Adequate separation of these products from warfarin should be assured to avoid an interaction. Similarly, timing of administration of these products should be investigated when a sub therapeutic INR is encountered and other contributing factors are ruled out.

Miscellaneous Warfarin-Nutrient and Lifestyle Interactions:

Tobacco products

The pharmacodynamics of warfarin should be carefully considered in patients using tobacco products. Some studies show no difference between smokers and nonsmokers in average warfarin dose used, but changes in dose may be necessary in patients who change their smoking status. An abrupt increase in smoking tobacco may cause a decrease in the INR while an abrupt decrease in smoking tobacco may cause an increase in the INR. Some reports have also shown contradictory results. Most of the available data consists of case reports. Tobacco products may affect the INR, especially when there are acute changes in the quantity used. Therefore, INRs should be monitored closely, and warfarin adjusted as necessary after tobacco cessation.

Assisting Current Smokers

During the First Encounter Teaching:

1. Ask patient if they currently smoke cigarettes, e-cigarettes (vape) or use other tobacco products like chewing tobacco or hookah.
    a. If patient has recently quit:
        i. Congratulate their efforts
        ii. Ask if any additional support is needed
    b. If patient is trying to quit:
        i. Congratulate patient for making an attempt
        ii. Ask if they would like additional support through our smoking cessation program
2. If patient indicates that they are a smoker, ask if they are interested in making a quit attempt
    a. If interested, connect with our smoking cessation program
        i. Provide telephone number - **(888) 427-7587**
        ii. Provide website information - **henryford.com/tobaccofree**
        iii. Refer through EPIC (best if possible)– **Meds & Orders > search "smoking" or "tobacco"**
    b. If not interested, let patient know if they do decide to quit and would like assistance, we can help with the referral to the smoking cessation program anytime
3. Document the patient's smoking status and stance on quitting in the Specialty Comments

Smoking Cessation Assistance:

1. HFHS - Certified Tobacco Treatment Specialists offer individual counseling and group classes
    a. Counseling by phone, extended hours:
    8 am - 8 pm Mon-Thu, 9 am - 4 pm Fri
    b. Virtual "Freedom From Smoking" classes
    c. **Free** for all HFHS patients and employees, regardless of insurance status
    d. 6 months of quit planning and tobacco treatment support
    e. Prescriptions overseen by Clinical Advisor (HFH pulmonologist)
    f. Progress documented in Epic
    g. Quit rates competitive with similar programs
2. More help with staying tobacco-free:
    a. MICHIGAN DEPARTMENT OF HEALTH AND HUMAN SERVICES (800) QUIT-NOW https://michigan.quitlogix.org/
    b. AMERICAN LUNG ASSOCIATION -(800) LUNG-USA select 2 for the Lung HelpLine or go to http://www.lung.org

Adapted from:

- HFHS Live Well, Tobacco Treatment Service 3.31.21
- A3C Tobacco Cessation Workflow-MHealthy Tobacco Consultation Service (MAQI²)

Alcohol:

Alcohol is another lifestyle factor that should be closely monitored in patients taking warfarin. Acute alcohol consumption may increase the anticoagulation effect by decreasing the metabolism of warfarin; chronic alcohol intake, however, may actually decrease the anticoagulation effect by increasing the warfarin metabolism.

The studies comparing warfarin alone and with alcohol consumption did not find a significant difference in effect on anticoagulation. Based on limited evidence from small studies, it may be safe to consume small amounts of alcohol while on concurrent warfarin therapy. Only one study had patients with indications for long-term warfarin; the other studies involved short-term use in healthy subjects or subjects without indications for the anticoagulant. One of these studies utilized one-time-only consumption of alcohol. Therefore, anticoagulation providers should monitor warfarin patients for alcohol consumption and educate them about the possible interaction between ethanol and warfarin.

Warfarin Adverse Events:

*Major determinants of warfarin induced bleeding are the intensity of the INR, specific patient characteristics, concomitant use of drugs that interfere with hemostasis, and length of therapy

Criteria for major bleeding include:

- Fatal bleeding
- Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome
- Bleeding causing a fall in hemoglobin level of 2g/dL or more, or leading to transfusion of two or more units of blood or red cells

Adverse Reaction	Signs & Symptoms	Mechanism	Management
Upper GI Bleed	"Coffee-ground" emesis Blood in emesis Melanotic stool (dark, tarry bowel movements) Massive upper GI bleed may have frank blood in stool Abdominal pain may be present or absent	Warfarin is thought to "unmask" existing lesions or enable major bleeding from an ordinarily minor source. Consider use of NSAIDs, antiplatelets, other past medical history.	Patient should be evaluated in an emergency department.
Lower GI Bleed	Bright red blood/clots in stool or on used toilet paper Abdominal pain may be present or absent	Warfarin is thought to "unmask" existing lesions or enable major bleeding from an ordinarily minor source. Consider medical history and other potential causes.	Visible bleeding warrants an evaluation in all cases.
Epistaxis	Drainage of blood from one or both nostrils Posterior drainage may also occur; blood may be swallowed or enter the mouth	Dry air, nasal sprays (steroids, etc.), colds, and other irritants may predispose to bleeding.	Insert a plug of cotton-wool or tissue-paper soaked in normal saline nasal spray into the bleeding nostril(s). Apply pressure (squeeze) to the nostrils (not the bridge). While sitting up, bend forward from the waist. Spit out any blood that trickles into the throat. Any chronic bleeding should be referred to an otolaryngologist (ENT).
Intracerebral Hemorrhage	Severe headache Vomiting Decreased level of consciousness Ataxia Aphasia	Spontaneous rupture of small vessels damaged by chronic hypertension, amyloid angiopathy, or vascular abnormalities.	Patients with signs & symptoms of stroke should be referred to the emergency department immediately.
Bruising	Characteristic discoloration ("black and blue") of skin in days following trauma	Increased bleeding is the result of damaged capillaries and venules from bruising. Warfarin exaggerates this bleeding response.	Higher rates of bruising are common in patients on warfarin. Bruises that are abnormally painful or spread beyond small, well-circumscribed areas should be evaluated.

Adverse Reaction	Signs & Symptoms	Mechanism	Management
Skin necrosis	Typically occurs 3-10 days after treatment initiation Most often effects extremities, but also adipose tissue and other areas Maculopapular rash Ecchymosis May lead to necrosis	The mechanism is not clearly understood. It is thought that imbalances between procoagulant and anticoagulant proteins early in therapy may be a cause.	There are no well-done studies showing differences in outcomes between treatments. General strategies include warfarin reversal with vitamin K and heparin administration. Prostacyclin has also been used. Approximately 50% of patients will require surgical intervention. Some experts advocate future therapy with low-weight molecular heparins.
"Purple toe syndrome"	Typically occurs 3-8 weeks after treatment initiation Blue-tinged discoloration of the bottom & sides of the toes Lesions blanch with pressure and elevation of the affected leg(s)	It is thought to be due to cholesterol microembolization into arterial circulation from atheromatous plaques.	There are no well-done studies showing differences in outcomes between treatments. General strategies include warfarin reversal with vitamin K and heparin administration. Some experts advocate future therapy with low-weight molecular heparins.
Birth defects, stillbirth, spontaneous abortion	See patient counseling section. Women of childbearing age must be counseled of these risks in advance before starting warfarin.	Not well determined	Use effective method of contraception. Inform anticoagulation physician/PCP if patient reports being pregnant.

Patients on Inappropriate Aspirin Therapy

1. During the course of patient medication review and/or patient interview, should it be discovered that the patient is on aspirin therapy and an indefinite length of anticoagulation treatment, there should be verification that the use of aspirin is appropriate as evidenced by the presence of one or more of the following comorbidities:

a. Appropriate for Coronary Artery Disease (including prior Myocardial Infarction, Percutaneous Coronary Intervention, Coronary Artery Bypass Graft)

i. ASA use inappropriate if MI/PCI/CABG > 1 year ago

ii. ASA use inappropriate if CAD diagnosis only with no history of events/revascularization

b. Appropriate for Peripheral Artery Disease (including prior bypass or stent placement)

c. Appropriate for Valve replacement (any type: mechanical or bio-prosthetic)

e. Appropriate for Left Ventricular Assist Device

2. If determined that the patient does not meet the appropriate use of aspirin therapy, the AC Practitioner will contact the patient's responsible anticoagulation physician of record and send a templated Telephone Encounter Form (TEF) or e-mail to the provider to suggest discontinuation of aspirin. This action will be documented in the Anticoagulation encounter note.

3. Within 7 days, the AC Practitioner will follow-up with the responsible anticoagulation physician to discuss the discontinuation of aspirin therapy.

a. The patient's responsible anticoagulation physician or AC Practitioner will contact the patient in regard to the discontinuation of aspirin therapy as ordered by the responsible anticoagulation physician.

b. Patient will receive a follow-up call by the AC Practitioner to ensure aspirin discontinuation and a letter will be mailed to the patient's home or entered into their MyChart per patient preference.

c. Aspirin is removed from the medication list if the physician authorizes discontinuation.

4. If the physician does not respond within the initial 7 days, the AC Practitioner will send one more attempt via TEF and/or e-mail.

5. If the physician does not respond within 14 days of the initial TEF and/or e-mail, then an Anticoagulation Co-Medical Director should be contacted.

6. If the responsible anticoagulation physician does not want to discontinue the patient's aspirin therapy, the AC Practitioner will document in the EHR and place a note with the date and indication to continue aspirin per responsible anticoagulation physician.

Reference(s)/Source(s): Douketis, James. Combination warfarin-ASA therapy: Which patients should receive it, which patients should not, and why? Thrombosis Research 127(2011) 513-517

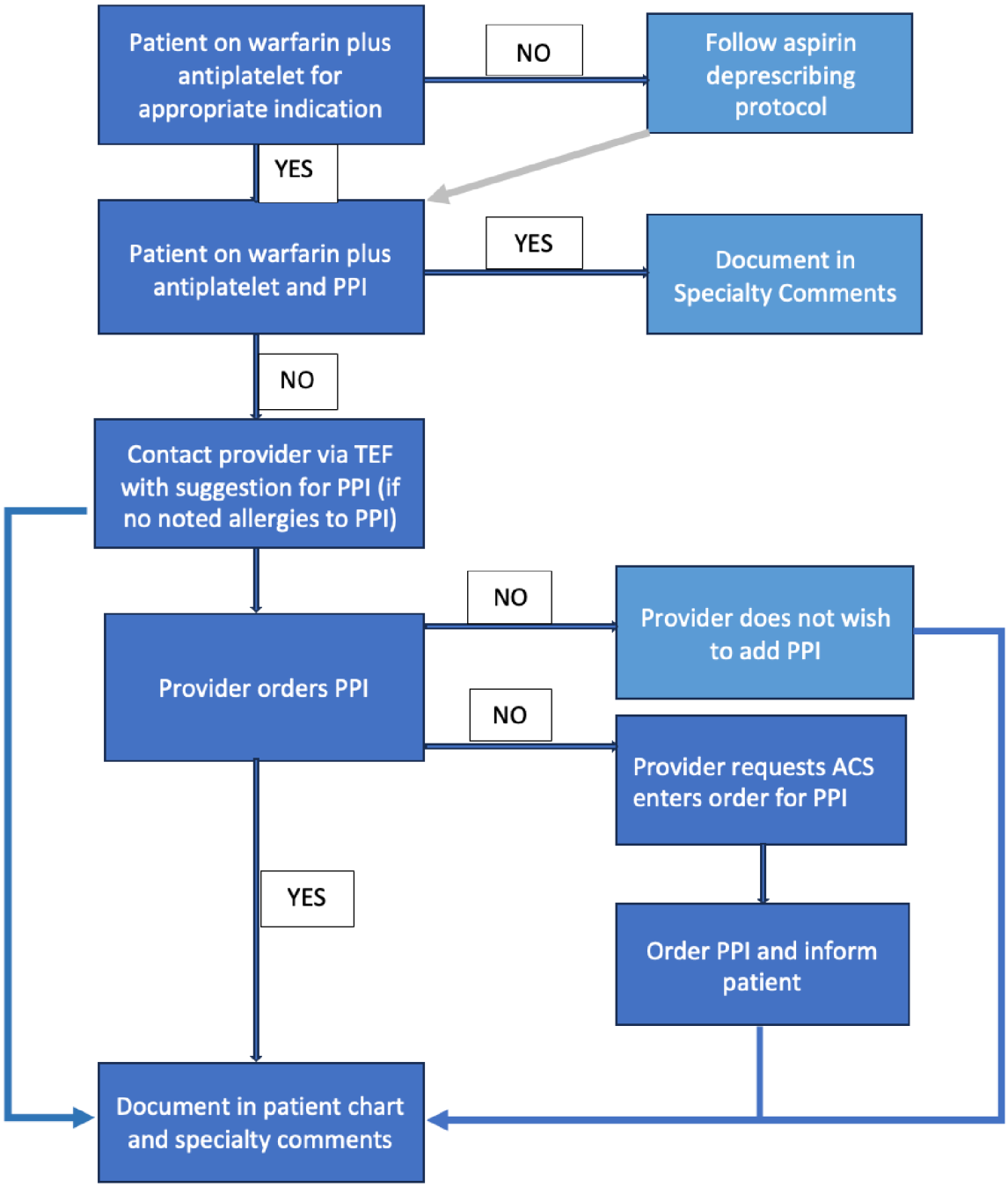
MAQI 2018

Process for Gastroprotection Quality Improvement Initiative

1. Patients who are on anticoagulation and appropriate or provider-recommended antiplatelet therapy should be screened for gastroprotective therapy use, such as a PPI or H2 Antagonist (this excludes patients with LVADs/Mechanical Support Devices as of 5.11.23)
    a. Anticoagulant + aspirin = PPI
        i. Omeprazole
        ii. Pantoprazole
        iii. Lansoprazole
        iv. Rabeprazole
        v. Esomeprazole
    b. Anticoagulant + P2Y12 Inhibitor (clopidogrel) = PPI (as above) or H2 Antagonist i. Famotidine
        ii. Nizatidine
        iii. Cimetidine*
2. Determine which patients should have recommendation for PPI
    a. Patient is on warfarin and an antiplatelet and no gastroprotection agent
    b. Patient does not have any PPIs on the allergy list
        i. If patient has an allergy or intolerance to any PPI
            1. Ensure that patient is eligible for antiplatelet therapy per ASA inappropriate use protocol
                a. If patient should stop ASA, contact provider
    2. Document patient review and allergy in the patient's chart in the progress note and Specialty Comments
    3. Open a new telephone encounter if patient has not yet had a message sent to the provider
    a. Create a new documentation note and contact provider via TEF using the following smartphrase in the body of the message: .ANTICOAGGASTROPROTECTION
4. Document in the progress note using smartphrase: .ANTICOAGGASTRODOC
5. Sign and close the encounter and add note to the Specialty Comments that the suggestion was made to the provider to start PPI.
6. The PPI order is intended to be entered by the provider but may be ordered by ACS Practitioner per verbal order (not via text or Halo) if requested.
    a. Enter order for PPI
    b. Contact patient to communicate recommendation to start a new PPI and answer any patient questions
    c. Send patient letter using a free form letter and the smartphrase: .ANTICOAGGASTROLETTER
    d. Document in the patient's chart that a PPI has been recommended for this patient and add a note to the Specialty Comments.

2. If provider orders the PPI for the patient, you have the option of sending a free form letter and using smartphrase: .ANTICOAGGASTROLETTER
3. If provider replies that they do not wish to start a PPI:
    a. Add note to encounter "provider does not wish to start PPI"
    b. Sign and close encounter
    c. Add note to the Specialty Comments

Gastroprotection Protocol Flowchart



References (May be shared with providers as requested)

1. Kumbhani DJ, Cannon CP, Beavers CJ, et al. 2020 ACC Expert Consensus Decision Pathway for Anticoagulant and Antiplatelet Therapy in Patients With Atrial Fibrillation or Venous Thromboembolism Undergoing Percutaneous Coronary
   Intervention or With Atherosclerotic Cardiovascular Disease: A Report of the American College of Cardiology Solution Set Oversight Committee. Journal of the American College of Cardiology. 2021;77(5):629-658. doi:10.1016/j.jacc.2020.09.011
2. Scally B, Emberson JR, Spata E, et al. Effects of gastroprotectant drugs for the prevention and treatment of peptic ulcer disease and its complications: a meta-analysis of randomised trials. Lancet Gastroenterol Hepatol. 2018;3(4):231-241. doi:10.1016/S2468-1253(18)30037-2
3. Bhatt DL, Scheiman J, Abraham NS, et al. ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol. 2008;52(18):1502-1517. doi:10.1016/j.jacc.2008.08.002
4. Ray WA, Chung CP, Murray KT, et al. Association of Proton Pump Inhibitors With Reduced Risk of Warfarin-Related Serious Upper Gastrointestinal Bleeding. Gastroenterology. 2016;6(151): 1105-1112. https://doi.org/10.1053/j.gastro.2016.08.054.
5. Clinical Pharmacology Online accessed 4/7/23
6. Prilosec® Package Insert accessed 6/5/23

Warfarin Initiation Guidelines:

When starting therapy in a warfarin naïve patient, the dosing algorithm does not always apply, as it is intended more for patients who are in steady state. The following offer basic guidelines to beginning warfarin therapy:

New Enrollment – Hospital discharge:

A. Check warfarin dose received during hospitalization
B. Compare warfarin dose to INRs drawn while IPD
C. Determine weekly dose to achieve current INR
D. Review record for pertinent anticoagulation-related issues (co-morbidities, contraindications, concomitant medications, short-term medications IE antibiotics)
E. Adjust weekly warfarin dose based on 5 mg or 10 mg nomogram attached. Consider using 10 mg nomogram for VTE patients with no co-morbidities as listed below
F. Advise patient to return in 3-5 days for INR.(based on the day of the week)
G. If newly started on warfarin at discharge, have patient return in 3 days for INR.

New Enrollment – Outpatient:

A. Verify patient's warfarin initiation date.
B. Ensure that prescribed dose is appropriate for patient based on patient's age, co-morbidities and concomitant medications. If inappropriate, adjust accordingly.
C. Patient should have INR drawn 3-5 days after initiation of warfarin therapy.

D. If INR is subtherapeutic or supratherapeutic after 3 days, adjust warfarin dosing schedule according to 5 mg or 10 mg nomogram attached, depending on comorbidities (see below)

E. After warfarin adjustment, if no other changes are occurring, patient should return in 7 days for INR.

F. Once patient is therapeutic for 4 consecutive weeks, patient may return in 2 weeks. If therapeutic after those 2 weeks, have patient return in 2 more weeks. If patient again therapeutic (now 8 weeks), may have patient return in 4 to 5 weeks.

G. If the patient's INR remains stable and reliable for a period of at least 6 months, with no dose changes, the patient may be considered for lengthier intervals of up to 12 weeks

Dosing considerations for patients over 65 years:

The CHEST guidelines recommend a reduced initial warfarin dose (< 5 mg/day) for elderly patients with:

-Congestive Heart Failure -Debilitation

-Liver Disease -Malnourishment

Co-morbidities that may affect anti-coagulation therapy:

-Congestive Heart Failure	-Chronic kidney disease	-Liver disease
-Debilitation	-Diabetes	-Thyroid disease
-GERD	-Cancer	-Hx of stroke/TIA
-Alcoholism	-Hx of DVT	-Hx of PE
-Malnourishment	-Mechanical Valve Replacement	

SAMe-TT_2R_2

The SAMe-TT_2R_2 score can help to determine if a patient will do well on warfarin or would be better off taking a DOAC. Patients with a high-risk score could mean that warfarin is more likely to be less effective and a DOAC should be considered.

Criteria	Description	Points
Sex	Female	1
Age	< 60	1
Medical history	>2 comorbidities*	1
Treatment	Amiodarone	1
Tobacco	Smoking within 2 years	2
Race	Non-Caucasian	2

*comorbidities include: previous stroke, diabetes mellitus, peripheral artery disease, coronary artery disease, liver disease, lung disease, renal disease, hypertension and heart failure

Low risk = 0-1 points High risk ≥ 2 points

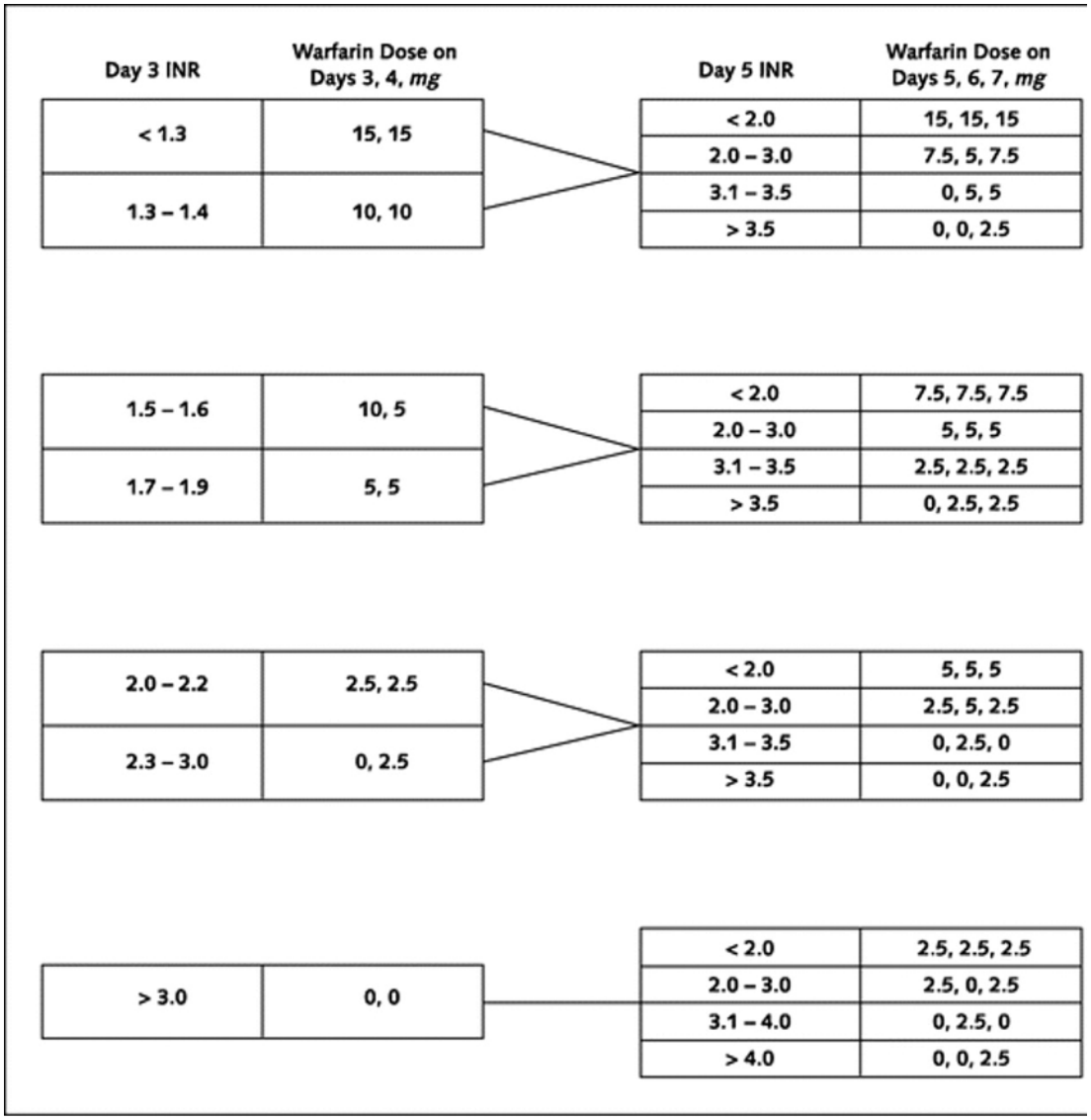
*Note: The HAS-BLED score (see page 56) should also be used to evaluate anticoagulated atrial fibrillation patients at initiation and throughout their therapy period, as some risks are modifiable (see page 57) and patients may be at more or less risk of bleeding as time progresses. (**European Heart Journal (2020) 00, 1-125 doi:10.1093/eurheartj/ehaa612**)

5mg "Loading" of Warfarin Nomogram:

Day	INR	Dosage
1		5 mg
2	< 1.5 1.5 – 1.9 2.0 – 2.5 >2.5	5 mg 2.5 mg 1 – 2.5 mg 0.0
3	<1.5 1.5 – 1.9 2.0 – 2.5 2.5 – 3.0 >3.0	5 – 10 mg 2.5 – 5 mg 0.0 – 2.5 mg 0.0 – 2.5 mg 0.0
4	<1.5 1.5 – 1.9 2.0 – 3.0 >3.0	10 mg 5 – 7.5 mg 0.0 – 5 mg 0.0
5	<1.5 1.5 -1.9 2.0 – 3.0 >3.0	10 mg 7.5 – 10 mg 0.0 – 5 mg 0.0
6	<1.5 1.5-1.9 2.0-3.0 >3.0	7.5 – 12.5 mg 5-10 mg 0.0 – 7.5 mg 0.0

Crowther. Ann Int Med; 127:33, 1997

10 mg "Loading" Dose Nomogram



Day 3 INR	Warfarin Dose on Days 3, 4, *mg*	Day 5 INR	Warfarin Dose on Days 5, 6, 7, *mg*
< 1.3	15, 15	< 2.0	15, 15, 15
		2.0 – 3.0	7.5, 5, 7.5
1.3 – 1.4	10, 10	3.1 – 3.5	0, 5, 5
		> 3.5	0, 0, 2.5
1.5 – 1.6	10, 5	< 2.0	7.5, 7.5, 7.5
		2.0 – 3.0	5, 5, 5
1.7 – 1.9	5, 5	3.1 – 3.5	2.5, 2.5, 2.5
		> 3.5	0, 2.5, 2.5
2.0 – 2.2	2.5, 2.5	< 2.0	5, 5, 5
		2.0 – 3.0	2.5, 5, 2.5
2.3 – 3.0	0, 2.5	3.1 – 3.5	0, 2.5, 0
		> 3.5	0, 0, 2.5
> 3.0	0, 0	< 2.0	2.5, 2.5, 2.5
		2.0 – 3.0	2.5, 0, 2.5
		3.1 – 4.0	0, 2.5, 0
		> 4.0	0, 0, 2.5

Kovacs M J et al. Ann Intern Med 2003;138:714-719

Considerations to using 10mg "loading" dose nomogram:
Patients **excluded** from studies to test the 10 mg warfarin initiation nomogram:

Baseline INR > 1.4 Platelet count < 50 K/uL age < 18 years

Required Hospitalization High risk for major bleeding (including interacting medications)

MAINTENANCE DOSING ALGORITHM:

For patients with assigned INR range of: 2.0 – 3.0 (GOAL 2.5)

INR	ACTION
≤ 1.5*	Increase weekly dose by 15%; repeat INR within 7 – 10 days
1.51 – 1.99*	If unexplained, increase weekly dose by 10%; repeat INR in 7 – 10 days
2.00 – 3.00**	No change
3.01 – 4.99*	If INR 3.01 – 3.99 do not hold warfarin *If high on two consecutive occasions, decrease weekly dose by 10%; If INR 4.00 – 4.99 hold for 1 day repeat INR within 7 days if ≥ 4.00, otherwise 7-10 days
5.00 – 9.99 (with no bleeding)	**Inform ACS Pharmacist******. Hold the next 1 or 2 warfarin doses, monitor more frequently and restart warfarin at a lower dose (decrease weekly dose by 15%) when INR therapeutic. Alternatively, hold 1 dose and administer vitamin K (1 to 2.5 mg) orally, if the patient is at an increased risk of bleeding.
≥ 10.0 (with no bleeding)	**Inform Physician**. Hold warfarin and give Vitamin K 2.5 – 5 mg PO***. Monitor more frequently and repeat Vitamin K if necessary.
Serious bleeding regardless of INR	**Inform physician immediately**. Refer to HFHS Reversal Guidelines

* Clinical and professional judgment may allow variation in application of algorithm (and should be included in chart documentation)

**If INR between 1.80 – 2.00 or 3.00 – 3.20, consider no change in dose with repeat INR in 7 – 10 days, for first occurrence ONLY.

For patients with assigned INR range of: INR 2.5 – 3.5 (GOAL 3.0)

INR	ACTION
≤ 1.5*	Increase weekly dose by 20%; repeat INR within 7 -10 days
1.51 – 2.49*	Increase weekly dose by 15%; repeat INR in 7 – 10 days
2.50 – 3.50**	No change
3.51 – 4.99	If INR 3.51 – 4.59 do not hold warfarin *If high on two consecutive occasions, decrease weekly dose by 10%; If INR 4.60 – 5.00 hold for 1 day repeat INR within 7 days if ≥ 4.00, otherwise 7-10 days
5.00 – 9.99 (with no bleeding)	**Inform ACS Pharmacist******. Hold the next 1 or 2 warfarin doses, monitor more frequently and restart warfarin at a lower dose (decrease weekly dose by 15%) when INR therapeutic. Alternatively, hold 1 dose and administer vitamin K (1 to 2.5 mg) orally, if the patient is at an increased risk of bleeding**.**
≥ 10.0 (with no bleeding)	**Inform Physician**. Hold warfarin and give Vitamin K 2.5 – 5 mg PO***. Monitor more frequently and repeat Vitamin K if necessary.
Serious bleeding regardless of INR	**Inform physician immediately**. Refer to HFHS Reversal Guidelines

* Clinical and professional judgment may allow variation in application of algorithm (and should be included in chart documentation)

**If INR between 2.3 – 2.5 or 3.50 – 3.70, consider no change in dose with repeat INR in 7 – 10 days, for first occurrence ONLY.

*****Preferred route of Vitamin K administration in NON-emergent situations is ORAL. Avoid Sub Q or I.M. administration.**

******Pharmacist to review patient's record to evaluate potential drug related causes, and patient's bleeding risk per CHEST guidelines and Pharmacist's clinical judgment. Vitamin K administration recommendations in line with CHEST 2012 guidelines, but are optional in light of recent findings (see references below).**

References for Algorithm

1. Crowther et al. Oral Vitamin K Versus Placebo to Correct Excessive Anticoagulation in Patients Receiving Warfarin; Ann Intern Med 2009; 150; 293-300.

2. Ageno W, et al. Oral Anticoagulant Therapy: Antithrombotic Therapy and Prevention of Thrombosis, Chest 2012; 141; e44S-e88S

3. Rose AJ et al. Prompt Repeat Testing After Out-of-Range INR Values A Quality Indicator for Anticoagulation Care, Circulation Volume 4, Issue 3, May 2011, Pages 276-282

Frequency of Assessment Guide:

The frequency of anticoagulation monitoring should be as follows:

During Initiation of Therapy (within the first 3-4 weeks of therapy):

- Average daily dosing method — within 2-5 days, then within 1 week
- After hospital discharge — if stable, (no med changes while IPD) within 2-5 days
  if unstable (INR issues or Medication changes while IPD), within 1-3 days
- First 3-4 weeks of therapy — at least weekly

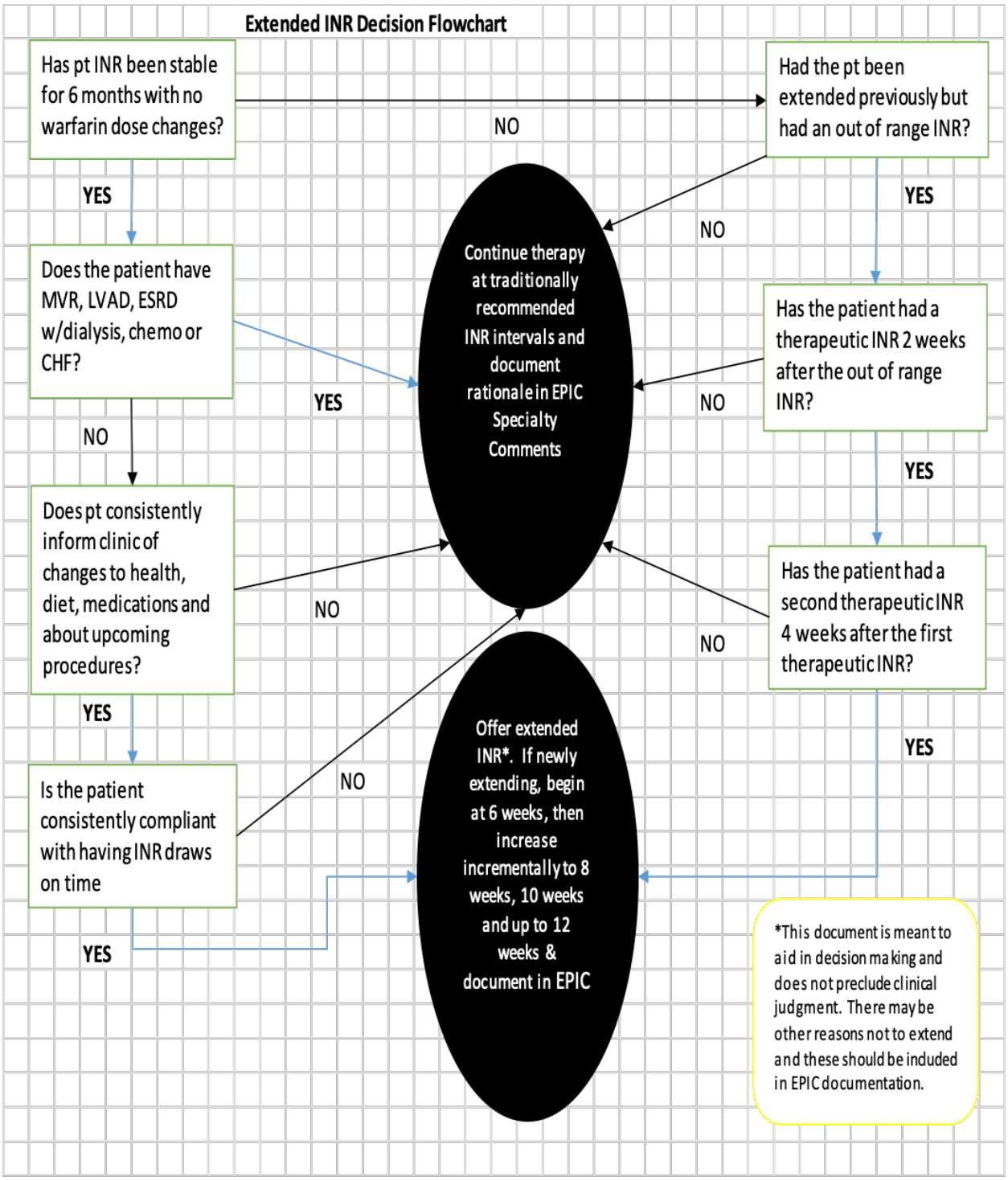
Maintenance Therapy (after the first 3-4 weeks of therapy):

- Dosage change today — in 7-10 days
- Dosage change < 2 weeks ago — in 2-3 weeks
- Dosage change > 2 weeks ago — in 3-5 weeks
- In stable and reliable patients — in up to 12 weeks

(Consistently therapeutic results and no dose changes in at least 6 consecutive months)

Extended INR Intervals:

In an effort to improve patient quality of life, and to reduce daily workload, patients whose INR results have been consistently therapeutic and have not had dose changes in at least 6 consecutive months should be advised to come in for INR draws at longer (up to 12 week) intervals. Please refer to the Extended INR Decision Flowchart below to determine who and when to extend.


Extended INR Decision Flowchart
Has pt INR been stable for 6 months with no warfarin dose changes?
NO
Had the pt been extended previously but had an out of range INR?
YES
YES
NO
Does the patient have MVR, LVAD, ESRD w/dialysis, chemo or CHF?
YES
Continue therapy at traditionally recommended INR intervals and document rationale in EPIC Specialty Comments
NO
Has the patient had a therapeutic INR 2 weeks after the out of range INR?
NO
YES
YES
Has the patient had a second therapeutic INR 4 weeks after the first therapeutic INR?
Does pt consistently inform clinic of changes to health, diet, medications and about upcoming procedures?
NO
NO
YES
YES
Is the patient consistently compliant with having INR draws on time
NO
Offer extended INR*. If newly extending, begin at 6 weeks, then increase incrementally to 8 weeks, 10 weeks and up to 12 weeks & document in EPIC
YES
*This document is meant to aid in decision making and does not preclude clinical judgment. There may be other reasons not to extend and these should be induded in EPIC documentation.

V. Prevention of Venous Thromboembolism and Post-thrombotic Syndrome:

Prevention of thromboembolism involves mechanical and pharmacological methods. Mechanical thromboprophylaxis includes graduated compression stockings (GCS) and intermittent pneumatic compression (IPC). Pharmacologic thromboprophylaxis may include heparin, low molecular weight heparin, Fondaparinux, or warfarin. Patients receiving warfarin for thromboprophylaxis consists mainly of patients undergoing major orthopedic procedures, such as hip arthroplasty, knee arthroplasty, or hip fracture surgery. According to the 2012 American College of Chest Physicians (ACCP) guidelines, the recommended warfarin duration of therapy for these specific indications may range from 10 to 35 days. The HFHS anticoagulation clinics do not routinely manage warfarin patients who receive warfarin for < 90 days.

In recent years, there has been increased emphasis on prevention of post-thrombotic syndrome (PTS), a late complication of deep venous thrombosis. PTS manifests as edema, hyperpigmentation, and ulceration and can occur in up to one-third of patients who have had prior DVT. Patients with DVT are at risk of developing the post thrombotic syndrome in the first years after the initial episode. This syndrome can range from mild, with some swelling and pain at the end of the day, to severe, with massive swelling and skin ulceration. Graduated elastic compression stockings to the knee with an ankle pressure of 30-40 mmHg fitted in the first weeks after the initial thrombosis and worn for 1-2 years reduce the risk of the post-thrombotic syndrome by about 50%. As an anticoagulation provider, you may suggest that your patients further discuss this issue with their physician.

Note that the CHEST 2016 guidelines recommend:

In patients with acute DVT of the leg, we suggest not using compressions stockings routinely to prevent PTS (Grade 2B).

Remarks: This recommendation focuses on prevention of the chronic complication of PTS and not the treatment of symptoms. For patients with acute or chronic symptoms, a trial of graduated compression stockings is often justified.

VI. Bridge Therapy Guidelines for Patients on Chronic Oral Anticoagulation:

The following guidelines may be utilized for peri-procedural bridge therapy. The physician of record will make the ultimate decision regarding bridge therapy and dosing regimen. ACS Practitioner must contact anticoagulation physician of record before initiation of bridge therapy regimen.

Anticoagulant	Minimal bleed risk	Low/moderate bleed risk	High bleed risk	All HFHS GI/Endo	Ortho/neuro surgery	Neuraxial anesthesia[3]
Warfarin	No hold	Hold 5 days prior STAT INR 7 days prior to procedure and adjust hold as needed Bridge if high thromboembolic risk only[4]	Hold 5 days prior STAT INR 7 days prior to procedure and adjust hold as needed Bridge if high thromboembolic risk only[4]	Hold 5 days prior STAT INR 7 days prior to procedure and adjust hold as needed Bridge if high thromboembolic risk only[4]	Hold 5 days prior STAT INR 7 days prior to procedure and adjust hold as needed Last dose enoxaparin 24 hours prior	Hold for 4-5 days and INR ≤ 1.4 STAT INR 7 days prior to procedure and adjust hold as needed Last dose enoxaparin ≥24 hours prior
Apixaban [1]	No hold	CrCl ≥ 30 mL/min – Hold 1 day	CrCl ≥ 30 mL/min- Hold 2 days	CrCl ≥ 30 mL/min- Hold 2 days	Hold 3 days	Hold 3 days
		CrCl < 30 mL/min- Hold 2 days	CrCl < 30 mL/min- Hold 3 days	CrCl < 30 mL/min- Hold 3 days		
Rivaroxaban[1]	No hold	CrCl ≥ 30 mL/min – Hold 1 day	CrCl ≥ 30 mL/min- Hold 2 days	CrCl ≥ 30 mL/min- Hold 2 days	Hold 3 days	Hold 3 days
		CrCl < 30 mL/min- Hold 2 days	CrCl < 30 mL/min- Hold 3 days	CrCl < 30 mL/min- Hold 3 days		
Dabigatran CrCl ≥ 50 mL/min	No hold	Hold 1 day	Hold 2 days	Hold 2 days	Hold 3 days	Hold 4 days
Dabigatran CrCl < 50 mL/min	No hold	Hold 2 days	Hold 4 days	Hold 4 days	Hold 5 days	Hold 5 days
Edoxaban[1]	No hold	CrCl ≥ 30 mL/min – Hold 1 day	CrCl ≥ 30 mL/min- Hold 2 days	CrCl ≥ 30 mL/min- Hold 2 days	Hold 3 days	Hold 3 days
		CrCl < 30 mL/min- Hold 2 days	CrCl < 30 mL/min- Hold 3 days	CrCl < 30 mL/min- Hold 3 days		

[1] **A longer duration of interruption may be required in some special cases, irrespective of the DOAC used. This may include patients with severe renal insufficiency (CrCl < 30 mL/min), impaired hepatic function, or patients taking CYP3A4 or P-glycoprotein inhibitors which may interfere with DOAC clearance**

[2]AF – 2023 ACC/AHA/ACCP/HRS Guidance *Circulation*. 2024;149:e1–e156. DOI: 10.1161/CIR.0000000000001193

[3] Tier 1 policy follows ASRA Guidance - Reg Anesth Pain Med. 2018 Apr;43(3):225-262

[4] **Decisions about interruption and bridging should only be made after assessment of individual patient- and procedure-related factors and discussions with the patient, management team, and proceduralist. See further guidance for interruption below.**

Bridging Suggestion [a]	Clinical Condition
Interrupt / LMWH Bridging Suggested ***Low/moderate/high bleeding risk*** Address any reversible patient risk factors such as high INR or aspirin use and consider bleed history before bridging; Bridging not suggested for colonoscopies with anticipated polypectomy; Consider delaying procedure, if possible, in high thrombotic risk patients with recent thromboembolism (within 3 months).	• AF: CHADsVASc ≥ 7; stroke/TIA/SE < 3 months ago, or rheumatic valvular heart disease • VTE: (DVT or PE) < 3 months, severe thrombophilia (eg. deficiency of protein C, protein S or antithrombin, homozygous factor V Leiden or prothrombin gene mutation or double heterozygous for each mutation, multiple thrombophilias), antiphospholipid antibodies, associated with vena cava filter, associated with active cancer with high VTE risk (shorter interruption periods may be acceptable for low/moderate bleed risk procedures) • MHV: Mechanical Mitral Valve with major risk factors for stroke (multiple prior strokes, prior perioperative stroke, or prior valve thrombosis), Mechanical Aortic Valve + Thrombosis risk factor [Caged ball or Tilting disc valve, AF, Prior Stroke/Embolism (<3 months), DM, HTN, CHF (LVEF < 40%) Age≥75] • Intra-cardiac Thrombus (LA, LV) < 3 months
Interrupt/No LMWH bridging suggested ***Low/moderate/high bleeding risk*** Shorter interruption periods may be acceptable for low/moderate bleed risk procedures	• AF: no prior stroke/TIA/SE or stroke/TIA/SE ≥ 3 mos ago • VTE: VTE past 3-12 mos, non-severe thrombophilia (eg heterozygous factor V Leiden or prothrombin gene mutation), recurrent VTE, active CA or recent history of CA (within 5 years, excluding non-melanoma skin cancer) or VTE > 12 mos and no other risk factors • MHV*: Bileaflet AV prosthetic. and one or more major risk factors for stroke, or Bileaflet AV prosth w/o AF and no other stroke risk factors
No LMWH Bridging Recommended ***Minimal procedural bleed risk with any of the above clinical conditions***	• Interruption may be appropriate if there is increased concern for bleeding due to patient factors (eg. dental extraction in a patient with poor dentition, a screening colonoscopy in a patient with history of polyps that may require resection, or coronary angiography with a femoral (instead of radial) access

For full list of procedures, see online appendix to the 2017 ACC Expert Consensus Decision Pathway for Periprocedural Management
*Bridging in moderate risk MHV may be considered on an individualized basis after weighing bleed risk with risk of thromboembolism
LMWH: Low-molecular-weight-heparin DVT: Deep Vein Thrombosis PE: Pulmonary Embolism VTE: Venous thromboembolism LA: Left Atrial LV: Left Ventricular AF: Atrial Fibrillation CHF: Congestive Heart Failure LVEF: Left Ventricular Ejection Fraction SE: Systemic Embolism

[a] Pre-Procedure: In patients who are receiving bridging anticoagulation with therapeutic-dose SC LMWH twice daily dose regimen, it is recommended to administer the last dose pre-procedure of LMWH 24 h before surgery or a procedure.

For those patients receiving once-daily LMWH, administer half the daily dose on the day prior to surgery/procedure.

Post-Procedure: It is recommended to resume therapeutic dose 24 hours after minor surgery/invasive procedure when there is adequate hemostasis. In patients undergoing major surgery/high bleeding risk surgery or procedure, it is recommended to resume full-dose LMWH/UFH 48 to 72 hours after procedure

Estimate Procedure Bleed Risk (examples)				
Minimal	**Low/Moderate**		**High**	
-Minor dermatologic procedures -Ophthalmologic (cataract) procedures -Minor dental procedures -Pacemaker or cardioverter-defibrillator device implantation	-Arthroscopy -Cutaneous/lymph node biopsies -Foot/hand surgery -Coronary angiography -GI endoscopy ± biopsy -Colonoscopy ± biopsy	-Abdominal hysterectomy -Laparoscopic cholecystectomy -Abdominal hernia repair -Hemorrhoidal surgery -Bronchoscopy ± biopsy	-Major surgery with extensive tissue injury -Cancer surgery, especially solid tumor resection -Major orthopedic surgery, including shoulder replacement surgery -Reconstructive plastic surgery -Major thoracic surgery -Urologic or GI surgery, especially anastomosis surgery -Transurethral prostate resection, bladder resection, or tumor ablation	-Colonic polyp resection -Bowel resection -Percutaneous endoscopic gastrostomy placement, endoscopic -Retrograde cholangiopancreatography -Surgery in highly vascular organs (kidneys, liver, spleen) -Cardiac, intracranial, or spinal surgery -Any major operation (procedure duration > 45 minutes) -Neuraxial anesthesia -Epidural injections

More bleeding risk tables found on pages 50-52 of this manual

Disclaimer: This document is for informational purposes only and does not, itself, constitute medical advice. This document is not a replacement for careful medical judgments by qualified medical personnel. There may be information in this document that does not apply to or may be inappropriate for the medical situation at hand.

For latest HF Health Guidance for anticoagulant interruption click link: Tier 1: Perioperative Medication Management Periprocedural Management -MAQI² Pocket Card

References:

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Revised 5.31.24

ENOXAPARIN BRIDGING ALGORITHM FOR WARFARIN PATIENTS

Day	Lab Draw	Lab Value	Action	Warfarin Dose	Enoxaparin
Pre-0p 7	Stat "Pre-Op INR" SCr Platelets	INR > 2.99 – Contact physician performing procedure	Postpone procedure or hold warfarin an extra day	Yes – unless INR supratherapeutic	No
		INR 2.00 – 2.99	None	Yes	No
		INR < 2.00, & MVR pt., contact ACS provider	Consider starting enoxaparin sooner	Yes – unless starting enoxaparin	Consider enoxaparin
Pre-Op 6	No			Yes – unless Pre-Op INR supratherapeutic or enoxaparin started*	No
Pre-Op 5	No	If Pre-Op INR < 2.00		No	Yes
		If Pre-Op INR ≥ 2.00		No	No
Pre-Op 4	No	If Pre-Op INR 2.0 – 2.99		No	Yes
		If Pre-Op INR > 2.99		No	No
Pre-Op 3	No			No	Yes
Pre-Op 2	No			No	Yes
Pre-Op 1	Stat INR Platelets	INR> 1.49, must notify physician performing procedure	Consider delay or give Vitamin K	No	Enoxaparin **am only** (½ daily dose for q24h renal dose). NO evening dose.
OR/ Procedure				Resume same pm dose if hemostasis is secured. If active bleeding or severe anemia obtain order from AC physician/physician champion prn	No enoxaparin given. Resume therapeutic dose 24 hours after procedure (48 to 72 hours for procedure with high post-op bleeding risk) *** If patient IPD, surgeon to consult with Internal Medicine Consult team.
Post-Op 4 – 10 of enoxaparin	Stat platelets	PLTs < 50 K/uL or ≥ 50% drop	Must notify AC physician, HIT risk	If PLT drop noted, AC physician to advise of further anticoagulation therapy	
Post-Op 5	Stat INR	INR in range		Yes	Discontinue enoxaparin
		INR subtherapeutic		Yes	Continue until INR in range or AC physician stops

* Warfarin will be discontinued 5 days prior to procedure unless directed otherwise by Surgeon/Provider performing procedure

** Monday procedures will require advanced notice by ACS to surgeon/provider that STAT INR needs to be drawn & checked prior to procedure

***Patients with mechanical valves OR A-fib patients with CHADS score ≥ 4 (one point each for: age >75y; HTN; DM; CHF, two points for previous CVA or TIA) must have discussion between AC physician and surgeon post-op if there is a possibility of delaying resumption of Lovenox

Reference:

Douketis, JD et al; The Perioperative Management of Antithrombotic Therapy; CHEST 2012; 141:e326S-e350S

Revised and Approved by CORE committee September 2013; Approved Ambulatory Nurse Council June 2004; Approved Adult Primary Care Council August 2000

Reviewed 5.31.24

Periprocedural Bridging and Surgical Bleeding Risks*

Bleeding risk category	Type of surgery/procedure
High bleeding risk - requiring interruption of anticoagulant therapy	• Any major surgery (which has a procedure duration > 45 min) • Breast cancer surgery • Cardiac surgeries (coronary artery bypass, heart valve replacement) • Cardiac procedures (complex left-sided ablation – pulmonary vein isolation; VT ablation) • Implantable cardioverter defibrillator or cardiac resynchronization therapy defibrillator • Intracranial or spinal surgery (head or neck) • Endoscopically guided fine-needle aspiration • Hepatic surgeries and procedures including liver biopsy • Left atrial appendage occlusion (Lariat procedure) • Major vascular surgery (aortic aneurysm repair, aortofemoral bypass) • Major urologic surgery (prostatectomy, bladder tumor resection, kidney biopsy, nephrectomy, transurethral prostate resection [TURP], urologic cancer surgery or tumor ablation) • Major orthopedic surgery (hip/knee joint replacement, prosthetic revision) • Major surgery with extensive tissue injury (eg. Cancer surgery, reconstructive surgery) • Biliary sphincterectomy • PEG placement • Pneumatic dilatation • Variceal treatment • Neurosurgeries • Plastic surgery (major reconstructive surgery) • Spinal surgeries or procedures (Spinal or epidural anaesthisia, laminectomy, lumbar diagnostic puncture) • Splenic surgeries or procedures • Thoracic surgery • Lung resection surgery • Intestinal anastomosis surgery/bowel resection • Abdominal aortic aneurysm repair • Abdominal vascular surgery, open • ICD/pacemaker lead extraction • Selected procedures: colonic polypectomy of large polyp, endoscopic retrograde cholangiopancreatography with sphincterectomy, kidney biopsy, nephrectomy
Intermediate bleeding risk – requiring interruption of anticoagulant therapy	• Left atrial appendage occlusion (WATCHMAN device) • Lung biopsy (percutaneous needle) • Chest drain insertion (larger drain) • Angiography/PCI (with transfemoral access) • Arterial revascularization, lower extremity (femoral, popliteal, tibial) • Deep venous reconstruction, lower extremity
Low bleeding risk – may or may not require interruption of anticoagulant therapy	• Laparoscopic cholecystectomy • Laparoscopic inguinal hernia repair • Abdominal hysterectomy • Carpal tunnel repair • Dental procedures- extraction of 3 or more teeth • Noncontract ophthalmologic procedures • Endoscopy with biopsy or tissue removal • Gastrointestinal endoscopy +/- biopsy, enteroscopy, biliary/pancreatic stent without sphincterotomy, endosonography without fine-needle aspiration • Hemorrhoidal surgery • Hydorocele repair • Coronary angiography • Selected procedures: thoracentesis, paracentesis, arthrocentesis, bone marrow aspiration, and biopsy • Pacemaker/defibrillator implantation • AF ablation (transvenous) • Dilatation and curettage • Cervical biopsy • Prostate or bladder biopsy • Breast biopsy (Data suggest the safety of performing low bleeding risk procedures in the presence of a therapeutic INR (INR < 3). Preprocedural DOAC interruption > 24 h vs < 24 h was not identified as a potential risk factor for major bleeding events) • axillary node biopsy • Angiography/PCI (with trans radial access)

* There is currently no prediction guide to estimate the risk for perioperative bleeding. Chart is provided to help determine which procedures require increased caution when using anticoagulants.

	• Shoulder/foot/hand surgery and arthroscopy
Minimal bleeding risk – may not require interruption of anticoagulant therapy	• Extractions of 1-2 teeth • Periodontal surgery • Incision of abscess • Implant positioning • Endoscopy without surgery • Skin biopsy or selected skin cancer removal • abscess incision or small dermatology excisions • Cataract removal/glaucoma procedures • Central catheter removal

Darvish-Kazem S, Douketis JD. Perioperative Management of Patients Having Noncardiac Surgery Who Are Receiving Anticoagulant or Antiplatelet Therapy: An Evidence-Based but Practical Approach. Semin Thromb Hemost 2012; 38:652-660

2012 ACCP Guidelines. Chest 2012;141(2_suppl):e326S-e350S.

Guidance for the practical management of warfarin therapy in the treatment of venous thromboembolism. JThromb Thrombolysis. 2016;41:187-205

Procedure Risk for Bleeding (overall) for GI Endoscopy Procedures

Bleeding risk category	Type of procedure
Higher risk	• Polypectomy • Biliary or pancreatic sphincterotomy • Treatment of varices • PEG placement • Therapeutic balloon-assisted enteroscopy • EUS with FNA • Endoscopic hemostasis • Tumor ablation • Cystgastrostomy • Ampullary resection • Endoscopic mucosal resection • Endoscopic submucosal dissection • Pneumatic or bougie dilation • Percutaneous endoscopic jejunostomy
Low risk	• Diagnostic (EGD, colonoscopy, flexible sigmoidoscopy) including mucosal biopsy -DO NOT HOLD ANTICOAGULANT • ERCP with stent (biliary or pancreatic) placement or papillary balloon-assisted enteroscopy • Capsule endoscopy • Enteral stent deployment (Controversial) • EUS without FNA • Argon plasma coagulation • Barrett's ablation

Adapted from: ASGE Standards of Practice Committee. The management of antithrombotic agents for patients undergoing GI endoscopy.Gastrointestinal Endoscopy Volume 83, No.1: 2016. http://dx.doi.org/10.1016/j.gie.2015.09.035

Updated guidance 2.24: Abraham et al. American College of Gastroenterology-Canadian Association of Gastroenterology Clinical Practice Guideline: Management of Anticoagulants and Antiplatelets During Acute Gastrointestinal Bleeding and the Periendoscopic Period. J Can Assoc Gastroenterol.2022 Apr;5(2):100-101

Pain Procedures and Potential Bleed Risk

Bleeding risk category	Type of procedure
High Risk	• Spinal cord stimulation trial and implant • Dorsal root ganglion stimulation • Intrathecal catheter and pump implant • Vertebral augmentation (vertebroplasty and kyphoplasty) • Percutaneous decompression laminotomy • Epiduroscopy and epidural decompression
Intermediate Risk	• Interlaminar ESIs (C, T, L, S) • Transforaminal ESIs (C, T, L, S) • Cervical facet MBNB and RFA • Intradiscal procedures (C, T, L) • Sympathetic blocks (stellate, T. splanchnic, celiac, lumbar, hypogastric) • Trigeminal and sphenopalatine ganglia blocks
Low Risk	• Peripheral nerve blocks • Peripheral joints and musculoskeletal injections • Trigger point injections including piriformis injection • Sacroiliac joint injection and sacral lateral branch blocks • Thoracic and lumbar facet MBNB and RFA • Peripheral nerve stimulation trial and implant • Pocket revision and implantable pulse generator/intrathecal pump replacement

ESI: Epidural steroid injection MBNB: medial branch nerve block (lumbar facet joint injection) C: Cervical T: Thoracic L: Lumbar S: Sacral RFA: Radiofrequency ablation

Reg Anesth Pain Med 2018;43: 225–262

HAS-BLED Score – estimates major bleeding risk for patients on warfarin for atrial fibrillation

	Condition	Points
H	Hypertension	1
A	Abnormal renal/liver function (1 point each)	1 or 2
S	Stroke (any previous history)	1
B	Bleeding history or disposition	1
L	Labile INRs (< 60% TTR)	1
E	Elderly (age ≥ 65 years)	1
D	Current drugs (medication) or alcohol use (1 pt each)	1 or 2
	TOTAL POINTS	

Total Points	Annual Major Bleed risk (%)*	Intracranial bleeds per 100-pt-yrs**	Major Bleed risk category
0	1.13		Low
1	1.02		Low
2	1.88	0.6	Intermediate
3	3.74	0.7	High
4	8.7	1.0	High
5	12.5	1.2	High

***major bleed = ICH or bleeding resulting in a hospitalization, a hemoglobin drop > 2 g/dl, or a blood transfusion

****Friberg L, Rosenqvist M, Lip G. Net Clinical Benefit in Patients with Atrial Fibrillation: A Report from the Swedish Atrial Fibrillation Cohort Study. Circulation. 2012; 125: 2298-2307. Doi: 10: 1161/ CIRCULATIONAHA.111.055079

Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest. 2010 Nov;138(5):1093-100.doi: 10.1378/chest

Table 9 Risk factors for bleeding with OAC and antiplatelet therapy

Non-modifiable	Potentially modifiable	Modifiable	Biomarkers
Age >65 years Previous major bleeding Severe renal impairment (on dialysis or renal transplant) Severe hepatic dysfunction (cirrhosis) Malignancy Genetic factors (e.g. CYP 2C9 polymor- phisms) Previous stroke, small-vessel disease, etc. Diabetes mellitus Cognitive impairment/dementia	Extreme frailty ± excessive risk of falls[a] Anaemia Reduced platelet count or function Renal impairment with CrCl <60 mL/min VKA management strategy[b]	Hypertension/elevated SBP Concomitant antiplatelet/NSAID Excessive alcohol intake Non-adherence to OAC Hazardous hobbies/occupations Bridging therapy with heparin INR control (target 2.0 - 3.0), target TTR >70%[c] Appropriate choice of OAC and correct dosing[d]	GDF-15 Cystatin C/CKD-EPI cTnT-hs von Willebrand factor (þ other coagulation markers)

CKD-EPI= Chronic Kidney Disease Epidemiology Collaboration; CrCl = creatinine clearance; cTnT-hs = high-sensitivity troponin T; CYP = cytochrome P; GDF-15 = growth differentiation factor-15; INR = international normalized ratio; NSAID = non-steroidal anti-inflammatory drug; OAC = oral anticoagulant; SBP = systolic blood pressure; TTR = time in therapeutic range; VKA = vitamin K antagonist.

[a]Walking aids; appropriate footwear; home review to remove trip hazards; neurological assessment where appropriate.

[b]Increased INR monitoring, dedicated OAC clinicals, self-monitoring/self-management, educational/behavioural interventions. [c]For patients receiving VKA treatment.

[d]Dose adaptation based on patient's age, body weight, and serum creatinine level.

European Heart Journal (2020) 00, 1-125 doi:10.1093/eurheartj/ehaa612

Lovenox Dose Rounding Table based on actual (total) body weight in kg

Dose required	Dose to be administered	Syringe size to order	Size of dose in ml
35 – 44 mg	40 mg	40 mg syringe	0.4 ml
45 – 54 mg	50 mg	60 mg syringe	0.5 ml
55 – 64 mg	60 mg	60 mg syringe	0.6 ml
65 – 74 mg	70 mg	80 mg syringe	0.7 ml
75 – 84 mg	80 mg	80 mg syringe	0.8 ml
85 – 94 mg	90 mg	100 mg syringe	0.9 ml
95 – 104 mg	100 mg	100 mg syringe	1 ml
105 – 112 mg	105 mg	120 mg syringe	0.7 ml
113 – 127 mg	120 mg	120 mg syringe	0.8 ml
128 – 142 mg	135 mg	150 mg syringe	0.9 ml
143 – 150 mg	150 mg	150 mg syringe	1 ml
> 150 mg*	150 mg*	150 mg syringe	N/A

* Per Lovenox manufacturer package insert, maximum dose is 150 mg SC q 12 hours.

The 120mg and 150mg syringes are graduated in 15 mg per 0.1 ml increment. Enoxaparin 60mg, 80mg, and 100mg syringes are graduated in 10mg per 0.1 increments.

For dosing in patients who weigh more than 150 kg, Lovenox dosing and administration must be determined by an anticoagulation clinic pharmacist**.

****Considerations for Enoxaparin Dosing in Morbid Obesity:** Clinical practice guidelines do not offer consensus recommendations regarding enoxaparin dosing in morbidly obese patients. In patients with morbid obesity, differences in enoxaparin pharmacokinetics may lead to altered enoxaparin exposure. Observational studies have described therapeutic enoxaparin requirements in patients with body mass indices of > 40-50 kg/m2 and weights of > 140-200 kg. These studies demonstrated increased risk of enoxaparin over-exposure, based on supratherapeutic anti-Xa levels, when standard dosing (1 mg/kg Q12 hours) was used according to actual body weight. These studies also showed that lower weight-based doses (~0.7-0.85 mg/kg Q12 hours based on actual body weight) had a greater association with anti-Xa values within goal range.

(See Appendix N for further information and references)

Peri-procedural Bridge Therapy:

PROCEDURE	KEY POINTS
ACS staff to be notified at least 2 weeks prior to procedure, patients advised not to schedule Monday procedures	New enrollment education should include education of patient on ACS advance notification for procedures/dental work
Review exclusion criteria: • Cr Cl 15- 30 ml/min (Contact the ACS Pharmacist) • If CrCl , < 15 ml/min (including dialysis patients), contact the anticoagulation physician since Lovenox is not recommended • Weight > 150 kg • Platelets < 50 K/ul • Platelets and CrCl/SCr to be checked within 6 months prior to scheduled procedure	Review affordability, ability to administer injections every 12 hours (or seek alternative caregiver, consider Home Care referral) If exclusion criteria met, contact provider
Decision to bridge to be decided by physician, communicated with ACS	Refer to Suggested Risk Stratification and Surgeries Associated with High Risk of Bleeding Tables
Unless longer warfarin hold is otherwise indicated, warfarin to be held no more than 5 days before procedure & communicated to patient.	INR to be checked one day prior to procedure
Patient education scheduled and completed (using Lovenox teaching guideline) Technique for injections to be taught by clinic initiating Lovenox therapy (i.e. IM, FP, Cardiology) in collaboration with teaching guidelines ACS/bridging team to coordinate Assess insurance status for Lovenox coverage	Patient education to include: • Ensuring capability for self-administration • Physician ordered stop dates for Plavix, Aggrenox, prasugrel, ASA, NSAIDs, COX-2 inhibitors • Information regarding herbal product use • Advice against ETOH consumption 7 days pre-op • Ensuring patient has lab order for STAT INRs • Identifying the labs processing STAT INRs
Lovenox prescription electronically sent to pharmacy, noting rounding of dose for ease of patient use Therapeutic dose LMWH = enoxaparin 1 mg/kg every 12 hours. For VTE pts = 1.5 mg/kg every 24 hours[1]	Inform surgeon or staff performing procedure

[1] **1.5 mg/kg every 24 hours not recommended for patients with atrial fibrillation, Mechanical Valve Replacement, cancer, obesity or in pregnancy**

When resuming warfarin post-procedure, certain patient populations may be at a higher risk for bleeding and warfarin dose, in such situations, should not be temporarily increased. Rather, such patients should be restarted on their previous warfarin dose:

- Major orthopedic knee procedures
- Colonoscopy with polypectomy
- Cardiac catheterization
- Hemorrhoidectomy
- Certain urologic procedures (e.g., bladder or prostate surgery)

Use of LMWH During Spinal Anesthesia/Injection increases risk of Epidural or Spinal Hematoma

a. Concomitant administration (pre or post-procedure) of drugs that affect hemostasis (Plavix, NSAIDs, ASA) may increase the risk of hemorrhage complications including spinal hematomas.
b. Pre-op LMWH – needle placement should occur at least 24 hours after last dose of LMWH if patient on bridging doses of LMWH. Needle placement should occur 10-12 hours after last dose for patient on prophylactic doses of LMWH.
c. Post-op LMWH – first dose of Lovenox should occur a minimum of 24 hours after epidural/spinal needle placement if patient on bridging dose of LMWH, i.e. enoxaparin 1mg/kg/q12h or 1.5 mg/kg/q24h.
d. Delay initiation of LMWH therapy, either prophylactic or bridging dose, for greater than 24 hours post-op if there is presence of blood during needle and catheter placement.
NOTE:
Prophylactic or low-dose LMWH = Lovenox 40 mg daily or 30 mg twice daily
Bridging or high dose LMWH = Lovenox 1mg/kg every 12 hours or 1.5 mg/kg every 24 hours.

Reversal of enoxaparin:

Protamine sulfate may be used to partially reverse Lovenox- within 8 hours of enoxaparin dose, 1 mg protamine slow I.V. will partially neutralize 1 mg of enoxaparin injected. If enoxaparin dose given more than 8 hours ago, 0.5 mg protamine per 1 mg Lovenox injected can be administered. Second infusion of 0.5 mg protamine per 1 mg enoxaparin administered can be given 2-4 hours after the first infusion, if the aPTT remains prolonged.

These practice parameters are designed as guidelines and as such are not a substitute for the best professional judgment of physicians or other health professionals taking into consideration the individual circumstances presented by the patient. Acceptable medical practice may include a variety of responses to a particular clinical problem and all rationale should be documented in the patient's chart.

Outpatient Treatment of Venous Thromboembolism (VTE):
DOACs are recommended over vitamin K antagonists for the treatment of VTE (see guidance below). For patients unable to use DOAC therapies, outpatient treatment of VTE may consist of utilizing low molecular weight heparin (LMWH) [e.g., enoxaparin (Lovenox)] along with warfarin. Once a stable level of anticoagulation is reached (minimum of 5 days of overlap and two consecutive therapeutic INRs must be achieved), low molecular weight heparin is discontinued and warfarin is continued alone. LMWH has been shown to be superior to unfractionated heparin for the treatment of DVT, particularly for reducing mortality and the risk for major bleeding during initial therapy. Additional trials are needed to examine the efficacy of LMWH for the treatment of pulmonary embolism, but reviews of existing trials indicate that LMWH is at least as effective as unfractionated heparin for these patients as well. The current HFHS protocol approves the use of enoxaparin 1mg/kg SC q 12 hours for the outpatient treatment of VTE.

A regimen of enoxaparin 1.5 mg/kg q 24 hours is also acceptable for treatment of VTE when the following criteria are met*:

1) Patient is **NOT** obese
2) Size of the dose (1.5 mg/kg) does **NOT** exceed 150mg per dose
3) Patient is **NOT** pregnant
4) Patient does **NOT** have cancer

*Use of enoxaparin 1.5 mg/kg once daily for the treatment of VTE is controversial. This dosing option is based on a single randomized, clinical trial comparing unfractionated heparin (UFH) to enoxaparin 1.5 mg/kg daily or 1 mg/kg twice daily in 900 patients with VTE [43]. While there was no difference in recurrent VTE or major bleeding between the groups as a whole, only 32 % of the patients enrolled had PE at the time of randomization. Patients with symptomatic PE, obesity and malignancy all had higher rates of recurrent VTE when treated with 1.5 mg/kg daily versus 1 mg/kg twice daily. [J Thromb Thrombolysis (2016) 41:165–186]
Current guidelines suggest that when enoxaparin is used for the treatment of VTE, it should be dosed at 1 mg/ kg twice daily and that the reduced dose delivered by 1.5 mg/ kg once daily be avoided [Chest 141(2)(Suppl):e419S–e494s; Chest 142:1074–1075]

Guidance for Treatment of Outpatient VTE:

ASH 2020 recommendations (Blood Advances; October 2020;4(19):4693-4738):

Recommendation 3. For patients with DVT and/or PE, the ASH guideline panel suggests using direct oral anticoagulants (DOACs) over vitamin K antagonists (VKAs) (conditional recommendation based on moderate certainty in the evidence of effects)

Remarks: This recommendation may not apply to certain sub- groups of patients, such as those with renal insufficiency (creatinine clearance < 30 mL/min), moderate to severe liver disease, or antiphospholipid syndrome.

Recommendation 4. For patients with DVT and/or PE, the ASH guideline panel does not suggest 1 DOAC over another (conditional recommendation based on very low certainty in the evidence of comparative effects).

Remarks: Factors, such as a requirement for lead-in parenteral anticoagulation, once- vs twice-daily dosing, and out-of-pocket cost may drive the selection of specific DOACs. Other factors, such as renal function, concomitant medications (eg, need for a concomitant drug metabolized through the CYP3A4 enzyme or P-glycoprotein), and the presence of cancer, may also impact DOAC choice.

CHEST 2021 recommendations (CHEST 2021, doi: https://doi.org/10.1016/ j.chest.2021.07.056.):

Guidance Statement:
15. In patients with VTE (DVT of the leg or PE) we recommend apixaban, dabigatran, edoxaban or rivaroxaban over VKA as treatment phase (first 3 months) anticoagulant therapy (strong recommendation, moderate-certainty evidence).

Comments: The choice of anticoagulant for treatment phase of VTE necessitates consideration of patient specific factors (e.g., renal function, direct patient expense, payor considerations, bleeding risk, anticipated compliance) drug availability and the patient's preferences. Guidance is driven by the comparable efficacy and improved safety of DOACs over traditional therapy. DOACs also offer greater convenience. Certain clinical situations favor VKA (e.g., extremes of weight, severe renal impairment, or presence of antiphospholipid syndrome). Cost may also drive the clinical decision.

Cancer-related VTE:

ASCO 2019 recommendations (J Clin Oncol 38:496-520):

Recommendation 4.2. For long-term anticoagulation, LMWH, edoxaban, or rivaroxaban for at least 6 months are preferred because of improved efficacy over vitamin K antagonists (VKAs). VKAs are inferior but may be used if LMWH or direct oral anticoagulants (DOACs) are not accessible. There is an increase in major bleeding risk
with DOACs, particularly observed in GI and potentially genitourinary malignancies. Caution with DOACs is also warranted in other settings with high risk for mucosal bleeding. Drug-drug

interaction should be checked prior to using a DOAC (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).

CHEST 2021 recommendations (CHEST 2021, doi: https://doi.org/10.1016/ j.chest.2021.07.056.):

Guidance Statement:
16. In patients with acute VTE in the setting of cancer ("cancer-associated thrombosis") we recommend an oral Xa inhibitor (apixaban, edoxaban, rivaroxaban) over LMWH for the initiation and treatment phases of therapy (strong recommendation, moderate-certainty evidence).

Remark: Edoxaban and rivaroxaban appear to be associated with a higher risk of gastrointestinal major bleeding than LMWH in patients with CAT and a luminal gastrointestinal malignancy while apixaban does not. Apixaban or LMWH may be the preferred option in patients with luminal GI malignancies.

HFHS Guidelines for VTE treatment:

DOACs are the first line choice for new VTE unless the patient has the following characteristics (see also pages 65 & 66 for patients who should avoid DOACs):

- Mechanical Heart Valve
- Atrial Fibrillation in the presence of moderate to severe mitral valve stenosis or mechanical mitral valve
- Left Ventricular Assist Device (LVAD)
- Pregnancy/Breast feeding/child-bearing age not on contraception
- Coagulation Disorder -Antiphospholipid Antibody Syndrome (APS)
- CrCl < 30 mL/min or dialysis patient (apixaban may be used)
- History of DOAC failure or recurrent VTE (Thromboembolic event or major bleeding event while compliant on an appropriate DOAC regimen)
- DOAC and Warfarin Failure
- Severe hepatic impairment (Child-Pugh Class C)
- Heparin-induced thrombocytopenia (HIT)Patients who are pregnant or breast feeding should be on LMWH, all others with the characteristics listed above should be on started on LMWH and bridged to warfarin, with an INR range of 2.0 – 3.0.

Patients with active cancer should be treated with LMWH or a DOAC, unless the patient has an intact Gastrointestinal or Genitourinary cancer, then the patient should use LMWH. (please see Policy Stat for latest HFHS Anticoagulation for VTE guidelines)

Summary of Outpatient treatment of VTE with Lovenox & warfarin:

Guidelines for Outpatient Treatment of VTE with Lovenox and Warfarin

PROCEDURE	KEY POINTS
1. When starting Lovenox, initiating department orders baseline INR, CBC, PLTs and SCr. (SCr to be checked within the past 6 months)	If not drawn, draw INR, CBC, PLTs and SCr
2. Anticoagulation education prior to initiation of therapy	Basic teaching done by discharging staff/thorough teaching completed by Ambulatory Anticoagulation Service (ACS)
3. Contact ACS for enrollment, enrollment form forwarded to ACS	
4. ACS staff to contact patient within 24 hours of receiving form (during regular business hours) Assessment to include: A. Review of exclusion criteria: a) eCrCl < 30 ml/min (SCr checked within 6 months of starting Lovenox therapy) b) Weight > 150 kg, (or female < 45 kg, male < 57 kg for non-weight based/prophylactic dosing) B. Review of inclusion criteria: Documented VTE C. Verify correct doses of Lovenox (based on weight and eCrCl) and warfarin. D. Verify quantities of Lovenox syringes and warfarin tablets on hand. E. Assess patient level of warfarin and Lovenox knowledge. F. Assess capability of self-administering Lovenox G. Review concomitant medications for warfarin drug interactions H. Assess aspirin, NSAID, Plavix, Aggrenox use I. Explain lab process, provide lab order J. Offer class, if applicable K. Provide next lab due date L. Reinforce importance of close communication with ACS	If exclusion criteria met, contact provider. If CrCl >15 ml/min and $\leq$ 30 ml/min, contact ACS Clinical Pharmacist Lovenox dose: 1mg/kg/q12h or 1.5 mg/kg/q24h Caution: 1.5 mg/kg/q24h is not recommended for obese or cancer patients. If patient unable to self-inject, consider alternative caregiver or Homecare referral Provide orders for STAT INRs, PLTs emphasizing need for early morning draw and same-day patient contact. Obtain ER contact name and telephone number. Be sure to have patient responsibility/authorization form signed.
5. Monitor INR every 1 to 2 days, adjust warfarin dose per "5 mg Loading of Warfarin Algorithm" (see appendix D)	Need for warfarin dose adjustment on same day
6. Check PLTs day 4-10 of Lovenox therapy, notify Dr. if PLTs are <50,000 or $\leq$ 50% of baseline	Heparin-Induced Thrombocytopenia may occur within 4-10 days
7. Assess for signs/symptoms of bleeding with each contact	
8. Discontinue Lovenox when the patient has 2 consecutive therapeutic INRs at least 24 hours apart	New VTEs must have 5 full days of Lovenox therapy (exceptions may include INR > 4.0, contact ACS provider for instructions)

Use of LMWH during spinal anesthesia/injection:

**** LMWH may increase the risk of epidural or spinal hematoma ****

a. Concomitant administration (pre or post-procedure) of drugs that affect hemostasis (i.e. Plavix, NSAIDs, or ASA) may increase the risk of hemorrhage complications including spinal hematomas.

b. Pre-op LMWH – needle placement should occur at least 24 hours after last dose of LMWH if patient on bridging doses of LMWH. Needle placement should occur 12 hours after last dose of patient on prophylactic doses of LMWH.

c. Post-op LMWH – first dose of Lovenox can be resumed 4 hours after low-risk pain procedures but at least 12-24 hours after intermediate- and high-risk pain procedures.

d. Delay initiating of LMWH therapy, either prophylactic or bridging dose for greater than 24 hours post-op if there is presence of blood during needle and catheter placement.

Reversal of Lovenox:

Protamine sulfate may be used to partially reverse Lovenox.

- Stop enoxaparin
- Within 8 hours of Lovenox dose, 1 mg protamine slow I.V. injection over 5-10 minutes will partially neutralize 1 mg of Lovenox injected.
- If Lovenox dose given more than 8 hours ago, 0.5mg protamine per 1 mg Lovenox injected can be administered as slow IV injection over 10 minutes.
- Second infusion of 0.5 mg protamine per 1 mg Lovenox administered can be given 2 to 4 hours after the first infusion, if the aPTT remains prolonged after 2-4 hours.

These practice parameters are designed as guidelines and as such are not a substitute for the best professional judgment of physicians or other health professionals taking into consideration the individual circumstances presented by the patient. Acceptable medical practice may include a variety of responses to a particular clinical problem.

Tier 1 Anticoagulation Reversal Guidelines

Information regarding Management of Anticoagulants for Watchman Procedure*

New policies regarding antithrombotic management for LAAC at HF Health and/or expert guidance could not be located as of this update to the manual. Please see abstract and link to article for informational purposes only below:

Mesnier J et al. Antithrombotic Management After Left Atrial Appendage Closure: Current Evidence and Future Perspectives.*CircCardiovascInterv*.2023;16:e012812.DOI:10.1161/CIRCINTERVENTIONS.122.012812

Abstract: Left atrial appendage closure (LAAC) is a validated alternative to chronic oral anticoagulation (OAC) to prevent embolic events related to nonvalvular atrial fibrillation (AF). In current practice, LAAC is mostly proposed to highly comorbid patients with an increased risk of both ischemic and bleeding events. Despite the high-risk features of this population, procedural success and long-term prevention of ischemic events following LAAC have been excellent. Still, major pitfalls, such as the occurrence of device-related thrombus (DRT), limit the extension of LAAC to a wider population. Bleeding complications after LAAC also remains an issue, especially during the intensive phase of antithrombotic therapy used to prevent DRT. Finding the most appropriate combination and duration of antithrombotic treatment is, therefore, critical, both for DRT and bleeding prevention. Considerable variations exist in the type and duration of antithrombotic regimens after the procedure. In this review, we provide an overview on the rationale for antithrombotic treatment after LAAC, evaluate current evidence regarding prevention of DRT/ischemic events and bleeding risk of the different antithrombotic regimens, and discuss future perspectives.

Device	Study	Antithrombotic treatment	Comments
WATCHMAN	PROTECT-AF PREVAIL	combination of warfarin and aspirin (81 mg/day) for 45 days, followed by DAPT with aspirin (325 mg/day) and clopidogrel (75 mg/day) up to 6 months and lifelong aspirin (325 mg/ day) thereafter.	Based on results of these studies, this antithrombotic regimen was approved by the FDA after WATCHMAN implantation
WATCHMAN FLX	PINNACLE FLX	antithrombotic treatment with a DOAC (apixaban or rivaroxaban was recommended) and concomitant low-dose aspirin during the first 45 days after LAAC	Study replaced VKA with DOAC (apixaban or rivaroxaban)
WATCHMAN FLX Amplatzer Cardiac Plug/Amulet	ANDES ADALA	Comparing DOAC versus DAPT following LAAC FDA approval of 45-day DAPT labeling for the WATCHMAN FLX, as an alternative to 45-day OAC plus aspirin.	Current European device labeling recommends DAPT for 3 months when standard therapy would not be possible after WATCHMAN or Amplatzer Cardiac Plug/Amulet implantation.

While controversial data exist regarding an increased risk of DRT with antiplatelet therapy compared to OAC, there is currently no definitive evidence regarding the optimal antithrombotic regimen to prevent DRT and ischemic events post-LAAC

CircCardiovascInterv.2023;16:e012812.DOI:10.1161/CIRCINTERVENTIONS.122.012812

6.5.2. Cardiac Surgery—LAA Exclusion/Excision

Recommendations for Cardiac Surgery—LAA Exclusion/Excision Referenced studies that support the recommendations are summarized in the Online Data Supplement.

COR	LOE	Recommendations
1	A	1. In patients with AF undergoing cardiac surgery with a CHA_2DS_2-VASc score ≥2 or equivalent stroke risk, surgical LAA exclusion, in addition to continued anti-coagulation, is indicated to reduce the risk of stroke and systemic embolism.[1–3]
1	A	2. In patients with AF undergoing cardiac surgery and LAA exclusion, a surgical technique resulting in absence of flow across the suture line and a stump of <1 cm as determined by intraoperative trans-esophageal echocardiography should be used.[1,4,5]
2b	A	3. In patients with AF undergoing cardiac surgery with CHA_2DS_2-VASc score ≥2 or equivalent stroke risk, the benefit of surgical LAA exclusion in the absence of continued anticoagulation to reduce the risk of stroke and systemic embolism is uncertain.[1–3]

From: 2023 ACC/AHA/ACCP/HRS guideline for the diagnosis and management of atrial fibrillation: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2024;149:e1–e156.doi:10.1161/CIR.0000000000001193

AC Forum Rapid Resource: Left Atrial Appendage Occulusion (LAAO) Devices for Prevention of Stroke and Systemic Embolism in Atrial Fibrillation

Purpose:
For patients receiving medical care from a Henry Ford Medical Group (HFMG) physician and for whom we have accepted into the Ambulatory Anticoagulation Service (ACS), the ACS Practitioner will work under said HFMG physician's delegated authority to manage patients on warfarin to provide peri-procedural INR monitoring and warfarin dosing adjustments for Structural Heart Disease and Electrophysiology prescribed warfarin pre- & post-Watchman procedure.

Background:

1. Watchman procedures are being done by Interventional (Structural Heart Disease) and Electrophysiology providers. The majority of the patient/anticoagulation management (ACC enrollment, patient communication, TEE scheduling, etc) is done by SHD and EP NPs/PAs
2. Nearly all patients who are candidates for the Watchman procedure are NOT on warfarin when the Watchman is planned and warfarin needs to be restarted, since prior anticoagulation has usually led to bleeding and/or adverse event.
3. It generally takes approximately 4 weeks during anticoagulation pre-procedure to:
    a. achieve a therapeutic INR
    b. have TEE scheduled and screened by Boston Scientific
    c. have Watchman procedure scheduled
4. INR Target 2.0 -3.0 advised pre-and post-procedure (keep toward 2 – 2.5 range pre-procedure)
5. TEE is scheduled and obtained 45 days post successful procedure, with Cardiology providers deciding/communicating with the patient regarding warfarin discontinuation.

Watchman Pre- & Post-Procedure Anticoagulation Management:

THERAPY PERIOD	INR RANGE	THERAPY DURATION
Pre-procedure	2.0-3.0 keeping toward **2.0 – 2.5**	4 weeks
Procedure	2.0-3.0 keeping toward **1.8 - 2.5**	**Test INR 4 days prior**
Post- procedure	2.0-3.0	45 days

Watchman Pre- & Post-Procedure Anticoagulation Management Enrollment Process:

1. If (re-)starting warfarin pre-Watchman procedure, then Cardiology provider should:
    a. order initial CBC, PT, and PTT
    b. complete EPIC ACS referral form
    c. prescribe initial warfarin dose choosing INR goal 2-3 and 3 month expected treatment duration
2. Cardiology providers will be responsible for:
    a. ordering TEEs
    b. notifying patients plus ACS personnel when/ if warfarin stopped at 45 days. When providing patient instructions to "stop warfarin and start aspirin/clopidogrel" following day 45 TEE result, Cardiology will look under Letters/Communication in EPIC and determine who is the ACS RN or PharmD managing patient's anticoagulation. Cardiology will then direct the EPIC clinic note or telephone note to this individual with clear notification of warfarin stopped/ "May disenroll from ACS"
    c. all antiplatelet agent (aspirin, clopidogrel, etc) prescribing post-procedure
3. ACS providers will be responsible for:
    a. ensuring appropriate INR range and length of warfarin therapy ordered
    b. scheduling INR draws
        - pre-procedure during titration phase
        - **4 days prior to procedure**
        - Post-procedure as needed to keep therapeutic

c. adjusting warfarin doses as necessary to achieve therapeutic INR results prior to scheduled Watchman procedure
d. assessing patients via telephone interview for signs/symptoms of bleeding and/or adverse events
e. ensuring that patients have been instructed by their Cardiology provider when to discontinue warfarin therapy

4. If there is no "Stop warfarin/Disenroll ACS" communication generated at around 45 days, ACS providers will review the patient case at 3 months from the start of warfarin therapy to confirm warfarin stoppage/no continued need for ACS services
5. If the above protocol is not followed by the Cardiology providers (e.g. they use DOACs in place of warfarin, or they start warfarin closer to the procedure than 2 weeks), approval for us to manage must be obtained by an HFMG Ambulatory Anticoagulation Service Co-Medical Director

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Approved by M. Hudson, MD; G. Krol, MD; P. Kuriakose, MD; V. Shah, MD; N. Ryan, PharmD 10.13.15
Updated 3.2024

Anticoagulation therapy around dental, dermatologic, and cataract extraction Procedures:

Minor **dental** procedures consist of single or multiple tooth extractions and endodontic (root canal) procedures. Studies that compared continuing warfarin therapy with interrupting treatment prior to a dental procedure showed there were no episodes of thromboembolism or major bleeding with either perioperative management strategy. Therefore, it is recommended to continue warfarin therapy in patients who are undergoing minor dental procedures. Pro-hemostatic agents, such as tranexamic acid and epsilon aminocaproic acid mouthwash given in conjunction with warfarin therapy are safe and may further minimize the risk of minor bleeding.

Therefore, coadministeration of an oral prohemostatic agent is recommended to decrease the risk for clinically relevant nonmajor and minor bleeding.

Dental procedures can also be classified according to risk of bleeding:

Minimal bleeding risk

- Extraction of 1-2 teeth
- Periodontal surgery
- Incision of abscess
- Implant positioning

Low bleeding risk

- Extraction of 3 or more teeth

Rules of thumb for warfarin and dental procedures:

- Minor dental procedures do not require interruption of warfarin therapy.
- Local interventions such as use of hemostatic agents, local anesthetics with a vasoconstrictor, absorbable hemostatic dressing, and suturing play a major role in minimizing bleeding complications.
- Evaluate risk for bleeding for each patient based on type of procedure and medical history.
- Avoid analgesics with antiplatelet effects post procedure, such as NSAID.
- Most minor dental procedures can be done while INR ≤ 3.0. Some references suggest going as high as INR of 4.0.
- Obtain INR within 24 hours before procedure (up to 72 hours if procedure falls on Mondays) and forward the result to the dentist's office before procedure.
- Tranexamic acid (TXA) has been the primary oral hemostatic agent used.
- Compared to local agents used during procedure, TXA is at least as effective.
- Disadvantages of TXA include additional cost and compliance (used qid for several days post procedure)
- Anecdotal data with another oral hemostatic agent, aminocaproic acid, is posted on www.clotcare.com (http://www.clotcare.com/clotcare/faq_amicarsolution.aspx)
- There is no place for LMWH bridge therapy in minor dental procedures.
- LMWH may be useful in more extensive oral surgeries, but data is lacking at this time.

Dental procedures and patients on chemotherapy or IV Biphosphonates:

- Oral side effects of chemotherapy include mucositis, oral infections, neurotoxicity (e.g., dental hypersensitivity), thrombocytopenia, dental changes, change in taste, dry mouth, bleeding tendency, and the development of osteonecrosis of the jaw (e.g., hypercalcemia of malignancy associated with bone metastases and multiple myeloma).

- In general, avoid extensive dental procedures around periods of receiving chemotherapy until mucositis resolves and platelet count is back to normal.

- Patients on IV bisphosphonates [e.g., zoledronic Acid (Zometa), pamidronate (Aredia)] should avoid extensive dental procedures where bone is exposed (e.g., extractions, implants, root planing or scaling) due to risk of osteonecrosis of the jaw. Tartar removal (dental cleaning) is acceptable.

- Postmenopausal women may receive zoledronic acid (Reclast) IV infusion once a year. The risk of osteonecrosis of the jaw is still a concern with extensive dental procedures.

- ***Anticoagulated patients may be more prone to bleeding if they have dental procedures around chemotherapy. Depending of the type of dental procedure, some of these patients may be exposed to a higher risk of osteonecrosis of the jaw if they are also on IV bisphosphonates. Some of these patients may not even be chemotherapy patients, but simply with osteoporosis. In such cases, dental interventions should be postponed if possible or addressed***.

Dermatologic procedures:

Minor **dermatologic** procedures include excisions of basal and squamous cell carcinomas, actinic keratosis, and malignant or premalignant nevi. Based on current literature, warfarin patients who are undergoing minor dermatologic procedures should continue warfarin therapy around the time of such procedures.

Cataract procedures:

Per UpToDate (July 2021), cataract surgery is considered a low-risk procedure for bleeding. In general, patients can be continued on their anticoagulant therapies. However, the decision to continue or discontinue anticoagulants should be made after a discussion with the proceduralist. Patients may have anticoagulants stopped prior to surgery due to patient-specific concerns, such as patients with previous bleeding complications or in cases where a larger incision is planned.

VII. Direct Oral Anticoagulants (DOACs) essential skills:

Direct Oral Anticoagulant (DOAC) Basics

DOACs affect the clotting cascade differently than warfarin. While warfarin is a vitamin K antagonist and causes a biologic depletion in clotting factors, DOACs directly antagonize specific clotting factors. Because DOACs do not rely on the gradual decrease of clotting factors, they have a quicker therapeutic onset and more predictable dosing than warfarin.

Dabigatran (Pradaxa ®) is a direct thrombin inhibitor, which inhibits both free and clot-bound thrombin. Dabigatran prevents thrombin-induced platelet aggregation and development of a thrombus by preventing the thrombin-mediated conversion of fibrinogen to fibrin during the coagulation cascade.

Apixaban (Eliquis®), rivaroxaban (Xarelto®), edoxaban (Savaysa®) and betrixaban (Brevyxx® currently not available in the U.S.), are selective factor Xa inhibitors and do not require antithrombin III for antithrombotic activity. These agents inhibit free factor Xa and prothrombinase activity. Apixaban also inhibits clot bound factor Xa. By inhibiting Factor Xa, they decrease thrombin generation and the development of a thrombus. Although Factor Xa inhibitors have no direct effect on platelet aggregation, they indirectly inhibit platelet aggregation induced by thrombin.

DOACs do not require regular INR monitoring, but they do require periodic lab draws for renal and hepatic function, as well as complete blood counts.
The anticoagulation pharmacists are involved in the process of converting from warfarin to these agents as follows:

1) The following data are evaluated before the conversion process can proceed:
    a. Calculated creatinine clearance (by Cockcroft Gault method using ABW instead of IBW)
    b. Proper indication
    c. Absence of contraindications

d. Appropriateness of dose
e. Age
f. Risk of bleeding
g. CHA2DS2-VASc score (Atrial Fibrillation patients)

If any of the above factors do not adhere to current standards, the prescriber must be contacted, and the issue must be resolved before patient is started on the newer anticoagulant.

2) Once all criteria listed above are met, the assigned AC Practitioner contacts the patient and goes over instructions on how to conduct the conversion from warfarin to the new anticoagulant (see below) and the patient education information on the new anticoagulant based on FDA Medication Guide.
3) The AC Practitioner will follow-up with the patients via the DOAC Dashboard, or as determined by clinical assessment in 2 weeks, 6 weeks, 3 months, then 6 months intervals to ensure:
    a. Appropriate indication and dosage
    b. Warfarin conversion/initiation of therapy
    c. Individualized treatment recommendations
    d. Follow-up with physician regarding treatment recommendations and plan
    e. Patient education (drug information monographs available on shared drive, in "Patient Education" Folder)
    f. Guidance for therapy interruption due to procedures
    g. Drug interaction prevention advice
    h. Compliance management
    i. Patient follow-up surveillance (renal function lab monitoring, post-hospitalization follow-ups)
    j. Adverse drug reaction monitoring and reporting (Patient flyers regarding management of minor bleeding and epistaxis on shared drive)
    k. Outpatient specific consultations to assist in appropriate medication selection

<u>Proper prescribing of DOACs</u>

1. Review indication for therapy

2. Check for appropriate medication dosing for indication
3. Review the patient's profile for the following:
   a. Difficult to maintain therapeutic INR with proper warfarin compliance
   b. Adequate renal function
   c. Adequate liver function
   d. Age
4. Contact the prescribing physician for discussion of any of the following (including but not limited to):
   a. Active pathological bleeding, at an increased risk for bleeding or previous history of GI bleed
   b. Patients with feeding tubes (dabigatran)
   c. Moderate/severe mitral stenosis or mechanical prosthetic heart valves (DOAC use not recommended)
   d. Left Ventricular Assist Device (LVAD) (DOAC use not recommended)
   e. Embolic Stroke of Undetermined Source (ESUS) (DOAC use not recommended)
   f. Transcatheter Aortic Valve Replacement (TAVR) (Per 2020 ACC/AHA Guidelines – "VKA is reasonable")
   g. Within 3 months of a biosprosthetic heart valve replacement (DOAC use not recommended)
   h. Valvular Atrial Fibrillation (in the presence of MVR or moderate/severe mitral stenosis)
   i. Severe hepatic impairment (DOAC use not recommended)
   j. Moderate hepatic impairment (Risk/Benefit discussion)
   k. Concomitant CYP3A4 and/or P-gp inhibitors/inducers (see specifications per agent)
   l. Patient financial burden due to limited income
   m. Patients with weight > 120 kg or BMI $\geq$ 40 (Risk/Benefit discussion; recent studies (2021) show standard doses may be used)
   n. Patients who have undergone bariatric surgery (Risk/Benefit discussion)

Medical Conditions	**Alternative Agent**
Mechanical Heart Valve or LVAD	Recommend Warfarin^{+}
Moderate to severe mitral stenosis	Recommend Warfarin^{+}
Pregnancy	Recommend LMWH
Breast Feeding	Recommend Warfarin^{+} or LMWH
Coagulation Disorder (e.g. Anti-phospholipid syndrome)	Recommend Warfarin^{+}
CrCl < 30 mL/min**	Recommend Warfarin^{+}
Dialysis	Recommend Warfarin^{+} apixaban may be used in Afib
Severe Liver disease (Child-Pugh C)	Recommend Warfarin^{+}

DOAC failure or recurrent VTE (Thromboembolic event or major bleeding event while compliant on an appropriate DOAC regimen)	Recommend Warfarin[+] or LMWH
DOAC and Warfarin failure	Recommend LMWH
LMWH failure (Thromboembolic event or major bleeding event while compliant on an appropriate LMWH regimen)	Recommend increasing LMWH dose by one-quarter to one-third OR Recommend DOAC
Heparin-induced thrombocytopenia	Warfarin with argatroban or fondaparinux bridge OR rivaroxaban
Obesity (specifically BMI $\geq$ 40 or weight >120 kg)	For VTE, standard doses of rivaroxaban or apixaban are appropriate options (not in setting of acute bariatric surgery). Warfarin, and LMWH (per manufacturer's recommendations) also options++

o. Patients with ESRD on hemodialysis (unless apixaban for AF)
p. Active infective endocarditis
q. Women who are pregnant or of childbearing potential who refuse to use a form of contraception or are breastfeeding (DOAC use not recommended)
r. Patients with Antiphospholipid Syndrome (DOACs not recommended)
s. Off-label indications (Risk/Benefit Discussion)
t. Severe renal impairment (CrCl < 30 mL/min) (Risk/Benefit Discussion)
u. Poor medication adherence
v. Treatment failure while on therapeutic warfarin or LMWH (Risk/Benefit Discussion)
w. Cancer patients with an acute diagnosis of VTE and a high risk of bleeding, including patients with luminal gastrointestinal cancers with an intact primary, patients with cancers at risk of bleeding from the genitourinary tract, bladder, or nephrostomy tubes, or patients with active gastrointestinal mucosal abnormalities such as duodenal ulcers, gastritis, esophagitis, or colitis (Lovenox monotherapy first choice, rivaroxaban or edoxaban, or apixaban acceptable alternatives)

Conditions suggesting alternate anticoagulation therapy to DOACs*

*Anticoagulant choice should be individualized based on patient characteristics
**CrCl < 25 mL/min if apixaban
[+]If acute VTE, patients initiated on warfarin should be bridged with LMWH for a minimum of 5 days until INR is therapeutic for two consecutive INR levels taken at least 24 hours a part
++Martin et al. Use of direct oral anticoagulants in patients with obesity for treatment and prevention of venous thromboembolism: Updated communication from the ISTH SSC Subcommittee on Control of Anticoagulation. JTH April 21, 2021 DOI: 10.1111/jth.15358

Therapy Management

1. Patients will receive medication counseling regarding DOAC use from the AC Pharmacist or Nurse (AC Practitioners), which will include but not be limited to, information regarding:
    a. Conversion between agents (warfarin and/or new agents)
    b. Proper administration and storage (drug monographs available on shared drive)
    c. Potential adverse drug events and when to contact physician
    d. Interruption of therapy for procedures
    e. Need for an I.D. bracelet/necklace indicating patient is on a blood thinner
    f. AC clinic telephone numbers and when to contact an AC Practitioner
    g. Additional counseling points to be provided at the discretion of the AC Pharmacist or Nurse
2. Upon request, AC Practitioners will work closely with the primary care physician and/or the physician performing the procedure to determine an appropriate length of DOAC interruption for procedures. Patients for whom DOAC therapy would be interrupted for procedures would be advised based on an empiric protocol anchored on whether major or minor surgery was being done, the extent of renal insufficiency, and patient risk for bleeding. (See pages 80 & 81)
3. AC Practitioners to provide physicians, other health care providers and patients with treatment recommendations, information regarding drug-drug and/or drug-disease interactions, and treatment plans.
4. AC Practitioners to provide clinical follow-up plan:
    a. 1 - 2 weeks after DOAC initiation
        i. Evaluate drug tolerance
        ii. Check for new medications and instruct patient to notify clinic of future medication changes
        iii. Check for adverse events
            (i) Review signs/symptoms of bleeding/bruising – assess HASBLED score
            (ii) Recommend emergency room visit should patient develop signs/symptoms of bleeding
        iv. Ensure compliance
            (i) Are they taking as prescribed?
            (ii) Can they afford refills?
        v. Check for upcoming procedures and instruct patient to notify clinic of future procedures in advance and as soon as they are scheduled.
    b. 6 weeks after DOAC initiation
        i. Evaluate drug tolerance (as above)
        ii. Check for new medications (as above)
        iii. Check for adverse events (as above)
        iv. Ensure compliance (as above)
        v. Check for upcoming procedures
    c. 3-month follow-up call (initially, with at minimum every 6 months thereafter **per chart on page 72 and Appendix G**) check of:
        i. SCr
        ii. Regularly assess weight and age (apixaban)
        iii. Calculated CrCl (use actual body weight)

iv. Hepatic function (in patients with a provider-documented history/suspicion of hepatic disease, liver function testing may be considered. See Child-Pugh scoring system)
(i) Rivaroxaban - Avoid use in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment or with any degree of hepatic disease associated with coagulopathy
(ii) Apixaban - No dose adjustment is required in patients with mild hepatic impairment. Because patients with moderate hepatic impairment may have intrinsic coagulation abnormalities and there is limited clinical experience with apixaban in these patients, dosing recommendations cannot be provided. Apixaban is not recommended in patients with severe hepatic impairment (Child-Pugh C).
(iii) Edoxaban – No dose adjustment necessary in patients with mild hepatic impairment (Child-Pugh A). Not recommended in patients with moderate or severe hepatic insufficiency (Child-Pugh B and C)

d. Annually assess (& adjust dose per package insert dosing instructions as necessary):
i. Hgb
ii. Hepatic function (via EHR documentation)
iii. Renal function (more frequently if renal insufficiency)
iv. Weight
v. Age
vi. Bleed risk using HASBLED score

5. AC Practitioners to perform post-IPD (with notification) follow-up to review:
a. Renal function (SCr, calculated CrCl)
b. Hepatic function (as needed)
c. New medications for potential drug-drug interactions
d. Potential drug-disease state interactions
6. The DOAC Dashboard will alert AC Practitioners to drug-drug interactions, required dose changes and duplicate anticoagulant orders. Please refer to PolicyStat usng this link for more information:

Tier 2: Direct Oral Anticoagulant (DOAC) Dashboard

Patient Tracking and Documentation

1. EPIC Anti Coag Tracking
a. Click on the EPIC button and choose Encounter
b. Choose your patient and click accept
c. In Encounter Selection box, choose "New" to create a new encounter
d. In New Encounter box, choose Type: "Anti-coag DOAC Visit and accept
e. In DOAC Track
i. Link DOAC episode
ii. Track Pt. Outreach
iii. Progress Note
iv. Patient Findings (if needed)
f. Sign visit
2. Add patient encounter to Remind Me folder (so that others may follow-up if necessary)
a. Include any comments necessary for next follow-up
3. Run Report for Next DOAC outreach

a. Click on EPIC button and choose Reports
b. Go to "Library"
c. Type "DOAC" in search box
d. Click on HF DOAC
e. Click Run

DOAC Dashboard Manual

Background

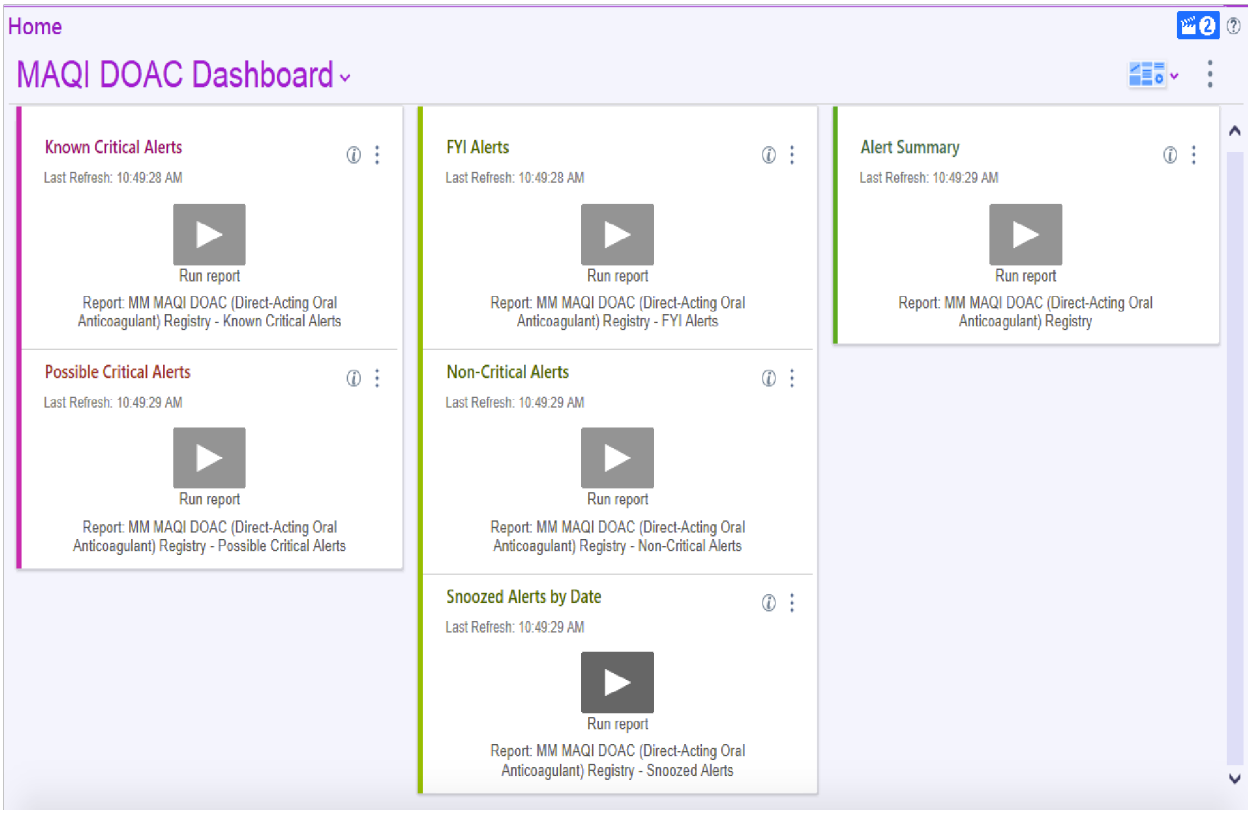
Anticoagulants remain a high-risk medication class due to their adverse event profile. Improving anticoagulation care continues to be a National Patient Safety Goal (NPSG) for The Joint Commission[1]. NPSG's for 2021 state facilities need to ensure their protocols are updated to cover all types of anticoagulants, including DOACs. The following required safety goals are often missed for those patients not enrolled in the anticoagulation clinic, which includes the majority of the patients on a DOAC currently in the HFMG:

- Have a written policy on the need for laboratory tests to adjust and monitor anticoagulant therapy.
- Establish a process to respond to adverse drug events and evaluate and anticoagulation safety practices.

The HFMG Ambulatory Anticoagulation Services (HFMG ACS) has been shown to provide safer management of anticoagulant therapy than the usual practice. Real life data outside clinical trials have shown that using a lower dose Direct Oral Anticoagulant (DOAC) therapy for patients that do not meet the criteria for dose adjustment may result in an increase embolic events and result in potentially preventable strokes in those with atrial fibrillation. Alternatively, using the standard dose DOAC for patients whose renal function suggest a lower dose is indicated may have worse outcomes with respect to bleeding risk.[2,3] Studies have suggested that DOACs are often prescribed at a non-FDA recommended dose[4,5,6], in addition receiving insufficient laboratory monitoring.[7] The HFMG ACS has worked in conjunction with the Michigan Anticoagulation Quality Improvement Initiative (MAQI^2) to improve the quality of anticoagulation management statewide, nationally and internationally. Together, a tool has been created and implemented to ensure safer management of DOAC therapy.

Procedure

1. Patients prescribed a DOAC within HFMG under the orders of an Internal Medicine, Family Medicine, Cardiology, Pulmonology or Hematology/Oncology provider will be automatically enrolled in the Ambulatory Anticoagulation Services (see Anticoagulation Service Policy and Procedure for enrollment process)
2. Patients will be included in the MAQI^2 DOAC Dashboard which extracts data from the Electronic Health Record (EHR) registry reports
3. Reports will be run and reviewed by ACS Practitioners on a regularly scheduled basis



a. Dashboard will appear when you open EPIC if assigned
b. Reports are also accessible from EPIC “Reports”

4. EHR corrections will be made under the delegated authority of the HFMG Provider (as described above):

    a. Correction of DOAC prescriptions

        i. Patient dosing instructions entered in an incorrect field (i.e. free-texted) will be entered in the appropriate field with the appropriate patient dosing instructions

        ii. Includes correction when no frequency or directions have been included in the order, or no strength has been selected

        iii. DOAC dosing adjustments will be made by ACS Pharmacists and Nurses. Medications will be ordered via EHR orders and will be cosigned by the responsible anticoagulation provider. Additionally, the provider will be notified of the new order via Halo and/or EHR messaging (TEF)

            1. Apixaban

a. Age, weight and SCr changes

i. Dose reduction to 2.5 mg twice daily if 2 of the following 3 criterion met for atrial fibrillation indication (dose increase to 5 mg twice daily if criterion not met and dose previously inappropriately reduced):

1. Age $\geq$ 80 years

2. Weight $\leq$ 60 kg

3. SCr $\geq$ 1.5 mg/dL

b. Venous Thromboembolism (VTE) treatment after 6 months therapy

i. Dose reduction to 2.5 mg twice daily if not also indication for atrial fibrillation

ii. Dose reduction will not be considered for patients with active CA, weight > 120 kg or BMI > 40, or recurrent VTE while on DOAC therapy

2. Rivaroxaban

a. Creatinine Clearance (CrCl) changes

i. Dose reduction to 15 mg once daily for CrCl $\leq$ 50 mL/min (atrial fibrillation indication)

ii. Dose increase to 20 mg once daily for CrCl > 50 mL/min (atrial fibrillation indication)

b. VTE treatment after 6 months therapy

i. Dose reduction to 10 mg once daily if not also indication for atrial fibrillation

ii. Dose reduction will not be considered for patients with active CA, weight > 120 kg or BMI > 40, or recurrent VTE while on DOAC therapy

3. Dabigatran

a. CrCl changes

i. Dose reduction to 75 mg twice daily for CrCl 15 – 30 mL/min (atrial fibrillation indication)

b. There are currently no FDA recommended reductions in dose after 6 months therapy for VTE

4. Edoxaban

a. CrCl changes

i. Dose reduction to 30 mg once daily for CrCl 15 – 50 mL/min (atrial fibrillation and/or venous thromboembolism indications)

ii. Dose increase to 60 mg once daily for CrCl > 50 mL/min (atrial fibrillation and/or venous thromboembolism indications

b. Weight changes

i. Dose reduction to 30 mg once daily for weight ≤ 60 kg (venous thromboembolism indications)

ii. Dose increase to 60 mg once daily for weight > 60

kg (venous thromboembolism indications)

c. There are currently no FDA recommended reductions in dose after 6 months therapy for VTE

b. Documentation of correct indication for DOAC therapy
c. Removal of duplicate active anticoagulant orders as appropriate
   i. Same DOAC listed multiple times as active orders
   ii. Discontinued DOAC and new DOAC listed as active orders
   iii. Warfarin and DOAC both listed as active orders
d. Ordering and tracking lab work no less than yearly and as needed
   i. Serum creatinine (SCr)
   ii. Liver function tests (LFTs)
e. Applying indications to DOAC orders

5. AC Practitioners will contact the responsible anticoagulation physician to:

a. Review off-label indications

b. Discuss existing or potential contraindications to DOAC use

c. Discuss drug-drug interactions between DOACs and potentially harmful interacting drugs

d. Report patient adverse events

e. Report issues of patient nonadherence to DOAC therapy

f. Discuss potential discontinuation of DOAC therapy

i. Apixaban

1. Discontinue for CrCl < 25 mL/min (venous thromboembolism indications)

ii. Rivaroxaban

1. Discontinue for CrCl < 15 mL/min (atrial fibrillation indication)

2. Discontinue for CrCl < 30 mL/min (venous thromboembolism indications)

3. Discontinue therapy if on dialysis (atrial fibrillation and/or venous thromboembolism indications)

iii. Dabigatran

1. Discontinue therapy for CrCl < 15 mL/min (atrial fibrillation)

2. Discontinue therapy for CrCl < 30 mL/min (venous thromboembolism indications)

3. Discontinue therapy if on dialysis (atrial fibrillation and/or venous thromboembolism indications)

iv. Edoxaban

1. Discontinue therapy for CrCl $\geq$ 95 mL/min or < 15 mL/min (atrial fibrillation indication)

2. Discontinue therapy for CrCl < 15 mL/min (venous thromboembolism indications)

3. Discontinue therapy if on dialysis (atrial fibrillation and/or venous thromboembolism indications)

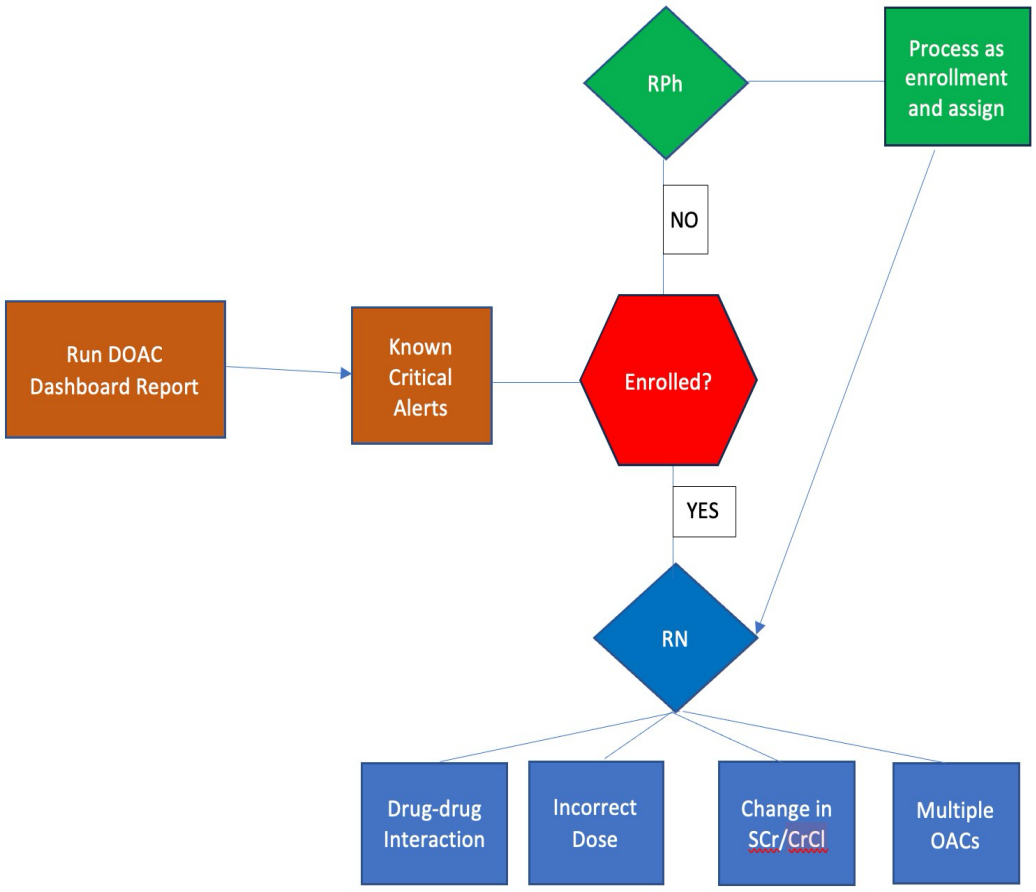
6. DOAC Dashboard management

a. Corrected issues in the EHR will automatically remove alerts from DOAC

Registry reports

b. Issues not requiring immediate action will be scheduled for later follow-up for 3 months (or less if sooner scheduled lab draw or office visit)
    i. Fluctuating SCr defined as a single SCr level requiring dose change ≥ 6 months of stable levels
    ii. Fluctuating weight defined as weight requiring dose change ≥ 6 months of stable weight
    iii. Non-FDA recommended dosing approved by physician after patient evaluation
        1. Lower dose due to history of bleeding or age 2. Higher dose despite age, weight, renal function

c. Recurring issues will be scheduled for later follow-up not more than two times (for total of 6 months) before addressed with the responsible anticoagulation physician and/or Anticoagulation Service physician champion



7. Addressing Alerts:
    a. **Possible Critical Alert – Current dose cannot be determined**

i. Will display if the Registry does not recognize the frequency of the DOAC on the medication list
    1. Prescriber free texted the instructions instead of using standard frequencies
    2. No frequency/directions in the order
    3. No strength selected

b. **Possible Critical Alert – Cannot determine indication**

i. Will display if more than one indication for anticoagulation is present on the patient's problem list
    1. Review patient problem list
    2. Review most recent provider note to review DOAC indication
    3. If indication is not obvious, consider the following logic (may be exceptions):

a. VTE within the past 6 months
b. VTE and AF are present, select AF
c. If AF and CAD/PAD are present (rivaroxaban only), select AF
d. If VTE and CAD/PAD are present (rivaroxaban only), select VTE

    4. Add indication
        a. Open DOAC Encounter
        b. Go to the DOAC tab and proceed to the DOAC Registry tab
        c. Select the appropriate indication (if VTE, you will need to include a date)
        d. Close encounter and sign when finished
    5. Do not need to document in a progress note because opening an encounter and modifying the smart form is recorded in EPIC

c. Possible Critical Alert – No Indication Found

i. Will display if no indication for anticoagulation is present on the patient's problem list
    1. Review problem list
    2. Review medical history, reviewing most recent provider notes
    3. Add indication
        a. Open DOAC Encounter
        b. Go to the DOAC tab and proceed to the DOAC Registry tab
        c. Select the appropriate indication (if VTE, you will need to include a date)
        d. Close encounter and sign when finished
    4. Do not need to document in a progress note, as described above

d. Possible Critical Alert – CONTRAINDICATED – Possible Mechanical heart valve

i. Will display if patient has a heart valve replacement noted on their problem list as the registry does not recognize whether this is a bioprosthetic or mechanical heart valve. ICD codes do not differentiate between mechanical and bioprosthetic.
    1. Review chart and verify patient has bioprosthetic valve
    2. Add correct valve
        a. Open DOAC Encounter
        b. Go to the DOAC.tab and proceed to the DOAC Registry tab
        c. Select appropriate heart valve type
        d. Close encounter and sign when finished
    3. Do not need to document in a progress note, as described above

e. Known Critical Alert – Change in SCr/CrCl

i. Will display changes in SCr for apixaban patient and CrCl for rivaroxaban, dabigatran and edoxaban patients. Also displays if there are changes in patient weight or age.
    1. Review lab values for trends in SCr
        a. If patient recently IPD discharge order a new level
        b. If patient not recently IPD discharge and SCr has been stable for ≥ 6 months, snooze out for 3 months
        c. If SCr has fluctuated borderline to that requiring dose change, snooze out for 3 months
        d. If SCr has changed over time, contact provider regarding dose change (see Protocol regarding dose changes)
    2. Review vitals for trends in weight
        a. If patient has had stable weight not requiring dose change
        ≥ 6 months, snooze out for 3 months
        b. If patient has had fluctuating weight changes borderline for dose change, snooze out for 3 months
        c. If patient has had trending toward weight change and is now at weight requiring dose change, contact provider
    3. Review CrCl
        a. Verify change requiring dose change by
            i. Calculating CrCl using C-G with actual body weight
            ii. Determining if weight and/or SCr changes are not one-time changes requiring dose change (as above)
        b. If CrCl requires dose change, follow dose change protocol under Procedure 4. If requires potential discontinuation, contact provider as per Procedure 5.

f. Known Critical Alert – Drug-Drug Interaction

i. Displays if patient has received medication order for a drug which interacts with their DOAC
    1. Review patient medication list
    2. Review chart for provider notes regarding interacting medication
    3. Contact patient to ask if they have been taking the interacting medication
    4. Contact provider to have interacting medication changed or DOAC dose decreased where applicable
        a. If provider aware of interacting medication and considers benefit to outweigh the risk, snooze for 3 months up to 2 times (total 6 months) and contact provider again about interaction
        b. If provider aware of interacting medication and does not want the medication changed or dose decreased after snoozing for 6 months, involve anticoagulation physician champion
        c. If after speaking to anticoagulation physician champion, would provider still like to keep interacting medications, document, and snooze out for 3 months

g. Known Critical Alert – Incorrect Dose

i. Displays if DOAC dose is not approved for patient indication per FDA recommendations
    1. Review DOAC dose in patient chart
    2. Verify correct dosing per FDA recommendations per dose correction protocol (see Procedure 4.a.iii)
    3. Correct dose per policy and send new prescription via EPIC
    4. Contact provider regarding dose change via HALO and/or TEF
        a. If provider aware of unapproved dose for patient indication and considers the benefit to outweigh the risk, snooze for 3 months up to 2 times (total 6 months) and contact provider again about dose change
        b. If provider aware of unapproved dose and does not want to change the dose after snoozing for 6 months, involve anticoagulation physician champion
        c. If after speaking to anticoagulation physician champion, provider would still like to keep patient on the unapproved dose, document, and snooze out for 3 months

h. Known Critical Alert – Multiple DOAC Medication

i. Process for working the reports: reviewing the list of patients
    1. While in chart, look at Medications tab and identify the multiple DOAC entries.
        a. Possible reasons for multiple DOAC entries:

i. Old, expired med remains on list after a new Rx was sent
ii. Pt was prescribed a starter pack of DOAC and prescribed a full prescription for med iii. Dose was changed and old Rx was not removed iv. Pt was prescribed a small dose to local pharmacy and a full prescription to mail order pharmacy
v. Pt was switched to another DOAC due to insurance reasons. Rx for previous DOAC was not removed
vi. Other

b. After identifying multiple DOAC issue and reason for alert, OPEN a DOAC Encounter to correct the issue and document

i. FYI Alert – VTE after 6 months

i. Displays if patient continues treatment for VTE and is potentially eligible for a dose reduction
   1. Review DOAC dose in patient chart
   2. Verify current dosing per FDA recommendations
      a. Apixaban 5 mg twice daily reduced to Apixaban 2.5 mg twice daily
      b. Rivaroxaban 20 mg once daily reduced to Rivaroxaban 10 mg once daily
   3. Adjust to recommended dose and order new prescription
   4. Notify provider of the change to the recommended dose via telephone encounter
   5. Contact patient and advise of recommended dose change

j. FYI Alert – Consider dose reduction for interacting medication

i. Displays if the patient is on an interacting medication for which a dose reduction may be warranted
   1. To be reviewed by an ACS Pharmacist
   2. If a dose reduction is necessary, ACS Pharmacist to order new prescription
   3. Notify provider of dose adjustment via telephone encounter
   4. Contact patient and advise of recommended dose change 8. After a NEW enrollment by a prescriber or after the FIRST switch to a DOAC:

a. Patient will receive first encounter education

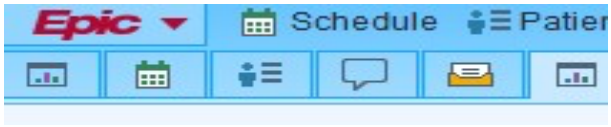
i. Patient education (drug information monographs available on shared drive, in “Patient Education” Folder, agreement form NOT required for DOAC patients) ii. Guidance for therapy interruption due to procedures

iii. Drug interaction prevention advice iv. Patient follow-up requirements (renal function lab monitoring, posthospitalization follow-ups)

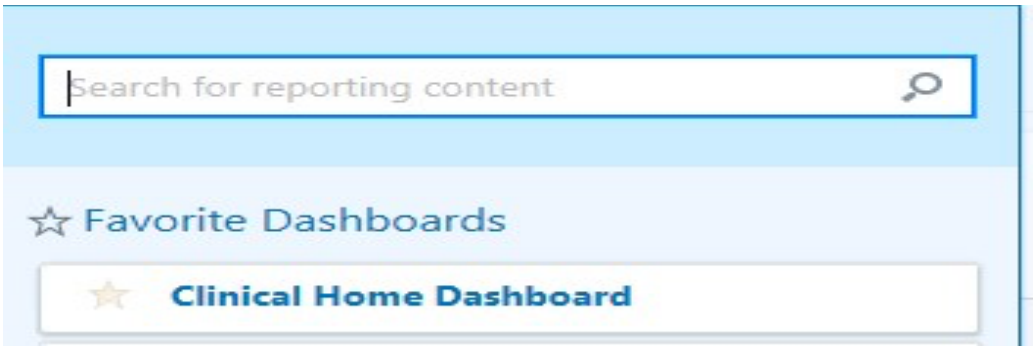
b. The AC Practitioner will follow-up with the patients after first 2 weeks(or as necessary) to discuss:
    i. Conversion from initial loading dose to maintenance dose (VTE indication)
    ii. Patient adverse events
    iii. Compliance management iv. Adverse drug reaction monitoring and reporting (Patient flyers regarding management of minor bleeding and epistaxis on shared drive)
c. The AC Practitioner will follow-up after hospital discharge per usual protocol

9. **<u>Accessing the DOAC dashboard</u>**:

A. First time opening reports: Open the EPIC button and choose "Reports". (Not "My Reports")



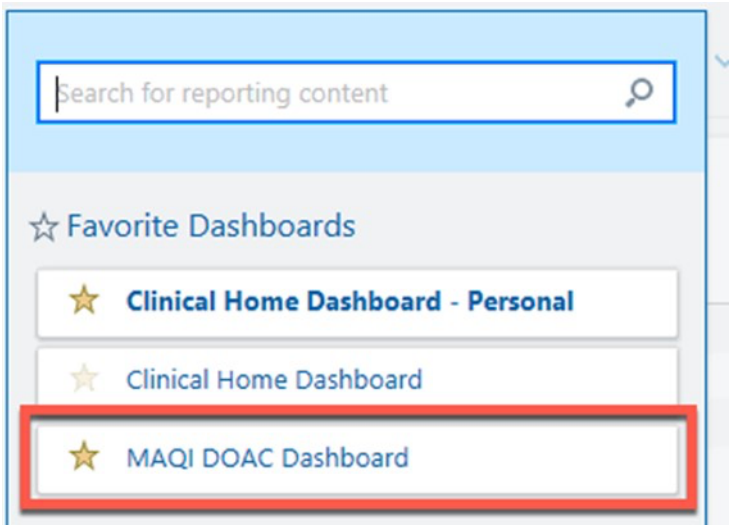
B. A new box will appear. From this box choose "My Dashboards"
C. Choose "Clinical Home Dashboard" from box.



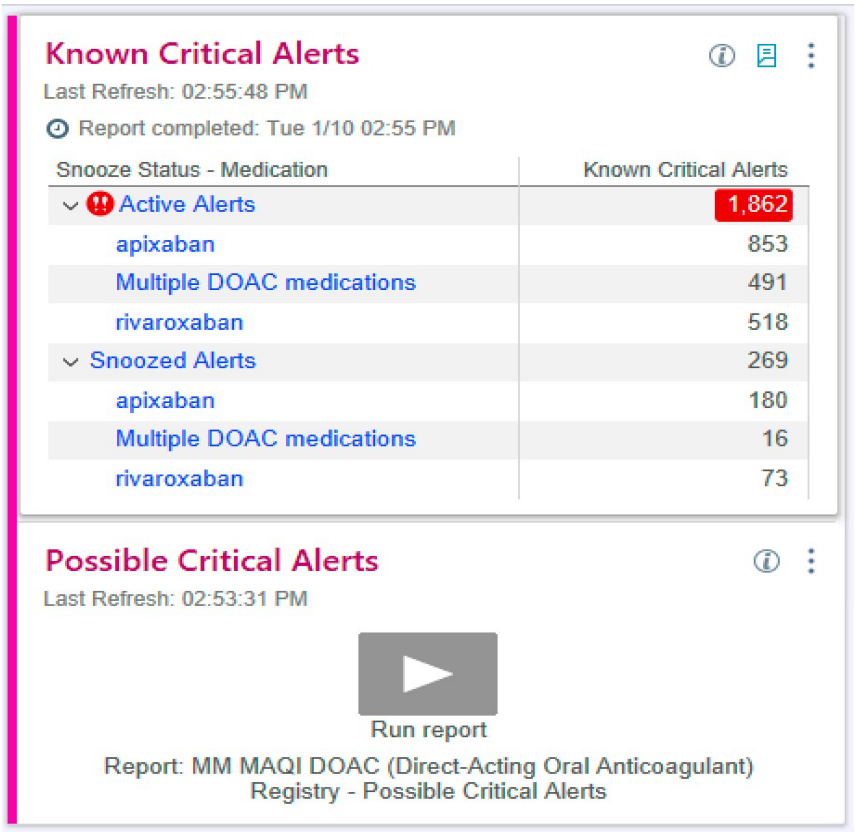
D. Next, click on the chevron beside "Clinical Home Dashboard"

E. Next Click on MAQI DOAC Dashboard.

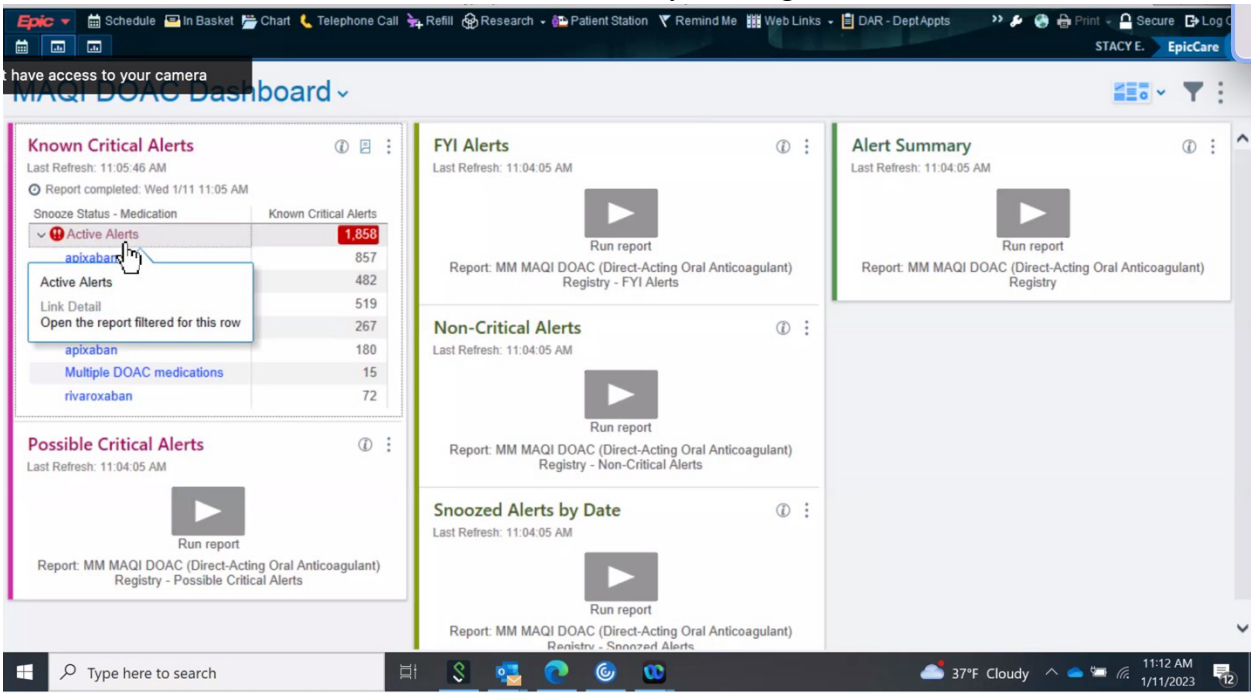
- *(Hint: When you hover over the dashboard, click on the yellow star that appears in the right-hand corner as noted above, prior to choosing it so it will appear in your Favorite Dashboard list from now on, at future sign-on, you will only need to choose the EPIC button and then "My Dashboards" to run the reports.)*



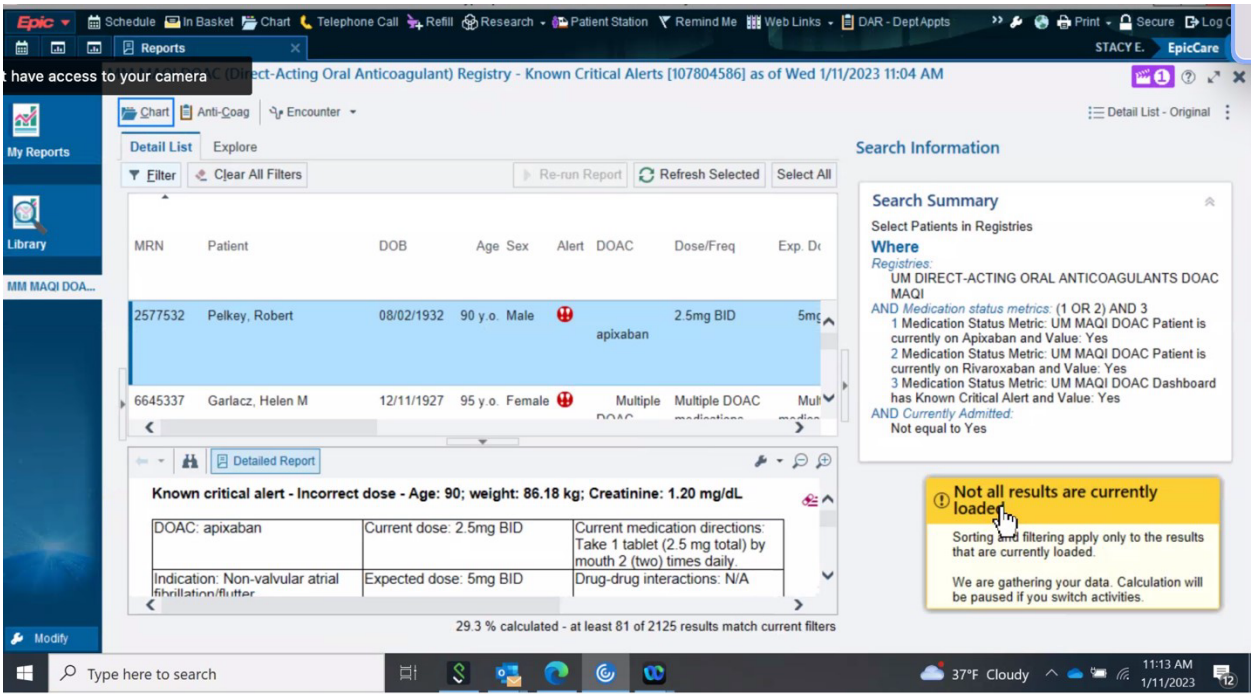
F. On the left side of this screen, you will have access to 2 types of reports: "**Known Critical Alerts**" and "**Possible Critical Alerts"**



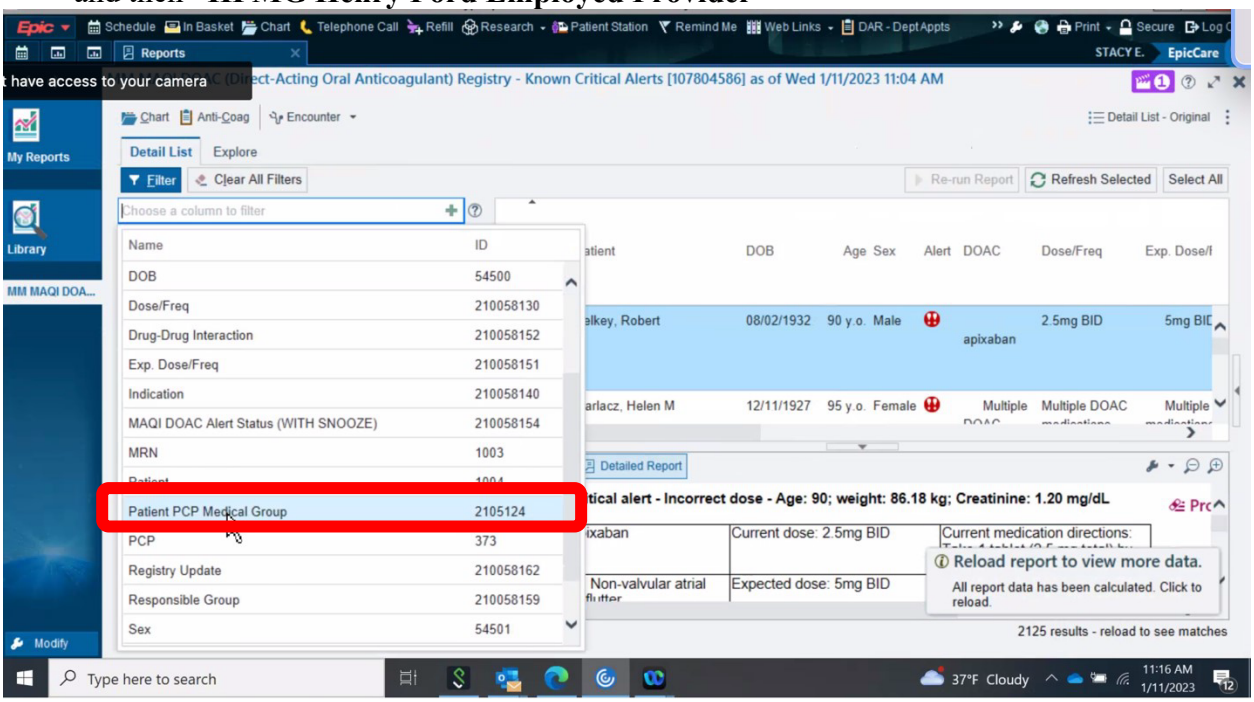
G. Run “Known Critical Alerts” by clicking the arrow

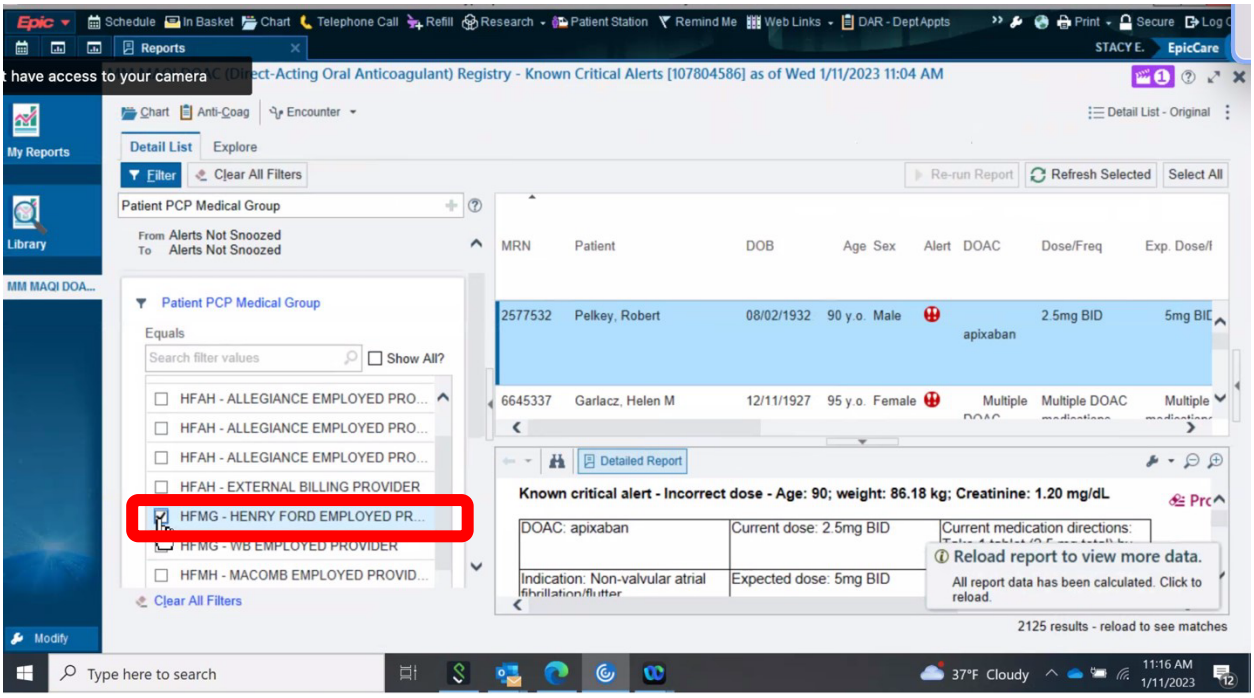


H. Wait until all results are loaded before filtering

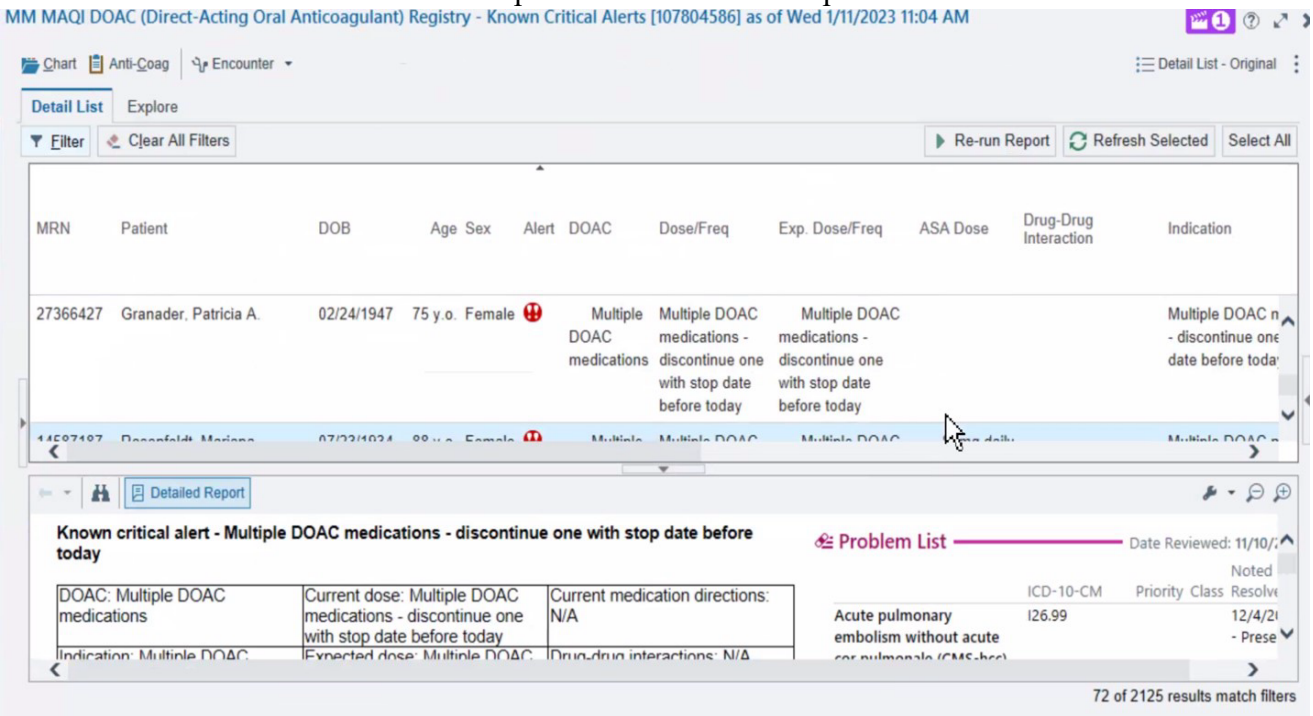


10. Once all results are loaded, click on "Filter" and then select **"Patient PCP Medical Group"** and then **"HFMG Henry Ford Employed Provider"**

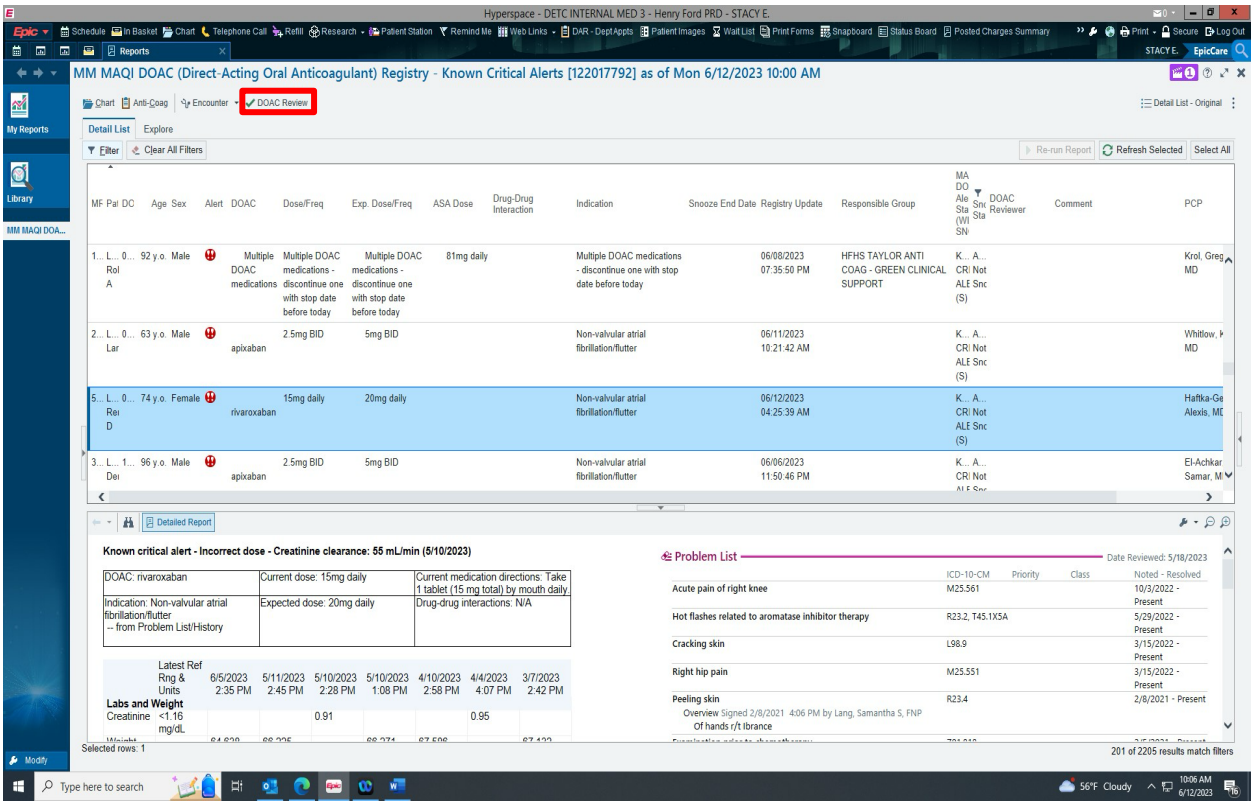




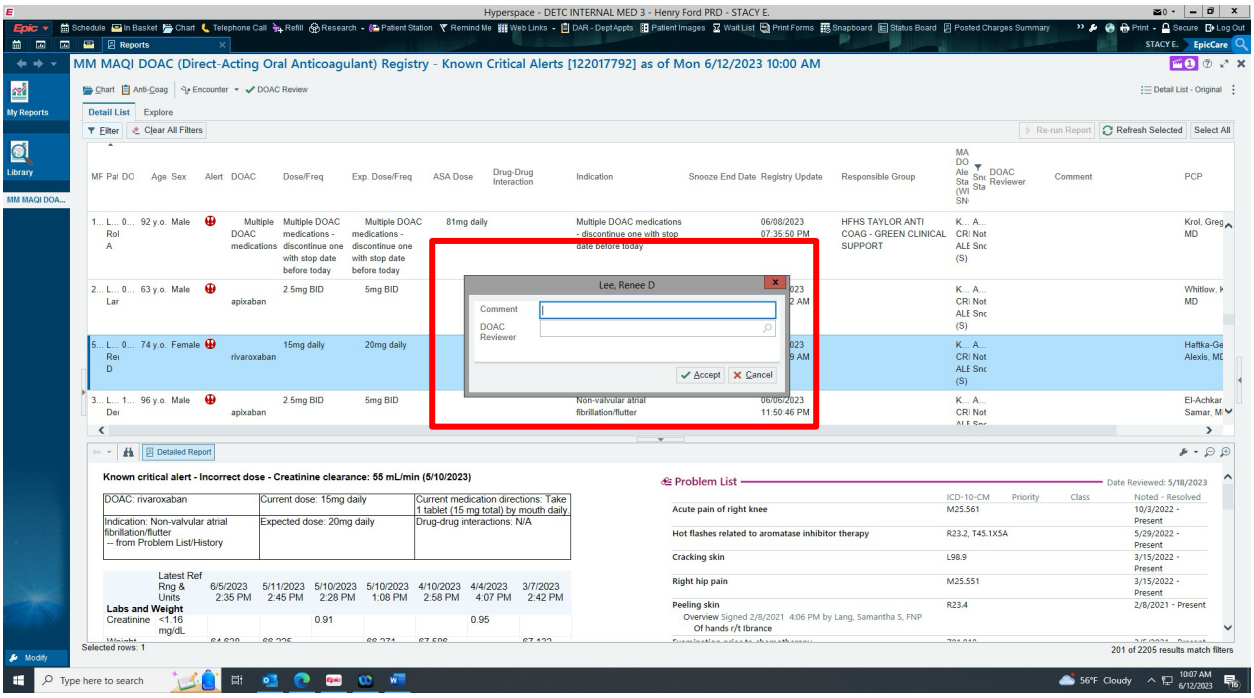
I. Start from the top of the list. Click on a patient to address an issue.

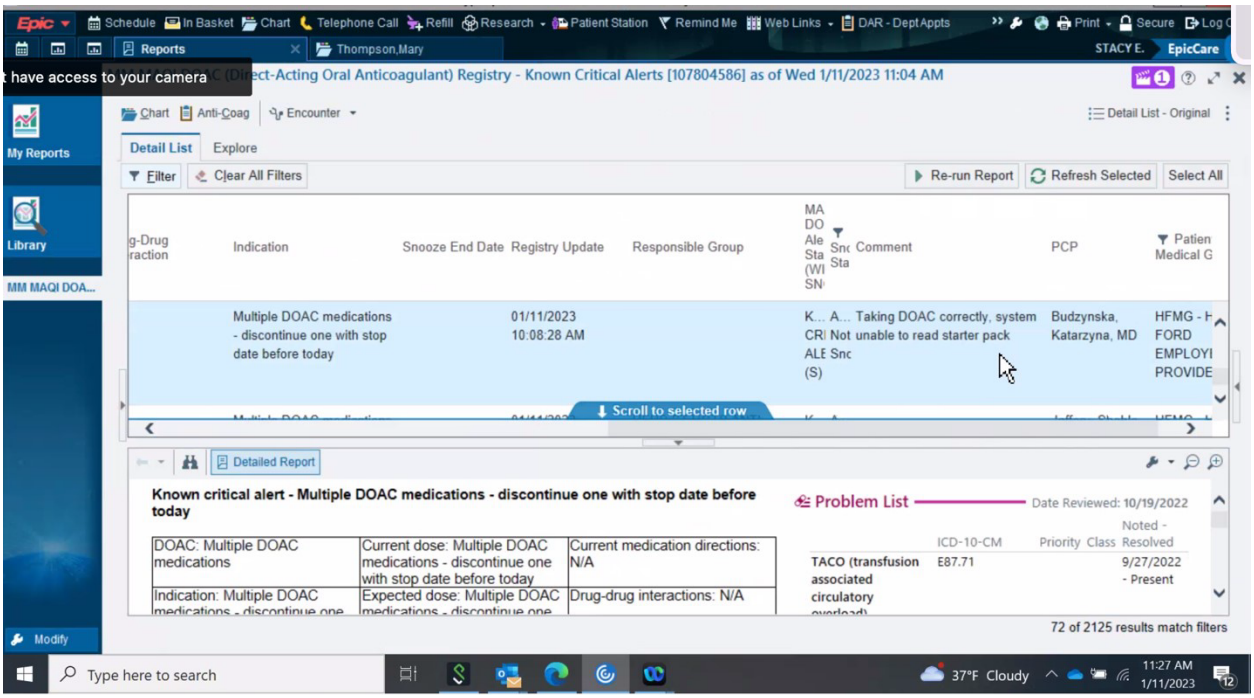


J. You can add a comment if needed so that you or others can follow-up more easily. Click on “DOAC Review” to open a pop-up (see next two screenshots)

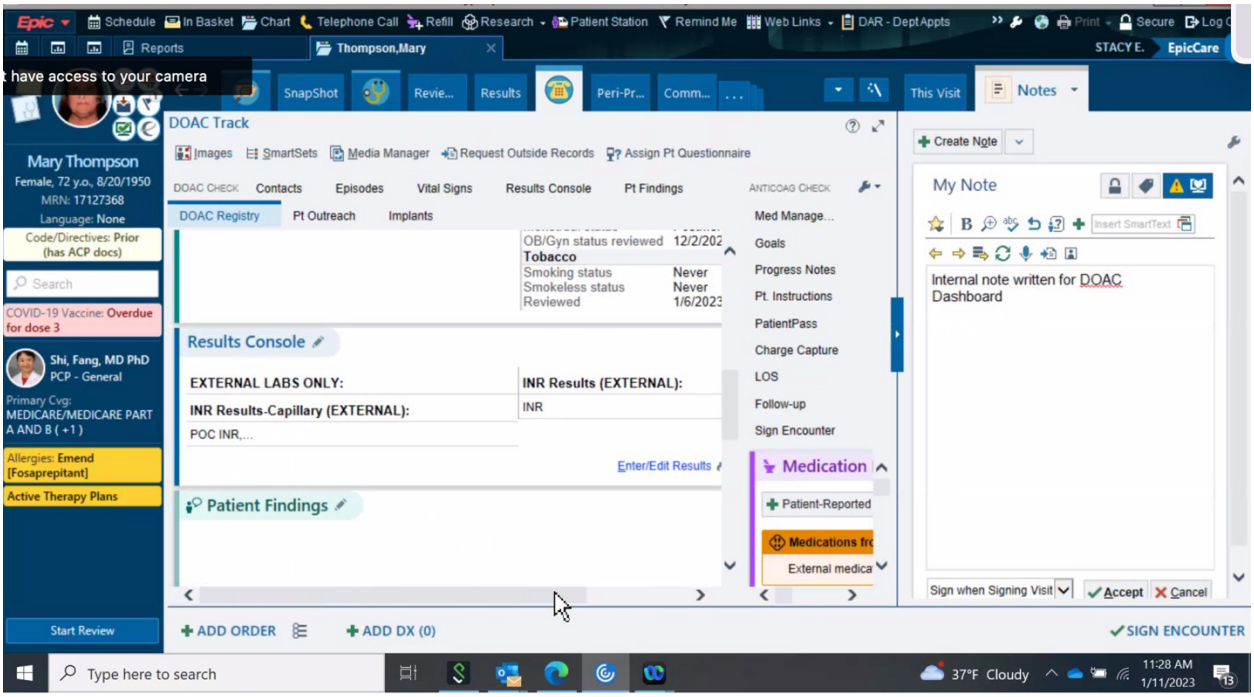


K. Enter comment and use the drop-down feature to find and enter your name as the reviewer.





L. Click on the EPIC button > Encounter > DOAC Track to work in the patient's chart. Here is where you would enter a note regarding the action taken.

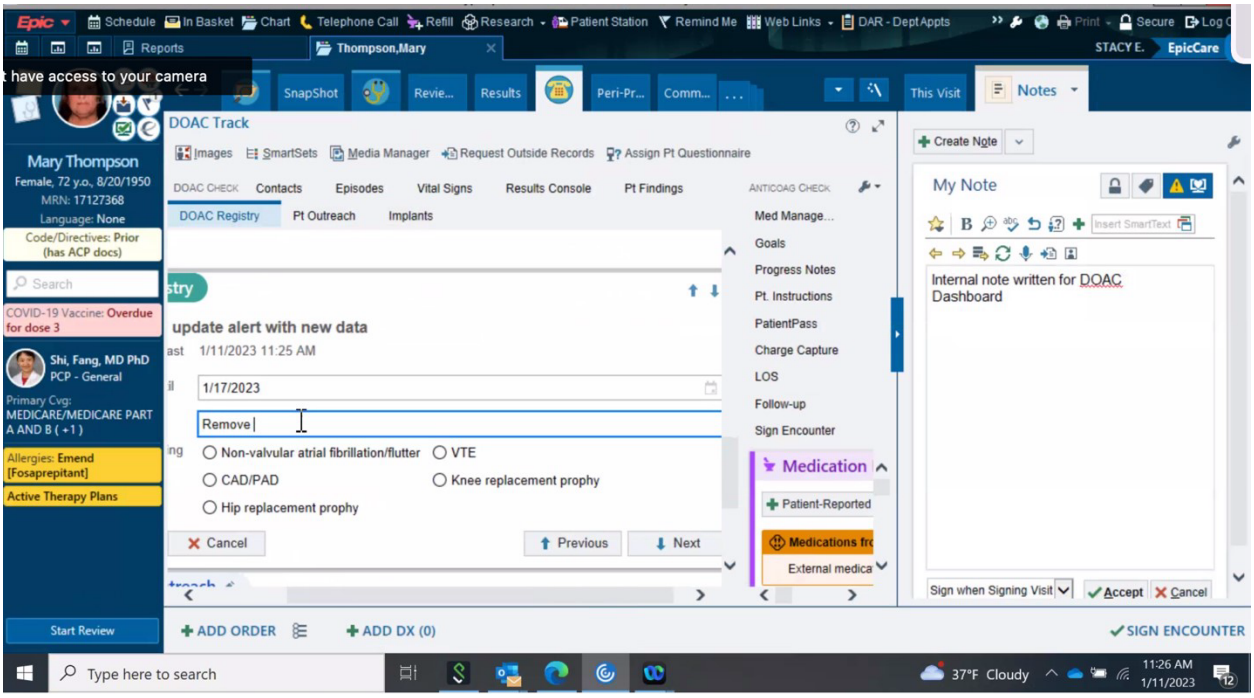


M. After you've entered your note, go to the DOAC Registry found on the DOAC Track page.

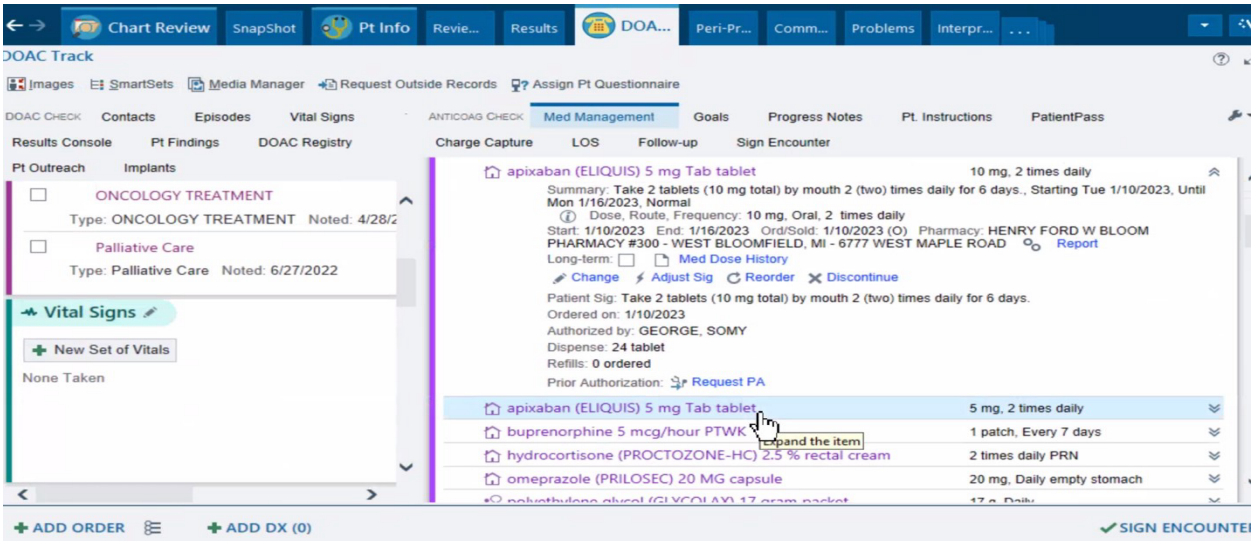
a. If you are not addressing the issue presently, you may either:

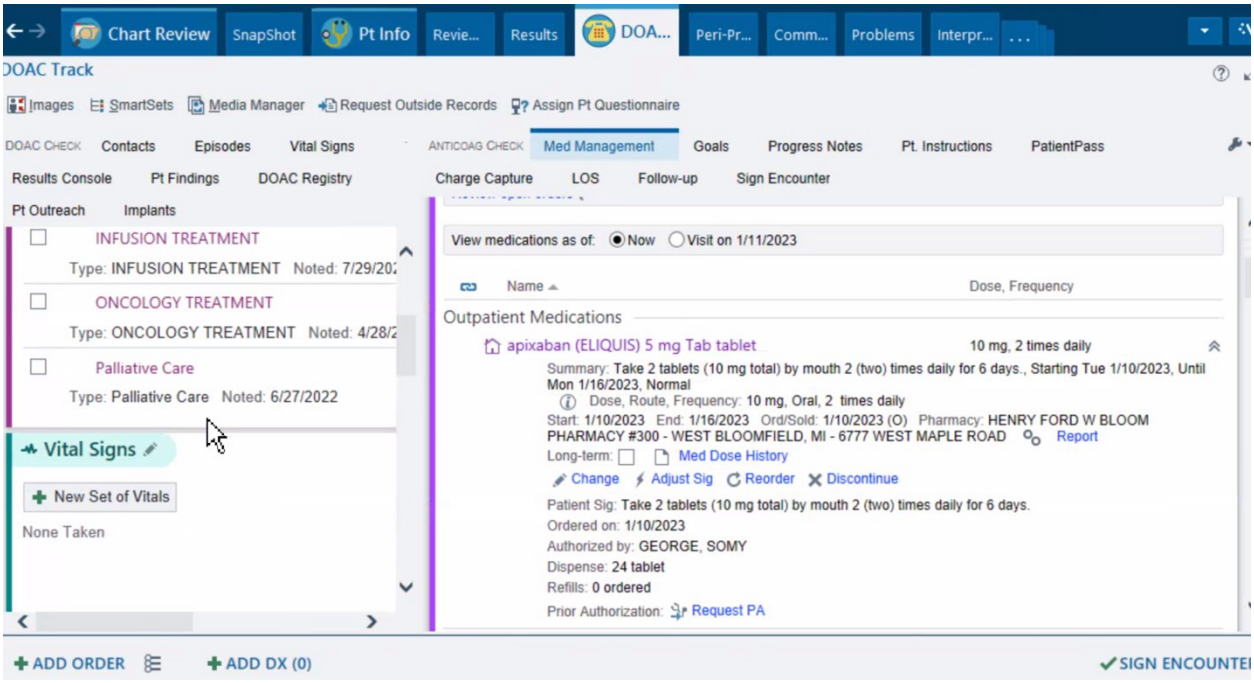
i. "SNOOZE" -Enter the date for follow-up and any comments which you would like to appear in the DOAC Dashboard

ii. Not "SNOOZE" and put something in the comment section to indicate current action being taken.



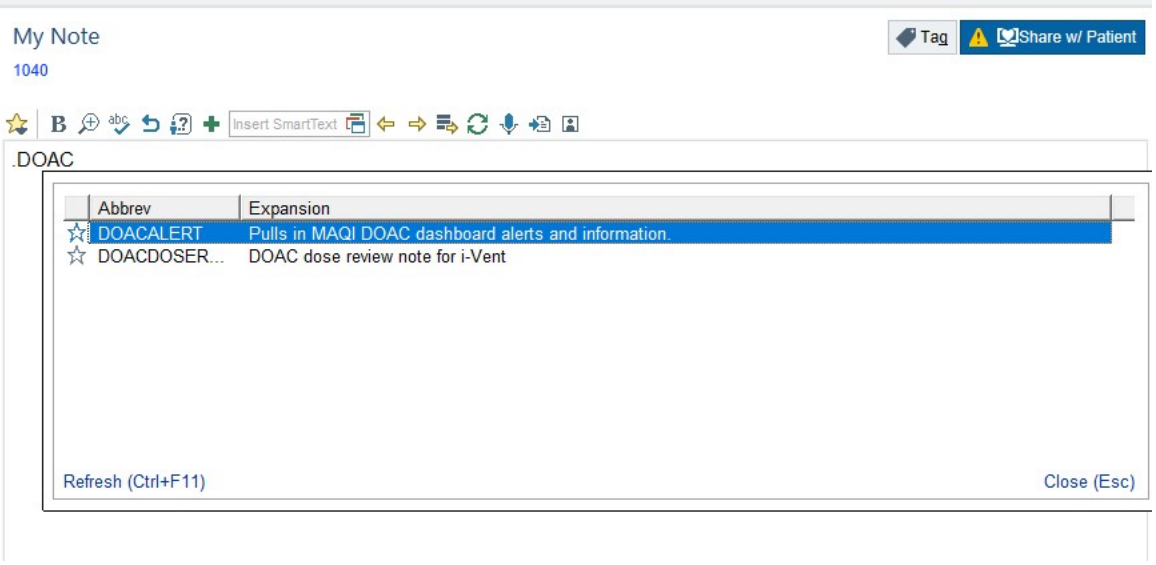
N. Multiple DOAC Medications Alert example:



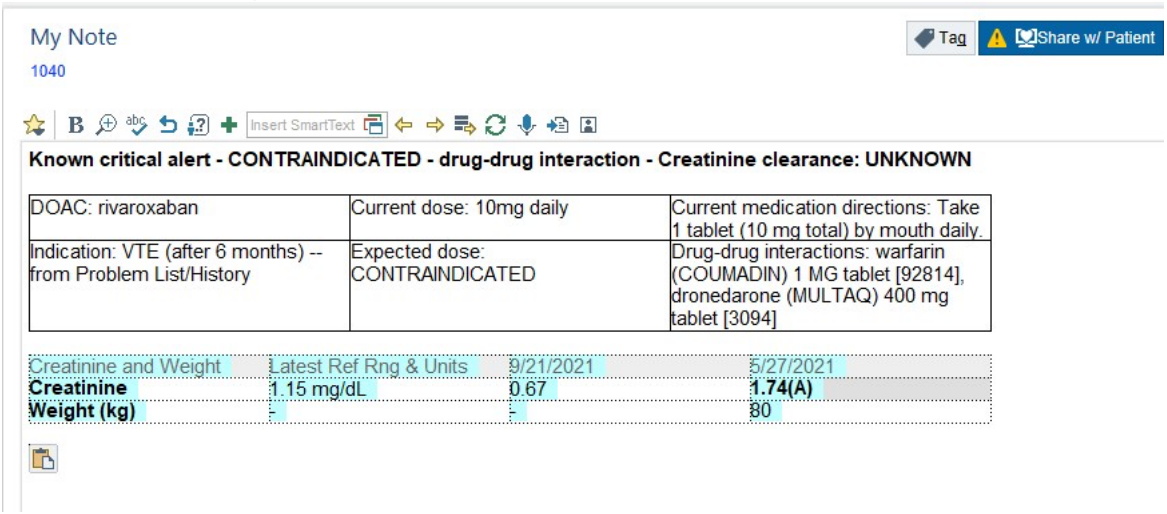


Smartphrase: “DOACALERT”:

Typing ‘.DOACALERT’ into a note section will allow the user to pull in the DOAC dashboard alert information captured by the DOAC registry print group.

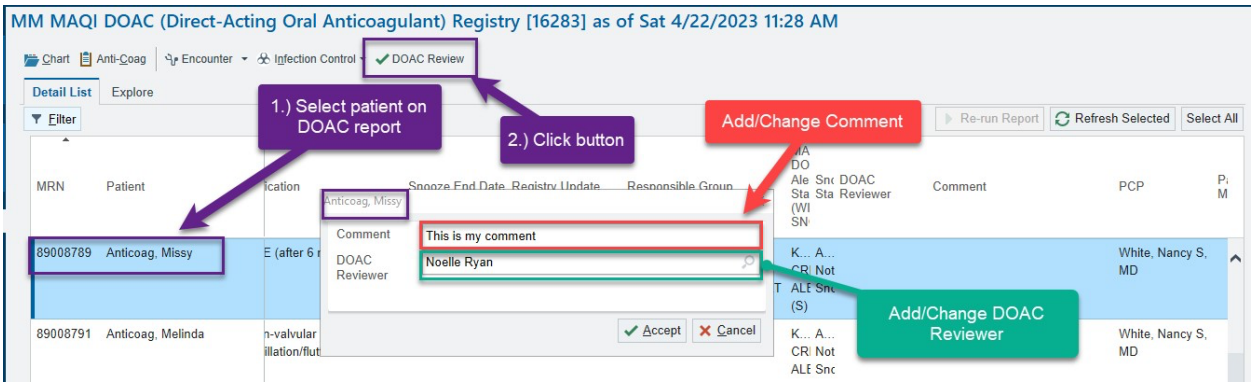


Note: Flowsheet Vitals section only pulls Creatinine and Weight results as requested by team



New Report toolbar button: 'DOAC Review'

With patient selected on report, end user can click 'DOAC Review' to launch DOAC Review smartform to add/change DOAC reviewer or Comment if desired.



Documented comment and DOAC reviewer will display in the MAQI DOAC report columns

Templates:

Pharmacist TEF to provider at enrollment from DOAC Registry

Your patient has been automatically enrolled in the *New* EPIC DOAC registry. This registry monitors for possible safety issues related to DOAC's, including drug-drug interactions, recommended dose corrections based on changes in SCr/CrCl and multiple anticoagulant medications active in a patient's chart, which will help prevent avoidable harm. A referral has been created in your name and sent to you for electronic signature to ensure we have a collaborative agreement.

If you have any questions regarding this enrollment, please feel free to contact me or one of the HFMG Anticoagulation Service Co-medical Directors, Dr. Scott Kaatz, or Dr. Gregory Krol.

Apixaban Dosing/Afib

Your patient has been automatically enrolled in the *New* EPIC DOAC registry. This registry monitors for possible safety issues related to DOAC's.

This patient is on apixaban (Eliquis ®) xx mg BID for atrial fibrillation. Based on their age, weight and creatinine, dosing guidelines recommend apixaban xx mg BID.

Age xx
Weight xx
Creatinine xx

Please respond to one of the following:

- Patient should remain on current dose. **Please let us know the reason for documentation**. With this we will automatically re-evaluate every 3 months.

- Patient's dose should be changed. With this we will contact patient and make the changes for you.

If you have any questions regarding this matter, please feel free to contact me or one the anticoagulation physician champions Dr. Scott Kaatz, or Dr. Gregory Krol

Thank you

Xarelto Dosing/Afib

Your patient has been automatically enrolled in the *New* EPIC DOAC registry. This registry monitors for possible safety issues related to DOAC's.

This patient is on rivaroxaban (Xarelto ®) XX mg daily for atrial fibrillation. Based on current creatinine clearance of <>50 mL/min guidelines recommend rivaroxaban XX mg daily.

Date XXX mL/min

Please respond to one of the following:

- Patient should remain on current dose. **Please let us know the reason so we can document**. With this we will automatically re-evaluate every 3 months and ask you to continue to confirm dose yearly for safety reasons.

- Patient's dose should be changed. With this we will contact the patient and make the changes for you.

If you have any questions regarding this issue please feel free to contact me or one the anticoagulation physician champions, Dr. Scott Kaatz, or Dr. Gregory Krol

Thank you

Medication Interaction

Your patient has been automatically enrolled in the EPIC DOAC registry. This registry monitors for possible safety issues related to DOAC's.

Currently they are taking apixaban/xarelto and XXXX. The severity between these medications is considered *major* and may result in an increase/decrease plasma concentration leading to an increased risk (bleeding / thromboembolic) events.

Could you please re-evaluate and respond to one of the following:

- You feel the patient is safe taking both medication and should continue. With this we will automatically re-evaluate safety every 6 months and ask you to continue to confirm.

    - One of the medications should be stopped or replaced with similar medication.
- Based on patient's medical history and being on both medications for long period of time, you feel the patient's risk is acceptable and patient can remain on the current medications. With this option we will continue to re-evaluate every 3 months for other safety issues

If you have any questions regarding this issue please feel free to contact me or one the anticoagulation physician champions, Dr. Scott Kaatz, or Dr. Gregory Krol

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Alert Weight and Creatinine Apixaban

The DOAC Dashboard System is alerting that the patient should be on increased dose of apixaban, 5 mg twice a day. Patient creatinine's are currently fluctuating to make change in apixaban dosing. Will remain current 2.5 mg twice a day dosing and reevaluate in 3 months.

The DOAC Dashboard System is alerting that the patient should be on decreased dose of apixaban, 2.5 mg twice a day. Patient creatinine's are currently fluctuating to make

change in apixaban dosing. Will remain on current 5 mg twice a day dosing and reevaluate in 3 months.

The DOAC Dashboard System is alerting that the patient should be on increased dose of apixaban 5.0 mg twice a day. Patient's weight is currently fluctuating to make change in apixaban dosing. Will remain on current 2.5 mg twice a day dosing and re-evaluate in 3 months.

The DOAC Dashboard System is alerting that the patient should be on decreased dose of apixaban 2.5 mg. twice a day. Patient's weight is currently fluctuating to make change in apixaban dosing. Will remain on current 5 mg twice a day dosing and reevaluate in 3 months.
.

Alert Weight and Creatinine Xarelto

The new DOAC Dashboard System is alerting patient should be on increased dose of rivaroxaban, 20 mg daily. Patient's creatinine clearance is currently fluctuating to make change in rivaroxaban dosing. Will remain on 15 mg daily and re-evaluate in 3 months.

The new DOAC Dashboard System is alerting patient should be on decreased dose of rivaroxaban, 15 mg daily. Patient's creatinine clearance is currently fluctuating to make change in rivaroxaban dosing. Will remain on 20mg daily and re-evaluate in 3 months.

Inappropriate Xarelto Dosing for DVT long term.

Your patient has been automatically enrolled in a *NEW* EPIC DOAC registry. This registry monitors for possible safety issues related to DOAC's.

This patient is currently on rivaroxaban (Xarelto ®) 15 mg daily for DVT. 15 mg daily dosing of Xarelto is currently not an approved dose for DVT long term treatment. Guidelines recommend 20 mg daily for treatment or 10 mg daily for secondary prevention after 6 months of treatment. We understand this patient has been on this dose for a while. Could you please review and verify patient should remain on this dose and let us know.

Thank you

If you have any questions regarding this issue please feel free to contact me or one the anticoagulation physician champions Dr. Scott Kaatz, or Dr. Gregory Krol

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In appropriate Apixaban Dosing for DVT long term.

Your patient has been automatically enrolled in a *NEW* EPIC DOAC registry. This registry monitors for possible safety issues related to DOAC's.

This patient is currently on apixaban 5.0 mg **daily** for DVT. Apixaban 5.0 mg daily is currently not an approved dose for DVT treatment. Guidelines recommend 5.0 mg **twice a day** for treatment or 2.5 mg **twice a day** for secondary prevention after 6 months of treatment. We understand this patient has been on this dose for a while. Could you please review and verify patient should remain on this dose and let us know.

If you have any questions regarding this issue please feel free to contact me or one the anticoagulation physician champions Dr. Scott Kaatz, or Dr. Gregory Krol

Reference(s)/Source(s)

1. www.jointcommission.org/-/media/tjc/documents/standards/national-patient-safetygoals/2021/npsg_chapter_ahc_jan2021.pdf - accessed 8.17.21 - NPSG.03.05.01
2. NHS Specialty Pharmacy Service. www.sps.nhs.uk Practice Guide to dosing of Direct Oral Anticoagulants in patients with renal impairment. Accessed 8/9/21
3. Yao X, Shah ND, Sangaralingham LR et al. Non-vitamin K antagonist oral anticoagulation dosing in patients with atrial fibrillation and renal dysfunction JACC 2017 69 (23) 2779-2790
4. JP Fava, KM Starr et al. Dosing challenges with direct oral anticoagulants in the elderly: a retrospective analysis**.** *Ther Adv Drug Saf.* 2018, Vol. 9(8) 405–414 DOI: 10.1177/ 2042098618774498
5. Steinberg B, Shrader P, Thomas L et al. Off label dosing of non-vitamin K antagonist oral anticoagulation and adverse outcomes. The Orbit II AF registry JACC 2016 68 (64) 2597-2604
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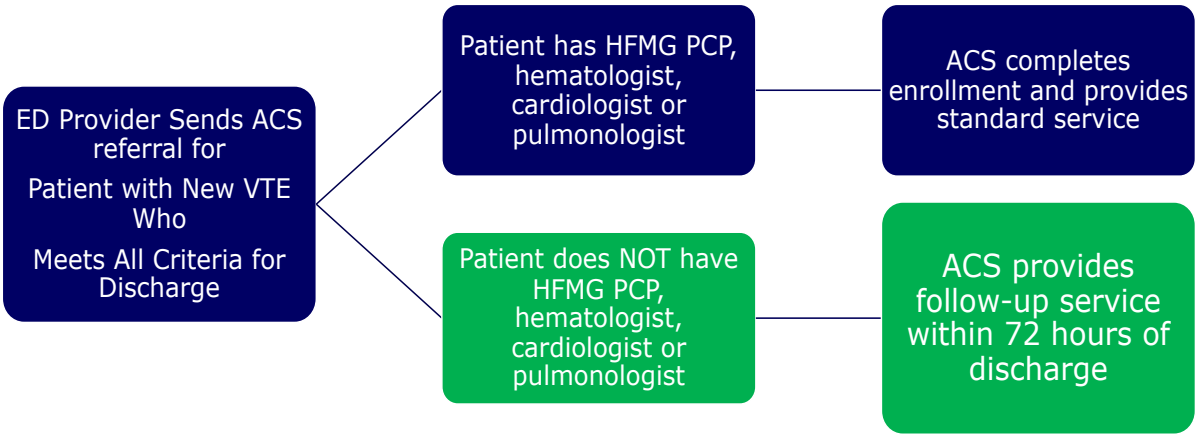
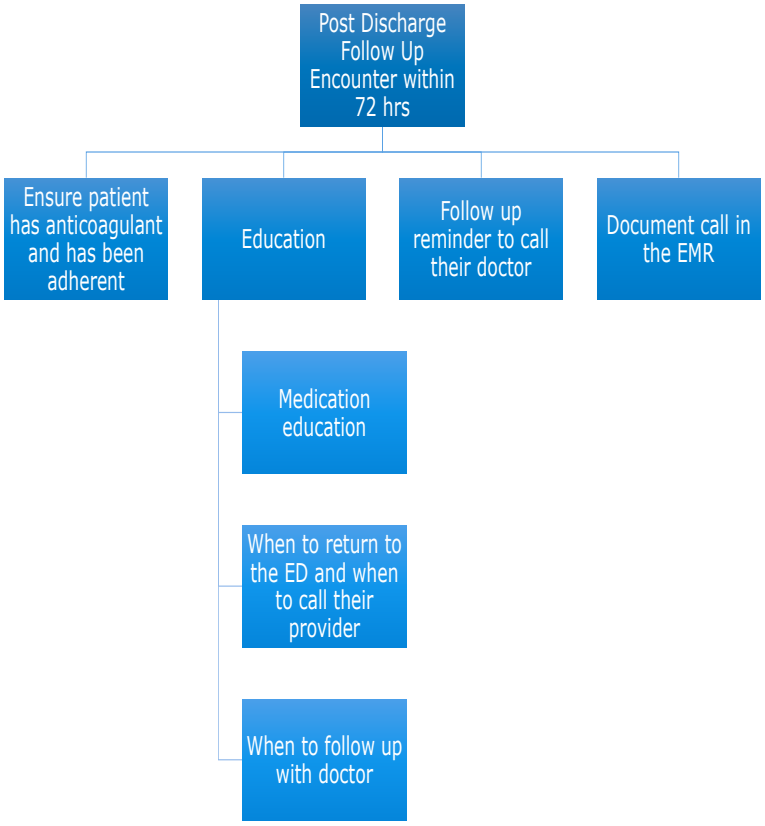
7. M Gruca et al. Creatinine monitoring patterns in the setting of direct oral anticoagulant therapy for non-valvular atrial fibrillation. J Throm Thrombolysis. 2019 October; 48(3): 500-505
8. ESC Guidelines.European Heart Journal (2020) 42, 373498 doi:10.1093/eurheartj/ehaa612
9. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014
   AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American heart association Task force on clinical practice guidelines and the heart rhythm society in collaboration with the Society of thoracic surgeons. Circulation 2019;140:e125–51.
10. Barnes, G, Sippola, E, Dorsch, M, Errickson, Joshua, Lanham, M & Allen, A, Applying population health approaches to improve safe anticoagulant use in the outpatient setting: the DOAC dashboard multi-cohort implementation evaluation study protocol, *Implementation Science*, 15(1)

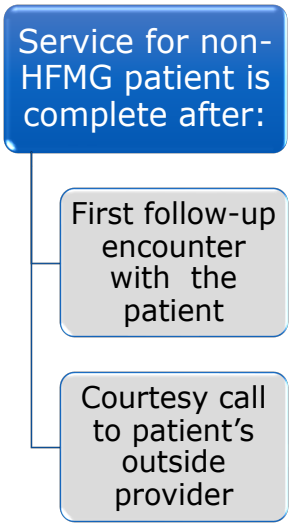
ACS Role in ED Transition of Care



ACS Service: Non-HFMG Patients



ACS Service: Non-HFMG Patients



DOCUMENTATION: Use specified dot phrases

.HFMGVTETOC
Patient enrolled into the anticoagulation clinic for *** monitoring with approval from PCP Dr. ***as the patient's designated anticoagulation physician for a diagnosis of "**Deep Venous Thrombosis**" **or** "**Pulmonary Embolism**" . New enrollment will be routed to the Henry Ford *** Anticoagulation clinic and patient will be contacted by their staff for new enrollment education.
Current *** dose prescribed ***. This dose is appropriate based on the patient's indication and CrCl:
Age:
Total body weight: kg
Serum Creatinine:
ECrCl: (using ABW)

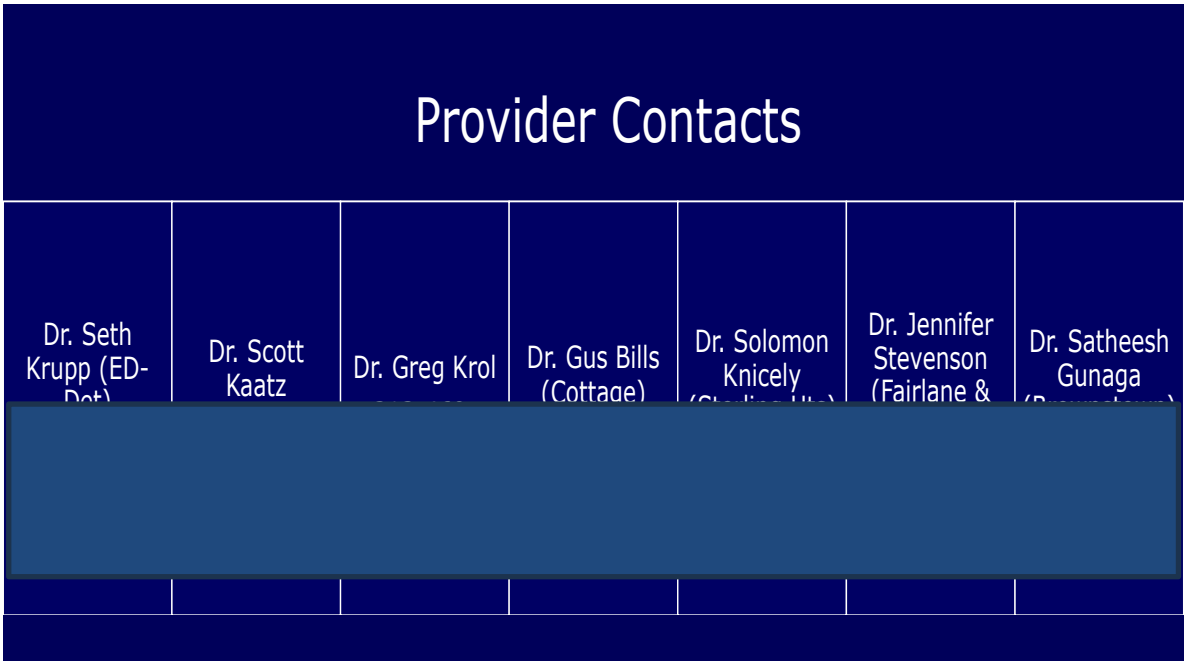
.NONHFMGVTETOC
Patient referred to the anticoagulation clinic by HFH-Detroit Emergency Department Dr. ***as the patient's designated anticoagulation physician for one-time ***(DOAC)** follow-up for a diagnosis of "**Deep Venous Thrombosis**" **or** "**Pulmonary Embolism**" .
Current *** dose prescribed ***. This dose is appropriate based on the patient's indication and eCrCl:
Age:
Total body weight: kg
Serum Creatinine:
eCrCl (using ABW):

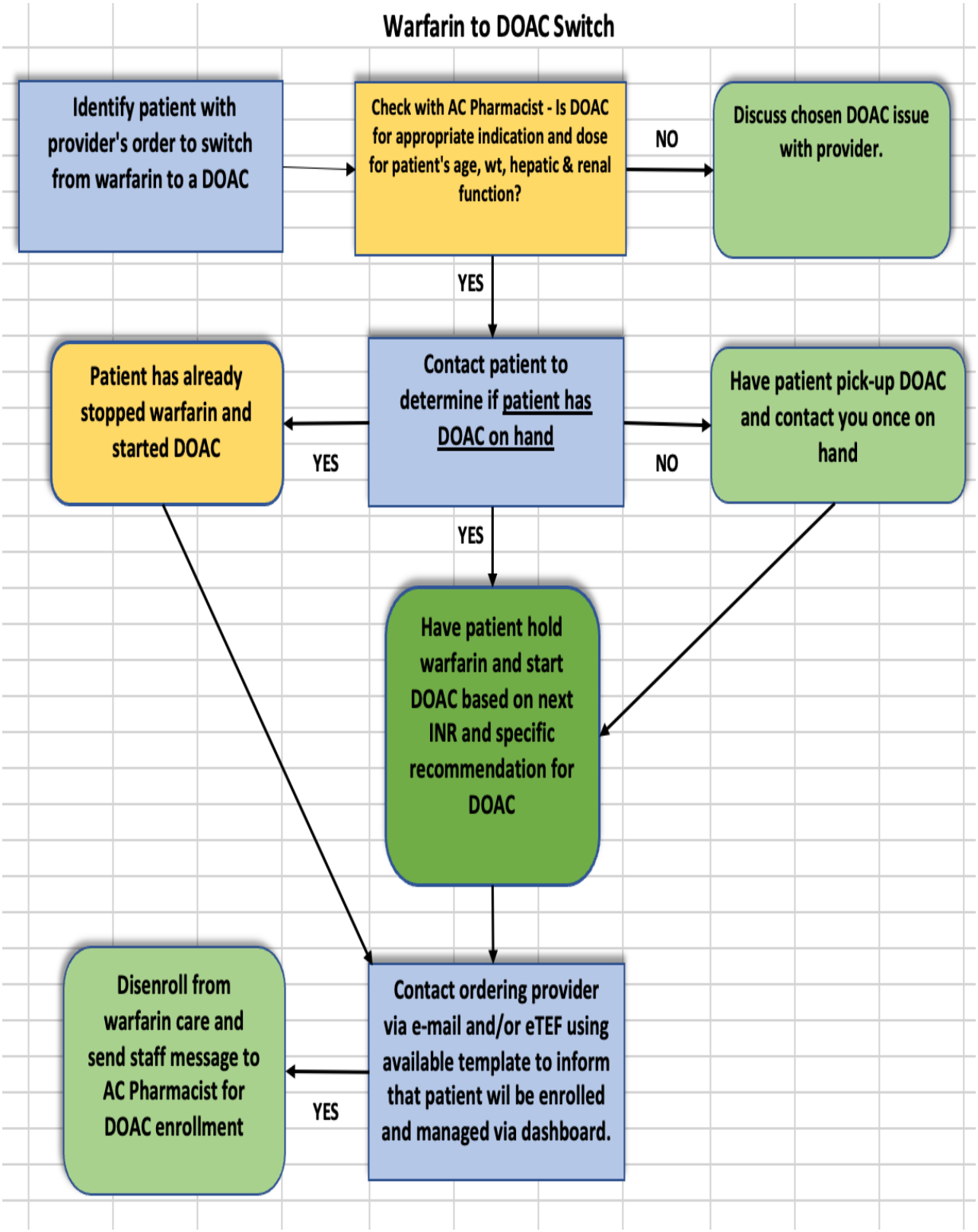
Patient identified using 3 identifiers. Patient verified having *** prescription in hand and medication education provided. Patient advised to contact their provider for a follow-up appointment, anticoagulant monitoring and prescription refills. Patient advised of signs/symptoms of bleeding or clotting and when to return to the Emergency Department or contact their physician. Patient understanding verified using teach-back confirmation. As a courtesy, patient's provider, *** at (**phone number)** was contacted and informed that the patient has been started on *** requiring a follow-up visit.

VTE TOC Log

- DATE
- MRN
- HFMG enrolled
- NONHFMG education provided
- DOAC prescribed
- DOAC dose correction required
- ED provider contacted
- ACS Physician champion contacted
- Time spent on entire encounter
- Comments
- RPh initials

ACS Service: Non-HFMG Patients




Warfarin to DOAC Switch
Identify patient with provider's order to switch from warfarin to a DOAC
Check with AC Pharmacist - Is DOAC for appropriate indication and dose for patient's age, wt, hepatic & renal function?
NO
Discuss chosen DOAC issue with provider.
YES
Patient has already stopped warfarin and started DOAC
Contact patient to determine if patient has DOAC on hand
Have patient pick-up DOAC and contact you once on hand
YES
NO
YES
Have patient hold warfarin and start DOAC based on next INR and specific recommendation for DOAC
Disenroll from warfarin care and send staff message to AC Pharmacist for DOAC enrollment
Contact ordering provider via e-mail and/or eTEF using available template to inform that patient wil be enrolled and managed via dashboard.
YES

Switching from a DOAC to Warfarin

DOAC	Procedure to Switch to Warfarin[11]
Dabigatran[25]	Start warfarin and overlap with dabigatran: • CrCl 50 mL/min, overlap 3 days • CrCl 30–50 mL/min, overlap 2 days • CrCl 15–30 mL/min, overlap 1 day • CrCl <15 mL/min, no recommendations can be made
Rivaroxaban[27]	Stop DOAC; start warfarin and LMWH at time of next scheduled DOAC dose and bridge until INR ≥ 2.0
Apixaban[24]	Stop DOAC; start warfarin and LMWH at time of next scheduled DOAC dose and bridge until INR ≥ 2.0
Edoxaban[26]	• For 60 mg dose, reduce dose to 30 mg and start warfarin concomitantly • For 30 mg dose, reduce dose to 15 mg and start warfarin concomitantly • Stop edoxaban when INR ≥ 2.0
Overlap is intended to avoid under-anticoagulation while warfarin effect is developing. When DOAC is overlapped with warfarin, measure INR just before next DOAC dose, as the DOAC can influence INR. As a general rule, we believe either approach (i.e., stop DOAC then start LMWH and warfarin; or overlap warfarin with DOAC, measure INR just before next the DOAC dose, and stop DOAC when INR is ≥ 2.0) can be used for all DOAC-to-warfarin transitions. Recommendations adapted from company's package inserts. A recent ASH consensus guideline suggests overlapping DOAC and VKA therapy until the INR is within the therapeutic range over using LMWH or UFH-bridging therapy for patients at low risk of thrombosis/bleeding (conditional recommendation based on very low certainty in the evidence about effects).[48]	

Abbreviations: ASH, American Society of Hematology; CrCl, creatinine clearance; DOAC, direct oral anticoagulant; INR international normalized ratio; IV, intravenous; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin; VKA, vitamin K agonist.

From: AC Forum DOAC Playbook v. 14 Final – accessed on 6.4.21

Follow-up Workflow for DOAC Patients (after initial, 2 week, 6 weeks, 3 months follow-up)

Action	Interval	Comments
Assess Labs • AC Practitioner to order SCr, Hgb, (PLTs if not WNL) • Have patient contact provider to determine if other labs may be needed	As needed	• If clinically indicated for conditions that may impact renal or hepatic function • Declining renal function may require a DOAC dose adjustment (see FDA package insert) Edoxaban is ***contraindicated*** for AF patients with CrCl > 95 ml/min
	Every 3 months	• Renal function if CrCl 15-30 ml/min
	Every 6 months	• Renal function if CrCl 30 – 60 ml/min or if ≥ 75 years old (especially if on dabigatran) or frail
	Yearly	• Hgb, renal and liver function (only if patient has documented history of hepatic dysfunction)
Assess compliance	**EACH VISIT:** • **Every 3 months if CrCl 15-30mL/min (or sooner as needed)** • **Every 6 months (or sooner as needed) otherwise**	• Note and calculate average adherence (using compliance tool in the manual) • Re-educate on importance of strict intake schedule • Inform about compliance aids (special boxes, smartphone applications, etc.) Note that dabigatran must remain in the original packaging
Assess for thromboembolism		• Systemic circulation (TIA, stroke, peripheral) • Pulmonary circulation
Assess for bleeding • In high-risk patients*, review **HAS-BLED** at every follow-up		• If nuisance bleeding (minor wound, nose bleeds, etc.) educate regarding preventative measures and encourage patient to diligently continue anticoagulation • If bleeding with impact on quality-of-life or with significant risk, consider changing the anticoagulation to prevent bleeding
Assess for other side effects		• Assess for relation to DOAC and decide whether to continue, temporarily stop or change to a different anticoagulant
Assess for new medications		• Prescription or over-the-counter drugs • Assess for P-gp inhibitors/inducers (if on dabigatran or edoxaban) or dual P-gp/CYP3A4 inhibitors (if on rivaroxaban or apixaban) • Assess for other medications that may increase risk of bleeding, such as antiplatelets or NSAIDs. • DOAC dose adjustments may be required if patient starts on interacting medications
Assess for optimal DOAC and correct dosing		• For new VTE patients on apixaban, **after first week** change dose from 10 mg BID to 5 mg BID • For new VTE patients on rivaroxaban, **at three weeks** change dose from 15 mg BID to 20 mg daily • For **ONLY VTE patients after 6 months** treatment (with NO thrombophilia, NO cancer, NO weight > 120 kg or BMI > 40, NO recurrent VTE while on DOAC therapy) - recommended dose for apixaban 2.5 mg BID - recommended dose for rivaroxaban 10 mg daily

Adapted from: Steffel J. et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J 2018 Apr 21;39(16):1330-1393.

*High risk includes patients with advanced age, prior stroke, DM or history of GI bleeding

	Dabigatran (Pradaxa)	**Rivaroxaban (Xarelto)**	**Apixaban (Eliquis)**	**Edoxaban (Savaysa)**
Converting from warfarin to new agent	Discontinue warfarin and start Pradaxa when the INR is below 2.0	Discontinue warfarin and start Xarelto as soon as the INR is below 3.0	Discontinue warfarin and start Eliquis when the INR is below 2.0	Discontinue warfarin and started edoxaban when INR $\leq$ 2.5
Converting from new agent to warfarin	Adjust the starting time of warfarin based on creatinine clearance as follows (using TBW): ❖ For CrCl 50 mL/min, start warfarin 3 days before discontinuing Pradaxa. ❖ For CrCl 30-50 mL/min, start warfarin 2 days before discontinuing Pradaxa. ❖ For CrCl 15-30 mL/min, start warfarin 1 day before discontinuing Pradaxa. ❖ For CrCl <15 mL/min, no recommendations can be made.	Discontinue Xarelto and begin both a parenteral anticoagulant and warfarin at the time the next dose of Xarelto would have been taken. Discontinue the parenteral anticoagulant when INR reaches an acceptable range. **OR** (if **not** new PE or DVT, cancer patient, hypercoagulable nor BMI > 40/wt > 120kg) Overlap Xarelto dose with warfarin dose until INR is in range: ❖ INR to be drawn just before next intake of Xarelto during concomitant administration	Discontinue Eliquis and begin both a parenteral anticoagulant and warfarin at the time the next dose of Eliquis would have been taken. Discontinue the parenteral anticoagulant when INR reaches an acceptable range. **OR** (if **not** new PE or DVT, cancer patient, hypercoagulable nor BMI > 40/wt > 120kg) Overlap Eliquis dose with warfarin dose until INR is in range ❖ INR to be drawn just before next intake of Eliquis during concomitant administration	**If taking edoxaban 60** mg/day, reduce dose to 30 mg/day and begin warfarin concomitantly **If taking edoxaban 30** mg/day, reduce dose to 15 mg/day and begin warfarin concomitantly **Then:** INR must be measured at least weekly and just prior to the daily dose of edoxaban to minimize the influence on INR measurements Once stable INR $\geq$ 2.0 is achieved, discontinue edoxaban and continue warfarin
Converting to/from an anticoagulant other than warfarin	❖ From a parenteral, start Pradaxa 0 – 2 hours prior to the next scheduled parenteral dose time ❖ To a parenteral, for CrCl $\geq$ 30 mL/min –wait 12 hours after last dose of Pradaxa ❖ To a parenteral, for CrCl < 30 mL/min- wait 24 hours after last dose of Pradaxa	❖ From an anticoagulant, start Xarelto 0 – 2 hours prior to next scheduled dose of the other anticoagulant ❖ To an anticoagulant, stop Xarelto and start at the time of the next scheduled Xarelto dose	❖ Discontinue the one taken and begin the other one at the next scheduled dose	❖ From LMWH, initiate edoxaban at the time of the next scheduled administration of LMWH ❖ From UFH, discontinue heparin and initiate edoxaban 4 hours later ❖ To a parenteral, discontinue edoxaban and start the parenteral anticoagulant at the time of the next dose of edoxaban

	Dabigatran (Pradaxa)	Rivaroxaban (Xarelto)	Apixaban (Eliquis)	Edoxaban (Savaysa)
Dosing based on specific indications **and** renal function [*Therapeutic uses only*]	**Nonvalvular Atrial fibrillation** ❖ For patients with CrCl >30 mL/min: 150 mg orally, twice daily ❖ For patients with CrCl 15-30 mL/min: 75 mg orally, twice daily ❖ For patients with CrCl < 15 mL/min or on dialysis, no dosing recommendations ❖ For patients with CrCl 30-50 mL/min, receiving P-gp inhibitor dronedarone or systemic ketoconazole: 75 mg orally, twice daily ❖ For patients with CrCl < 30 mL/min receiving P-gp inhibitor, avoid administration **Treatment of DVT, PE** ❖ CrCl ≥ 30 mL/min: 150 mg orally twice daily **after** 5 to 10 days parenteral anticoagulation ❖ CrCl < 30 mL/min or dialysis: AVOID ❖ P-gp inhibitor co-administration if CrCl < 50 mL/min: AVOID	**Nonvalvular Atrial Fibrillation** ❖ For patients with CrCl >50 mL/min: 20 mg PO once daily with food ❖ For patients with CrCl ≤ 50 mL/min: 15 mg PO daily with food **Treatment of DVT, PE** ❖ **15 mg PO twice daily** with food for the first 21 days for the initial treatment of acute DVT or PE. After the initial treatment period, **20 mg PO once daily** with food for the remaining treatment ❖ **CrCl ≤ 30 mL/min- Avoid use** **Reduction in the Risk of Recurrence of DVT and/or PE in patients at continued risk for DVT and/or PE** ❖ **10 mg po once daily** with or without food after at least 6 months of standard anticoagulation treatment **Patients with CrCl < 30 ml/min** were excluded from the Einstein-DVT and Einstein-PE. Due to an expected increase in rivaroxaban exposure, AVOID Xarelto for DVT or PE in patients with CrCl < 30 ml/min.	**Nonvalvular Atrial fibrillation** ❖ 5 mg taken orally twice daily ❖ 2.5 mg twice daily in patients with any **2** of the following characteristics: • age ≥80 years • body weight ≤60 kg • serum creatinine ≥1.5 mg/dL ❖ The recommended dose for nonvalvular atrial fibrillation patients with end-stage renal disease (ESRD) maintained on hemodialysis is 5 mg twice daily. Reduce dose to 2.5 mg twice daily if one of the following patient characteristics (age ≥80 years or body weight ≤60 kg) is present ❖ When Eliquis is coadministered with drugs that are strong dual inhibitors of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) (e.g., ketoconazole, itraconazole, ritonavir), the recommended dose is 2.5 mg twice daily ❖ In patients already taking 2.5 mg twice daily, coadministration of Eliquis with strong dual inhibitors of	**Nonvalvular Atrial Fibrillation** ❖ 60 mg taken orally once daily (CrCl > 95 ml/min: Do not use d/t increased risk of ischemic stroke) ❖ For patients with CrCl 15 – 50 ml/min: 30 mg taken orally once daily **Treatment of DVT, PE** ❖ In patients who have been initially treated with a parenteral anticoagulant for 5-10 days: ➢ > 60 kg: 60 mg taken orally once daily ➢ ≤ 60 kg: 30 mg taken orally once daily ❖ For patients with CrCl 15 – 50 ml/min or who use certain P-gp inhibitors: 30 mg taken orally once daily

	Dabigatran (Pradaxa)	Rivaroxaban (Xarelto)	Apixaban (Eliquis)	Edoxaban (Savaysa)
		CAD/PAD ❖ **2.5 mg orally twice daily** with aspirin 75-100 mg orally once daily **VTE prophylaxis for acutely ill** ❖ **10 mg orally once daily** in hospital and after hospital discharge for a total recommended duration of 31 to 39 days	CYP3A4 and P-gp should be avoided. **Treatment of DVT and PE**: ❖ The recommended dose is 10 mg taken orally twice daily for 7 days, followed by 5 mg taken orally twice daily. **Reduction in the Risk of Recurrence of DVT and PE:** ❖ The recommended dose of ELIQUIS is 2.5 mg taken orally twice daily after at least 6 months of treatment for DVT or PE	
Spinal/Epidural Anesthesia or Puncture [Package Insert Recommenda-tions] *see below for Periprocedural management and ASRA recommendations for interventional pain procedures	❖ Consider longer hold times than stated in periprocedural management section in patients undergoing major surgery, spinal puncture, or placement of a spinal or epidural catheter or port, in whom complete hemostasis may be required.	❖ An epidural catheter should not be removed earlier than 18 hours after the last administration of Xarelto. ❖ The next Xarelto dose is not to be administered earlier than 6 hours after the removal of the catheter. ❖ If traumatic puncture occurs, the administration of Xarelto is to be delayed for 24 hours.	❖ Indwelling epidural or intrathecal catheters should not be removed earlier than 24 hours after the last administration of ELIQUIS. ❖ The next dose of ELIQUIS should not be administered earlier than 5 hours after the removal of the catheter. ❖ The risk may also be increased by traumatic or repeated epidural or spinal puncture. ❖ If traumatic puncture occurs, delay the administration of ELIQUIS for 48 hours.	❖ Indwelling epidural or intrathecal catheters should not be removed earlier than 12 hours after the last administration of SAVAYSA. ❖ The next dose of SAVAYSA should not be administered earlier than 2 hours after the removal of the catheter. The risk may also be increased by traumatic or repeated epidural or spinal puncture.
Drug interactions	❖ Avoid concomitant use of P-gp	❖ Avoid concomitant use of Xarelto with	❖ The dose of Eliquis should be	❖ Avoid concomitant use of P-gp

	Dabigatran (Pradaxa)	Rivaroxaban (Xarelto)	Apixaban (Eliquis)	Edoxaban (Savaysa)
*drug lists are not exhaustive	inducers (e.g., rifampin) ❖ In patients with CrCl 30-50 mL/min, consider reducing the dose of Pradaxa to 75 mg twice daily when given concomitantly with the P-gp inhibitor dronedarone or systemic ketoconazole*. ❖ The use of P-gp inhibitors (**verapamil, amiodarone, quinidine, and clarithromycin**)* does not require a dose adjustment of Pradaxa. These results should <u>not</u> be extrapolated to other P-gp inhibitors. ❖ The concomitant use of Pradaxa and P-gp inhibitors in patients with CrCl 15-30 mL/min should be <u>avoided</u>.	combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir/ritonavir erythromycin, fluconazole and conivaptan)* ❖ Avoid concomitant use of Xarelto with drugs that are combined P-gp and strong CYP3A4 inducers (e.g., **carbamazepie, phenytoin, rifampin, St. John's wort**)*	decreased to 2.5 mg twice daily when it is coadministered with drugs that are strong dual inhibitors of CYP3A4 and P-gp, (e.g., ketoconazole, itraconazole, ritonavir)* ❖ In patients already taking Eliquis at a dose of 2.5 mg twice daily, avoid coadministration with strong dual inhibitors of both CYP3A4 and P-gp. ❖ Avoid concomitant use of Eliquis with strong dual inducers of CYP3A4 and P-gp (e.g., **rifampin, carbamazepine, phenytoin, St. John's wort**)* as such drugs will decrease apixaban levels.	inducers (e.g. rifampin) ❖ For Non-valvular A-Fib, no dose reduction is recommended when coadministered with P-gp inhibitors ❖ For DVT/PE treatment, Dose reduction recommended when coadministered with P-gp inhibitors
Monitoring parameters	❖ Assess renal function <u>prior</u> to initiation of treatment with Pradaxa. <u>Periodically</u> assess renal function as clinically indicated (i.e., more frequently in clinical situations that may be associated with a decline in renal function). Adjust therapy accordingly. ❖ Discontinue Pradaxa in patients	❖ Patients who develop acute renal failure while on Xarelto should discontinue the treatment. ❖ Avoid use in patients with Child-Pugh B (moderate) or Child-Pugh C (severe) hepatic impairment, or with any hepatic disease associated with coagulopathy due to an increased bleeding risk	❖ No dose adjustment required for mild hepatic impairment ❖ No dosing recommendation for patients with moderate hepatic impairment ❖ Not recommended in patients with severe hepatic impairment	❖ Assess renal function prior to initiation of treatment with edoxaban. Periodically assess renal function as clinically indicated (i.e. more frequently in clinical situations that may be associated with a decline in renal function). Adjust therapy accordingly. ❖ Discontinue edoxaban in patients who

	Dabigatran (Pradaxa)	Rivaroxaban (Xarelto)	Apixaban (Eliquis)	Edoxaban (Savaysa)
	who develop acute renal failure while on Pradaxa and consider alternative anticoagulant therapy.			develop acute renal failure while on edoxaban and consider alternative anticoagulant therapy. ❖ No dose adjustment required for mild (Child-Pugh A) hepatic impairment ❖ Not recommended for patients with moderate-to-severe (Child-Pugh B/C) hepatic impairment
Impact on coagulation lab tests	May raise the Ecarin clotting Time (ECT), PTT, thrombin time (TT)	May raise the INR, PTT	May raise the INR, PTT	May influence INR measurements if not drawn just prior to the daily dose of edoxaban
Black Box Warning	WARNING: (A)PREMATURE DISCONTINUATION OF PRADAXA INCREASES THE RISK OF THROMBOTIC EVENTS (B)SPINAL/EPIDURAL HEMATOMA: **Epidural or spinal hematomas may occur in patients treated with PRADAXA who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Monitor patients frequently for signs and symptoms of neurological impairment and if observed, treat urgently. Consider the benefits and risks before neuraxial intervention in patients who are or who need to be anticoagulated** **See full prescribing information for complete boxed warning**	WARNING: (A)PREMATURE DISCONTINUATION OF XARELTO INCREASES THE RISK OF THROMBOTIC EVENTS (B)SPINAL/EPIDURAL HEMATOMA: **Epidural or spinal hematomas have occurred in patients treated with XARELTO who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Monitor patients frequently for signs and symptoms of neurological impairment and if observed, treat urgently. Consider the benefits and risks before neuraxial intervention in patients who are or who need to be anticoagulated.** **See full prescribing information for complete boxed warning**	WARNING: (A)PREMATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOTIC EVENTS (B)SPINAL/EPIDURAL HEMATOMA: **Epidural or spinal hematomas may occur in patients treated with ELIQUIS who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:** **• use of indwelling epidural catheters** **• concomitant use of other drugs that affect hemostasis, such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants** **• a history of traumatic or repeated epidural or spinal punctures** **• a history of spinal deformity or spinal surgery**	WARNING: (A) REDUCED EFFICACY IN NONVALVULAR ATRIAL FIBRILLATION PATIENTS WITH CREATININE CLEARANCE (CRCL) > 95 ML/MIN (B)PREMATURE DISCONTINUATION OF SAVAYSA INCREASES THE RISK OF ISCHEMIC EVENTS (C) SPINAL/EPIDURAL HEMATOMA: **Epidural or spinal hematomas may occur in patients treated with SAVAYSA who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures** **See full prescribing information for complete boxed warning.**

	Dabigatran (Pradaxa)	Rivaroxaban (Xarelto)	Apixaban (Eliquis)	Edoxaban (Savaysa)
			• optimal timing between the administration of ELIQUIS and neuraxial procedures is not known Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated See full prescribing information for complete boxed warning.	

CHILD-PUGH SCORE

Note: ACS Practitioners are not expected to diagnose whether a patient has hepatic dysfunction, but rather be aware if it is indicated in a DOAC patient's problem list.

Clinical and Biochemical Measurements	Points Scored for Increasing Abnormality		
	1	2	3
Hepatic encephalopathy (grade)	None	1 and 2	3 and 4
Ascites	Absent	Mild	Moderate
Total bilirubin (mg/dl)	< 2.0	2.0 - 3.0	> 3.0
Serum albumin (g/dl)	> 3.5	2.8 - 3.5	< 2.8
Prothrombin time (sec. prolonged over normal 10-14 sec) or Prothrombin time INR	< 4 or < 1.7	4 - 6 or 1.7 - 2.2	> 6 or >2.2

Chronic liver disease is classified into Child-Pugh class A to C, employing the added score from above

Points	Class	One year survival	Two year survival
5-6	A	100%	85%
7-9	B	81%	57%
10-15	C	45%	35%

https://www.mdcalc.com/calc/340/child-pugh-score-cirrhosis-mortality

Child-Pugh Pearls

- Originally designed to predict mortality in cirrhosis patients
    - Created in 1964 to guide selection of patients who would benefit from an elective surgery for portal decompression
    - A = Good hepatic function, B = moderately impaired, C = advanced hepatic dysfunction
    - Historically used for liver transplant allocations
- Validated as a predictor of post-op mortality after portocaval shunt surgery
- Predicts mortality risk associated with other major operations
    - Abdominal surgery mortality rate
        - A = 10%
        - B = 30%
        - C = 70% - 80%
    - Elective surgery is contraindicated in Child class C patients
- Predicts all-cause mortality risk and development of other complications from liver dysfunction, like variceal bleeding
    - Overall mortality at one year
        - A = 0%
        - B = 20%
        - C = 55%

Periprocedural Management of DOACs

Develop a Procedural Plan

PRE-Procedure[49]							
DOAC Type	Surgery/ Procedure Bleeding Risk	PRE-Procedure Interruption of DOAC					
		Day -5	Day -4	Day -3	Day -2	Day -1	Day 0
Dabigatran CrCl < 50 mL/min	High	√	X	X	X	X	No DOAC taken on the day of surgery/ procedure
	Low	√	√	√	X	X	
Dabigatran CrCl ≥ 50 mL/min Rivaroxaban Apixaban Edoxaban	High	√	√	√	X	X	
	Low	√	√	√	√	X	

POST-Procedure						
DOAC Type	Surgery/ Procedure Bleeding Risk	POST-Procedure Resumption of DOAC*				
		Day 0	Day +1	Day +2	Day +3	Day +4
Any DOAC	High	No DOAC taken on the day of surgery/ procedure	X	√	√	√
	Low		√	√	√	√

KEY		
Take Dose	Flexibility of Dose Timing	Do NOT Take Dose
√	√	X

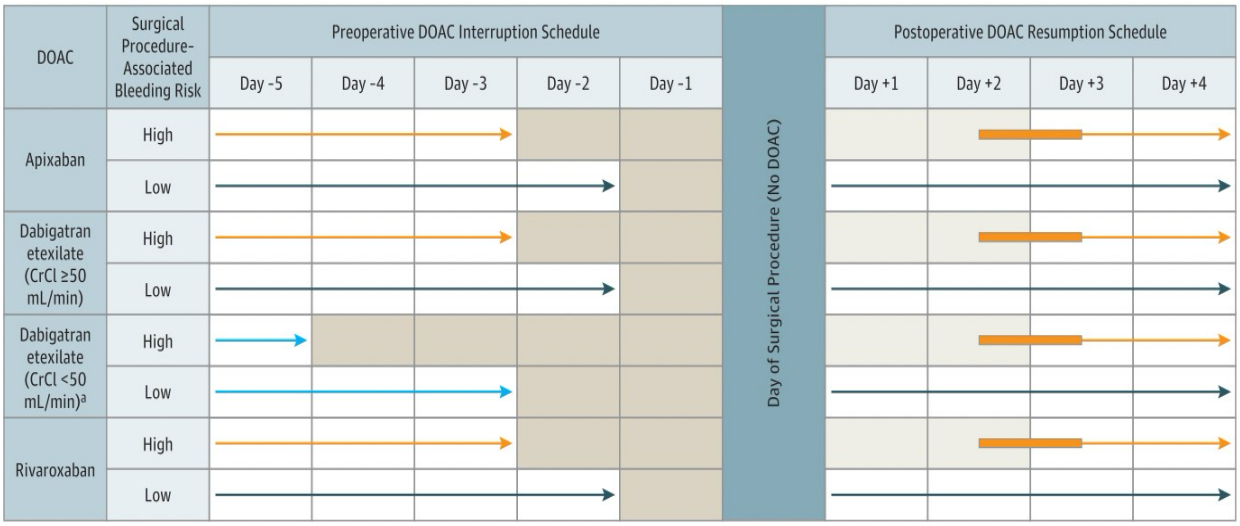
Abbreviations: CrCl, creatinine clearance; DOAC, direct oral anticoagulant.

**According to the American Society of Regional Anesthesia, patients having neuraxial anesthesia or epidural pain procedures should discontinue dabigatran 120 hours and apixaban/edoxaban/rivaroxaban 72 hours prior to procedure. The DOAC may be resumed at least 6 hours after catheter removal or according the surgery/procedure bleeding risk timeframe provided above, whichever is longer.*[51]

From: AC Forum DOAC Playbook v.14 final – accessed 6.4.21

For current HF Health Guidance: Tier 1: Perioperative Medication Management Periprocedural Management (DOAC)

Figure. Perioperative Direct Oral Anticoagulant (DOAC) Management Protocol



No DOAC was taken on certain days (shaded) and on the day of the elective surgery or procedure. The light blue arrows refer to an exception to the basic management, a subgroup of patients taking dabigatran with a creatinine clearance (CrCl) less than 50 ng/mL. The orange arrows refer to patients having a high-bleed-risk surgical procedure. Dark blue arrows refer to patients having a low-bleed-risk surgical procedure. The thickened orange part of arrows refer to flexibility in the timing of DOAC resumption after a procedure.

[a] Cancer diagnosed within 3 months or has been treated within 6 months or metastatic.

These practice parameters are designed as guidelines and as such are not a substitute for the best professional judgment of physicians or other health professionals taking into consideration the individual circumstances presented by the patient. Acceptable medical practice may include a variety of responses to a particular clinical problem and all rationale should be documented in the patient's chart

Direct Oral Anticoagulant

Potential Drug Interaction Table

NOTE: For quick reference only. Please check Lexicomp (UpToDate), Micromedex and/or Clinical Pharmacology for most recent updates.

CYP or Transporter System	Examples (Lists are not exhaustive)
CYP-3A4 inhibitors	Strong inhibitors: Boceprevir, clarithromycin***, conivaptan, grapefruit juice*, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole Moderate inhibitors: Amprenavir, aprepitant, atazanavir, ciprofloxacin, diltiazem, darunavir/ritonavir, erythromycin, fluconazole, fosamprenavir, grapefruit juice*, imatinib, verapamil Weak inhibitors: Alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, fluvoxamine, ginkgo, goldenseal, isoniazid, nilotinib, oral contraceptives, ranitidine, ranolazine, tipranavir/ritonavir, zileuton
CYP-3A4 inducers	Strong inducers: Carbamazepine, phenytoin, rifampin, St. John's wort** Moderate inducers: Bosentan, efavirenz, etravirine, modafinil, nafcillin Weak inducers: Amprenavir, armodafinil, Echinacea, pioglitazone, prednisone, rufinamide
P-glycoprotein inhibitors	Strong P-gp inhibitors: Clarithromycin***, conivaptan, itraconazole, ketoconazole, lopinavir and ritonavir Moderate P-gp inhibitors: Diltiazem, dronedarone, erythromycin, verapamil Weak P-gp inhibitors: Ranolazine, amiodarone, quinidine, azithromycin, felodipine Other P-gp inhibitors: Captopril, carvedilol, cyclosporine
P-glycoprotein inducers	Carbamazepine, fosphenytoin, phenytoin, rifampin, St John's wort**, tipranavir/ritonavir
Combined 3A4/P-gp Inhibitors	Strong 3A4 AND P-gp inhibitors: Itraconazole, lopinavir/ritonavir, clarithromycin, ritonavir, ketoconazole, indinavir/ritonavir, conivaptan Moderate 3A4 AND P-gp inhibitors: Verapamil, erythromycin, diltiazem, dronedarone Weak 3A4 AND P-gp inhibitors: Quinidine, ranolazine, amiodarone, felodipine, azithromycin
Combined 3A4/P-gp Inducers	Carbamazepine, phenytoin, rifampin, St John's wort**

* The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (e.g., high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (e.g., low dose, single strength).

** The effect of St. John's wort varies widely and is preparation-dependent.

***Clarithromycin does not require DOAC dose adjustment

Strong CYP Inhibitors: ≥ 5-fold increase in AUC or > 80% decrease in CL

Moderate CYP inhibitors: ≥ 2 but < 5-fold increase in AUC or 50-80% decrease in CL

Weak CYP inhibitors: ≥ 1.25 but < 2-fold increase in AUC or 20-50% decrease in CL

Commonly Used Medications Which Can Increase the Risk of Renal Dysfunction

Drug class	**Generic Drug names**
Loop diuretics	Furosemide Ethacrynic acid Bumetanide Torsemide
Thiazide-like diuretics	Hydrochlorothiazide Chlorothiazide Methyclothiazide
Angiotensin Converting Enzyme Inhibitors (ACEI's)	Captopril Enalapril Lisinopril Fosinopril Benazepril Moexipril Trandolapril Quinapril HCl Ramipril
Angiotensin Receptor Blockers (ARB)	Losartan Olmesartan Medoxomil Valsartan Candesartan Cilexetil Telmisartan Irbesartan
Biguanide	Metformin
NSAIDs	Ibuprofen Mefenamic Acid Naproxen. Meloxicam Diclofenac. Nabumetone Fenoprofen. Oxaprozin Indomethacin. Piroxicam Ketoprofen. Sulindac Ketorolac. Tolmetin Sodium Toradol

Direct Oral Anticoagulants Prescribing Check List for Primary Care Providers

Drug	Factors to consider Upon Prescribing
Dabigatran etexilate (Pradaxa)	☐ Verify indication is for nonvalvular atrial fibrillation **or** treatment of VTE [i.e., deep vein thrombosis (DVT) or pulmonary embolism (PE)] ☐ Calculate CrCl using Cockroft-Gault with Actual Body Weight, not Ideal Body Weight ☐ Verify that patient can afford paying for the drug on long-term basis ☐ Assess age (age > 75 years is associated with higher GI bleeding) ☐ Assess renal function (creatinine clearance) upon prescribing and dose accordingly ☐ Assess renal function periodically during therapy as clinically indicated and adjust therapy accordingly ☐ Assess past medical history (contraindicated in Mechanical prosthetic heart valve, may aggravate symptoms of dyspepsia, gastro-esophageal reflux disease, esophagitis, erosive gastritis, and gastrointestinal ulcer) ☐ Instruct patients not to chew, break, or open capsules.
Rivaroxaban (Xarelto)	☐ Verify indication is for either nonvalvular atrial fibrillation **or** treatment of venous thromboembolism (VTE) [i.e., deep vein thrombosis (DVT) or pulmonary embolism (PE)], CAD, PAD or VTE prophylaxis in acutely ill patients ☐ Calculate CrCl using Cockroft-Gault with Actual Body Weight, not Ideal Body Weight ☐ Verify that patient can afford paying for the drug on long-term basis ☐ Assess past medical history for history or susceptibility to gastrointestinal (GI) bleeding (higher rate of GI bleeding in atrial fibrillation trial) ☐ Verify the proper dose for the proper indication. Dose for atrial fibrillation is **DIFFERENT** than that for treatment of VTE. Always specify to take rivaroxaban with food. ☐ Assess renal function (creatinine clearance) and dose accordingly. ☐ Avoid giving rivaroxaban to patients receiving drugs with combined P-glycoprotein and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir/ritonavir, and conivaptan) or drugs with combined P-glycoprotein and strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's wort)
Apixaban (Eliquis)	☐ Verify indication is for nonvalvular atrial fibrillation (avoid in patients with prosthetic heart valves) **or** treatment of venous thromboembolism (VTE) [i.e., deep vein thrombosis (DVT) or pulmonary embolism (PE)] ☐ Verify the proper dose for the proper indication. Dose for atrial fibrillation is **DIFFERENT** than that for treatment of VTE. ☐ Verify that patient can afford paying for the drug on long-term basis ☐ Reduced dose of 2.5mg PO bid should be given if patient has **at least 2** of the following characteristics: ✓ age ≥80 years ✓ body weight ≤60 kg ✓ serum creatinine ≥1.5 mg/dl ☐ Reduced dose of 2.5mg PO bid should be given when apixaban is coadministered with drugs that are strong dual inhibitors of CYP3A4 and P-gp, (e.g., ketoconazole, itraconazole, ritonavir, or clarithromycin) ☐ Avoid apixaban if the patient qualifies for a dose of 2.5 mg bid (see above), **AND** patient is also on drugs with strong dual inhibitors of both CYP3A4 and P-glycoprotein (e.g., ketoconazole, itraconazole, ritonavir, or clarithromycin) ☐ Avoid concomitant use of apixaban with strong dual inducers of CYP3A4 and P-glycoprotein (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) because such drugs will decrease exposure to apixaban

Edoxaban (Savaysa)	☐ Verify indication is for nonvalvular atrial fibrillation or treatment of venous thromboembolism (VTE) [i.e. deep vein thrombosis (DVT) or pulmonary embolism (PE). Avoid in patients with prosthetic heart valves. ☐ Verify that patient can afford paying for the drug on long-term basis ☐ Assess past medical history for history or susceptibility to gastrointestinal (GI) bleeding ☐ Assess renal function (serum creatinine, creatinine clearance) and dose accordingly ☐ Avoid edoxaban in patient with CrCl > 95 ml/min, as this will reduce the efficacy of edoxaban ☐ Reduced dose (30 mg po daily) should be given for CrCl 15 – 50 ml/min ☐ For DVT/PE treatment, a reduced dose (30 mg po daily) should be given for patients $\leq$ 60 kg ☐ Avoid giving edoxaban to patients receiving drugs that are P-gp inducers (e.g. rifampin) ☐ For DVT/PE treatment, dose reduction is recommended when coadministered with P-gp inhibitors ☐ Not recommended for patients with moderate-to-severe hepatic impairment (Child-Pugh B/C)

These practice parameters are designed as guidelines and as such are not a substitute for the best professional judgment of physicians or other health professionals taking into consideration the individual circumstances presented by the patient. Acceptable medical practice may include a variety of responses to a particular clinical problem and all rationale should be documented in the patient's chart.

Apixaban	Indication	Dose		Modifiers	Renal	Hepatic Impairment Child-Pugh Class	Pregnancy/Lactation	Reversal
	NVAF	Recommended dose	5 mg twice daily	If taking 5 mg or 10 mg twice daily, decrease dose by 50% if concomitant CYP3A4 and Pgp inhibitors. AVOID if dose already at 2.5 mg twice daily AVOID concomitant strong inducers of CYP3A4 and P-gp	ESRD on HD: Not adequately studied in large-scale clinical trial,* AM J Med 2017; 130(9): 10 15-1023 *For patients with AF At elevated risk for stroke and who have end-stage CKD (CrCl<15 mL/min) or are on dialysis, it might be reasonable to prescribe evidence-based dose of apixaban 2023ACC/AHA/ACCP/HRSA AF Guidelines	B. No advice C. AVOID	Cat B	Coagulation Factor Xa(recombinant) (Andexxa ®) approved 2018 Indication: life-threatening or uncontrolled bleeding IV bolus followed by continuous IV infusion Activated oral charcoal decrease absorption of apixaban and decrease plasma concentration
		If two of the following: Age ≥ 80 yo, Wt ≤ 60 kg, or SCr ≥ 1.5 mg/dl	2.5 mg twice daily					
	VTE	10 mg twice daily for first 7 days; after 7 days, transition to 5 mg twice daily					Unknown if excreted in human milk, D/C breastfeeding or drug	
	VTE risk reduction	2.5 mg twice daily AFTER at least 6 mo of treatment dose						
	VTE prophylaxis	Hip Replacement (initial dose 12—24 hr after surgery)	2.5 mg twice daily					
		Knee Replacement (initial dose 12-24 hr after surgery)	2.5 mg twice daily					

Transition from warfarin	
Discontinue warfarin and start apixaban when the INR is < 2	
Transition to warfarin	
One approach is to d/c apixaban and begin both a parenteral anticoagulant and warfarin at the time of the next dose of apixaban would have been taken. D/C parenteral agent when INR reaches acceptable range. NOTE: apixaban affects INR	
Transition from apixaban to anticoagulants other than warfarin (oral or parenteral)	
Stop apixaban	Begin taking new anticoagulant other than warfarin at usual time of the next dose of apixaban
Transition from anticoagulants other than warfarin to apixaban	
Stop the anticoagulant	Begin apixaban at the usual time of the next dose of the anticoagulant other than warfarin
Temporary interruptions for Surgery or Invasive Procedures (especially epidural or spinal) - SEE PERI-PROCEDURAL GUIDE	
Patient Education Highlights	
Take with or without food. Can crush tablets and add to applesauce or D5W if trouble swallowing or can deliver via NG tube	
NVAF – Non-Valvular Atrial Fibrillation VTE - Venous Thromboembolism	

Rivaroxaban	Indication	Dose		Modifiers	Renal	Hepatic Impairment Child-Pugh Class	Pregnancy/ Lactation	Reversal
	NVAF	CrCl>50 mL/min	20 mg daily with food	AVOID concomitant P-gp and strong CYP3A4 inhibitors AVOID concomitant P-gp and strong CYP 3A4 inducers	ESRD on HD: Not adequately studied in large-scale clinical trial, use in this population should be avoided whenever possible AM J Med 2017; 130(9): 10 15-1023	B. AVOID C. AVOID	Use caution in pregnancy du to potential for obstetric hemorrhage and/or emergent delivery	Coagulation Factor Xa(recombinant) (Andexxa ®) approved 2018 Indication: life-threatening or uncontrolled bleeding IV bolus followed by continuous IV infusion
		CrCl 15-50 mL/min	15 mg daily with food					
		CrCl < 15	AVOID					
		CrCl 15-80 mL/min AND combined P-gp + moderate CYP3A4 inhibitors	AVOID					
	VTE	CrCl > 30 mL/min	15 mg twice daily with food for first 21 days				Has been detected in human milk. Insufficient data for recommendations	
			After 21 days, transition to					
			20 mg once daily with food for remaining treatment					
		CrCl<15mL/min	AVOID					
	VTE risk reduction	10 mg daily with or without food after at least 6 months standard anticoagulant therapy						
	CAD or PAD	2.5 mg twice daily with or without food in combination with ASA (75mg – 100 mg) daily						
	VTE prophylaxis	Hip Replacement	10 mg daily with or without food					
		Knee Replacement	10 mg daily with or without food					
		Acute Illness	10 mg daily with or without food (total of 31-39 days IPD + post-D/C)					
		CrCl< 15 mL/min	AVOID					

Transition from warfarin	
Discontinue warfarin and start rivaroxaban when the INR is <3	
Transition to warfarin	
Discontinue rivaroxaban and begin both a parenteral anticoagulant and warfarin at the time the next dose of Xarelto would have been taken. Discontinuing the parenteral anticoagulant when INR reaches an acceptable range. NOTE: Rivaroxaban affects INR	
Transition from rivaroxaban to anticoagulants other than warfarin (oral or parenteral)	
Stop rivaroxaban	Begin taking new anticoagulant other than warfarin at usual time of the next dose of rivaroxaban
Transition from anticoagulants other than warfarin to rivaroxaban	
From an anticoagulant, start rivaroxaban 0 – 2 hours prior to next scheduled evening dose of the other anticoagulant	Omit administration of other drug
Temporary interruptions for Surgery or Invasive Procedures (especially epidural or spinal) - SEE PERI-PROCEDURAL GUIDE	
Patient Education Highlights	
Take 15 and 20 mg dose with food. May crush pills and mix with applesauce or water if trouble swallowing or delivery via NG or gastric tube, follow with meal or enteral feeding	
NVAF – Non-Valvular Atrial Fibrillation VTE - Venous Thromboembolism CAD – Coronary Artery Disease PAD – Peripheral Artery Disease	

Dabigatran	Indication	Dose		Modifiers	Renal	Hepatic Impairment Child-Pugh Class	Pregnancy/ Lactation	Reversal
	NVAF	CrCl>30 mL/min	150 mg twice daily	AVOID P-gp inducers	ESRD on HD: Not adequately studied in large-scale clinical trial, use in this population should be avoided whenever possible AM J Med 2017; 130(9): 10 15-1023	B. large inter-subject variability. No evidence of consistent change in exposure or pharmacodynamics	May increase risk of bleeding in fetus and neonate	For life threatening emergencies or urgent surgery: idarucizumab (Praxibind®) IV in 2 divided doses Hemodialysis can remove
		CrCl 15-30 mL/min	75 mg twice daily					
		CrCl < 15 mL/min	AVOID					
		CrCl 30 – 50 mL/min AND P-gp inhibitors	75 mg twice daily					
		CrCl 15-30 mL/min AND P-gp inhibitors	AVOID					
	VTE	CrCl >30 mL/min	150 mg twice daily after 5-10 day lead-in with parenteral agent (no overlap)				Breastfeeding NOT recommended	
		CrCl ≤ 30 mL or HD	No recommendation					
		CrCl < 50 and P-gp inhibitor	AVOID					
	VTE risk reduction	CrCl > 30 mL/min	150 mg twice daily					
		CrCl ≤ 30 or HD	No recommendation					
		CrCl<50 and P-gp inhibitor	AVOID					
	VTE prophylaxis	Hip Replacement CrCl > 30 mL/min	110 mg daily for first day, then 220mg once daily					
		CrCl <50 AND P-gp inhibitor	AVOID					
		CrCl< 30 mL/min or HD	No recommendation					

Transition from warfarin		
Discontinue warfarin and start dabigatran when the INR is <2		
Transition to warfarin		
CrCl ≥ 50 mL/min	Start warfarin 3 days before discontinuing	Note: dabigatran can increase the INR. INR will better reflect warfarin's effect after dabigatran stopped at least 2 days
CrCl 30-50 mL/min	Start warfarin 2 days before discontinuing	
CrCl 15-30 mL/min	Start warfarin 1 day before discontinuing	
CrCl < 15 mL/min	No recommendations	
Transition from Oral to Parenteral		
Currently on parenteral	Start 0-2 hours before the time of next dose of parenteral drug or at time of d/c of IV heparin	
Currently on dabigatran	If CrCl ≥ 30 mL/min- wait 12 hours. If CrCl < 30 mL/min – wait 24 hours after last dose of dabigatran before initiating parenteral	
Temporary interruptions for Surgery or Invasive Procedures (especially epidural or spinal) - SEE PERI-PROCEDURAL GUIDE		
Patient Education Highlights		
Must remain in original container. Use open bottle within 120 days. Blister packs available. Swallow capsules whole, do not open, break or chew. Take with full glass of water.		
NVAF – Non-Valvular Atrial Fibrillation VTE - Venous Thromboembolism		

Edoxaban	Indication	Dose		Modifiers	Renal	Hepatic Impairment Child-Pugh Class	Pregnancy/ Lactation	Reversal
	NVAF	CrCl>95mL/min	AVOID	AVOID P-gp inducers	HD: No data	B. AVOID C. AVOID	Insufficient data	None
		CrCl 51- 95 mL/min	60 mg once daily					
		CrCl 15 – 50 mL/min	30 mg once daily					
		CrCl < 15 mL/min	AVOID					
	VTE	CrCl > 50 mL/min	60 mg once daily AFTER 5-10 day lead-in with parenteral agent (no overlap)				Breastfeeding NOT recommended	
		CrCl 15-50 mL/min	30 mg once daily					
		CrCl < 15 mL/min	AVOID					
		If Weight ≤ 60 kg	30 mg once daily					
		If P-gp inhibitor	30 mg once daily					

Transition from warfarin		
Discontinue warfarin and start edoxaban when the INR is <2.5		
Transition to warfarin		
Oral option: If taking 60 mg, decrease dose to 30 mg	Begin warfarin concomitantly. Once stable INR ≥2, D/C edoxaban	Note: Measure INR at least weekly and just prior to daily edoxaban to minimize influence on INR value
Oral option: If taking 30 mg, decrease dos to 15 mg	Begin warfarin concomitantly. One stable INR ≥2, D/C edoxaban	
Parenteral option: D/C edoxaban	Begin parenteral and warfarin at time of next scheduled edoxaban dose. Once stable INR ≥2, D/C parenteral	
Transition from Oral to Parenteral or DOAC		
Currently on parenteral or DOAC	D/C other anticoagulant or LMWH and start edoxaban at time of next scheduled dose	
Currently on IV Heparin	D/C infusion and start edoxaban 4 hours later	
Currently on edoxaban	D/C edoxaban and start other non-warfarin anticoagulant or parenteral at the time of the next edoxaban dose	
Temporary interruptions for Surgery or Invasive Procedures (especially epidural or spinal) - SEE PERI-PROCEDURAL GUIDE		
Patient Education Highlights		
Can take with or without food. Do not double up for missed dose. Instruct patients who cannot swallow the tablet whole to crush SAVAYSA, combine with 2 to 3 ounces of water or applesauce and ingest immediately. Instruct patients who require a gastric tube to crush the SAVAYSA tablet and mix it with 2 to 3 ounces of water before administering immediately via the gastric feeding tube.		
NVAF – Non-Valvular Atrial Fibrillation VTE - Venous Thromboembolism		

Patient Anticoagulation Medication Counseling Basics

Patient Advice	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Missed Dose	Take missed dose if before 12:00 pm on the same day and call your AC Practitioner	Take as soon as possible the same day, but at least 6 hrs before next scheduled dose, otherwise call AC Practitioner/provider	If missed at 15 mg dose, can take 30 mg one time to make up, otherwise call AC Practitioner/provider	Take as soon as possible the same day, otherwise call AC Practitioner/provider	Take as soon as possible the same day otherwise call AC Practitioner/provider
	DO NOT DOUBLE DOSE TO MAKE UP A MISSED DOSE				
Food Concerns	Take with or without food; consistency with high vitamin K containing foods	With or without food, with a full glass of water	With food for 15 mg & 20 mg doses. With or without food for 10mg	With or without food	With or without food
Weekly Pill Planner	Can help with medication adherence	MUST store in the original container, keep sealed and use in 120 days after opening	Weekly pill planner can be used and may help with medication adherence		
Medication Administration	Can crush, mix with food	Swallow whole, DO NOT CUT, OPEN OR CRUSH	Can crush, mix with food or water for NG tube	Can crush, mix with food or D5W for NG tube	No data regarding crushing
Drug-drug Interactions (see package insert, Micromedex, Clinical Pharmacology online and/or anticoag guidelines for complete list)	Numerous; report all medication changes to AC Practitioner	Avoid giving to patients receiving drugs that are P-gp inducers (e.g. rifampin)	Avoid giving to patients receiving drugs with combined P-glycoprotein and strong CYP3A4 inhibitors or drugs with combined P-glycoprotein and strong CYP3A4 inducers	Avoid concomitant use with strong dual inducers of CYP3A4 and P-glycoprotein. If possible, reduce dose for concomitant use of apixaban with strong dual inhibitors of CYP3A4 and P-gp	Avoid giving to patients receiving drugs that are P-gp inducers (e.g. rifampin)
Medication Changes	Contact AC Practitioner/provider for any medication changes, including OTCs and herbal supplements				
Procedures Scheduled	Contact AC Practitioner as soon as procedure is scheduled				
S&S Bleeding/Thrombosis	Report signs and symptoms of bleeding and potential clotting (see guidelines for when to call provider or go to ED)				
Pregnancy (or planning)/Breastfeeding	Contact AC Practitioner/provider if pregnant or planning to become pregnant. Inform AC Practitioner or provider if breastfeeding				
Medication Alert	Carry an ID wallet card or an I.D. bracelet/necklace indicating patient is on a blood thinner to alert emergency medical responders				
Medication Discontinuation	DO NOT DISCONTINUE unless otherwise instructed by provider or AC Practitioner				

Reversal Agent	DOAC dose	DOAC timing since last dose	Dose of reversal agent	Resume DOAC
Andexxa ® (Factor Xa)	Rivaroxaban ≤ 10mg	Within 8 hours or unknown timing	400 mg IV bolus @ 30mg/min followed by 4 mg/min continuous IV infusion up to 120 minutes	As medically appropriate
	Apixaban ≤ 5 mg	At 8 hours or more		
	Rivaroxaban > 10mg or unknown	Within 8 hours of timing of last dose	800 mg IV bolus @ 30mg/min followed by 8 mg/min continuous IV infulsion for up to 120 minutes	
	Apixaban > 5mg or unknown			
Praxbind ® (Idarucizumab)	Dabigatran at any dose	N/A	5 g IV once, in conjunction with standard supportive, medically appropriate measures; second dose of 5 g IV if needed	Dabigatran therapy may be initiated 24 hours after administration of idarucizumab

For most updated use of reversal agents at Henry Ford Health click on the link below:

Tier 1: Anticoagulation Reversal Guidelines

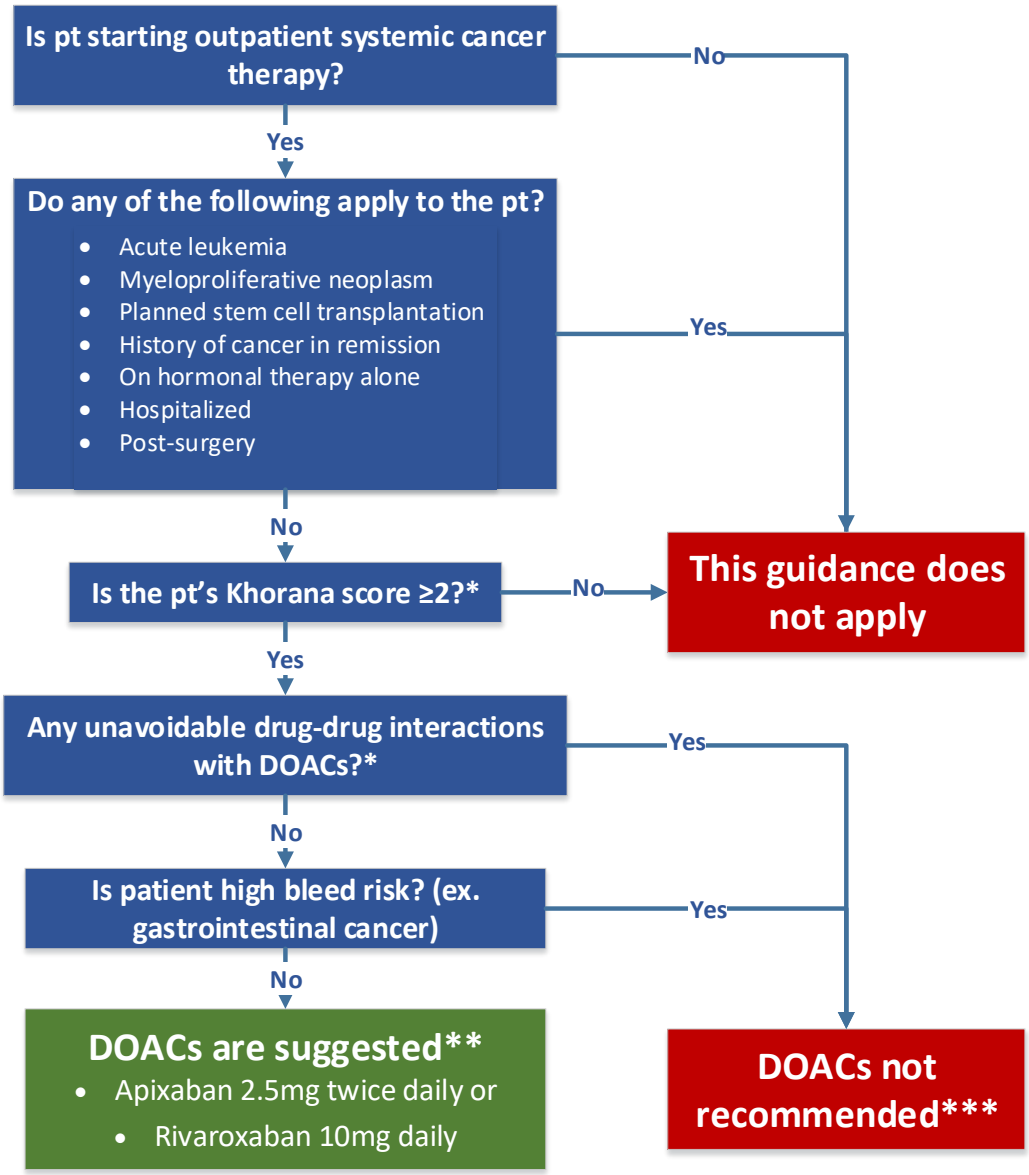
DOAC Use for Cancer Related VTE

CHEST 2021; 160(6):e545-e608:
Recommendation 16. In patients with acute VTE in the setting of cancer (cancer-associated thrombosis) we recommend an oral Xa inhibitor (apixaban, edoxaban, rivaroxaban) over low molecular weight heparin (LMWH) for the initiation and treatment phases of therapy (strong recommendation, moderate-certainty evidence). Remark: ***Edoxaban and rivaroxaban appear to be associated with a higher risk of GI major bleeding than LMWH in patients with cancer-associated thrombosis (CAT) and a luminal GI malignancy, while apixaban does not. Apixaban or LMWH may be the preferred option in patients with luminal GI malignancies.***

ASH Guidelines for VTE Patients with Cancer (Blood Advances. 23 February 2021:5(4)929-930):
Recommendation 20. For patients with cancer and VTE, the ASH guideline panel suggests DOAC (apixaban or rivaroxaban) or LMWH be used for initial treatment of VTE for patients with cancer (conditional recommendation, very low certainty in the evidence of effects)
Good practice statement 1. Patients with cancer are at increased risk for VTE, as well as major bleeding. Any consideration of thromboprophylaxis or treatment for patients with cancer should be based on an assessment of the patient's individual risk for thrombosis and major bleeding after full discussion of the potential benefits and harms.

VTE Prevention in Ambulatory Cancer Patients

Patients with active cancer have an increased risk of VTE. Two recent trials (AVERT[1] and CASSINI[2]) have shown that DOACs can reduce VTE risk in ambulatory cancer patients initiating chemotherapy. The following flowchart is based on a guidance statement from the International Society on Thrombosis and Haemostasis.[3]



*See the following page for the Khorana score calculation. Consult with a pharmacist or hematologist to evaluate for potential DOAC drug-drug interactions.

** Apixaban or rivaroxaban recommended since they were used in the AVERT and CASSINI trials. Treatment up to 6 months after initiation of chemotherapy is suggested. Regular monitoring of platelet counts and bleeding risk complications is recommended.[3]

*** In high-risk ambulatory cancer patients where primary thromboprophylaxis is planned but with concerns for safety of DOACs (such as in patients with concern of drug interaction or high risk of gastrointestinal bleeding), prophylactic doses of LWMH is suggested.[3]

Khorana Score

Patient Characteristic	Risk Score
Cancer location: stomach or pancreas (very high risk)	2
Cancer location: lung, lymphoma, gynecologic, bladder, testicular (high risk)	1
Pre-chemotherapy platelet count ≥ 350 $X10^9$/L	1
Hemoglobin < 10 g per deciliter or use of red blood cell growth factors	1
Pre-chemotherapy leukocyte count > 11 x 10^9/L	1
Body Mass Index ≥ 35 kg/m^2	1

VTE Risk	Total Score
Low	0
Intermediate	1-2
High	≥3

[1]Carrier M, et al. Apixaban to Prevent Venous Thromboembolism in Patients with Cancer (AVERT trial). N Engl J Med 2019; 380:711-719. DOI: 10.1056/NEJMoa1814468
[2]Khorana A, et al. Rivaroxaban for Thromboprophylaxis in High-Risk Ambulatory Patients with Cancer. N Engl J Med 2019; 380:720-728. DOI: 10.1056/NEJMoa1814630
[3]Wang T, et al. The use of direct oral anticoagulants for primary thromboprophylaxis in ambulatory cancer patients: Guidance from the SSC of the ISTH. J Thromb Haemost. 2019;17:1772–1778.
[4]Khorana A, et al. Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood (2008) 111 (10): 4902-4907. doi.org/10.1182/blood-2007-10-116327

VIII. Patient Education & Phone Interviews (Warfarin/Enoxaparin):

The majority of Anticoagulation Clinic encounters are done via telephone. The following outlines examples of basic encounter sessions that may be used for telephone interviews.

First Encounter Teaching Session:

Confirm discharge or initial instructions provider has given to patient

- What instructions were given to the patient?
- Is patient self-injecting Lovenox?
- Is the patient currently taking the warfarin?
- How many days has the patient been taking warfarin/Lovenox?

Confirm dose of warfarin

- Confirm brand, shape and color of warfarin tablet
- How many tablets is the patient taking daily?
- What time is the patient taking the warfarin?
- Explain weekly dosing concept.

Review purpose of warfarin

- Does the patient know why they are taking warfarin?
- Explain pathophysiology of disease state and purpose for warfarin.

Review lab process

- Importance of bloodwork as prescribed.
- Assure patient has received lab order.
- Explain the procedure for coming into the lab.
- Explain blood tests that are to be run (Protime and INR).
- Instruct patient to look for the "blue topped tube."

Briefly review effects of sub-/supratherapeutic INRs

- Explain prioritization of INR values (Urgent, High and Regular)
- Review signs/symptoms of bleeding: melena, hematuria, hemoptysis, epistaxis, petichea, unusual hematoma or internal bleeding following injury due to fall or head trauma. (Flyers regarding care and prevention of minor wound bleeding and epistaxis available on shared drive)
- Review signs/symptoms of thromboembolism: Chest pain, shortness of breath, sudden severe headache, sudden vision changes, numbness/tingling/weakness on one side of the body, or swelling of an extremity that may have area of warmth/tenderness/redness.

Review the function and process of the Anticoagulation Clinic

- Review our role and delegated authority of the anticoagulation physician.
- Review timeliness of communicating INR results once received.
- Adjust warfarin dose per lab results and other factors that influence warfarin therapy.
- Review clinic hours.
- Provide clinic telephone numbers.

Review briefly the factors that affect INR results

- Drastic changes in diet; lack of consistency
- Medications (prescription and non-prescription)
- ETOH
- Health changes (fever, vomiting, diarrhea, fluid retention and glucose control)
- Herbal supplementation

Review communication

- Explain patient agreement and privacy forms.

- Emphasize importance of contacting us if they have not been contacted within 48 hours of having blood drawn for an INR.
- Confirm emergency contact information.
- Emphasize importance of having a working telephone number or reliable contact.

Review Adverse Effects of Anticoagulation Therapy

- Bleeding side effects (major & minor) and measures to take if/when they occur.
- Counsel women of childbearing age that warfarin is contraindicated in pregnancy and it can cause spontaneous abortion, stillbirth, neonatal death, and preterm birth. An effective method of contraception must be used while a woman of childbearing age is on warfarin. The patient should also be advised to contact her healthcare provider regarding warfarin therapy as soon as she recognized she is pregnant. If so, Lovenox is a safe antithrombotic agent to use during pregnancy.

Closing

- Review warfarin/Lovenox doses.
- Review next lab due date.
- Ask patient if they smoke tobacco and if so, would they like help quitting (see page 30)
- Answer any questions patient may have.
- If available, offer patient education class.
- Send patient packet containing:
    - Warfarin Patient Education (available from HFHS printshop)
    - Patient Responsibility and Agreement Form
    - Laboratory location information
    - Flyers for managing nuisance bleeding (optional- on shared drive)

Follow-up teaching:

Verify that the patient has reviewed the patient education packet

- Answer any questions.
- Verify that the Anticoagulation Clinic Patient Agreement/Privacy form was signed.

Process INR result

- Review interpretation of the INR and meaning of sub-/supratherapeutic INR.
- Review signs/symptoms of sub-/supratherapeutic INR
- Verify warfarin dose, ask about missed doses.
- Enquire regarding changes in medications, diet or health.
- Instruct regarding warfarin dose.
- Advise next lab due date.

Review diet/vitamin K consistency

- Review importance of maintaining consistency in intake of vitamin K rich foods or vitamin K supplements.
- Review foods high in vitamin K.
- Review supplements high in vitamin K.

Review effects of herbal products

- Identify sources of herbal products.
- Emphasize consistency in consumption.

Review medication/health changes

- Review chart and medication list before and/or during patient encounter
- Emphasize importance of notifying the anticoagulation clinic with any medication changes (prescription or non-prescription).

- Identify drugs that may have a large impact on warfarin therapy: antibiotics; antiplatelet (e.g., aspirin, clopidogrel, prasugrel; NSAIDs); pain medications, antiarrhythmic, etc.
- Emphasize importance of contacting the anticoagulation clinic with any changes in health or hospitalizations.

Review effects of ETOH consumption

- Review cautions with ETOH (elevated INR, increased risk of GI bleeding, increased risk of injury).
- Emphasize clinic recommendation to avoid ETOH.
- ETOH consumption should be discussed with physician.

Review importance of compliance

- Describe actions to take for missed doses.
- Review importance of medication adherence.
- Emphasize importance of compliance with lab and physician visits.

Review clinic recommendations

- Dental procedures.
- Medical procedures.
- Travel procedures.

Review prescription refill/lab order procedures

- Anticoagulation clinic can refill warfarin and Lovenox prescriptions, but others will require a call to the pharmacy or physician’s office.
- Anticoagulation clinic can order bloodwork related to anticoagulation (PT/INR, Hgb, platelet counts and biochemical profiles).
- Require 24 hours notification for orders as listed above.
- Messages for these services may be left on voicemail.

DOAC Patient Education:

- What is anticoagulation and how do DOACs work
- If on warfarin in the past, how are DOACs different from warfarin
    - No INR monitoring required
    - No need for frequent dose adjustments
    - No Vit K interactions
    - Much quicker onset of action
    - Likely more expensive
- Why does patient need to start taking a DOAC
    - Indication and risks of condition
- The expected duration of treatment
- How to take the DOAC (dose, frequency, timing, with food?)
    - Dabigatran – take with or without food with large glass of water. DO NOT CRUSH or open the capsule
    - Rivaroxaban – take with evening meal or largest meal of the day
    - Apixaban – take with or without food
    - Edoxaban – take with or without food
- The importance of not skipping doses
    - Missing even one dose increases the risk of thromboembolic events
    - The impact of one missed dose may be more detrimental with a once-daily dosing regimen
    - One extra dose (i.e., doubling dose) provides much a much higher peak concentration and can lead to bleeding
- What to do about missed doses
- Ask if the patient smokes and if so, would they like help quitting (see page 30)

Dosing Issue	Twice Daily Dosing (BID)	Once Daily Dosing (QD)
Missed	• Forgotten dose may be taken up to 6 hours after scheduled intake • If patient has increased stroke and decreased bleeding risk, forgotten dose may be taken any time up to next scheduled dose	• Forgotten dose may be taken up to 12 hours after the scheduled intake • Beyond 12-hour period, dose can be skipped, and next scheduled dose may be taken • If patient has increased stroke risk, 12-hour period may be extended
Doubled	• Next dose may be taken 24 hours after the doubled dose	• Next dose may be taken per normal dosing regimen (without skipping next daily dose)
Uncertainty	• Start with next dose at 12-hour interval	• If increased thrombotic risk, take tablet and resume planned dosing regimen • If low thrombotic risk, wait until next scheduled dose

Adapted from Steffel J et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *European Heart Journal*, Volume 39, Issue 16, 21 April 2018, Pages 1330–1393, https://doi.org/10.1093/eurheartj/ehy136

- Signs/symptoms of bleeding or clotting
- Medications that can increase the risk of bleeding
    - Aspirin/antiplatelets
    - NSAIDs
    - Other anticoagulant use
    - Interacting medications
- Drug-drug interactions to watch for
    - Strong CYP3A4 and P-gp inhibitors/inducers
- Lab monitoring that will need to be done and how often
    - Hgb/Hct, PLT
    - SCr
    - Liver function
- What to do about taking DOACs around procedures/surgeries
- How to store DOACs

    - Pradaxa ® (dabigatran) must be kept in the original container
- Necessary lifestyle changes
    - Avoid contact sports
    - Fall prevention
    - Pregnancy prevention
- When and how to notify the anticoagulation clinic/physician
    - Signs/symptoms of bleeding or clotting (flyers regarding care and prevention of minor wound bleeding and epistaxis available on shared drive)
    - Changes in other medications
    - Changes in health
    - Hospitalizations
    - Upcoming procedures
- When to seek immediate medical attention
    - Signs/symptoms of major bleeding
- Send patient packet containing:
    - Specific DOAC Patient Education Monograph (if needed, available in shared drive, Patient Education folder)
    - Patient Responsibility and Agreement Form
    - Flyers for managing nuisance bleeding (optional- on shared drive)

Assessing compliance:

Dose Regimen	# missed doses/time period to qualify for 20% (mark as non-adherent)
Daily	• **1 out of 7 days** • **3 out of 2 weeks** • **6 out of 4 weeks** • **12 out of 8 weeks**
Twice Daily	• **3 out of 7 days** • **6 out of 2 weeks** • **12 out of 4 weeks** • **24 out of 8 weeks**

Adherent to medication if taken as prescribed more than 80% of the time (WHO, 2003)

DOAC Adherence is particularly important:

- **DOACs have a shorter duration of action than warfarin and require STRICT adherence**
  - **Impact of one missed dose may be more detrimental with a once daily dosing regimen**
  - **One extra dose provides a much higher peak concentration which may lead to bleeding**
- **Limited laboratory monitoring tests means fewer patient encounters, which leads to less adherence monitoring**
- **Adherence rates improve with appropriate selection of patients and through anticoagulation monitoring services**

Home Medication Reconciliation Update for Patient Adherence

Conway SE et al. Laboratory and Clinical Monitoring of Direct Acting Oral Anticoagulants; What Clinicians Need to Know. Pharmacotherapy 2017;37(2):236-248

IX. Workflow:

EPIC is the software program used to monitor patient INRs in the Anticoagulation Clinics. EPIC contains all the essential information pertaining to a patient's warfarin therapy, including, but not limited to:

Name	Warfarin tablet strength
Birthdate	Warfarin dosing schedule
MRN	INR history
Address	Current INR result
Anticoagulation physician	Contact information

EPIC allows anticoagulation clinic practitioners to retrieve information that would be vital to patient care. It also allows the clinic to communicate information regarding patients to one another, as well as to the patient's anticoagulation physician and other providers, via electronic medical record documentation. **All pertinent positives should be included in any documentation in EPIC, especially (but not limited to) advice given and the evidence and/or reasoning behind that advice.**

"Workflow" is a descriptor for how we prioritize tasks and manage patients' warfarin therapy. The following contains useful information for organizing and processing patient INR results.

Recommended Prioritization of Daily Tasks:

The daily task list of the Anticoagulation Clinic Practitioner (may be prioritized per clinic demand and as decided by Practitioner clinical judgment):

a. Open EPIC In Basket Results Folder
b. Retrieve any voicemail messages
c. Contact the patients with the "urgent" priority results, high priority first
d. Contact the patients with "high" priority results next, oldest results first
e. Contact all patients currently on Lovenox therapy that have results reported
f. Contact new enrollees

g. Contact recently discharged patients
h. Contact patients with "regular" priority results, oldest results first (alternatively, "regular" results may be addressed early in the day via sending a letter only, without a phone call, for patients who have been stable for more than 2 consecutive months. Patients must be made aware that this will be an option).
i. Contact DOAC patients scheduled for follow-up
j. Send prescription requests to pharmacy via EPIC
k. Send laboratory order requests via EPIC and document lab expiration date in "Specialty Comments" and on a "Sticky Note"
l. Prepare letters for posting
m. Print the workflow inbox prior to leaving at the end of the day
n. Maintain a list of high-risk/high-priority patients to ensure safe hand-off of care as necessary

- Please check voicemail and return phone messages every ½ to 1 hour throughout the day

Prioritization of INR results:

"Urgent" value	<1.5 or >5
"High" value	1.5 – 2.0 or 3.5 – 5.0
"Regular" value	2.0 – 3.0

Steps for Processing "Urgent" Results:

<u>If INR is < 1.5:</u>

1. Patient assessment of the following to determine possible cause for subtherapeutic INR:

- Verify warfarin dose
- Verify warfarin color/tablet strength
- Verify compliance with warfarin dose- Did the patient miss any doses since previous INR?
- Verify whether the patient is new to warfarin therapy.
- Look for previous dose adjustment for short-term medication that was not revised after course of medication was completed

- Ask about medication changes, such as antibiotics, thyroid supplements or anti-arrhythmic. Were any medications started or stopped recently?
- Look for recent office visit, ER visit, hospital discharge or new provider notes that would indicate possible changes in drug therapy or reasons to hold warfarin.
- Ask about dietary changes that would include the addition or increase in consumption of foods rich in vitamin K, herbal products or nutritional supplements (like Boost or Ensure).
- Ask if the patient has recently discontinued ETOH consumption.

2. Adjust dose per algorithm
3. Review and assess patient for signs/symptoms of clot formation or stroke
4. Verify that the patient's PT/INR lab order does not expire before their next advised blood draw

<u>If INR is > 5:</u>

1. Contact patient and assess the following to determine a possible cause for supratherapeutic INR:

- Review and assess patient for signs/symptoms of bruising or bleeding
- Verify whether patient is new to warfarin therapy
- Verify warfarin dose
- Verify warfarin tablet color/strength
- Ask if the patient has a newly diagnosed condition or has had a recent illness such as fever, diarrhea, vomiting, worsening CHF, thyroid changes, cancer, liver impairment or others
- Ask patient about over-the-counter medication use
- Ask about changes in routine medications, or whether the patient has started or stopped any medications recently

- Look in the electronic record for recent office visits, ER visits, hospital discharges or new provider notes. Ask patient about any physician visits outside of the System
- Enquire regarding changes in dietary habits
- Look for a previous dose adjustment for short-term medication that was not revised after the course of medication was completed
- Assess ETOH use

2. Advise patient to hold warfarin dose per protocol
3. Reinforce the need to avoid activities that may result in injury
4. Reinforce the need for immediate ER visit if bleeding or excessive bruising occur
5. Notify Anticoagulation Pharmacist if INR $\leq$ 9.99 with no bleeding. Notify Anticoagulation Physician of record if INR $\geq$ 10 and/or patient has signs or symptoms of bleeding, to determine preferred course of action regarding need for patient going to the ER or use of vitamin K (if INR >10)
6. Call patient (or contact person) with any instructions given by physician
7. Place MRN and INR on STAT board if patient advised to hold warfarin until next INR
8. Verify that the patient's PT/INR lab order does not expire before their next advised blood draw

Steps for Processing "High" Results:

If INR is >1.5 and <1.99:

1. Patient assessment of the following to determine possible cause for subtherapeutic INR:
   - Verify warfarin dose
   - Verify warfarin color/tablet strength
   - Verify compliance with warfarin dose- Did the patient miss any doses since previous INR?
   - Verify whether the patient is new to warfarin therapy.

- Look for previous dose adjustment for short-term medication that was not revised after course of medication was completed
- Ask about medication changes, such as antibiotics, thyroid supplements or anti-arrhythmics. Were any medications started or stopped recently?
- Look for recent office visit, ER visit, hospital discharge or new provider notes that would indicate possible changes in drug therapy or reasons to hold warfarin.
- Ask about dietary changes that would include the addition or increase in consumption of foods rich in vitamin K, herbal products or nutritional supplements (like Boost or Ensure).
- Ask if the patient has recently discontinued ETOH consumption.

2. Adjust dose per algorithm

1. Review and assess patient for signs/symptoms of clot formation or stroke
2. Verify that the patient's PT/INR lab order does not expire before their next advised blood draw

<u>If the INR > 3.5 and </= 4.99</u>:

1. Contact patient and assess the following to determine a possible cause for supratherapeutic INR:

- Review and assess patient for signs/symptoms of bruising or bleeding
- Verify whether patient is new to warfarin therapy
- Verify warfarin dose
- Verify warfarin tablet color/strength
- Ask if the patient has a newly diagnosed condition or has had a recent illness such as fever, diarrhea, vomiting, worsening CHF, thyroid changes, cancer, liver impairment or others
- Ask patient about over-the-counter medication use
- Ask about changes in routine medications, or whether the patient has started or stopped any medications recently

- Look in the electronic record for recent office visits, ER visits, hospital discharges or new provider notes. Ask patient about any physician visits outside of the System
- Enquire regarding changes in dietary habits
- Look for a previous does adjustment for short-term medication that was not revised after the course of medication was completed
- Assess ETOH use

2. Hold and/or adjust warfarin dose per dosing Algorithm
3. Review and assess patient for signs/symptoms of bruising or bleeding
4. Advise patient to seek immediate medical attention should unusual bruising, epistaxis lasting longer than 10 – 15 minutes, melena, hemoptysis or hematuria occur.
5. Verify that the patient's PT/INR lab order does not expire before their next advised blood draw

Steps for Processing "Regular" Results:

1. Contact patient and inform them of therapeutic INR
2. Verify current warfarin tablet color, strength and dosing schedule
3. Ask if patient has had changes in:
   - Prescription medications
   - Over-the-counter medications
   - Vitamin usage
   - Diet
   - Medical conditions

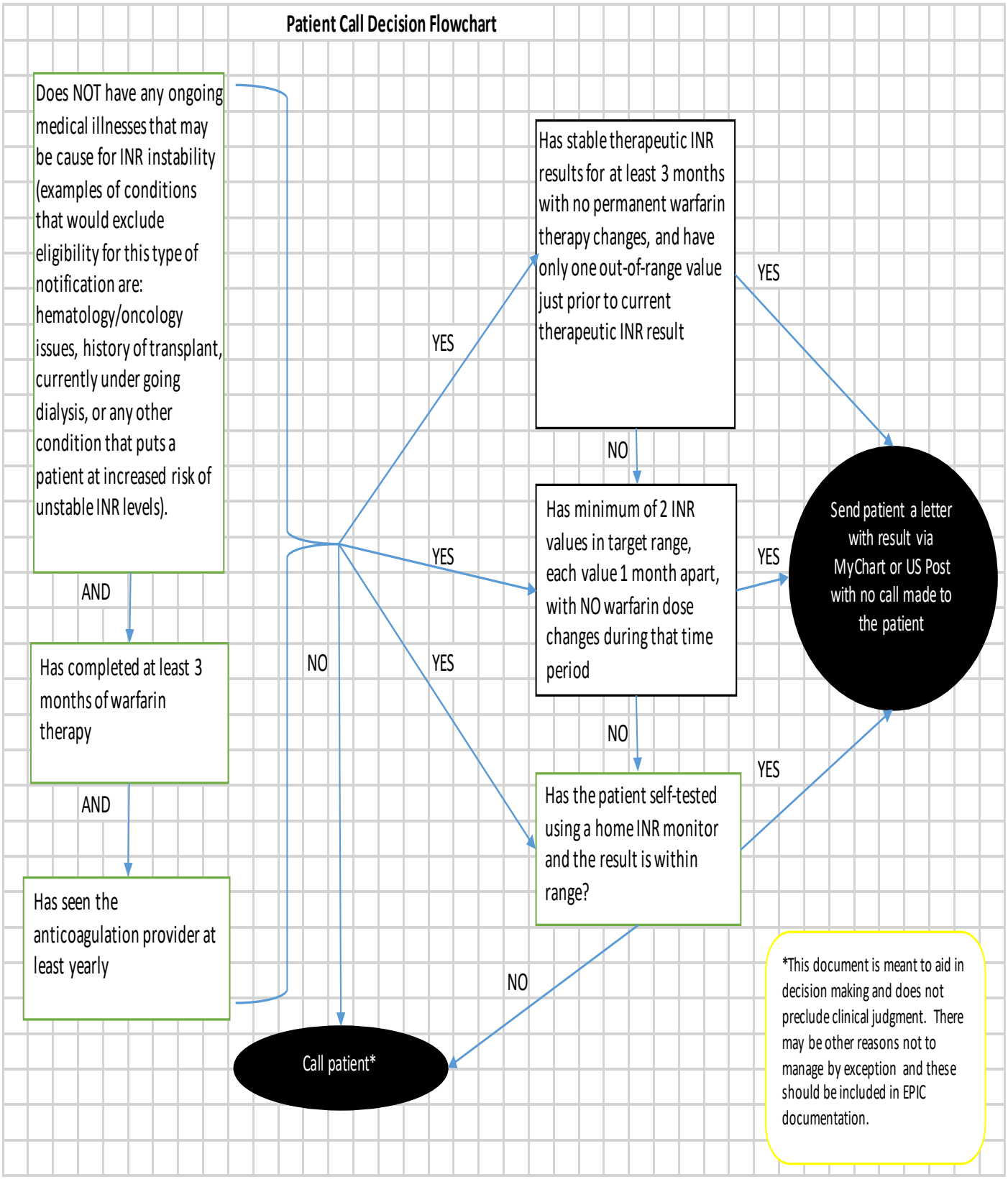
4. Ask patient if they have any upcoming procedures planned/scheduled
5. Advise patient per dosing algorithm
6. Verify that the patient's PT/INR lab order does not expire before their next advised blood draw

Causes of elevated INR to Review:

1. Verify tablets strength & dose
2. Acute illness
3. Diarrhea (prolonged)/Vomiting
4. Decreased food or beverage intake
5. Starting new medications (or stopping medications)
6. Taking other medications including vitamins & other OTC
7. Taking more warfarin than prescribed
8. Eating less vitamin K-rich food
9. Excessive alcohol consumption
10. Starting herbal health products
11. Cranberry or pomegranate juice (controversial)
12. Any change in tablet shape or color?
13. Disease state interactions (CHF, hyperthyroidism)
14. Significant decrease in smoking (e.g., smoking cessation)

Causes of decreased INR to Review:

1. Verify tablets strength & dose
2. Starting new medications (or stopping medications)
3. Taking other medications including vitamins & OTC (e.g., Metamucil)
4. Eating more vitamin K-rich food (e.g., green tea, V8 juice, liver meat,etc)
5. Enteral feedings or supplements (e.g., Ensure, Boost, Glucerna, Jevity,.etc.)
6. Soy-containing foods or drinks
7. Any change in tablet shape or color?
8. Significant increase in physical activity & exercise
9. Significant increase in smoking
10. Any changes in thyroid status (hypothyroidism decreases INR, check TSH)


Patient Call Decision Flowchart
Does NOT have any ongoing medical illnesses that may be cause for INR instability (examples of conditions that would exclude eligibility for this type of notification are: hematology/oncology issues, history of transplant, currently under going dialysis, or any other condition that puts a patient at increased risk of unstable INR levels).
AND
Has completed at least 3 months of warfarin therapy
AND
Has seen the anticoagulation provider at least yearly
NO
YES
Has stable therapeutic INR results for at least 3 months with no permanent warfarin therapy changes, and have only one out-of-range value just prior to current therapeutic INR result
YES
NO
Has minimum of 2 INR values in target range, each value 1 month apart, with NO warfarin dose changes during that time period
YES
NO
Has the patient self-tested using a home INR monitor and the result is within range?
YES
NO
Send patient a letter with result via MyChart or US Post with no call made to the patient
Call patient*
*This document is meant to aid in decision making and does not preclude clinical judgment. There may be other reasons not to manage by exception and these should be included in EPIC documentation.

Patient Enrollment:

A patient will be eligible for enrollment to the anticoagulation clinic provided they meet all of the following criteria:

- A documented need for anticoagulant therapy with an appropriate target INR.
- Presents with one of the following diagnoses for warfarin therapy:
  - Arterial Thrombus (arterial embolism, arterial insufficiency)
  - Atrial Fibrillation (a-flutter)
  - Cardiomyopathy (intra-cardiac thrombus, CHF
  - Coronary Atherosclerosis (aneurysm
  - Hypercoagulable State (antiphospholipid or anticardiolipin antibody) (**warfarin only**)
  - Left Ventricular Assist Device (LVAD) (**warfarin only**)
  - Mechanical Aortic Valve (**warfarin only**)
  - Mechanical Mitral Valve (**warfarin only**)
  - Peripheral Vascular Occlusive Disease
  - Pulmonary Embolism
  - Pulmonary HTN
  - Stroke (cerebral vascular disease, carotid disease, cerebral sinus thrombus)
  - Venous Thromboembolism (PE, DVT of upper or lower extremity)
  - Other Diagnosis - **require approval by one of the physician champions**
- Ability to attend clinic appointments / have blood drawn as instructed.
- Accessible or contact accessible by telephone to facilitate follow-up.
- Patients must be willing to be active participants in their care
- Patient / patient's caregiver should have the capacity to understand the condition and implications of anticoagulation therapy.
- Patient has an HFMG-assigned PCP, Cardiologist, or Heme/Onc physician who has assumed responsibility for the management of the patient's medical/surgical problems and evaluates the patient at least once every 12 months.

Both inpatient house staff and outpatient clinic physicians can refer patients to the anticoagulation clinic provided there is an HFMG senior staff physician to assume responsibility for the patient's anticoagulation. Enrolling physicians will complete the Patient Referral Form found in EPIC under "Meds & Orders" section. In blank field,

physician can enter "anticoag" to open the referral form. Referral forms will be reviewed, and patients will be assigned by an ACS Pharmacist who vets all referrals. Enrolled patients will be entered in an in basket which is assigned to a specific Anticoagulation (ACS) Practitioner. The ACS practitioner will contact the newly enrolled patient for first encounter teaching and follow-up.

Process for division of referrals/staff messages for Pharmacist review:

- Assigned Pharmacist will review (and keep track of) old and new staff messages and new enrollments pending (note need for follow up if still pending from previous assignment).
- Divide the new staff messages and enrollments:
  - Is the patient still IPD?
  - Did a pharmacist review already and has familiarity with the case? (avoid duplicity of effort)
  - Is the case more urgent?
  - Is the case a referral for another department/service?
  - Is it just a quick question or more involved matter?
- Take in account the schedule:
  - If case is more urgent, who is off the next day and may not be able to complete follow up in a timely manner?
  - Who is double-covering or has a very heavy in-basket?
    - All pharmacists working in CB, CR or SR will be assigned referrals.
    - If the number of referrals would give any of the pharmacists in CB, CR or SR more than 2, the overflow will go to the pharmacist(s) working on other in baskets. (i.e. 3 pharmacists covering LVAD inbaskets and there are 7 referrals)
- Further considerations when assigning referrals for vetting:
  - all pharmacists also have other responsibilities besides their in-basket assignments, including (but not limited to):
    - reviewing critical INRs
    - interventions
    - incoming staff messages/patient calls for their patients
    - order review
    - working on the DOAC Dashboard

Inpatient Admission:

Patients' results will be managed by the Ambulatory ACS while out-patient. If the patient is hospitalized INR results will not come into the In Basket Results folder in EPIC. Care of the patient by the ACS staff will resume upon the patient's discharge. While the patient is hospitalized, their

therapy will be followed by the inpatient staff physicians and may include a team member of the Pharmacist-Directed Anticoagulation Service (PDAS).

Hospital Discharge:

Each Anticoagulation Clinic site will run an EPIC Anticoag patient discharge report daily in the morning. Once discharged, the ACS staff will review the patient's discharge instructions for warfarin dose, or changes in health, diet or other medications. ACS staff will adjust the warfarin doses accordingly as necessary and assign the next lab due date per protocol, if not assigned by the inpatient bedside PDAS pharmacist managing the patient prior to discharge.

Patient Disenrollment:

It is the responsibility of patients receiving anticoagulation therapy to be adherent to routine assessment and monitoring appointments to maintain health status and reduce the risk for serious complications of therapy. It is the responsibility of the Anticoagulation practitioners to provide methods to assist patients in complying with follow-up requirements.

Patients, who are considered at risk for complications of anticoagulant therapy due to non-compliance with routine physician assessment, and/or lab monitoring, and/or practitioner recommendations, will be addressed in a standardized fashion and ultimately disenrolled from the Henry Ford Ambulatory Anticoagulation Service if the risks associated with non-compliance outweigh the benefits of therapy. Patients residing in a nursing home, rehabilitation center or assisted living center who are not being monitored by the Henry Ford Ambulatory Anticoagulation Service, will be disenrolled if remaining inpatient for an extended period. It is recognized that there may be extenuating circumstances that require diversion from this policy.

Patients are to undergo routine assessment by their anticoagulation physician of record at least once yearly. Patients on shorter therapy duration (i.e. 3 or 6 months) are to be evaluated by the anticoagulation physician of record prior to scheduled disenrollment. During the course of INR monitoring, when a patient's electronic medical record indicates that the **patient has not been evaluated by his/her anticoagulation physician of record within the past year**, the anticoagulation practitioner will:

- Instruct the patient at the time of the encounter that an appointment must be made with the patient's anticoagulation physician of record
- Include in the patient's letter/calendar that (s)he is due for routine assessment by the anticoagulation physician of record
- Inform the anticoagulation physician of record that the patient is due for an appointment and request that the physician advise whether patient should continue to be monitored by the Ambulatory Anticoagulation Service
- Document ordered continuation of anticoagulation monitoring via continuation referral form (EPIC)

Patients new to HFMG will be required to be seen in the office of the responsible Anticoagulation Physician of record at a scheduled follow-up appointment after hospital discharge; typically, 1 to 2 weeks post discharge. During INR monitoring, when patient's electronic medical record indicates that **the patient has not been evaluated by his/her anticoagulation physician of record with an office visit following hospital discharge**, the anticoagulation practitioner will:

- Instruct the patient at the time of the encounter that an appointment must be made with the patient's anticoagulation physician of record. New HFMG patients will be given 7 days to comply.
- Include in the patient's letter/calendar that (s)he must schedule and keep an appointment with the Anticoagulation Physician of record within the next 7 days.

- If the patient does not comply with the request to schedule and keep an appointment with the anticoagulation physician of record within the 7 days, the anticoagulation practitioner will:
    - Advise the patient that they have 7 additional days with which to schedule and keep an appointment.
    - Include in the patient's letter/calendar that (s)he must schedule and keep an appointment with the Anticoagulation Physician of record within the next 7 days, or face disenrollment.
- If the patient does not comply with the request to schedule and keep an appointment and it has been 30 days or more since hospital discharge, the anticoagulation practitioner will:
    - Inform the anticoagulation physician of record that the patient is due for an appointment and request that the physician advise whether patient should continue to be monitored by the Ambulatory Anticoagulation Service.
- If the Anticoagulation Physician of record deems that the patient should be disenrolled at any point during the first 30 days or more of therapy, the anticoagulation practitioner will:
    - Place a call to the patient informing them that they are being disenrolled from the Ambulatory Anticoagulation Service for non-compliance.
    - Process and mail a modified version of compliance letter #3 via certified mail, return receipt requested, which informs the patient that they are disenrolled from the program and must contact the anticoagulation physician of record for further treatment.
- Submit EPIC "Documentation" note with cc to the responsible anticoagulation physician, and e-mail the anticoagulation physician of record, notifying of disenrollment and details in EPIC.
- Document patient disenrollment in EPIC.
- Block patient from Ambulatory Anticoagulation Service.

When a patient appears as **due for lab monitoring** in the inbox for the **first time**, the anticoagulation practitioner will:

- Place a reminder call to the patient

- Process and mail compliance letter #1, if in the anticoagulation practitioner's judgment, the patient would require a letter for reminder reinforcement or the patient could not be contacted by phone
- Set out the "action date" 7 days
- Place a brief note in an EPIC document regarding patient reminders

When the patient appears as due for lab monitoring for the **second consecutive time**, the anticoagulation practitioner will:

- Place a reminder call to the patient
- Process and mail compliance letter #2
- Notify the anticoagulation physician of record via letter, with copy of patient's compliance letter #2
- Set out the "action date" 10 days
- Place a brief note in an EPIC document regarding steps as described above

When the patient appears as due for lab monitoring for the **third consecutive time**, the anticoagulation practitioner will:

- Place a call to the patient informing them that they are being disenrolled from the Ambulatory Anticoagulation Service for non-compliance
- Process and mail compliance letter #3 via certified mail, return receipt requested, which informs the patient that they are disenrolled from the program and must contact the anticoagulation physician of record for further treatment
- Contact the anticoagulation physician of record
- Send a copy of the patient compliance letter #3 to the anticoagulation physician of record
- Document patient disenrollment ("Discontinue Therapy") in EPIC Anticoag Track in the Anticoag Episode

If a provider requests re-enrollment of a patient that has been disenrolled for non-compliance, the physician will be required to monitor the patient for a minimum of 4 PT/INR results within 6 weeks and provide proof of patient compliance during that time before the patient may be re-enrolled.

When patients have three consecutively **documented incidences of willful non-compliance** with the recommendations of the Anticoagulation Clinic practitioners (including, but not limited to, warfarin dosing recommendations) or display as many acts of belligerence toward an anticoagulation practitioner, they will be disenrolled from the program. In this instance, the anticoagulation practitioner will take the following actions:

- Document each incident, carefully including all facts (not opinion) of the encounter
- Upon the second consecutive incident, contact the patient's anticoagulation physician of record to relay the concerns for patient safety and the need for physician intervention
- Upon the third consecutive incident, follow-up with a free-form letter to the patient indicating that the Anticoagulation Service will no longer follow the patient for reasons previously documented and that a copy of this letter will be sent to the anticoagulation physician of record
- Upon sending a letter to the patient, contact the anticoagulation physician of record and send a copy of the patient letter.

Patients enrolled in the clinic on an anticoagulant may be disenrolled if they cannot be contacted for initialization of management. Every effort should be made to contact the patient. However, if the patient cannot be reached within 2 weeks from referral, and all channels for contact have been exhausted, the responsible anticoagulation physician should be notified and the patient should be disenrolled.

When patients are residing in **skilled nursing, assisted living or rehabilitation facilities**, the patient's anticoagulation will be managed by the facility's house physician staff, if the patient is not being managed by their HFMG anticoagulation physician of record. In this instance the anticoagulation practitioner will follow these steps:

- Inform the patient or patient's contact person of record to contact the anticoagulation clinic when the patient is discharged, or leave a message for the patient to do the same when they return home and patient will not be disenrolled
- Contact the responsible facility physician after a period of 6 weeks, if the patient continues to reside in a skilled nursing, assisted living or rehabilitation facility, **to determine if patient will be discharged**. **If the patient will potentially be discharged within the subsequent 6 weeks**, the responsible physician at the facility should be advised to contact the anticoagulation clinic when the patient has been discharged from the facility and anticoagulation clinic contact information should be provided.
- Inform the anticoagulation physician of record that **patients continuing to reside in a skilled nursing facility, rehabilitation center or assisted living facility indefinitely** will be discharged from the program, but may be re-enrolled by the anticoagulation physician of record after discharge.

Renewal of Patient Referral:

Because patient conditions may change over time, it is recommended that we ensure that physicians review the patient's anticoagulation therapy at least yearly. If the patient is not seen by the responsible anticoagulation physician during the course of a year, then the responsible anticoagulation physician must be contacted to ensure that our service should continue to monitor the patient's anticoagulation therapy under the physician's delegated authority. This also applies if the physician does not document that the patient's anticoagulation therapy has been addressed or reviewed in the past year. The responsible anticoagulation physician should be contacted via TEF following the process outlined in Appendix J.

Role of the Responsible Anticoagulation Physician:

As nurses and pharmacists, we are limited in our scope of practice regarding making medical decisions. For this reason, we work under the

delegated authority of the responsible anticoagulation physician via collaborative agreement. This means that we are allowed to dose anticoagulant medications, make anticoagulant medication dosage adjustments, and order refills and lab draws. However, if a medical decision must be made, the responsible anticoagulation physician must be contacted, as (s)he has the final authority regarding:

- Whether the proceduralist's recommended length of warfarin hold for a scheduled procedure is acceptable for their specific patient
- Whether or not to bridge with enoxaparin
- Verbal order for enoxaparin
- Responsibility for patient enrollment
- DOAC dose changes
- Stopping an anticoagulant

Faxed INR results:

There are occasions when a patient's INR will be drawn outside the HFHS System and processed at an outside lab. On these occasions (i.e. vacationers, temporary residence changes or home care nurse draws) a faxed INR result will be received. These results are promptly entered into EPIC via an "Abstract Encounter" and forwarded to the appropriate Anticoagulation Clinic site pool for the day in which they had been drawn. For example, if a patient had the blood work drawn January 1st, and the result was received January 2nd, the INR result would be entered for January 1st, as that is the draw date.

Once the lab has been entered, the faxed result is treated in the same manner as a result received in the EPIC In Box Results folder. The fax is then bundled with other recent faxes and sent to medical records for scanning into EPIC.

Home INR Testing:

For patients who qualify, at home INR testing may be an option. For the sake of safety and consistency, patients enrolled in the HFHS Ambulatory Anticoagulation Services may obtain a home INR meter from Acelis (formerly known as Alere). However, patients may obtain a home INR monitor from other sources, such as RealTime and mdINR. Patients must have an approved anticoagulation related diagnosis (atrial fibrillation, MVR, or VTE) and have been on warfarin therapy for at least three months.

The home INR monitor company is responsible for delivering the meters to the patients and the patient education regarding use of the meter. Once the patient has been trained, they will test their INR once weekly, up to once monthly, depending on the physician's order. The patient will get the result from the home INR meter and call Acelis's designated telephone number. The patient can use the telephone keypad to enter the INR. Once received, the computer at Acelis will generate an INR results sheet with the patient's information (name, birth date, INR result, date drawn, etc) and fax it to the Anticoagulation Clinic. At that point, the INR result is processed like any other faxed result (see above).

Potential Home INR Monitor limitations:

- May have limitations to their use included in their operating guides and/or package inserts
- Some may not be used for patients with:
    - APS
        - Per CoaguChek XS PT package insert: Anti-phospholipid antibodies (APA) like Lupus antibodies (LA) may falsely prolong coagulation times, i.e. they may cause false-high INR values and false-low Quick values. Where APA are known to be present, a result should be obtained using an APA insensitive laboratory method.
        - Per CoaguSense manual: Liver diseases, congestive heart failure, thyroid dysfunction, Lupus, antiphospholipid antibody syndrome (APS) and other diseases or conditions can affect the action of oral blood thinners and the INR value.
        - The literature primarily supports the exclusion of fingerstick point-of-care testing in patients with APS (Perry, Samsa, & Ortel, 2005)

- Anemia
    - Per CoaguCheck XS PT package insert: Hematocrit ranges between 25-55 % (nml 40-54% for men, 36-48% for women) do not significantly affect test results.
    - Per CoaguSense: not sensitive to HGB or HCT levels
- Heparin or LMWH (enoxaparin) within the last 12 – 24 hours
    - Per CoaguCheck XS PT package insert: No significant effect on test results for Heparin concentrations up to 0.8 U/mL (therapeutic 0.3 – 0.7 U/mL) or Low molecular weight heparins (LMWH) up to 2 IU anti-factor Xa activity/mL (therapeutic 0.5 -1.2 IU/mL)
    - Per CoaguSense manual: This test system is not recommended for patients who have recently taken or are currently taking any type of Heparin anticoagulants.
- Direct thrombin inhibitors
    - Per CoaguCheck XS PT package insert: The CoaguChek XS System should not be used for patients being treated with any direct thrombin inhibitors, including Hirudin, Lepirudin, Bivalirudin and Argatroban.
- DOACs
    - Per CoaguCheck XS PT package insert: INR results from patients treated with Direct Oral Anticoagulants (DOACs) e.g. rivaroxaban, apixaban, edoxaban, betrixaban and dabigatran may be influenced and should be confirmed with an alternative laboratory method.
    - Per CoaguSense manual: The system should also not be used to monitor patients on direct oral anticoagulants (DOACs) including Factor Xa and Direct Thrombin inhibitors.
- FDA.gov states that other conditions that may affect some meters more that others include:
    - Certain medications, for example some antibiotics
    - Environment: humidity, altitude and temperature

- When in doubt, ask the patient to check their operating manual or package insert

Procedure for Critical INR results & Lovenox renal dose adjustments:

When a patient with an INR result of > 5 but $\leq$ 9.99 is identified and patient has no bleeding, the nurse will call the pharmacist on duty (refer to pharmacist schedule) and leave a message with patient's name and MRN for pharmacist to do further evaluation regarding the critical INR result. The nurse will need to contact the patient first and enter a preliminary note in Workflow Internal Notes. The pharmacist will review such notes and contact the anticoagulation clinic nurse for further discussion about the

patient. Discussion will focus on possible causes for the elevated INR (e.g., drug-drug, drug-disease state interaction). Once a plan of care is finalized, the nurse will enter a final anticoagulation clinic note in EPIC, followed by a pharmacist EPIC note. This pharmacist's EPIC note will be sent to the responsible anticoagulation physician so the responsible anticoagulation physicians will be notified of all critical INRs and the rationale behind actions taken. In this manner, a record will then be readily available for any healthcare provider who may need it, as well.

Similarly, when a Lovenox patient has a calculated creatinine clearance of < 30 ml/min, the anticoagulation clinic nurse will leave a message for the pharmacist on duty (refer to pharmacist schedule) and leave the patient's name and MRN for pharmacist to verify the creatinine clearance calculation and final Lovenox dosing recommendation. The pharmacist will calculate patient's creatinine clearance and contact the anticoagulation clinic nurse for final recommendation for Lovenox dose. Once a plan of care is finalized, the nurse will enter a final anticoagulation clinic note in EPIC, followed by a pharmacist EPIC note that will also be sent to the responsible anticoagulation physician as an update.

In cases where creatinine clearance is slightly above 30 ml/min, the anticoagulation nurse must call the anticoagulation physician for a final approval of Lovenox renal dose.

Procedure for antithrombotic therapy in patients with AF treated with oral anticoagulation undergoing percutaneous coronary intervention:

Patients who undergo percutaneous coronary intervention (PCI) with stent placement are routinely started on antiplatelet therapy. For patients on oral anticoagulant therapy (OAC), this can increase the risk of bleeding, particularly in the GI tract. The Ambulatory Anticoagulation Services has established guidelines to ensure patient safety while on Triple Oral Antithrombotic Therapy (TOAT).

Below is a summary of the 2021 North American expert consensus-derived recommendations on the antithrombotic management of patients with atrial fibrillation treated with OAC undergoing PCI as presented by the American Heart Association. These are in line with the 2020 Joint European Consensus Document, as well.

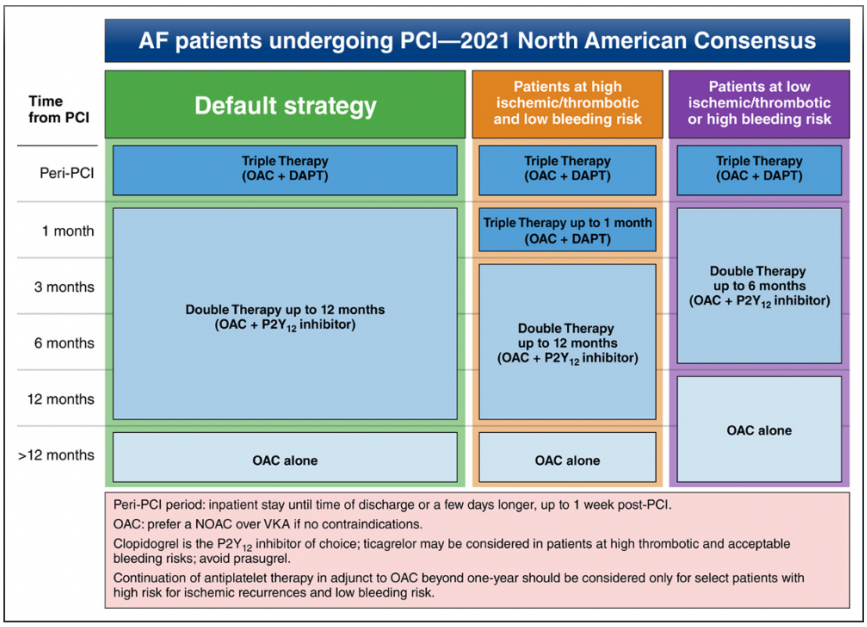


Figure 2. Management of antiplatelet therapy in patients with atrial fibrillation (AF) undergoing percutaneous coronary intervention (PCI) treated with an oral anticoagulant: 2018 North American Consensus Update. A double-therapy regimen, consisting of oral anticoagulant therapy (OAC) plus a $P2Y_{12}$ inhibitor, should be considered for most patients immediately after the peri-PCI period (Default Strategy). Aspirin should be used during the peri-PCI period, defined as inpatient stay until time of discharge, generally 1 to 2 days after PCI, and in some patients continued for 1 week after PCI. A non–vitamin K antagonist oral anticoagulant (NOAC) should be preferred over a vitamin K antagonist (VKA) unless contraindicated. Clopidogrel is the $P2Y_{12}$ inhibitor of choice; ticagrelor may be an alternative in patients with high thrombotic and acceptable bleeding risk; prasugrel should be avoided. It is reasonable to continue aspirin for up to 1 month after PCI (ie, triple therapy) in patients at high thrombotic risk and who have an acceptable risk of bleeding. Extending aspirin therapy beyond 1 month after PCI is not recommended. $P2Y_{12}$-inhibiting therapy should be discontinued at 1 year in most patients; earlier discontinuation (eg, 6 months) can be considered in patients at low ischemic or high bleeding risk; continuation of antiplatelet therapy beyond 1 year should be considered only in select patients with high risk for ischemic recurrences and low bleeding risk. DAPT indicates dual antiplatelet therapy.

Dominick J. Angiolillo MD, PhD et al. Antithrombotic Therapy in Patients with Atrial Fibrillation Treated with Oral Anticoagulation Undergoing Percutaneous Coronary Intervention, A North American Perspective – 2021 Update. Circulation 2021;143(6):583-596

Henry Ford Health System Cardiologists currently use the following protocol for antiplatelet therapy in patients with atrial fibrillation undergoing PCI with OAC:

1) For patients with ACS and/or low bleeding risk:
   a) 1 to 3 months TOAT with ASA + Clopidogrel + DOAC or warfarin
   b) At the end of treatment period, discontinue ASA
2) For patients with ACS and high bleeding risk:
   a) TOAT with ASA + Clopidogrel + DOAC or warfarin peri-PCI only **OR**
   b) 1 to 4 weeks TOAT with ASA + Clopidogrel + DOAC or warfarin, at the end of the treatment period, discontinue ASA
3) For all warfarin patients on TOAT, lower INR range to 2.0 – 2.5 during treatment period

When managing a patient on OAC plus antiplatelet therapy, AC Practitioners should:

1) Review the patient's antiplatelet therapy dosing to ensure that patients are prescribed lowest doses possible.
   a) Aspirin 75 mg to 100 mg daily (i.e. 81 mg)
   b) Clopidogrel 75 mg daily
   c) DOACs (at established stroke prevention doses, unless lower doses due to renal adjustment or have been specifically tested in TOAT)
      i) Rivaroxaban 20 mg daily
      ii) Apixaban 5 mg twice daily
      iii) Dabigatran 150 mg twice daily
      iv) Edoxaban 60 mg daily
2) Review medical record for proton-pump inhibitor (PPI) order and recommend this therapy to the anticoagulation physician of record and/or cardiologist if not ordered
3) Note the following in EPIC Specialty Comments:
   a) Date of PCI procedure
   b) Antiplatelet therapy and dose
   c) Need for more frequent INR monitoring
   d) Date that aspirin should be discontinued
4) Exercise due diligence in ensuring that INR results at the higher end of the patient's therapeutic range are proactively addressed by adjusting warfarin therapy accordingly.
5) Schedule the patient to return for INR check weekly, if not sooner, during the first 4 weeks of triple therapy. Patients should not be on extended interval INR monitoring during triple therapy management.
6) After completion of requisite period of TOAT, the ACS Practitioner will contact the patient's cardiologist and responsible anticoagulation physician to ensure discontinuation of aspirin

7) Responsible anticoagulation physician or cardiologist should be the one to document instructions for discontinuation of antiplatelet therapy in EPIC**, unless clearly** stated in a communication to the Anticoagulation Clinic.
8) Relay patient reported signs/symptoms of bleeding to responsible anticoagulation physician of record and cardiologist. Antithrombotic therapy changes should be communicated to the anticoagulation physician of record.
9) Document all encounters in patient's electronic medical record

ACE Rapid Resource: Antithrombotic Management of Patients Receiving Oral Anticoagulation Post-Acute Coronary Syndrome (ACS) or Post-Percutaneous Coronary Intervention (PCI)

Pregnancy and Breastfeeding

Atrial Fibrillation:

For women receiving oral anticoagulant therapy for prevention of stroke/TE in Atrial Fibrillation who become pregnant, CHEST guidelines suggest discontinuation of the warfarin between weeks 6 and 12 and replacement with LMWH twice daily (with dose adjustment according to weight and target anti-Xa level 4-6 hours post-dose 0.8-1.2 U/ml). If the patient is switched back to an oral anticoagulant after 12 weeks, the oral anticoagulant should be replaced by adjusted dose LMWH (target anti-Xa level 4 to 6 hours post-dose 0.8-1.2 U/ml) in the 36th week of gestation.

For women on treatment with long-term vitamin K antagonists who are attempting pregnancy and are candidates for LMWH substitution, CHEST guidelines suggest performing frequent pregnancy tests and use LMWH instead of VKA when pregnancy is achieved, rather than switching to LMWH while attempting pregnancy.

For pregnant or breastfeeding women, CHEST guidelines suggest avoiding the use of DOACs. For lactating women using warfarin or UFH who wish to breastfeed, CHEST guidelines suggest continuing the use of warfarin, LMWH or UFH.

Lipp G, et al. Antithrombotic Therapy for Atrial Fibrillation CHEST Guideline and Expert Panel Report. CHEST 2018; 154(5):1121-1201

Venous Thromboembolism (VTE):

Antithrombotic therapy is recommended for patients who are pregnant and experience acute VTE. Low Molecular Weight Heparin (LMWH) is recommended over unfractionated heparin (UFH) or any oral anticoagulant. Pregnant women may receive either once or twice daily LMWH dosing and routine monitoring of anti-FXa levels to guide dosing is not suggested. For women with combined thrombophilia or who are homozygous for the Factor V Leiden mutation or prothrombin gene mutation, regardless of family history, postpartum antithrombotic prophylaxis is suggested.

Women who are diagnosed with acute VTE and are breastfeeding are recommended to use UFH, LMWH, warfarin, fondaparinux or danaparoid. The agents with greatest experience in this patient population and the best evidence for safety are warfarin, acenocoumarol and LMWH. Direct Oral Anticoagulants (DOACs) are not recommended.

Bates S, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: venous thromboembolism in the context of pregnancy. Blood Advances 2018 2:3317-3359; doi: https://doi.org/10.1182/blodavances.2018024802

Anticoagulationtoolkit.org; MAQI2 accessed 4.29.20

Procedure for managing patients discharged on fondaparinux (Arixtra):

Occasionally, patients may be discharged from the hospital on Arixtra (fondaparinux) because they cannot take Lovenox (enoxaparin). This agent may only be managed by the HFHS Ambulatory Anticoagulation Services for the purpose of bridging patients to therapeutic on warfarin for a new DVT or PE, or for those patients previously on warfarin upon hospital discharge status post procedure. The Ambulatory Anticoagulation Services will not be managing patients on Fondaparinux for the purpose of bridging for warfarin interruption. When a patient is using this agent until therapeutic on warfarin, warfarin management in regard to frequency of INR and dosing is the same as for patients becoming therapeutic on Lovenox.

Dosing Considerations:

- The patient's total (actual) body weight should be used to determine dose required.
- Use fondaparinux with caution in elderly patients. Monitor these patients closely for signs and symptoms of bleeding.
- Calculate the patient's creatinine clearance to ensure accuracy. If the patient's creatinine clearance is less than 30 ml/min, fondaparinux is contraindicated.
- Use caution in the treatment of DVT or PE in patients weighing less than 50 kg. Monitor these patients closely for signs and symptoms of bleeding, as their clearance is decreased.
- The half-life (t ½) of fondaparinux is 17 to 21 hours. After discontinuation of fondaparinux, its anticoagulant effects may persist for 2 to 4 days in patients with normal renal function and even longer in those with renal impairment.
- Fondaparinux is recommended for Acute Coronary Syndromes and prophylaxis of Venousthromboembolism in patients with prior confirmed Heparin Inducted Thrombocytopenia (HIT) – though Thrombocytopenia (HIT) can occur with fondaparinux administration.

Dosing (should be continued for at least 5 days until INR of 2-3 with warfarin):

- Adults weight < 50 kg = 5 mg SC once daily

  weight 50 to 100 kg = 7.5 mg SC once daily
  weight > 100 kg = 10 mg SC once daily (Maximum recommended dose)

- Renal impairment: CrCl > 50 ml/min – no dosage adjustment necessary
  CrCl = 30 – 50 ml/min: Use with caution in this setting; no specific dosing guidelines available

  CrCl $\leq$ 30 ml/min: CONTRAINDICATED

Monitoring:

Effectiveness

Parameter	Range	Frequency
PT/INR (during warfarin bridging)	2.0 to 3.0	Baseline then every 3 to 5 days
Thromboembolism	No clot formation	Daily (patient self-evaluation for signs/symptoms of clotting) Review with patient every 3 to 5 days at telephone encounter.

Toxicity

Parameter	Range	Frequency
CrCl	$\leq$ 30 ml/min	Baseline
Hemorrhage	Hematochezia, hematuria, epistaxis, hematemesis, hematoma	Daily (patient self-evaluation for signs/symptoms of bleeding) Review with patient every 3 to 5 days at telephone encounter.
Platelet Count	$\leq$ 100 K/uL or drop $\geq$ 50% from baseline	Baseline, then every 3 to 5 days with INR

Precautions specific to the Henry Ford Health System:

- When neuraxial anesthesia (epidural/spinal anesthesia) or spinal puncture is employed, notify acute pain service prior to initiation of fondaparinux. Patients anticoagulated or scheduled to be anticoagulated with fondaparinux for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis. The risk of these events is increased by the use of indwelling epidural cathethers for administration of analgesia or by the concomitant use of drugs affecting hemostasis such as non-steroidal anti-inflammatory drugs (NSAIDS), platelet inhibitors or other anticoagulants. The risk also appears to be increased by traumatic or repeated epidural or spinal puncture. Patients should be frequently monitored for signs and symptoms of neurological impairment. If neurologic compromise is noted, urgent treatment is necessary.

- It is recommended that surgical providers consult hematology/oncology for discussion regarding alternative antithrombotic therapies for patients who are

unable to use a low molecular weight heparin (LMWH), such as enoxaparin, for peri-procedural bridge therapy.

Reversal of Anticoagulation:

Click link below for latest anticoagulation reversal guidelines at Henry Ford Health:

Tier 1: Anticoagulation Reversal Guidelines

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Appendix A

Selected Warfarin-Herbal Product Interactions

Source: *Natural Medicines – Comprehensive Database*

Herbal Product	Interaction Rating	Details
Alfalfa	Major	Alfalfa contains large amount of vitamin K. Concomitant use can reduce the anticoagulant activity of warfarin.
Aloe	Moderate	Aloe latex has stimulant laxative effects. In some people aloe latex can cause diarrhea. Diarrhea can increase the effects of warfarin, increase international normalized ratio (INR), and increase the risk of bleeding. Advise patients who take warfarin not to take excessive amounts of aloe vera.
Beer	Major	Acute alcohol intoxication and beer hops can decrease metabolism and increase effects of warfarin (Coumadin). In contrast, chronic intoxication can induce metabolism of warfarin, reducing therapeutic effectiveness
Bishop's weed	Moderate	There is some concern that bishop's weed might have additive effects with anticoagulant or antiplatelet drugs and possibly increases the risk of bleeding. The bergapten constituent of bishop's weed has antiplatelet effects.
Bladderwrack	Moderate	Bladderwrack seems to have anticoagulant effects. Theoretically, taking bladderwrack with antiplatelet or anticoagulant drugs might increase the risk of bruising and bleeding.
Capsicum	Moderate	Theoretically, capsicum might increase the effects and adverse effects of antiplatelet drugs
Chinese Black Fungus (AKA Cloud Ear, Tree Ear)	Major	Known as a "natural blood thinner" and has been compared to warfarin. Purported to decrease clot formation by decreasing platelet aggregation and protecting blood vessel elasticity. Also said to reduce cholesterol. Patients on warfarin or other anticoagulants should be advised to avoid this mushroom and any foods that may contain it, such as Chinese hot and sour soup, as it may cause an increase in the INR and risk for bleeding.
Coenzyme Q-10	Moderate	Concomitant use might reduce the anticoagulation effects of warfarin. Coenzyme Q-10 is chemically similar to menaquinone and might have vitamin K-like procoagulant effects. Four cases of decreased warfarin efficacy thought to be due to coenzyme Q-10 have been reported. However, there is some preliminary clinical research that suggests coenzyme Q-10 might not significantly decrease the effects of warfarin in patients that have a stable INR. Closely monitor patients taking warfarin and coenzyme Q-10. Dose adjustment may be necessary.
Cranberry	Moderate	There is contradictory evidence about the effect of drinking cranberry juice on warfarin. Case reports have linked cranberry juice consumption to increases in the international normalized ratio (INR) in patients taking warfarin, resulting in severe spontaneous bleeding and excessive post-surgical bleeding. Daily consumption of cranberry sauce for one week has also been linked to an increase in INR in one case report. In a small study in healthy young men, two weeks of treatment with cranberry capsules, equivalent to 57 grams of fruit daily, produced a 30% increase in the area under the INR-time curve after a single 25 mg dose of warfarin. However, a clinical study in patients stable on warfarin reported that drinking cranberry juice 250 mL daily for 7 days does not significantly increase INR. Researchers speculated that flavonoids in cranberry might inhibit the cytochrome P450 2C9 (CYP2C9) isoenzyme, which could reduce the metabolism of warfarin and increase the anticoagulant effect. However, contradictory pharmacokinetic research shows that drinking cranberry juice 240 mL daily or 600 mL daily does not significantly affect CYP2C9 in humans. It has also been

Herbal Product	Interaction Rating	Details
		suggested that cranberry increases the sensitivity of clotting factors to the effects of warfarin, but this needs further clarification.
Danshen	Major	Concomitant use might increase the risk of bleeding due to decreased platelet aggregation. Danshen has been reported to have antithrombotic effects; avoid concomitant use. There have been several case reports of increased international normalized ratio (INR) after concomitant use of danshen and warfarin. Elevations in INR have occurred as early as 3-5 days after start of danshen. Danshen might increase the rate of absorption and decrease the elimination rate of warfarin. Avoid concomitant use.
Devil's claw	Moderate	Purpura has occurred in a patient taking warfarin and devil's claw concurrently, suggesting over-anticoagulation. Devil's claw should be avoided or used cautiously in patients taking warfarin. Warfarin dose adjustments may be necessary.
Dong Quai	Major	Concomitant use increases the anticoagulant effects of warfarin and the risk of bleeding. In one case, after 4 weeks of dong quai 565 mg once or twice daily, INR increased to 4.9. INR normalized 4 weeks after discontinuation of dong quai. Dong quai is thought to inhibit platelet activation and aggregation
Echinacea	Moderate	Echinacea appears to inhibit CYP1A2 enzymes in humans. Theoretically, echinacea might increase levels of drugs metabolized by CYP1A2.
Evening primrose	Major	Evening primrose oil, which contains gamma-linolenic acid (GLA), could have anticoagulant effects. Theoretically, taking evening primrose oil with other anticoagulant or antiplatelet drugs might increase the risk of bruising and bleeding.
Feverfew	Moderate	Some evidence suggests that feverfew may inhibit platelet aggregation. However, this has not been demonstrated in humans. Theoretically, feverfew might have additive effects and increase the risk of bleeding when used with these drugs.
Flaxseed	Moderate	There is some evidence that the oil contained in flaxseed can decrease platelet aggregation. Theoretically, using flaxseed oil in combination with anticoagulant or antiplatelet drugs might have additive effects and increase the risk of bleeding.
Flaxseed oil	Moderate	There is some evidence that flaxseed oil might decrease platelet aggregation and increase bleeding time. Theoretically, using flaxseed oil in combination with anticoagulant or antiplatelet drugs might have additive effects and increase the risk of bleeding.
Garlic	Moderate	Garlic might enhance the effects of warfarin (Coumadin) as measured by the International Normalized Ratio (INR). Theoretically, garlic might also enhance the effects and adverse effects of other anticoagulant and antiplatelet drugs
Ginger	Moderate	Preliminary evidence suggests that ginger might inhibit thromboxane synthetase and decrease platelet aggregation. There is one case report that ginger increases the INR when taken with phenprocoumon, which has similar pharmacological effects as warfarin. However, research in healthy people suggests that ginger has no effect on INR, or the pharmacokinetics or pharmacodynamics of warfarin. Until more is known, monitor INRs closely in patients taking significant amounts of ginger.
Ginko	Major	Ginkgo leaf might increase the anticoagulant effects of warfarin and risk of bleeding. Ginkgo is thought to have antiplatelet effects and might have additive effects when used with warfarin. There is also some evidence that ginkgo leaf extract can inhibit cytochrome P450 2C9, an enzyme that metabolizes warfarin. This could result in increased warfarin levels. However, research in healthy people suggests that ginkgo has no effect on INR, or the pharmacokinetics or

Herbal Product	Interaction Rating	Details
		pharmacodynamics of warfarin. There is also some preliminary clinical research that suggests ginkgo might not significantly increase the effects of warfarin in patients that have a stable INR; however, these contradictory findings are in small-scale, short-term studies that may not have the power to detect a small or moderate effect on bleeding risk. Until more is known, monitor INRs closely in patients taking ginkgo.
Ginseng	Major	American ginseng can decrease the effectiveness of warfarin therapy. Healthy patients receiving warfarin 5 mg daily, who also take American ginseng 1 gram twice daily, seem to have a significantly reduced international normalized ratio (INR)
Glucosamine	Major	Taking glucosamine alone or in combination with chondroitin might increase the anticoagulant effects of warfarin (Coumadin) and increase the risk of bruising and bleeding. In one case, a 71 year-old man taking warfarin had his international normalized ratio (INR) increase from 2.3 to 4.7 after increasing the dose of a glucosamine-chondroitin supplement from glucosamine hydrochloride 500 mg and chondroitin sulfate 400 mg to glucosamine hydrochloride 1500 mg and chondroitin sulfate 1200 mg daily. In another case, very high-dose glucosamine (3000 mg/day) plus high-dose chondroitin sulfate (2400 mg/day) combined with warfarin resulted in a significantly increased INR. Additionally, 20 voluntary case reports to the U.S. Food & Drug Administration (FDA) have linked glucosamine plus chondroitin with increased INR, bruising, and bleeding events in patients who were also taking warfarin. There have also been 20 additional case reports to the World Health Organization (WHO) that link glucosamine alone to increased INR in patients taking warfarin. Chondroitin is a small component of a heparinoid and might have weak anticoagulant activity. Glucosamine is also a small component of heparin, but is not thought to have anticoagulant activity; however, preliminary animal model research suggests that it might have antiplatelet activity. Patients taking warfarin should be advised to avoid or use glucosamine cautiously.
Licorice	Major	Licorice seems to increase metabolism and decrease levels of warfarin in animal models. This is likely due to induction of cytochrome P450 2C9 (CYP2C9) metabolism by licorice
Melatonin	Moderate	There are isolated case reports of minor bleeding and decreased prothrombin **activity** (i.e., a rise in INR) in people taking melatonin with warfarin (Coumadin). The mechanism, if any, of this interaction is unknown. Theoretically, melatonin might increase the effect of anticoagulant or antiplatelet drugs.
Peppermint	Moderate	There's preliminary evidence that peppermint oil might inhibit cytochrome P450 2C19 (CYP2C19). So far, this interaction has not been reported in humans. However, watch for an increase in the levels of drugs metabolized by CYP2C19 in patients taking peppermint oil.
Policosanol	Major	Policosanol can inhibit platelet aggregation. Theoretically, taking policosanol with other antiplatelet or anticoagulant drugs might increase the risk of bruising and bleeding.
Red clover	Moderate	There's preliminary evidence that red clover might inhibit cytochrome P450 2C9 (CYP2C9). So far, this interaction has not been reported in humans. However, watch for an increase in the levels of drugs metabolized by CYP2C9 in patients taking red clover.
Resveratrol	Moderate	Resveratrol seems to have antiplatelet effects. Theoretically, taking resveratrol with other antiplatelet or anticoagulant drugs might increase the risk of bruising and bleeding. Resveratrol may inhibit CYP-3A4.

Herbal Product	Interaction Rating	Details
Saw palmetto	Moderate	Theoretically, saw palmetto might increase the risk of bleeding when used concomitantly with these agents. Saw palmetto is reported to prolong bleeding time.
St. John's wort	Major	St. John's wort can decrease the therapeutic effects of warfarin. Taking St. John's wort significantly increases clearance of warfarin, including both the R-isomer and S-isomer of warfarin. This suggests that St. John's wort induces CYP1A2 and CYP3A4, which metabolize R-warfarin and CYP2C9, which metabolizes S-warfarin. St. John's wort can also significantly decrease International Normalized Ratio (INR) in people taking warfarin. In addition, warfarin physically interacts with hypericin and pseudohypericin, active constituents of St. John's wort. When the dried extract is mixed with warfarin in an aqueous medium, up to 30% of warfarin is bound to particles, reducing its absorption. Taking warfarin at the same time as St. John's wort might reduce warfarin bioavailability.
Turmeric	Moderate	Concomitant use of turmeric with these drugs might increase the risk of bleeding due to decreased platelet aggregation. Turmeric has been reported to have antiplatelet effects.
Vitamin E	Moderate	Use of more than 400 IU of vitamin E per day with warfarin might prolong prothrombin time (PT), INR, and increase the risk of bleeding, due to interference with production of vitamin K-dependent clotting factors. At a dose of 1000 IU per day, vitamin E can antagonize vitamin K dependent clotting factors even in people not taking warfarin. The risk for vitamin E interaction with warfarin is greater in people who are already deficient in vitamin K. Limited clinical evidence suggests that doses up to 1200 IU daily may be used safely by patients taking warfarin, but this may not be applicable in all patient populations. Monitor INR closely in patients taking warfarin who start vitamin E in doses of 400 IU or more.
Willow Bark	Major	Concomitant use theoretically might increase the risk of bleeding due to decreased platelet aggregation. Willow bark has antiplatelet effects, but less so than aspirin.
Wintergreen	Major	Concomitant use of topical wintergreen oil-containing products and warfarin can increase INR and bleeding risk due to systemic absorption of the methyl salicylate contained in wintergreen oil. Topical analgesic gels, lotions, creams, ointments, liniments, and sprays can contain up to 55% methyl salicylate.

Appendix B
ANTICOAGULATION CLINIC ORIENTATION CHECKLIST

Week 1 – Day 1

A. Physical Set-up of clinic:
   - Front desk
   - Locate fire extinguishers
   - Locate exits
   - Locate restrooms
   - Locate unit supplies
   - Locate printer

B. Check Access
   - EPIC
   - Webex
   - Outlook
     - Own e-mail
     - Group e-mail (HFHSAACS@hfhs.org)
   - Shared drive
   - OneHenry
     - PolicyStat

C. Review Anticoagulation Services Training Manual
   - Purpose
   - Where to find most commonly used information
   - Where to keep a copy for quick reference
   - Frequency of update and where information in manual comes from

D. How to access to physicians
   - E-mail
   - Mobile phone #s
   - Halo
   - Electronic Telephone Encounter Forms (eTEF)

E. Review clinic process – shadowing preceptor
   - Documentation
   - Lab orders
   - Results
   - Overdue INR Results
   - Online Drug/Disease state Resources
   - Monthly/Bi-annual ACS meetings
     - Share meeting schedule

Week 1 – Day 2

A. Review clinic process – shadowing preceptor
    - Processing regular INR results
    - Faxes
    - Enrollments
    - Lovenox (enoxaparin) Bridging
    - Message returns
    - DOAC Dashboard

Week 2

A. Continuation of week 1

B. Review of clinic process
    - Process regular INR results
    - DOAC Dashboard
    - Discharge report

C. Coordinate warfarin dose for procedures
    - Lovenox (enoxaparin) bridging procedures

Week 3

A. Continuation of weeks 1-2

B. Review of clinic process
    - Process high INR results
    - Prescription ordering
    - Entering faxed results into EHR

Week 4

A. Continuation of weeks 1-3

B. Review of clinic process
    - Process urgent results
    - Enrollment processing (pharmacist)
    - VTE TOC (pharmacist)
    - LVAD monitoring (pharmacist)

Week 5

A. Continuation of weeks 1-4

B. Review of clinic process
    - Process urgent results
    - Discharges
    - DOAC Dashboard assignments (pharmacist)

Weeks 7-12

A. Continuation of previous weeks, DOAC Management training, identify areas for continued education

B. Take competency exam

APPENDIX C

Job Descriptions

Position title: Physician Champion (AC Co-Medical Directors, AC Research & Education Advisors)
Department: Ambulatory Anticoagulation Service
Reports to: Ambulatory Anticoagulation Service Medical Co-Directors
General Summary:
The Physician Champion acts as a medical resource for the Ambulatory Anticoagulation Service practitioners, providing guidance and assistance when needed during the usual course of patient care. It has been estimated that the clinic requires one physician champion per 800 patients enrolled in the clinic. The anticipated time an anticoagulation physician is expected to spend on anticoagulation service duties is 40 hours. Ambulatory Anticoagulation Service Medical Co-Directors are considered physician champions and are expected to adhere to the duties as described below.
Principle Duties and Responsibilities:

1. Provides patient anticoagulation management when the Anticoagulation physician of record is unavailable and/or unable to provide such therapy decisions.
2. Answers practitioner questions regarding patient bridging therapy.
3. Available to see patients in scheduled office visits in order to make decisions regarding bridging therapy.
4. Attends the majority of CORE Committee meetings.
5. Attends quarterly staff meetings as possible. As 1 to 2 medical providers should be in attendance at each meeting, the physician champion may alternate or share this responsibility with other physician champions.
6. Moderates 1 or 2 staff monthly teleconferences and/or bi-annual staff meetings per year.
7. Attends the yearly HFHS/DMC-sponsored Antithrombotic Symposium.
8. Familiar with CHEST guidelines and is up-to-date with most recent recommendations.
9. Attends (as encouraged) national meetings related to antithrombotic therapies, such as the Anticoagulation Forum meetings held bi-yearly.
10. Those physicians who are Medical Co-Directors would also be expected to:
    a. Chair the quarterly staff meetings
    b. Chare the CORE Committee meetings
    c. Assume responsibility for overseeing the health care providers who actually manage patients' anticoagulation therapy.
    d. Maintain knowledge level as system expert
    e. Work closely with other departments/regions as advocates for the Ambulatory Anticoagulation Service
    f. Maintain availability for patient anticoagulation management when the anticoagulation physician of record is not available and/or not able to make an anticoagulation related decision.

Compensation:

1. Time off for Annual HFHS/ DMC Antithrombotic Symposium, for which the fee will be waived and the meeting will not count toward the yearly CME limit.
2. Time off with pay to attend a National meeting to increase knowledge base, which does not count toward the eight non-participant days.

Position title: Pharmacist – Anticoagulation Clinic
Department: Ambulatory Anticoagulation Services
Reports to: Area manager
General Summary:
The Pharmacist assumes responsibility for the day-to-day comprehensive, patient-oriented ambulatory anticoagulation services provided on his/her shift. This individual is responsible for the assessment of patients, evaluation/adjustment of anticoagulation/antithrombotic therapy per protocol and interpretation of laboratory results as they are related to anticoagulants/antithrombotics. The Pharmacist works under the general supervision of the Manager for the Ambulatory Anticoagulation Services. This individual assists the Manager in identifying problems, which exist in his/her assigned area of practice and cooperates in the resolution of these problems. The Pharmacist participates in training pharmacy students in anticoagulation management. This individual facilitates the quality improvement process, staff training, policies, procedures and overall operations of the Anticoagulation Clinic.
Principal Duties and Responsibilities:

1. Identifies and monitors the pharmaceutical needs of the patients.
2. Appropriately provides patient counseling regarding the proper use of their medications, including but not limited to anticoagulants.
3. Demonstrates ability to effectively manage anticoagulation/antithrombotic therapies. Contributes to protocols for anticoagulation management, computer based records keeping, communication, and policies and procedures ensuring accurate PT/INR test results.
4. Demonstrates expertise in clinical assessment, planning intervention and evaluation of patients in the anticoagulation clinic, therefore has specialized knowledge necessary to assist other anticoagulation clinic practitioners with patient care decisions.
5. Demonstrates competence in technical aspects of PT/INR testing and obtaining other indicated laboratory samples.
6. Demonstrates competence in maintaining a safe environment for staff and patients.
7. Maintains the complete anticoagulation record in the electronic medical record (EPIC). Demonstrates competence in appropriate documentation.
8. Actively seeks to establish/maintain positive working relationships with staff, physicians and management.
9. Provides continuing education for staff, physicians, and management from knowledge base, communicating current trends in anticoagulation.
10. Provides orientation and training to new staff in regard to anticoagulation management and proper documentation.
11. Participates in training of pharmacy students and residents.
12. Contributes to quality improvement process by monitoring patient clinical progress, clotting and hemorrhagic events and patient management trends.
13. Contributes to ongoing improvement, cost control and quality measures.
14. Participates in professional development activities.
15. Attends required meetings and serves on designated committees as requested.

Knowledge, Skills and Abilities Required:

1. Must be a graduate of an accredited School of Pharmacy.
2. Must be licensed to practice pharmacy in the State of Michigan.
3. He/she should demonstrate acumen in oral and written communication skills which enable him/her to contribute effectively in the dissemination of drug information to all levels of health personnel in the system.
4. Must demonstrate knowledge of managed care.
5. Displays knowledge and understanding of the current guidelines for managing anticoagulation, associated risks and patient assessment.
6. Ability to react calmly and effectively in emergency situations.
7. Ability to establish and maintain effective working relationships with patients, clinic and medical staff.

8. Ability to contribute to educational needs of patients, families and associated health professionals within anticoagulation services.
9. Must demonstrate the ability to work effectively with others in developing improved services for patients.
10. Computer literacy desired.
11. Good oral and written command of the English language.

Competency Assessment:
Competency assessment and evaluation is based on Product Line performance evaluation and is subject to the following criteria:

1. Competence assessed during the initial employment and orientation process and departmental standards met.
2. Competence maintained during the evaluation year to include Product Line standards, objectives, in-service and continuing education.
3. Competence assessed during the evaluation year through performance evaluation process.
4. Licensure, certification or registration required.
5. Requirements related to patient safety, infection control, quality assurance or other performance standards.
6. Competence assessed based on age specific groups.

Age(s) of patients who may be served by this position:

Adult (18 to 64 years)
Geriatric (65 years and older)

Position title: RN Ambulatory I – Anticoagulation Clinic
Department: Ambulatory Anticoagulation Services
Reports to: Area manager
General Summary:
Under general supervision of the Ambulatory Anticoagulation Clinic Manager, the RN- Ambulatory I performs the day-to-day comprehensive, patient-oriented ambulatory anticoagulation services provided on his/her shift. This individual is responsible for the assessment of patients, evaluation/adjustment of anticoagulation/antithrombotic therapy per protocol and interpretation of laboratory results as they are related to anticoagulants/antithrombotics. This individual assists the Manager in identifying problems, which exist in his/her assigned area of practice and cooperates in the resolution of these problems. The RN-Ambulatory I demonstrates clinical competence and engages in patient teaching.

Principal Duties and Responsibilities:

1. Identifies and monitors the anticoagulation needs of the patients.
2. Appropriately counsels patients regarding the proper use of their anticoagulant/antithrombotic medications.
3. Demonstrates ability to effectively manage anticoagulation/antithrombotic therapies.
4. Performs assessment of health habits, safety issues, availability of support systems, family network and coping mechanisms.
5. Performs functions/tasks determined as necessary or delegated by physician or physician extender.
6. Assesses patient complaints, and advises patients according to established protocols.
7. Utilizes prepared materials to teach patients, according to established protocols.
8. Demonstrates competence in technical aspects of PT/INR testing and obtaining other indicated laboratory samples.
9. Demonstrates competence in maintaining a safe environment for staff and patients.
10. Maintains the complete anticoagulation record in the electronic medical record (EPIC). Demonstrates competence in appropriate documentation.
11. Actively seeks to establish/maintain positive working relationships with staff, physicians and management.
12. Provides orientation and training to new staff in regard to anticoagulation management and proper documentation.
13. Contributes to ongoing improvement, cost control and quality measures.
14. Participates in professional development activities.
15. Attends required meetings and serves on designated committees as requested.

Knowledge, Skills and Abilities Required:

1. Must be a graduate of an accredited School of Nursing.
2. Must be licensed as a Registered Nurse by the Michigan State Board of Nursing.
3. He/she should demonstrate acumen in oral and written communication skills which enable him/her to contribute effectively in the dissemination of information to all levels of health personnel in the system.
4. Must demonstrate knowledge of managed care.
5. Displays knowledge and understanding of the current guidelines for managing anticoagulation, associated risks and patient assessment.
6. Ability to react calmly and effectively in emergency situations.
7. Ability to establish and maintain effective working relationships with patients, clinic and medical staff.
8. Ability to contribute to educational needs of patients, families and associated health professionals within anticoagulation services.
9. Must demonstrate the ability to work effectively with others in developing improved services for patients.
10. Computer literacy desired.
11. Good oral and written command of the English language.

Competency Assessment:
Competency assessment and evaluation is based on Product Line performance evaluation and is subject to the following criteria:

1. Competence assessed during the initial employment and orientation process and departmental standards met.
2. Competence maintained during the evaluation year to include Product Line standards, objectives, in-service and continuing education.
3. Competence assessed during the evaluation year through performance evaluation process.
4. Licensure, certification or registration required.
5. Requirements related to patient safety, infection control, quality assurance or other performance standards.
6. Competence assessed based on age specific groups.

Age(s) of patients which may be served by this position:
Adult (18 to 64 years)
Geriatric (65 years and older)

Position title: LPN– Anticoagulation Clinic
Department: Ambulatory Anticoagulation Services
Reports to: Area manager and/or Nurse Leader

General Summary:
Under general supervision of the Ambulatory Anticoagulation Clinic Manager or a registered nurse, uses sound nursing judgment in support of the medical staff treatment plan. Adheres to nursing and teaching protocol and functions as directed by nurse leader.

Principal Duties and Responsibilities:

1. Identifies and monitors the anticoagulation needs of the patients.
2. Appropriately counsels patients regarding the proper use of their anticoagulant/antithrombotic medications.
3. Demonstrates ability to effectively manage anticoagulation/antithrombotic therapies.
4. Performs assessment of health habits, safety issues, availability of support systems, family network and coping mechanisms.
5. Performs functions/tasks determined as necessary or delegated by physician or physician extender.
6. Assesses patient complaints, and advises patients according to established protocols.
7. Utilizes prepared materials to teach patients, according to established protocols.
8. Demonstrates competence in technical aspects of PT/INR testing and obtaining other indicated laboratory samples.
9. Demonstrates competence in maintaining a safe environment for staff and patients.
10. Maintains the complete anticoagulation record in the electronic medical record (EPIC). Demonstrates competence in appropriate documentation.
11. Actively seeks to establish/maintain positive working relationships with staff, physicians and management.
12. Provides orientation and training to new staff in regard to anticoagulation management and proper documentation.
13. Contributes to ongoing improvement, cost control and quality measures.
14. Participates in professional development activities.
15. Attends required meetings and serves on designated committees as requested.

Knowledge, Skills and Abilities Required:

1. Must be a graduate of an approved practical nursing program.
2. Must be licensed as a Licensed Practical Nurse by the Michigan State Board of Nursing.
3. He/she should demonstrate acumen in oral and written communication skills which enable him/her to contribute effectively in the dissemination of information to all levels of health personnel in the system.
4. Must demonstrate knowledge of managed care.
5. Displays knowledge and understanding of the current guidelines for managing anticoagulation, associated risks and patient assessment.
6. Ability to react calmly and effectively in emergency situations.
7. Ability to establish and maintain effective working relationships with patients, clinic and medical staff.
8. Ability to contribute to educational needs of patients, families and associated health professionals within anticoagulation services.
9. Must demonstrate the ability to work effectively with others in developing improved services for patients.
10. Computer literacy desired.
11. Good oral and written command of the English language.

Competency Assessment:

Competency assessment and evaluation is based on Product Line performance evaluation and is subject to the following criteria:

1. Competence assessed during the initial employment and orientation process and departmental standards met.
2. Competence maintained during the evaluation year to include Product Line standards, objectives, in-service and continuing education.
3. Competence assessed during the evaluation year through performance evaluation process.
4. Licensure, certification or registration required.
5. Requirements related to patient safety, infection control, quality assurance or other performance standards.
6. Competence assessed based on age specific groups.

Age(s) of patients which may be served by this position:
Adult (18 to 64 years)
Geriatric (65 years and older)

Position title: CMA – Anticoagulation Clinic
Department: Ambulatory Anticoagulation Services
Reports to: Area manager

General Summary:
Under general supervision of the Ambulatory Anticoagulation Clinic Manager, the Certified Medical Assistant in the Ambulatory Anticoagulation Service provides much of the administrative assistant duties for the clinic. Adheres to certification requirements of medical assistant.

Principal Duties and Responsibilities:

1. Accepts and enters patient enrollment forms into the electronic medical record.
2. Triages enrollments to Anticoagulation Practitioners
3. Answers phones/voicemail messages
4. Triages urgent calls to Anticoagulation Practitioners
5. Enters faxed labs into the electronic medical record
6. Returns patient calls as appropriate
7. Notifies patients regarding missed lab dates
8. Processes patient disenrollments
9. Mails new patient packets and patient dosing calendars
10. Monitors patient hospital discharges
11. Orders necessary clinic supplies

Knowledge, Skills and Abilities Required:

1. Must be a graduate of an accredited medical assistant program.
2. Must be certified by the board of the American Association of Medical Assistants.
3. He/she should demonstrate acumen in oral and written communication skills which enable him/her to contribute effectively in the dissemination of information to all levels of health personnel in the system.
4. Must demonstrate knowledge of managed care.
5. Displays knowledge and understanding of the current guidelines for managing anticoagulation, associated risks and patient assessment.
6. Ability to react calmly and effectively in emergency situations.
7. Ability to establish and maintain effective working relationships with patients, clinic and medical staff.
8. Ability to contribute to educational needs of patients, families and associated health professionals within anticoagulation services.
9. Must demonstrate the ability to work effectively with others in developing improved services for patients.
10. Computer literacy desired.
11. Good oral and written command of the English language.

Competency Assessment:
Competency assessment and evaluation is based on Product Line performance evaluation and is subject to the following criteria:

1. Competence assessed during the initial employment and orientation process and departmental standards met.
2. Competence maintained during the evaluation year to include Product Line standards, objectives, in-service and continuing education.
3. Competence assessed during the evaluation year through performance evaluation process.
4. Licensure, certification or registration required.
5. Requirements related to patient safety, infection control, quality assurance or other performance standards.
6. Competence assessed based on age specific groups.

Age(s) of patients which may be served by this position:
Adult (18 to 64 years)
Geriatric (65 years and older)
Position title: Certified Pharmacy Technician – Anticoagulation Clinic
Department: Ambulatory Anticoagulation Services
Reports to: Area manager

General Summary:
Under the supervision of the Ambulatory Anticoagulation Service Manager, the Certified Pharmacy Technician (CPhT) ensures that patients follow-up with their advised lab visits and physician office visits. The CPhT identifies patients who have been discharged from the hospital and notifies Anticoagulation Practitioners so that follow-up advice can be dispensed.
Principal Duties and Responsibilities:

1. Identifies patients who are hospitalized and monitors for their discharge so that Anticoagulation Practitioners can be notified.
2. Identifies and contacts patients who are overdue for recommended lab visits.
3. Identifies and contacts patients who are overdue for recommended office visits.
4. Starts patient disenrollment process.

Knowledge, Skills and Abilities Required:

1. Must be a graduate of an accredited Pharmacy Technician training program.
2. Must be certified by the Michigan State Board of Pharmacy.
3. He/she should demonstrate acumen in oral and written communication skills which enable him/her to contribute effectively in the dissemination of drug information to all levels of health personnel in the system.
4. Must demonstrate knowledge of managed care.
5. Displays knowledge and understanding of the current guidelines for managing anticoagulation, associated risks and patient assessment.
6. Ability to react calmly and effectively in emergency situations.
7. Ability to establish and maintain effective working relationships with patients, clinic and medical staff.
8. Must demonstrate the ability to work effectively with others in developing improved services for patients.
9. Computer literacy desired.
10. Good oral and written command of the English language.

Competency Assessment:
Competency assessment and evaluation is based on Product Line performance evaluation and is subject to the following criteria:

1. Competence assessed during the initial employment and orientation process and departmental standards met.
2. Competence maintained during the evaluation year to include Product Line standards, objectives, in-service and continuing education.
3. Competence assessed during the evaluation year through performance evaluation process.
4. Licensure, certification or registration required.
5. Requirements related to patient safety, infection control, quality assurance or other performance standards.
6. Competence assessed based on age specific groups.

Age(s) of patients who may be served by this position:
Adult (18 to 64 years)
Geriatric (65 years and older)

Appendix D

Quick Reference Guides

Questions to ask Lovenox (Enoxaparin) Bridge Therapy Patients

Date of INR Result	Questions to Ask
One week before procedure	Verify latest height and weight if not available already Which lab to have STAT orders drawn Which pharmacy to forward Lovenox Rx (prefer HFHS b/c they stock most common strengths) Go over bridge therapy scheduled day-by-day with patient and ask patient to read it back Request that next labs (day before procedure) be done as early in the day as possible
Day before procedure	Verify **no** Lovenox (Enoxaparin) PM does is given (if on q12h Lovenox regimen) or that they injected half the usual dose (if on q24h Lovenox regimen) the AM before Remind patient **NOT** to inject Lovenox on the morning of procedure Any bleeding side effects, esp. around injection site Remind patient to obtain clear instructions from surgeon regarding resumption of warfarin AND Lovenox. Ask about time of procedure so you can project when should hear from patient post-procedure How many Lovenox syringes are left, in case patient requires refills
Day of procedure	Ask for post-procedure instructions given by surgeon regarding warfarin and Lovenox For GI procedures, ask if biopsy or polypectomy was done as that may influence decisions regarding warfarin dosing. Other procedures that fall into this category include cardiac catheterization, orthopedic procedures (hip or knee replacement), hemorrhoidectomy For epidural injection, begin Lovenox 24 hours after procedure and give the regular (stable) dose of warfarin (do not blast) Ask if patient has adequate Lovenox supply left
Bridge Out (period after procedure	Any bleeding side effect Verify warfarin and Lovenox doses taken since last clinic encounter Give warfarin dosing instructions Ask if patient has adequate Lovenox supply left

Daily Task Reminders

Work Assignment	How to do it?
Answer phones/Voicemail	Answer phone when rings. Pay particular attention to the provider line, if applicable (e.g., physician, PDAS, another clinic, personal call). Check voicemail every ½ to 1 hour
Discharges	This refers to patients being recently discharged from the hospital. • EPIC > Reports > My Reports > Library > Search using "Anti" > HF Anticoagulation Patients with recent hospital discharge – highlight and click run button (on the right) • once report comes up, click on Filters > scroll down to responsible group and click > select responsible group from menu below > click apply. • Click on Filters > select Last Discharge > enter desired discharge dates in From and To search boxes below > click apply • You should now have a report for your clinic for only the dates you've specified • Once the report results are available (see above) view the results and then select Options > Export to file • In the Save In drop down, be sure to select your corp ID directory (e.g. fflinst1 on \corp\hfhs\home…H:) • In the Save as Type drop down menu, select *.tsv (tab delimited) • Enter a name for the file and click save • Navigate to the folder where you saved the file then open • Print • (it may also be possible to click on the print icon in the EPIC tool bar and print the report from there, depending on your computer set up) Call patient to schedule next appointment if PDAS had not done that already. Check if patient was discharged home, rehab, or nursing home, or elsewhere. If discharged other than home, place note in TEAM REMINDERS and date out (extend) MANAGE GOALS – INR return date 2 weeks from today. May also ask family to call us when patient goes home. Ask for warfarin dosage changes Ask for medication changes. In **Discharge Summary**, look for next appointment with doctors so we can consolidate appointments.
Enrollments	Contact new enrollee and go over teaching points (see New Enrollment Note). Try to limit to 15 minutes, as more information can be reviewed at the next few encounters. If INR level is needed sooner than new packet/lab card reaches patient by mail, make a temporary lab order (sheet) and fax it to the appropriate lab (see outpatient Lab Directory). Certain labs do STAT INR and this information is listed in the directory. If lab does not do STAT, the sample automatically is processed downtown (Main HFH). Try to do enrollments as early in day as possible after "high" priority INRs are done. Do not leave for late part of day.
Highs	Look into ACS DOCUMENTS and DOCUMENTS in CHART in EPIC to see if new meds, procedures, All Documents, or changes are applicable. Call patient to find about reason(s) for High INR level. Leave message if patient not available. Instruct in message whether to take extra dose or hold dose. Reflect that in CALL LOG

Work Assignment	How to do it?
	Before scheduling next INR, look into APPOINTMENTS to see if can consolidate visits. Click on PATIENT GOALS, then MANAGE GOALS and enter date for next INR Click on CALL LOG (click "Contact Type" and "Successful Attempt" buttons) Click appropriate button (contacted) then SAVE Click on PATIENT MEDICATION SCHEDULE to adjust warfarin dose, as necessary, then SAVE and QUICK PRINT or BATCH PRINT
Lovenox (peri-procedural)	On 1st encounter upon calling patient regarding upcoming bridge therapy, cover the following points: Cover the 5 points on Lovenox questionnaire (# of days to hold warfarin, Rx insurance coverage, Pharmacy name & phone #, injected SQ before, and what clinic to do teaching. Review bridge schedule with patient **and** mail it afterwards Remind patient to have labs drawn of day before procedure at a HFHS facility that does STATs. Remind patient NOT to present lab card. For phone contact on day before procedure, remind patient not to inject Lovenox tonight or tomorrow morning and to call ACS after procedure with surgeon's instructions for resuming warfarin and Lovenox. For patients on Lovenox q24 (renal dysfunction), make sure Lovenox is dosed every AM (not PM). Give ½ dose on morning day before procedure. Height and weight can be obtained from office notes or from EPIC. It may also be entered in Internal medicine office notes. For HAP patients, give 1 box of Lovenox with 2 refills; for BCBS patients, give 3 boxes with no refills. Note writing: Day before procedure, use Lovenox template Notify / Letter / Free form template Include in letter whether patient injected SC before, ability to inject, location where instructions were given, Rx coverage, and where Rx was sent (encourage using HFHS pharmacies). **Do not give warfarin loading doses in bridge therapy patients if:** **Orthopedic knee procedures (seem to notice more bleeding)** **Colonoscopy with polypectomy** **Cardiac cath.** **Hemorrhoidectomy** **Epidural Injection** **s/p bladder or prostate surgery** For newly formed thrombus (e.g., DVT, PE, atrial or ventricular thrombus), need to have 2 consecutive therapeutic INRs before discontinuing Lovenox. Heart Failure and Transplant team manages Lovenox bridge therapy for their patients only if procedure is a cardiac procedure (e.g., Cardiac cath, pacemaker, ablation). For all other procedures, we need to manage Lovenox bridge therapy. The surgeon determines when to resume anticoagulation therapy after procedure. The anticoagulation physician, **not** the surgeon, must approve any changes in Lovenox dosing that deviate from protocol.

Work Assignment	How to do it?
	Lovenox regimen **MUST** be approved by anticoagulation physician even when it is written by a different specialist who will do the procedure (e.g. GI, surgery).
Lovenox (New VTE)	This applies to patients who were newly placed on Lovenox at the hospital and discharged on Lovenox and warfarin for new DVT/PE. Add patient to Lovenox patients list and complete all fields (name, MRN, wt, CrCl, ..etc) Project when next INR is needed based on when warfarin started. We order an INR within no later than 3 days from discharge date. Circle it in pencil on the list. Enter this date under DUE FOR INR column. Project when next PLT is needed. We order PLT at 4 days after heparin/Lovenox was started. Pre-Lovenox PLT is usually done at the hospital earlier. Call patient and go over new enrollment First Encounter teaching session. In addition to warfarin information, go over Lovenox information. Ask patient which lab is closest to them and enter in LAB column on list. Ask patient to draw labs before 12 Noon so we can receive results on time. Assure patient has enough Lovenox dispensed, otherwise ask which pharmacy do they fill their meds at and issue additional refills. Need 2 consecutive INRs and 5 days of UFH/LMWH before Lovenox is DC'd. Fax Lab order as **STAT** (request it for 10-14 days). Put lab fax # on back of form.
Regulars	Early every AM, evaluate who needs only a letter sent (patients with at least 3 therapeutic consecutive INRs or consistently stable with only 1 previous INR out of range, this INR in range). Look into DOCUMENTS to see if new meds, appointments (procedures), All documents, or changes are applicable. Before scheduling next INR, look into APPOINTMENTS to see if can consolidate visits. Click on PATIENT GOALS, then MANAGE GOALS and enter date for next INR and click SAVE. Click on ACS DOCUMENTS Click on "Results Letter – Stable INR" Sign Print letter- PATIENT MEDICATION SCHEDULE, QUICK PRINT OR BATCH PRINT
Urgent	After talking to patient, call and notify AC pharmacist of INR > 5. Don't forget to put patient on board so they won't be lost to follow-up. Look into DOCUMENTS to see if new meds, procedures, All Documents, or changes are applicable. Before scheduling next INR, look into APPOINTMENTS to see if can consolidate visits. Click on PATIENT GOALS, then MANAGE GOALS and enter date for next INR Click on ANTICOAGULATON SERVICE NOTE to enter documentation
CrCl calculation – Clinical Pharmacology	Clinical Pharmacology Creatinine clearance by Cockroft-Gault equation Clinical Calculators

Appendix E

Recommended Templates

Note for new DOAC patient:

Patient started on (***) _ mg (***) daily on (***) for indication of (***).
Age: _ years

Patient weight (date):

Patient height (date):

BMI:

Last SCr (date):

Last Hgb (date):

eCrCl (C-G) using TBW:

(***) dose prescribed: _ mg (***) daily. Based on manufacturer's recommendations and current clinic guidelines, (***) dose is appropriate.

Patient was counseled on the following items, based on FDA-approved Medication Guide.

- Notify your physician and the anticoagulation clinic of any change in medications, including OTC products and herbals.
- Do not take NSAIDs without prior approval of physician
- Do not drink grapefruit juice (may raise drug levels)
- Notify your physician and the anticoagulation clinic of any upcoming procedures
- May take (***) with (***) food
- If you miss a dose, take it as soon as you remember. Do not take more than one dose at the same time to make up for a missed dose (Rivaroxaban-can make up missed dose within 12 hours, Apixaban-can make up missed dose within 6 hours)
- Possible side effects include bleeding, allergic reactions, swelling of face or tongue, wheezing or difficulty breathing or chest tightness.
- Signs and symptoms of bleeding were covered along with situations when to seek emergency care
- Signs and symptoms of stroke or thrombosis were covered and suggested emergency care in such situations
- Do not run out. Always request your refills in advance.

I also mailed patient the (***) Medication Guide for reference and encouraged patient to call our clinic at (248) 3XX-XXX0 if there are further questions.

Next clinic encounter is scheduled for _.

REVISED: Warfarin Anticoagulation template for progress note:

Patient identifiers (3) (phone no, name, DOB)

Tablet strength (color verified):

Patient reported dosing regimen:

Marijuana products/nicotine?

INR lab order expiration date?

Eligible for extended testing?

Upcoming procedure?

LOV with responsible anticoagulation physician:

ASSESSMENT: If INR level is out of range: potential reason? (see patient findings)

PLAN: (Dose adjustment made, patient advice including s/s to watch for with sub/supra tx INR)

Patient letter sent via: (MyChart/mail)

For full details regarding patient anticoagulation therapy management, look for the "anti coag visit" note under the "Encounters" tab in the "Chart Review"

Providers may contact the Henry Ford Anticoagulation Clinic at 1-833-XXXXXXX or (1-833-2XX-XXX2)

REVISED DOAC anticoagulation template for follow-up progress note:

Patient identifiers (3) (phone no, name, DOB)

Anticoagulant:

Dose/regimen:

Missed/extra doses? (Rivaroxaban-can make up missed dose within 12 hrs, Apixaban-can make up missed dose within 6 hrs)

Patient weight (date):

Patient height (date):

BMI:

Last SCr (date):

Last Hgb (date):

eCrCl (C-G) using TBW:

Any documentation of change in liver function (unless dabigatran)?

Upcoming procedure?

LOV with ACS responsible physician?

ASSESSMENT: DOAC dose still appropriate?

Review of medications: any new interacting? New OTC/vitamins/supplements (herbals)?

PLAN: Patient advice: (Review s/s of bleeding and clotting, remind no grapefruit, take rivaroxaban with FOOD)

NEXT DOAC ENCOUNTER DUE:

Patient letter sent via : (MyChart/mail)

For full details regarding patient anticoagulation therapy management, look for the "anti coag visit" note under the "Encounters" tab in the "Chart Review"

Providers may contact the Henry Ford Anticoagulation Clinic at 1-833-ANTICOAG or (1-833-268-4262)

Patient letters:

Dear Mr. Flintstone,

We are working with Dr. *** to manage your blood thinner, Eliquis ®. Please remember the following points while you are on this medication:

Your current Eliquis tablet strength is *** mg.
Your current Eliquis dose is ***.

Please contact the anticoagulation clinic of any change in medications. Call anticoagulation clinic before you begin taking any non-prescription products or herbals.

Notify the anticoagulation clinic of any upcoming procedures or if you miss a dose.

While on your blood thinner DO NOT take non-steroidal anti-inflammatory drugs, such as ibuprofen (Motrin®, Advil®) or naproxen (Aleve®) without prior approval of physician.

Do not eat grapefruit or drink grapefruit juice as interacts with blood thinning medication and may increase the risk of bleeding.

Possible side effects include bleeding. Seek immediate medical attention if you experience any signs and symptoms of bleeding, including blood in the urine or stool, dark color stools, vomiting up blood or coffee-ground-like material or if you experience any bleeding that does not stop.

Seek immediate medical attention if you experience any symptoms like numbness, tingling, weakness on one side, slurred speech, abrupt changes in vision, shortness of breath or swelling of the extremities.

Do not run out of your blood thinner. Always request your refills in advance.
Do NOT stop this medication without further advice from your doctor.

For women of child-bearing age who are pregnant or plan to become pregnant discuss which blood thinners to take if needed with your physician as it is not known if will harm your unborn baby. Tell your doctor right away if you become pregnant during treatment with blood thinners.

Please call us if you have any questions or concerns. We will contact you again on *** for a brief follow-up on your blood thinner therapy. Your safety is our main goal!

Sincerely,

HFHN COLUMBUS
HFMC COLUMBUS ANTICOAGULATION
39450 W 12 MILE RD
NOVI MI 48377
Dept: 833-268-4262
Fax 248-344-4191

Dear Mr. Flintstone,

We are working with Dr. *** to manage your blood thinner, Xarelto® (or rivaroxaban), please remember the following points while you are on this medication:

Your current Xarelto® tablet strength is {***}
Your current Xarelto® dose is {***}

Please contact the anticoagulation clinic of any change in medications. Call anticoagulation clinic before you begin taking any non-prescription products or herbals.

Notify the anticoagulation clinic of any upcoming procedures.

While on your blood thinner DO NOT take non-steroidal anti-inflammatory drugs, such as ibuprofen (Motrin®, Advil®) or naproxen (Aleve®) without prior approval of physician.

It is best to take Xarelto® with the evening meal for maximal absorption.

If you miss a dose of Xarelto®, Take Xarelto® as soon as you remember on the same day. Take your next dose at your regularly scheduled time. Do not double your dose, unless you are taking 15 mg twice a day for the first 21 days of your Xarelto® therapy.

Do not eat grapefruit or drink grapefruit juice as interacts with blood thinning medication and may increase the risk of bleeding.

Possible side effects include bleeding. Seek immediate medical attention if you experience any signs and symptoms of bleeding, including blood in the urine or stool, dark color stools, vomiting up blood or coffee-ground-like material or if you experience any bleeding that does not stop.

Seek immediate medical attention if you experience any symptoms like numbness, tingling, weakness on one side, slurred speech, abrupt changes in vision, shortness of breath or swelling of the extremities.

Do not run out of your blood thinner. Always request your refills in advance.
Do NOT stop this medication without further advice from your doctor.

For women of child-bearing age who are pregnant or plan to become pregnant discuss which blood thinners to take if needed with your physician as it is not known if will harm your unborn baby. Tell your doctor right away if you become pregnant during treatment with blood thinners.

Please call us if you have any questions or concerns. We will contact you again on *** for a brief follow-up on your blood thinner therapy. Your safety is our main goal!

Sincerely,

HFHN COLUMBUS
HFMC COLUMBUS ANTICOAGULATION
39450 W 12 MILE RD
NOVI MI 48377
Dept: 833-268-4262
Fax 248-344-4191

APPENDIX F

ICHECK'D DOAC Initiation Checklist

I = indication:

Why is the patient receiving the DOAC and is it a valid indication?

- Atrial Fibrillation
- VTE treatment
- VTE prophylaxis
- prevention of CV events

C = concomitant medications:

Is the patient receiving any interacting medications?

- Cytochrome P450 enzyme subtype 3A4 (CYP3A4) and/or P-glycoprotein inhibitors
- Cytochrome P450 enzyme subtype 3A4 (CYP3A4) and/or P-glycoprotein inducers

H = history:

Does the patient have a medical history?

- Mechanical Heart Valve
- Moderate to severe mitral stenosis
- Anti-phospholipid Syndrome
- Pregnant/nursing
- DOAC failure or recurrent VTE
- Hepatic impairment (Child-Pugh class B or higher)

E = education:

Provide the patient/caregiver information

- Review risk of bleeding
- Contact provider or clinic when DOAC therapy needs to be interrupted for procedures

C = compliance:

Missing or skipping doses may increase the risk of a blood clot since DOACs have a short half-life

K = kidney function:

Serum creatinine value needed prior to DOAC initiation and while receiving the DOAC in follow up

- Calculate the creatinine clearance using the Cockcroft-Gault formula with actual body weight
- Serum creatinine value used in dosing apixaban for Atrial Fibrillation

D = dose correct for indication:

Monitor for any changes that may be needed based on

- Kidney function for Atrial Fibrillation
- Loading dose followed by maintenance dose for Acute VTE

Adapted with permission from MAQI^2 Anticoagulationtoolkit.org accessed 5.1.20

APPENDIX G

Routine DOAC Management Follow-up Checklist

Assess Labs

- **3 months** (first 3 months, then every 3 months if CrCl 15 - 30 ml/min)
    - Renal Function (using Cockroft-Gault formula and actual body weight)
    - SCr
    - Assess weight and age (apixaban)
- **6 months** (first 6 months, then every 6 months if CrCl 30 – 60 ml/min)
    - Renal function (using Cockroft-Gault formula and actual body weight)
    - SCr
    - Assess weight and age (apixaban)
- **Yearly**
    - Hgb
    - Renal function
        - SCr
        - CrCl (using Cockroft-Gault formula and actual body weight)
    - Assess weight
    - Assess age
    - Liver function
        - Look for documentation of hepatic impairment, infection, cancer, etc
        - Child-Pugh class C should be switched to warfarin (responsible physician should be contacted)
        - Child-Pugh class B requires risk/benefit discussion for patients on factor Xa inhibitors (responsible physician should be contacted)
- **As needed** (if clinically indicated for conditions that may impact renal or hepatic function)
- **If labs have not been completed at the expected interval, they may be ordered and then the physician and patient should be notified of the need for blood work**
- **Declining renal function may require a DOAC dose adjustment (see manual for DOAC dosing information)**
- **Edoxaban is contraindicated for atrial fibrillation in patients with CrCl > 95**

Assess for Drug Tolerance (each visit, minimum every 6 months, sooner if necessary)

- Assess for side effects
    - Evaluate link to DOAC use
- Discuss with responsible provider and determine whether to
    - Continue
    - Temporarily stop
    - Change to different anticoagulant

Assess for New Medications (each visit, minimum every 6 months, sooner if necessary)

- Assess for P-gp inhibitors/inducers (if on dabigatran or edoxaban)
- Assess for dual P-gp/CYP3A4 inhibitors (if on apixaban or rivaroxaban)
- Assess for other medications that may increase risk of bleeding such as antiplatelets
- Instruct patient to notify clinic if future medication changes

- **DOAC dose adjustments may be required if patients start taking interacting medications (Check Clinical Pharmacology Online or Micromedex and drug interactions section of manual)**

Assess for Thromboembolism (each visit, minimum every 6 months, sooner if necessary)

- During interview ask about
    - Sudden headache
    - Sudden visual changes
    - Numbness/tingling/weakness on one side of the body
    - Swelling in an extremity with area of warmth/redness on an arm or leg
    - Chest pain/shortness of breath
- Check chart for documentation of stroke/TIA

Assess for Bleeding (each visit, minimum every 6 months, sooner if necessary)

- During interview ask about
    - melena
    - hematuria
    - hemoptysis
    - epistaxis
    - petechia
    - unusual hematoma
    - internal bleeding following injury due to fall or head trauma.
- If minor (nuisance) bleeding, are preventative measures possible?
    - Flyers regarding care of nuisance bleeding (nose bleeds, wound care) are available on the shared drive (West Bloomfield > AAS > Columbus Files)
    - Motivate patient to diligently continue anticoagulation
- If bleeding with impact on quality of life or with significant risk, is prevention possible?
    - Contact responsible physician regarding potential change of anticoagulant

Assess for Compliance (each visit, minimum every 6 months, sooner if necessary)

- Use WHO assessment chart in manual to determine compliance based on the number of doses missed during specific time period
    - Considered adherent to medication therapy if taken as prescribed more than 80% of the time
- Discuss importance of maintaining strict dosing schedule
- See manual for information regarding missed doses, doubled doses or uncertainty if dosed
- Inform about compliance aids using special boxes, smartphone apps, etc (Dabigatran must remain in its original packaging)

Assess for Upcoming Procedures (each visit, minimum every 6 months, sooner if necessary)

- Review chart for appointments
- Inform patient to contact clinic if scheduled for upcoming procedures requiring the interruption of anticoagulant therapy

Patient Tracking and Documentation

- EPIC Anti Coag Tracking
    - Click on the EPIC button and choose Encounter
    - Choose your patient and click accept

    - In Encounter Selection box, choose “New” to create a new encounter
    - In New Encounter box, choose Type: “Anti-coag DOAC Visit and accept
    - In DOAC Track
        - Link DOAC episode
        - Track Pt. Outreach
        - Progress note
        - Patient Findings (if needed)
    - Sign visit
- Add patient encounter to Remind Me folder (so that others may follow-up if necessary)
    - Include any comments necessary for next follow-up
- Run Report for Next DOAC outreach
    - Click on EPIC button and choose Reports
    - Go to “Library”
    - Type “DOAC” in search box
    - Click on “HF DOAC”
    - Click “Run”

Send patient letters

- After initial encounter
    - DOAC letter templates can be found in manual
    - Send DOAC drug monograph (in shared drive > West Bloomfield > AAS > Columbus files > Patient Education folder) as needed
- If change in DOAC or DOAC dosing (includes reduction after 6 months DOAC therapy for continued VTE prophylaxis)
- As needed after hospital discharge, patient procedure, change in health or change in other medications

References

Steffel J et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *European Heart Journal*, Volume 39, Issue 16, 21 April 2018, Pages 1330–1393, https://doi.org/10.1093/eurheartj/ehy136

Oertel LB. Practical Issues with Transitioning to DOAC Clinic. Anticoagulation Forum Conference, Ft. Lauderdale, FL 4.12.19

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APPENDIX H

DOAC EDUCATION LETTERS

apixaban (Eliquis®) Education

What is apixaban?

Apixaban is medicine that prevents blood clots from forming.

What should I know about apixaban?

Take apixaban at the same time every day as prescribed by your doctor. **Do not change the amount you take or stop taking this medicine.** If you suddenly stop taking apixaban, it can increase your risk of blood clots.

You can take apixaban with or without food. You do not need to change the type or amount of food you eat.

Do not drink alcohol, use tobacco products, or use medical or recreational marijuana products.

If you miss a dose, take the missed dose when you remember it, on the day you missed the dose. Take your next dose at your normal time. Do not take more than 1 dose of apixaban at the same time.

Your doctor may want to have a blood test done from time to time to check the health of your kidneys and liver. You will not need to have blood tests done to check the amount of medicine in your body.

Keep apixaban in the bottle it came in, in a cool, dry place, away from direct light.

You should not take apixaban if you have an artificial heart valve, active bleeding or severe liver disease.

What are some of the side effects?

Bleeding is the most common side effect of apixaban. Some medicines or conditions may cause you to bleed more easily. Talk to your doctor if you:

- Take prescription and over-the-counter medicines, vitamins, herbal products, and supplements.
- Have severe kidney or liver disease, if you are older than 80 or weight less than 132 pounds.
- Take blood thinners, antidepressants, or non-steroidal anti-inflammatory medicines (also known as NSAIDs; like ibuprofen), heparin, warfarin, clopidogrel (Plavix), ticagrelor (Brilinta), prasugrel (Effient)ketoconazole, erythromycin, phenytoin, St John's wart, ritonavir, carbamazepine, or rifampin.
- Have any changes in your health or if you become pregnant
- Plan to have a medical or dental procedure or surgery.
- Have changes in your medicines, dietary supplements, vitamins, herbal products, or over-the-counter medicines

Call 911 or go to the Emergency Department if you have signs of:

- **Allergic reaction**: hives, difficulty breathing, swelling of your face, lips, tongue or throat.
- **Spinal blood clot**: back pain, numbness or muscle weakness in your lower body, or loss of bladder or bowel control.
- **Blood clot**: shortness of breath, chest pain, redness, swelling, heat or pain in any limb.
- Unusual bleeding that won't stop, excessive bruising, or excessive menstrual bleeding
- Stool that is red or looks like black tar.
- Urine that is red, coffee colored, or cola colored.

- Unusual bleeding in the nose or gums.
- Coughing up blood or vomit that looks like coffee grounds blood.
- A serious fall or you hit your head.
- Other serious symptoms or changes.

rivaroxaban (Xarelto®) Education

What is rivaroxaban?

Rivaroxaban is medicine that stops blood clots from forming.

What should I know about rivaroxaban?

Take rivaroxaban at the same time every day as prescribed by your doctor. **Do not change the amount you take or stop taking this medicine.** If you suddenly stop taking rivaroxaban, it can increase your risk of blood clots.

If you have been prescribed 10mg tablets, take them with or without food.

If you have been prescribed the 15mg or 20mg tablets, take them **with food**.

You do not need to change the type or amount of food you eat.

If you take rivaroxaban 1 time each day and miss a dose, take the missed dose as soon as you remember on the day you missed to dose Take your next dose at your normal time the next day. Do not take more than 1 dose of rivaroxaban at the same time.

If you take rivaroxaban 2 times each day and miss a dose, take the missed dose as soon as you remember. You may take 2 doses at the same time to make up a missed dose.

Do not drink alcohol, use tobacco products, or use medical or recreational marijuana products.

Your doctor may want to have a blood test done from time to time to check the health of your kidneys.

You will not need to have blood tests done to check the amount of medicine in your body.

Keep rivaroxaban in a cool dry place, away from direct light.

You should not take rivaroxaban if you have an artificial heart valve.

What are some of the side effects?

Bleeding is the most common side effect of rivaroxaban. Some medicines or conditions may cause you to bleed more easily. Talk to your doctor if you:

- Take prescription and over-the-counter medicines, vitamins, herbal products, and supplements.
- Take antibiotics, antifungals, seizure medicines, HIV medicines, TB medicines, non-steroidal anti-inflammatory medicines (also known as NSAIDs; like ibuprofen), or blood thinners.
    - Especially talk to your doctor if you take ketoconazole, erythromycin, phenytoin, St John's Wart, ritonavir, carbamazepine, or rifampin.
- Have a bleeding disorder, hemorrhagic stroke, uncontrolled high blood pressure, stomach or intestinal bleeding or ulcer.
- Have changes in your health or if you become pregnant
- Plan to have a medical or dental procedure or surgery.
- Change your medicines, dietary supplements, vitamins, herbal products, or over-the-counter medicines

Call 911 or go to the Emergency Department if you have signs of:

- **Allergic reaction**: hives, difficulty breathing, swelling of your face, lips, tongue or throat.
- **Blood clot:** shortness of breath, chest pain, redness, swelling, heat or pain in any limb.
- **Spinal blood clot:** back pain, numbness/weakness in lower body, or loss of bladder or bowel control.
- **Stroke:** dizziness, visual changes or severe headache, numbness or weakness in any limb, slurred speech or difficult speaking.
- Bleeding that won't stop, excessive bruising, or excessive menstrual bleeding.
- Blood in stool that is red or looks like black tar.
- Blood in urine that is red, coffee colored, or cola colored
- Coughing up blood or vomit that looks like coffee grounds

- Unusual bleeding from nose or gums.
- Excessive menstrual bleeding.
- Serious fall, or if you hit your head.
- Other serious symptoms or changes.

dabigatran (Pradaxa®) Education

What is dabigatran?

Dabigatran is a medicine that stops blood clots from forming.

What should I know about dabigatran?

Take dabigatran at the same time every day as prescribed by your doctor. **Do not change the amount you take or stop taking this medicine.** If you suddenly stop taking dabigatran, it can increase your risk of blood clots.

You can take dabigatran with or without food. The capsules must be swallowed whole. You do not need to change the amount or type of food you eat.

Do not drink alcohol, use tobacco products, or use medical or recreational marijuana products.

If you miss a dose, take the missed dose when you remember it, on the day you missed the dose. Do not take a missed dose less than 6 hours before the next scheduled dose. Do not take more than 1 dose at a time.

Your doctor may want to have a blood test done from time to time to check the health of your kidneys. You will not need to have blood tests done to check the amount of medicine in your body.

Keep dabigatran in the bottle it came in, in a dry place, away from direct light.

You should not take dabigatran if you have an artificial heart valve or active bleeding.

What are some of the side effects?

Bleeding is the most common side effect of dabigatran. You may also experience stomach pain, indigestion, or heartburn. Some medicines or conditions may cause you to bleed more easily. Talk to your doctor if you:

- Take prescription, over-the-counter medicines, vitamins, herbal products, and supplements.
- Have a stomach or intestinal ulcer or bleeding
- Are older than 75.
- Take medicines that treat or prevent blood clots or take non-steroidal anti-inflammatory medications (also known as NSAIDs; like ibuprofen)
    - Especially talk to your doctor if you take St John's wart, tipranavir, carbamazepine or rifampin.
- Change your medicines, dietary supplements, herbal products, vitamins, or over-the-counter medicines.
- Have any changes in your health or if you become pregnant.
- Plan to have medical or dental procedures or surgeries.

Call 911 or go to the Emergency Department if you have signs of:

- **Allergic reaction**: hives, difficulty breathing, swelling of your face, lips, tongue or throat.
- **Stroke**: dizziness, visual changes or severe headache, numbness or weakness in any limb, slurred speech or difficult speaking.
- **Spinal blood clot**: back pain, numbness or muscle weakness in your lower body, or loss of bladder or bowel control.
- **Blood clot:** shortness of breath, chest pain, or redness, swelling, hear, or pain in any limb.
- Bleeding that won't stop, excessive bruising, or excessive menstrual bleeding.
- Stool that is red or looks like black tar.

- Urine that is red, coffee colored, or cola colored.
- Coughing up blood or vomit that looks like coffee grounds.
- Uncontrolled bleeding from nose or gums.
- Excessive menstrual bleeding.
- A serious fall, or you hit your head.
- Other serious symptoms or changes.

edoxaban (Savaysa®) Education

What is edoxaban?

Edoxaban is medicine that stops blood clots from forming. It is also used to treat certain types of blood clots.

What should I know about edoxaban?

Take edoxaban at the same time every day as prescribed by your doctor. **Do not change the amount you take or stop taking this medicine.** If you suddenly stop taking edoxaban, it can increase your risk of blood clots.

You can take edoxaban with or without food.

Do not drink alcohol, use tobacco products, or use medical or recreational marijuana products.

If you miss a dose, take the missed dose when you remember it, on the day you missed the dose. Skip the missed dose if it is almost time for your next dose. Do not take more than 1 dose of edoxaban at the same time.

Your doctor may want to have blood tests done from time to time to check the health of your kidneys and liver. You will not need to have blood tests done to check the amount of medicine in your body.

Keep edoxaban in the bottle it came in in a dry place away from direct light.

You should not take edoxaban if you have an artificial heart valve. You may not be able to take edoxaban if you have abnormal kidney function. Your doctor will check your kidney function before you start edoxaban.

What are some of the side effects?

Bleeding is the most common side effect of edoxaban. You may also experience low red blood cells, a rash, or poor liver function. Some medicines or conditions may cause you to bleed more easily. Talk to your doctor if you:

- Take certain medicines such as aspirin, non-steroidal anti-inflammatory medicines (also known as NSAIDs; like ibuprofen), heparin, warfarin, clopidogrel (Plavix), ticagrelor (Brillinta), or prasugrel (Effient).
- Take antifungals or antibiotics medicines such as ketoconazole, itraconazole, azithromycin, clarithromycin, erythromycin, ritonavir, cyclosporine, or rifampin.
- Take other prescription medicines, especially verapamil or quinidine, over-the-counter medicines, vitamins, herbal products, and supplements.
- Have a bleeding disorder, uncontrolled high blood pressure, a hemorrhagic stroke, stomach or intestinal bleeding, or ulcer.
- Change your medicines, dietary supplements, vitamins, herbal products, or over-the-counter medicines.
- Have any changes to your health or if you become pregnant.
- Plan to have a medical or dental procedure or surgery.

Call 911 or go to the Emergency Department if you have signs of:

- **Allergic reaction**: hives, difficulty breathing, swelling of your face, lips, tongue or throat

- **Spinal blood clot**: back pain, numbness or muscle weakness in your lower body, or loss of bladder or bowel control.
- Bleeding that won't stop, excessive bruising, or excessive menstrual bleeding.
- Stool that is red or looks like black tar.
- Urine that is red, coffee colored, or cola colored.
- Coughing up blood or vomit that looks like coffee grounds.
- A serious fall or you hit your head.
- Other serious symptoms or changes.

Appendix I

ALLOWABLE CMS ICD-10 DIAGNOSIS CODES FOR HOME INR MONITORING

PRIMARY HYPERCOAGULABLE STATE

- D68.51 Activated protein C resistance
- D68.52 Prothrombin gene mutation
- D68.59 Other primary thrombophilia
- D68.61 Antiphospholipid syndrome
- D68.62 Lupus anticoagulant syndrome

PHLEBITIS & THROMBOPHLEBITIS

- I80.11 Right femoral vein
- I80.12 Left femoral vein
- I80.13 Femoral vein, bilateral
- I80.221 Right popliteal vein
- I80.222 Left popliteal vein
- I80.223 Popliteal vein, bilateral
- I80.231 Right tibial vein
- I80.232 Left tibial vein
- I80.233 Tibial vein, bilateral
- I80.211 Right iliac vein
- I80.212 Left iliac vein
- I80.213 Iliac vein, bilateral
- I80.241 Right peroneal vein
- I80.242 Left peroneal vein
- I80.243 Peroneal vein, bilateral
- I80.251 Right calf muscular vein
- I80.252 Left calf muscular vein
- I80.253 Calf muscular vein, bilateral
- I80.291 Other deep vessels of right lower extremity
- I80.292 Other deep vessels of left lower extremity
- I80.293 Other deep vessels of lower extremity, bilateral

PULMONARY EMBOLISM & INFARCTION

- I26.01 Septic, with acute cor pulmonale
- I26.09 Other, with acute cor pulmonale
- I26.90 Septic pulmonary embolism without acute cor pulmonale
- I26.93 Single subsegmental pulmonary embolism without acute cor pulmonale
- I26.94 Multiple subsegmental pulmonary emboli without acute cor pulmonale
- I26.99 Other pulmonary embolism without acute cor pulmonale

ATRIAL FIBRILLATION

- I23.6 Thrombosis of atrium, auricular appendage, and ventricle as current complications

- I48.0 Paroxysmal atrial fibrillation
- I48.11 Longstanding persistent atrial fibrillation
- I48.21 Permanent atrial fibrillation

OTHER

- I27.24 Chronic thromboembolic pulmonary hypertension
- I27.82 Chronic pulmonary embolism
- I67.6 Nonpyogenic thrombosis of intracranial venous system
- O87.3 Cerebral venous thrombosis in the puerperium
- Z79.01 Long term (current) use of anticoagulants

HEART VALVE REPLACEMENT

- Z95.2 Presence of prosthetic heart valve

VENOUS EMBOLISM AND THROMBOSIS OF THE DEEP VESSELS OF THE LOWER EXTREMITY, AND OTHER SPECIFIED VEINS/UNSPECIFIED SITES

ACUTE CHRONIC DESCRIPTION

- I82.210 I82.211 Superior vena cava
- I82.290 I82.291 Other thoracic veins
- I82.411 I82.511 Right femoral vein
- I82.412 I82.512 Left femoral vein
- I82.413 I82.513 Femoral vein, bilateral
- I82.421 I82.521 Right iliac vein
- I82.422 I82.522 Left iliac vein
- I82.423 I82.523 Iliac vein, bilateral
- I82.431 I82.531 Right popliteal vein
- I82.432 I82.532 Left popliteal vein
- I82.433 I82.533 Popliteal vein, bilateral
- I82.441 I82.541 Right tibial vein
- I82.442 I82.542 Left tibial vein
- I82.443 I82.543 Tibial vein, bilateral
- I82.A11 I82.A21 Right axillary vein
- I82.A12 I82.A22 Left axillary vein
- I82.A13 I82.A23 Axillary vein, bilateral
- I82.B11 I82.B21 Right subclavian vein
- I82.B12 I82.B22 Left subclavian vein
- I82.B13 I82.B23 Subclavian vein, bilateral
- I82.C11 I82.C21 Right internal jugular vein
- I82.C12 I82.C22 Left internal jugular vein
- I82.C13 I82.C23 Internal jugular vein, bilateral

OTHER SPECIFIED

ACUTE CHRONIC DESCRIPTION

- I82.451 I82.551 Embolism and thrombosis of right peroneal vein
- I82.452 I82.552 Embolism and thrombosis of left peroneal vein
- I82.453 I82.553 Embolism and thrombosis of peroneal vein, bilateral
- I82.461 I82.561 Embolism and thrombosis of right calf muscular vein

- I82.462 I82.562 Embolism and thrombosis of left calf muscular vein
- I82.463 I82.563 Embolism and thrombosis of calf muscular vein, bilateral
- I82.491 I82.591 Embolism and thrombosis of other specified deep vein of right lower extremity
- I82.492 I82.592 Embolism and thrombosis of other specified deep vein of left lower extremity
- I82.493 I82.593 Embolism and thrombosis of other specified deep vein of lower extremity, bilateral
- I82.890 I82.891 Embolism and thrombosis of other specified veins

DEEP VEINS

ACUTE CHRONIC DESCRIPTION

- I82.621 I82.721 Right upper extremity
- I82.622 I82.722 Left upper extremity
- I82.623 I82.723 Upper extremity, bilateral

OTHER VENOUS EMBOLISM & THROMBOSIS

- I82.0 Budd-Chiari syndrome
- I82.220 Acute, inferior vena cava
- I82.221 Chronic, inferior vena cava
- I82.3 Renal vein
- Z86.718 Personal history of other venous thrombosis and embolism

1. CMS Manual System PUB 100-20 Medicare Claims Processing. Centers for Medicare & Medicaid Services (CMS) Transmittal 2200 Date:November 8, 2018.

OCTOBER 10, 2019

APPENDIX J

REFERRAL RENEWAL PROCESS

TEF to the Responsible Anticoagulation Provider:

1. Reason: ***Advice*** Date: (pops in automatically)

   Comment: ***Hello Dr ***. If you would like Anticoagulation Services to continue to manage this patient's anticoagulant (***), please submit a "Renewal of Ambulatory Anticoagulation Monitoring" in EPIC. This form may be found under Meds & Orders by typing "REF11112A" or "Renewal" in the search box. Thank you.***

2. The encounter is then "routed" to the physician without closing the encounter re "send and close workspace".
3. After the doctor enters the referral, he will send a response back to us, such as "referral entered" in the "notes" area of the encounter.

Workflow outline for processing Anticoagulation Renewal Orders:

1. Sign in to the HFMG Anticoagulation Enrollment Pool
2. Keep track of the renewal orders that you had requested from providers and look for them to show up in the "Orders" folder
3. Complete the order to take it out of the HFMG Anticoagulation Enrollment Pool
4. Update the Specialty Comment for each patient receiving a renewal order
5. In a patient care "Documentation" encounter, indicate the acknowledgment that the renewal to continue monitoring anticoagulation therapy under (provider name here) was received on (date here)

Appendix K

FREQUENTLY ASKED QUESTIONS

- **How do you determine if a physician belongs to HFMG?**
  - On henryford.com search for the physician by name
    - If the physician has an HFMG Crest by their name or on their white coat, they are HFMG
- **How do you create a Smartphrase?**
  - While in a note, right click and select "create smartphrase"
  - Type in the content of your smartphrase and save
- **What critical INR results should be reviewed by the AC Pharmacist?**
  - Per policy, critical INR values between 5 and 10 without bleeding should be reviewed by the AC pharmacist
  - Per policy, critical INR values > 10 or patients with bleeding should be reported and reviewed by the patient's responsible anticoagulation physician
- **When determining if a patient should be bridged, what is considered severe thrombophilia?**
  - deficiency of protein C, protein S, or antithrombin; antiphospholipid antibodies; multiple abnormalities
- **How do you "bridge" a patient from a DOAC to warfarin?**
  - Apixaban
    - One approach is to discontinue apixaban and begin both a parenteral anticoagulant (enoxaparin) and warfarin at the time of the next dose of apixaban is taken. Discontinue parenteral agent when INR reaches acceptable range.
    - Patient may continue apixaban and start warfarin at the time the next dose of apixaban would have been taken. INR levels should be drawn 4 hours before next apixaban dose. Continue both until the INR reaches acceptable range. NOTE: apixaban can affect the INR
  - Rivaroxaban
    - Discontinue rivaroxaban and begin both a parenteral anticoagulant and warfarin at the time the next dose of rivaroxaban would have been taken. Discontinuing the parenteral anticoagulant when INR reaches an acceptable range.
    - Patient may continue apixaban and start warfarin at the time the next dose of rivaroxaban is taken. INR levels should be drawn 4 hours before next rivaroxaban dose. Continue both until the INR reaches acceptable range. NOTE: rivaroxaban affects INR
  - Dabigatran

        - CrCl > 50 mL/min – start warfarin 3 days before discontinuing dabigatran
        - CrCl 30 – 50 mL/min – start warfarin 2 days before discontinuing dabigatran
        - CrCl 15-30 mL/min – start warfarin 1 day before discontinuing
        - Note: dabigatran can increase the INR. INR will better reflect warfarin's effect after dabigatran stopped at least 2 days
    - Edoxaban
        - If taking 60 mg, decrease dose to 30 mg and begin warfarin concomitantly. Once stable INR $\geq$ 2, discontinue edoxaban
        - If taking 30 mg, decrease dose to 15 mg and begin warfarin concomitantly. Once stable INR $\geq$ 2, discontinue edoxaban
        - Parenteral option: Discontinue edoxaban and begin parenteral and warfarin at the time of the next scheduled edoxaban dose. Once stable INR $\geq$ 2, discontinue parenteral
        - Note: Measure INR at least weekly and just prior to daily edoxaban to minimize influence on INR value

❖ **What is the weight limit recommended for DOAC therapy?**

- Standard doses of apixaban or rivaroxaban recommended for patients weighing $\geq$ 120 kg or BMI $\geq$ 40

❖ **What are the current recommendations for DOAC use in cancer patients?**

- DOACs recommended over LMWH recommended over warfarin for cancer related VTE
- Rivaroxaban, edoxaban and apixaban have been studied and are acceptable
- LMWH should be used in patients with GI and GU cancers

❖ **What DOACs can you use for patients with PEG tubes?**

- Apixaban
    - Can crush tablets and add to applesauce or D5W if trouble swallowing or can deliver via NG tube
- Rivaroxaban
    - May crush pills and mix with applesauce or water if trouble swallowing or delivery via NG or gastric tube, follow with meal or enteral feeding
- Edoxaban
    - Instruct patients who cannot swallow the tablet whole to crush SAVAYSA, combine with 2 to 3 ounces of water or applesauce and ingest immediately.
    - Instruct patients who require a gastric tube to crush the SAVAYSA tablet and mix it with 2 to 3 ounces of water before administering immediately via the gastric feeding tube.
- **DO NOT USE** Dabigatran for patients with feeding tubes
    - Capsules must be swallowed whole, **do not open, break or chew**

❖ **How do you disenroll a DOAC patient?**

- Patients who may not be reached after several tries or will not follow recommendations may be disenrolled
- Disenrollment letters can be found in EPIC

Appendix L

Recommended Actions to Address Drug-drug Interactions

Tetracycline: Doxycycline Tetracycline Minocycline Demeclocycline	May increase INR. Mechanism unknown, but postulated mechanisms include: A tetracycline-induced reduction in prothrombin activity. reduction in GI flora essential for vitamin K production	Monitor INR and adjust dose if needed.
Macrolides: Erythromycin (E-mycin) Clarithromycin (Biaxin) Azithromycin (Zithromax)	May increase INR. Warfarin clearance decreased by approximately 14% due to possible inhibition of CYP3A4 by erythromycin. Azithromycin can have a delayed effect on the INR	Decrease warfarin dose by 30% and repeat INR in 5 days.
Metronidazole (Flagyl) – consider both oral and vaginal	Increase INR Inhibits CYP2C9	Decrease warfarin dose by 30-35% and repeat INR in 5 days.
Sulfonamides: SMZ-TMP (Bactrim/Septra)	Increase INR Mechanism may be multifactorial.	Decrease warfarin dose by 10-20% prior to starting sulfonamide and repeat INR in 5 days.
Fluconazole (Diflucan)	Increase INR Potent inhibitor of CYP2C9, potent inhibitor of CYP2C19 and moderate inhibitor of CYP3A4	Decrease warfarin dose by 10-20% and repeat INR in 3 to 5 days.
Quinolones : Levofloxacin (Levaquin) Moxifloxacin (Avelox) Norfloxacin (Norflox) Ciprofloxacin (Cipro)	Increase INR per number of case reports Mechanism difficult to identify	Early and more frequent monitoring recommended (every 3 to 5 days).
Dicloxacillin	Decrease INR The mechanism of this interaction has not been fully investigated, but dicloxacillin has been shown to induce both CYP3A4 and CYP2C9, enzymes responsible for warfarin metabolism	Increase warfarin dose 50% – 70% within a week of antibiotic initiation and repeat INR in 5 days. Effects may be evident for weeks following discontinuation of dicloxacillin.
Nafcillin	Decrease INR Proposed increased warfarin metabolism through moderate CYP3A4 induction and the R-enantiomer of warfarin is a CYP3A4 substrate.	Increase warfarin dose up to 50% within a week of antibiotic initiation and repeat INR in 5 days. High-dose (e.g., 12 g/day IV) nafcillin added to established warfarin therapy may warrant a 2- to 5-fold increase in warfarin dosage within 2

		weeks of starting therapy. The dosage of warfarin may be reduced to pretreatment levels within 4 weeks of discontinuing nafcillin therapy
Daptomycin (Cubicin) Telavancin (Vibativ)	False elevation in INR (in vitro effect or drug-lab interaction)	Draw INR **before** daptomycin or telavancin IVPB is infused.
Rifampin Rifapentine (Priftin) Rifabutin (Mycobutin)	Decrease INR The mechanism of this interaction is due to rifampin-mediated induction of the CYP enzymes responsible for vitamin K antagonist metabolism (eg, CYP3A4, CYP2C9, CYP1A2). Rifabutin and rifapentine will likely affect vitamin K antagonists in a similar fashion to rifampin, but to a lesser extent.	Increase warfarin dose up to 50% within 5 to 7 days of antibiotic initiation and repeat INR in 5 days. A 2- to 3-fold increase in the daily dose of warfarin may be needed within a week of starting rifamycins to maintain appropriate anticoagulation. Once the rifamycin is discontinued, the dose of warfarin will need to be decreased. May take at least 1 to 2 weeks following discontinuation for warfarin effects to return to previous levels.
Isoniazid	Increase INR weak CYP3A4 inhibitor and the R-enantiomer of warfarin is a CYP3A4 substrate.	Monitor INR closely and adjust accordingly. Weak evidence of increased warfarin effects.
Griseofulvin	Decrease INR Unclear mechanism, but commonly believed that griseofulvin enhances the hepatic metabolism of warfarin via induction of CYP1A2 and/or 2C9	May need to increase dose by 40% within 2 weeks of initiation of antibiotic. The interaction between warfarin and griseofulvin may require up to 12 weeks to fully manifest and may be more significant with the ultramicrocrystalline formulation of griseofulvin.

3. Interaction between Antiretrovirals and warfarin

Drug Class	Drug generic name	Abbreviation	Brand name (single entity)	Brand name (Combination product)
CCR5 Inhibitor	Maraviroc	MVC	Selzentry	-
Fusion Inhibitor	Enfuvirtide	T20	Fuzeon	-
Integrase strand transfer inhibitors (INSTIs)	Dolutegravir	DTG	Tivicay	Triumeq [Abacavir + dolutegravir + lamivudine]
	Elvitegravir	EVG	Vitekta	Genvoya [Elvitegravir + cobicistat + emtricitabine + tenofovir] Stribild [Elvitegravir + cobicistat + emtricitabine + tenofovir]
	Raltegravir	RAL	Isentress	-
Nonnucleoside reverse transcriptase inhibitors (NNRTIs)	Efavirenz	EFV	Sustiva	Atripla [Efavirenz + emtricitabine + tenofovir]
	Etravirine	ETR	Intelence	-
	Nevirapine	NVP	Viramune	-
	Rilpivirine	RPV	Edurant	Odefsey [Emtricitabine + rilpivirine + tenofovir] Complera [Emtricitabine + rilpivirine + tenofovir]

Drug Class	Drug generic name	Abbreviation	Brand name (single entity)	Brand name (Combination product)
Nucleoside reverse transcriptase inhibitors (NRTIs)	Abacavir	ABC	Ziagen	Epzicom [Abacavir + lamivudine] Triumeq [Abacavir + dolutegravir + lamivudine] Trizivir [Abacavir + lamivudine + zidovudine]
	Emtricitabine	FTC	Emtriva	Atripla [Efavirenz + emtricitabine + tenofovir] Genvoya [Elvitegravir + cobicistat + emtricitabine + tenofovir] Stribild [Elvitegravir + cobicistat + emtricitabine + tenofovir] Odefsey [Emtricitabine + rilpivirine + tenofovir] Descovy [Emtricitabine + tenofovir] Truvada [Emtricitabine + tenofovir] Complera [Emtricitabine + rilpivirine + tenofovir]
	Lamivudine	3TC	Epivir	Epzicom [Abacavir + lamivudine] Triumeq [Abacavir + dolutegravir + lamivudine] Trizivir [Abacavir + lamivudine + zidovudine] Combivir [Lamivudine + zidovudine]
	Tenofovir	TDF TAF	Viread Vemlidy	Atripla [Efavirenz + emtricitabine + tenofovir] Genvoya [Elvitegravir + cobicistat + emtricitabine + tenofovir] Stribild [Elvitegravir + cobicistat + emtricitabine + tenofovir] Odefsey [Emtricitabine + rilpivirine + tenofovir] Descovy [Emtricitabine + tenofovir] Truvada [Emtricitabine + tenofovir] Complera [Emtricitabine + rilpivirine + tenofovir]
	Zidovudine	ZDV	Retrovir	Trizivir [Abacavir + lamivudine + zidovudine] Combivir [Lamivudine + zidovudine]
Protease inhibitors (PIs)	Atazanavir	ATV	Reyataz	Evotaz [Atazanavir + cobicistat]
	Darunavir	DRV	Prezista	Prezcobix [Darunavir + cobicistat]
	Fosamprenavir	FPV	Lexiva	-
	Lopinavir	LPV	-	Kaletra [lopinavir + ritonavir]
	Indinavir	IDV	Crixivan	
	Ritonavir	RTV	Norvir	Kaletra [lopinavir + ritonavir]
	Saquinavir	SQV	Invirase	-
	Tipranavir	TPV	Aptivus	-
Pharmacokinetic enhancers/boosters	Cobicistat	COBI	Tybost	Evotaz [Atazanavir + cobicistat] Prezcobix [Darunavir + cobicistat] Genvoya [Elvitegravir + cobicistat + emtricitabine + tenofovir]

Drug Class	Drug generic name	Abbreviation	Brand name (single entity)	Brand name (Combination product)
				Stribild [Elvitegravir + cobicistat + emtricitabine + tenofovir]
	Ritonavir	RTV	Norvir	Kaletra [lopinavir + ritonavir]

Table-1 Current classes of ARV drugs:

Drug Class	Drug generic name	P-glycoprotein	2C9	3A4	2C19
CCR5 Inhibitor	Maraviroc				
Fusion Inhibitor	Enfuvirtide				
Integrase strand transfer inhibitors (INSTIs)	Dolutegravir				
	Elvitegravir		Inducer	Substrate	
	Raltegravir				
Nonnucleoside reverse transcriptase inhibitors (NNRTIs)	Efavirenz		Inhibitor	Inhibitor	Inhibitor
	Etravirine	Inducer	Inhibitor	Inducer	Inhibitor
	Nevirapine			Inducer, substrate	
	Rilpivirine				
Nucleoside reverse transcriptase inhibitors (NRTIs)	Abacavir				
	Emtricitabine				
	Lamivudine				
	Tenofovir				
	Zidovudine				
Protease inhibitors (PIs)	Atazanavir	Inhibitor		Inhibitor	
	Darunavir		Inducer	Inhibitor	
	Fosamprenavir	Inhibitor		Inhibitor, weak inducer	
	Lopinavir			Inhibitor	
	Inidinavir				
	Ritonavir	Inhibitor	Inducer	Inhibitor	Inducer
	Saquinavir	Inhibitor		Inhibitor	
	Tipranavir	Inducer		Inhibitor	
Pharmacokinetic enhancers/boosters	Cobicistat	Inhibitor		Inhibitor	
	Ritonavir	Inhibitor	Inducer	Inhibitor	Inducer

Table-2 Selected mechanisms of ARV-associated drug interactions:

Drug Class	Drug abbreviation	Warfarin	Dabigatran	Apixaban	Rivaroxaban	Edoxaban
Integrase strand transfer inhibitors (INSTIs)	EVG/c EVG + PI/r	Possible ↓ in INR since Elvitegravir (EVG) induces 2C9.	↑ dabigatran possible No dosage adjustment for dabigatran if CrCl >50 mL/min. Avoid coadministration	↑ apixaban expected (AVOID)	↑ rivaroxaban expected (AVOID)	↑ edoxaban expected (AVOID)

Drug Class	Drug abbreviation	Warfarin	Dabigatran	Apixaban	Rivaroxaban	Edoxaban
			if CrCl <50 mL/min.			
Nonnucleoside reverse transcriptase inhibitors (NNRTIs)	EFV, NVP	↑ or ↓ warfarin possible. Monitor INR and adjust warfarin dose accordingly.	-	-	-	-
	ETR	↑ warfarin possible. Monitor INR and adjust warfarin dose accordingly.	-	-	-	-
Protease inhibitors (PIs)		PI/r possibly ↓ warfarin. Monitor INR closely when stopping or starting PI/r and adjust warfarin dose accordingly. No data on ATV/c, DRV/c interactions. Monitor INR closely when stopping or starting PI/c and adjust warfarin dose accordingly. If switching between RTV and COBI, the effect of COBI on warfarin is not expected to be equivalent to RTV's effect on warfarin.	All RTV-boosted PIs, ATV/c, DRV/c may Possibly ↑ dabigatran. No dosage adjustment if CrCl >50 mL/min. Avoid coadministration if CrCl <50 mL/min.	All PIs ↑ apixaban expected [AVOID]	All PIs ↑ rivaroxaban. [AVOID]	All PIs ↑ edoxaban. [AVOID]

Table-3 Drug interactions between ARVs and anticoagulants:

EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; PI/r = ritonavir-boosted protease inhibitor; EFV = efavirenz; NVP = nevirapine; ETR = etravirine; ATV/c = atazanavir/cobicistat; DRV/c = darunavir/cobicistat; RTV = ritonavir; COBI, c = cobicistat

3. Interactions of Analgesics and Anti-inflammatory Drugs with Warfarin

Drug	Mechanism Impact on INR	Management of Interaction (Recommendations based on patient using these agents consistently daily. As needed, use does not usually require dosage adjustment)
Aspirin (ASA)	Increase INR Inhibit platelet aggregation	Concomitant use of warfarin and ASA not recommended for most indications. If prescribed by physician, check indication and seek to discontinue if possible
Tylenol (Acetaminophen; APAP)	Increase INR Absolute mechanism unknown	daily acetaminophen doses exceeding 1.3 or 2 g/day for multiple consecutive days, should have their INR tested within 3-5 days of the first acetaminophen dose, consider lowering warfarin dosage per algorithm
NSAIDs - See limited examples of non-selective NSAID below: Ibuprofen (Motrin, Advil, Nuprin) Naproxen (Aleve, Naprosyn) Indomethacin (Indocin) Diclofenac (Voltaren)	Increase INR Inhibit platelet aggregation	Concomitant use of warfarin and NSAIDs not recommended. If cleared by physician, monitor for s/s of bleeding and lower warfarin dose as needed per algorithm. Advise patient regarding risks for GI bleed.
COX-2 Inhibitors: Celecoxib (Celebrex) Meloxicam (Mobic)	May increase risk for GI bleeding. Have little to no effect on platelet function and bleeding time at therapeutic doses.	Concomitant use with warfarin not recommended, however if patient requires an NSAID, these may be associated with fewer hospitalizations for GI bleeding events compared to non-selective NSAIDs.
Opioids	Alone have no effect on INR	No warfarin adjustment necessary.
Opioid combination products containing acetaminophen: Vicodin, Lortab, Lorcet, Norco, Zydone, Fioricet, Percocet	May increase INR due to large (>2 gm/d) doses of acetaminophen	Monitor INR and titrate warfarin dose according to algorithm.
Corticosteroids: Prednisone Methylprednisolone Prednisolone Dexamethasone	High dose corticosteroids Increase INR. Lower doses may have variable effects (may increase or decrease INR) Mechanism of action unknown	Corticosteroids alone may increase the risk for GI bleeding. For corticosteroid "bursts," decrease warfarin dose by 10% to 15% and recheck INR in 5 to 7 days. For lower-dose corticosteroids, monitor INR weekly and adjust warfarin dose according to algorithm.

4: Interactions of Lipid Lowering Drugs with Warfarin

Drug	Mechanism & Impact on INR	Management of Interaction
HMG CoA Reductase Inhibitors: Lovastatin (Mevacor) Fluvastatin (Lescol) Simvastatin (Zocor) Pravastatin (Pravachol) Rosuvastatin (Crestor) Atorvastatin (Lipitor)	Lovastatin and fluvastatin most likely to elevate the INR due to inhibition of CYP2C9. Case reports of elevated INR after simvastatin initiation in patients stable on warfarin. Pravastatin and rosuvastatin may have a modest effect	Monitor for increased effects of oral anticoagulants if an HMG-CoA reductase inhibitor is initiated/dose increased, or decreased effects if discontinued/dose decreased, adjust accordingly.

Drug	Mechanism & Impact on INR	Management of Interaction
	Atorvastatin has no known interaction with warfarin	No warfarin adjustment necessary.
Fibric Acid Derivatives: Fenofibrate (Tricor) Gemfibrozil (Lopid)	May increase INR due Suggested mechanisms: displacement of warfarin from protein binding sites increased affinity of anticoagulant for binding sites altered anticoagulant metabolism	May warrant a 25% to 33% decrease in warfarin dose if fibric acid derivative started. May take up to two weeks for interaction to occur. Monitor INR weekly and adjust accordingly.
Bile acid sequestrants: Cholestyramine Colestipol	Decreases INR. Binds to warfarin in the GI tract with concomitant administration.	Separate the administration of vitamin K antagonists and cholestyramine by at least 4 hours to minimize this interaction. Because dose separation may not eliminate the effects of this interaction, monitor for decreased INR and adjust accordingly.

5: Interaction of Gastroenterological Drugs with Warfarin

Drug	Mechanism & Impact on INR	Management of Interaction
Cimetidine (Tagamet)	Increase INR Inhibits metabolism	Avoid. Substitute other H2 antagonist such as ranitidine (Zantac) or famotidine (Pepcid) If unavoidable, monitor for increased bleeding and adjust warfarin dose per INR
Proton Pump Inhibitors: Omeprazole (Prilosec) Lansoprazole (Prevacid) Pantoprazole (Protonix) Esomeprazole (Nexium) Rabeprazole (Aciphex)	Increase INR Suspected PPI mediated inhibition of R-warfarin metabolism via CYP2C19	Monitor for signs of bleeding and INR results. Adjust warfarin dose accordingly
Sucralfate (Carafate)	Decrease INR Mechanism most likely involves sucralfate binding to warfarin within the GI tract and thereby reducing warfarin absorption	Administer warfarin at **least 2 hours** before or **at least 6 hours** after sucralfate to avoid moderate interaction
Fiber-containing products (e.g., Metamucil)	Decreased absorption of warfarin when given in proximity to warfarin.	Per the psyllium manufacturers, administration of other prescribed oral drugs should be separated from the administration of psyllium by at least 2 hours.
Aprepitant (Emend)	Increase or decrease in the exposure of warfarin is possible	INR should be closely monitored during the 2-week period (particularly at 7 to 10 days) after the initiation of an aprepitant or fosaprepitant dosage regimen cycle, regardless of the indication or dose.

6: Interactions of Cardiovascular Drugs with Warfarin

Drug	Mechanism & Impact on INR	Management of Interaction
Amiodarone (Cordarone)	Increase INR Inhibit metabolism	Monitor INR every week and adjust dose down. May need 30-50% reduction over weeks. May take several months to see effect. Monitor INR every week and titrate dose up if drug discontinued.
Dronedarone (Multaq)	Increase INR Dronedarone is moderate inhibitor of CYP-3A4 Onset of interaction, if it occurs, is 7-10 days	1) Repeat INR 1 week after starting dronedarone 2) Adjust warfarin dose accordingly.
Quinidine	INR/PT might be unchanged in the face of increased bleeding Additive hypoprothrombinemia associated with concomitant administration	Monitor INR closely if quinidine is added to warfarin therapy.
Propafenone (Rhythmol)	Increase INR inhibit metabolism	Lower warfarin dose by 20-30%
Ethacrynic Acid (Edecrin)	Increase INR Plasma protein displacement	Data is very limited but may need to monitor closely when added to warfarin therapy and decrease warfarin dose accordingly. May also consider recommending a loop-diuretic instead.
Spironolactone (Aldactone)	Decreased INR due to diuresis-induced increase in clotting factor levels	Closely monitor the INR if coadministration of warfarin with spironolactone is necessary

7: Interactions of Antiepileptic Drugs with Warfarin

Drug	Mechanism & Impact on INR	Management of Interaction
Carbamazepine (Tegretol)	Decrease INR Induces metabolism	50% increase in warfarin is recommended within a few weeks of carbamazepine initiation. Effect of induction can last up to one month after carbamazepine discontinued, therefore, monitor INR weekly.
Phenytoin (Dilantin) and Fosphenytoin	Induction or inhibition or altered protein binding sites	Monitor INR more closely. May see initial increase in INR secondary to altered protein binding; then after longer use see decrease INR secondary to increase metabolism
Phenobarbital Primidone (Mysoline)	Decrease INR Induces metabolism	Monitor for decreased therapeutic effects of oral anticoagulants if a barbiturate is initiated/dose increased (anticoagulant dose increases of 30% to 60% may be needed, depending on INR results). Effect of induction can last up to one month after barbiturate discontinued. An increased frequency of INR/PT monitoring should be considered for the period

Drug	Mechanism & Impact on INR	Management of Interaction
		immediately following barbiturate initiation/dosage changes.
Valproic acid and derivatives	Increase INR Displacement of warfarin from binding sites	Monitor INR closely when valproic acid/valproate sodium is initiated. May need to lower warfarin dose by 20-30%
Felbamate (Felbatol)	Increase INR Probable Inhibition of metabolism	Monitor INR weekly when felbamate is initiated or discontinued. (Micromedex). Lexapro and Clinical Pharmacology report no known interaction

8: Interactions of Sedatives and Psychotropic Drugs with Warfarin

Drug	Mechanism & Impact on INR	Management of Interaction
SSRIs Fluoxetine (Prozac) Fluvoxamine (Luvox) Paroxetine (Paxil) Sertraline (Zoloft) Citalopram (Celexa) Escitalopram (Lexapro)	Increase INR Inhibition of metabolism (CYP2C9) Inhibition of metabolism (CYP1A9) Mechanism unknown Mechanism unknown	Monitor INR weekly at initiation of SSRI. Consider lowering warfarin dose by 10%. Onset is delayed. Upon discontinuation of SSRI effect can still last for another month. Therefore, monitor INR weekly.
quetiapine	Increase INR	Increase monitoring of INR and signs/symptoms of bleeding for several weeks after starting quetiapine or after increasing quetiapine dose. Similarly, quetiapine discontinuation and/or dose reduction may also be associated with changes in INR and warfarin dose requirements.
Trazodone (Deseryl)	Decrease INR	Increase warfarin dose by 10% and monitor INRs weekly.
Wellbutrin (Bupropion)	Reports of increased PT/INR post-market Mechanism unknown	Prudent to monitor INR closely when initiating bupropion with patients stable on warfarin therapy and adjust accordingly if necessary. If used for smoking cessation, may see elevation in the INR due to discontinuation of tobacco use.

9: Interaction between Miscellaneous Drugs and Warfarin

Drug	Mechanism & Impact on INR	Management of Interaction
Antithyroid Drugs Propylthiouracil (PTU) Methimazole (Tapazole)	May **increase the INR** due to anti-vitamin K properties, but as hyperthyroidism is corrected, the **INR can decrease** due to changes in the clearance of endogenous clotting factors	Monitor weekly when antithyroid drug is added or discontinued, or thyroid status changes, and adjust warfarin for INR
Thyroid Hormones Levothyroid (Synthroid)	Altered catabolism of vitamin K clotting factors Increase INR	Decrease dose of warfarin by 10%. If patient's thyroid dose is being titrated, be sure to adjust dose upward accordingly (10% increments). Monitor

Drug	Mechanism & Impact on INR	Management of Interaction
		INRs as often as patient is being monitored for thyroid function. Effect may not be seen for up to 3 months.
Allopurinol	Increase INR	Monitor INR weekly and decrease warfarin dose accordingly as needed
Bosentan (Tracleer)	Decreased INR Bosentan is significant inducer of liver metabolism isoenzymes CYP2C9 and CYP3A4.	Onset of interaction is about 10-14 days Warfarin dosage increase is necessary when bosentan is added to a warfarin regimen
Miconazole (topical)	Inhibits metabolism Increase INR	Empiric reduction in warfarin dose (of 10-20%) together with extra monitoring of warfarin response (ie, INR testing, signs/symptoms of bleeding) to guide any further dose adjustment
Detrol (tolterodine)	May be related to decreased gastrintestinal transit due to anticholinergic effect increasing absorption of warfarin Increase INR	Three case reports of elevated INR within two weeks of starting tolterodine. Monitor INRs more closely after starting or stopping tolterodine.
Smokeless Tobacco	Increase Vitamin K ingestion	Monitor INR. May need to increase dose of warfarin.
azathioprine	Decrease INR Warfarin concentrations decreased Mechanism of drug interaction unknown	Monitor INR weekly and increase warfarin dose accordingly when Azathioprine is added for patient stable on warfarin. Conversely, INR should be monitored weekly once azathioprine discontinued and warfarin dose decreased accordingly.
Mercaptopurine	Decrease INR reported Mechanism of action unknown Increased risk of bleeding due to thrombocytopenia	Monitor INR weekly when Mercaptopurine added to stable patient or the dose is increased and increase warfarin dose as necessary. Warfarin dose adjustments may be required when mercaptopurine is discontinued.
Tramadol	Increased INR	Evaluate INR closely and frequently. Adjust warfarin dose accordingly.
Influenza vaccinations	No known drug interaction	Close monitoring of INR values is not required after influenza vaccination in patients on stable long-term VKA regimens.
Marijuana (cannibus)	Increase INR Cannabis constituents delta-9-tetrahydrocannabinol (THC), cannabidiol (CBD), and cannabinol inhibit the cytochrome P450 2C9 (CYP2C9)-mediated 7-hydroxylation of S-warfarin in a concentration-dependent manner.	Monitor INR and adjust warfarin accordingly. Promote consistency with use. There are also three case reports of patients chronically taking warfarin that developed a spike in international normalized ratio (INR) after smoking cannabis or taking medical cannabis orally.

10: Selected interaction between anti-cancer Drugs and Warfarin (also see text below regarding chemotherapy-warfarin interactions)

Drug	Mechanism & Impact on INR	Management of Interaction
Capecitabine (Xeloda)	Inhibition of CYP2C9 metabolism of warfarin Significant rise in INR noted Effects may be delayed several days to several months after concurrent therapy was initiated or 1 month after stopping capecitabine therapy	Warfarin dosage reduction **up to** 50% may be necessary. Many of the reported interactions have resulted in severe bleeding, large INR changes, and/or substantial reductions in warfarin dose requirements. (Age greater than 60 and a diagnosis of cancer independently predispose patients to an increased risk of coagulopathy)
Tamoxifen	Increase INR inhibition of CYP2C9-mediated warfarin metabolism Combined use of tamoxifen with warfarin is **contraindicated in U.S. labeling** due to risk of excessive anticoagulant response and resultant increased risk of bleeding (Lexicomp 2022)	A significant warfarin dosage reduction may be necessary…"in those in which the combination was continued, significant reductions in warfarin dose requirements (of approximately 35-60%) were noted" (Lexicomp 2022) Monitor INR frequently.

(Updated 8.1.2021 through 1.14.22 – NR)

Appendix M

HFMG Ambulatory Anticoagulation Services Physician Champions (Contact information for Providers Only – NOT for patient use)

All ACS Physician Champions may be reached via HALO:

Roles/Teams > search **HFMG Anticoag Service Physician Champion** to contact group.

Co-Medical Directors:

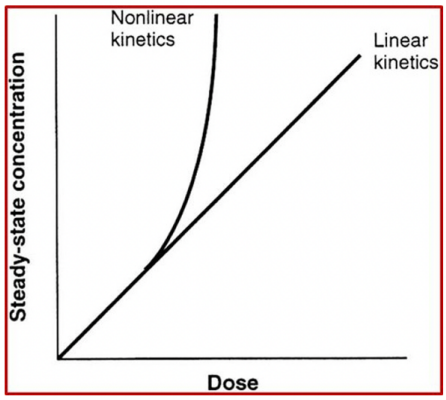
- Gregory Krol, MD ph: (313) 4XX-XXX6
- Michael Hudson, MD ph: (313) 5XX-XXX6
- Phillip Kuriakose, MD ph: (313) 5XX-XXX2
- Scott Kaatz, DO, MSc ph: (248) 3XX-XXX8

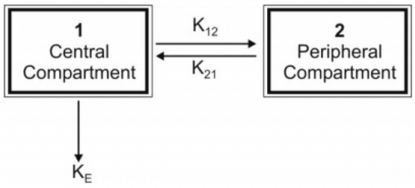
Appendix N

Enoxaparin Use in Obesity

Overview

- Enoxaparin is a hydrophilic molecule
- The volume of distribution of enoxaparin approximates blood volume
  - On this basis, it would be considered to have a small V_d (4-5 liters)
- Drugs that are primarily hydrophilic have difficulty passing through lipid membranes and remain mostly in vascular space and lean muscle mass
- Other common drugs for context (for 70 kg patient)
  - Apixaban V_d ~ 21 liters
  - Fentanyl V_d ~ 28 liters
  - Rivaroxaban V_d ~ 50 liters
  - Vancomycin V_d ~50 liters
  - Propofol V_d ~ 4200 liters
  - Amiodarone V_d ~ 4620 liters
- For drug therapies with moderate to large V_d, as the patient's body size increases, space for the drug to distribute into also increases
- Blood volume, which approximates enoxaparin V_d, does **not** increase linearly with increases in body weight
  - Therefore, there is a strong physiologic basis for potential over exposure to small V_d drugs (like enoxaparin) in morbid obesity
  - *Non-linear pharmacokinetics*





Guideline Commentary on Enoxaparin Dosing in Morbid Obesity	
Recommendations from the ICM-VTE: General. *J Bone Joint Surg Am*, 2022 Mar 16;104(Suppl 1):4-162.	No comment regarding enoxaparin dosing in obesity
American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. *Blood Adv* (2020) 4 (19): 4693–4738.	No comment regarding enoxaparin dosing in obesity
2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation. Circulation. 2019;140:e125–e151.	No comment regarding enoxaparin dosing in obesity
Antithrombotic Therapy for VTE Disease: Second Update of the CHEST Guideline and Expert Panel Report. *CHEST* 2021; 160(6):2247-2259	No comment regarding enoxaparin dosing in obesity
Antithrombotic Therapy for VTE Disease CHEST Guideline and Expert Panel Report. *CHEST* 2016; 149(2):315-352	No comment regarding enoxaparin dosing in obesity
2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation. *Circulation*, 2014;130:e199-e267	No comment regarding enoxaparin dosing in obesity

Studies Describing Enoxaparin Dosing in Morbid Obesity						
Reference	**Design**	**N**	**BMI Weight**	**Treatment Received**	**Findings**	**Comments**
Clin Pharmacol Ther. 2002 Sep;72(3):308-18. doi: 10.1067/mcp.2002.127114.	Open label pharmacokinetic study	24	Obese: 33.2 ± 9.7 Nonobese: 31.3 ± 10.1	Enoxaparin 1.5 mg/kg SUBQ daily, ×4 days	No bleeding noted. This was otherwise an open label trial in healthy volunteers. Anti-Xa activity, exposure at steady-state was 16% higher in obese volunteers than in nonobese volunteers (p = 0.001)	Small open label study Not designed to assess safety/efficacy

Thromb Res. 2005;116(1):41-50.	Nonrandomized, open label, prospective	233	Mean weight 78 kg 81 patients had BMI > 30	Enoxaparin 1.5 mg/kg daily or 1 mg/kg bid; no maximum dose	Mean anti-Xa activity was similar between patients with a BMI ≥18 and ≤30 kg/m2 and those with a BMI >30 kg/m2 for both daily and BID dosing	BMI on the lower end among population Difficult to note exact BMIs
J Thromb Thrombolysis. 2011 Aug;32(2):188-94.	Case series	26	Median weight 162 kg (106–243) Median BMI 49.5 kg/m2 (40.1–98.1)	Median starting dose 0.8 mg/kg BID	Anti-Xa at goal 46% Anti-Xa above goal 38% Unable to be interpreted 15% 40% of patients above goal had a bleeding event compared to none of the at goal patients No thrombotic events occurred	Among the 10 patients with anti-Xa levels above goal, the median initial dose was 0.85 mg/kg (range 0.75–1) versus 0.74 mg/kg (range 0.51–1) for patients at goal Severe cases of morbid obesity represented
J Thromb Thrombolysis. 2015;39:516-521.	Retrospective observational cohort	31	Median weight 138 kg (105-197) Median BMI 46.2 kg/m2 (40.1–62)	Enoxaparin 0.75 mg/kg based on actual body weight for patients with a weight > 200 kg or BMI ≥ 40 kg/m2	Anti-Xa at goal 48% Anti-Xa above goal 36% Anti-Xa below goal 16% Bleeding (n =2) Thrombosis (n = 1)	Of the 24 patients who achieved an anti-Xa level in goal range at some point during their admission, the mean enoxaparin dose needed to achieve this therapeutic anti-Xa was 0.71 mg/kg twice daily Small study
Clin Appl Thromb Hemost. 2015;21:513-520.	Prospective observational cohort	41	Median weight 138.1 kg (95.3-266.7) Median BMI 45.6 (36.8-92.1) Fifteen patients weighed 150 kg	Median weight-based and absolute enoxaparin dose was 0.90 mg/kg and 120 mg every 12 hours	Anti-Xa at goal 38.9% Anti-Xa above goal 50% Anti-Xa below goal 11.1% Median dose of enoxaparin that resulted in therapeutic Xa was 0.83 mg/kg 19.5% experienced bleeding, only one of which was major No thrombotic complications	Univariable logistic regression identified mg/kg dosing based on ABW as an independent predictor of having a supratherapeutic anti-Xa level at steady state Median dose of enoxaparin supratherapeutic anti-Xa and 0.98 mg/kg
Pharmacotherapy. 2015;35:1007-1015.	Retrospective observational cohort	99	Mean weight 146.3 +/- 31.0 kg Mean BMI 50.6 +/- 9.85 kg/m2	Standard FDA dosing 1 mg/kg Q12 for CrCl > 30 ml/min or Q24 if < 30 ml/min	Anti-Xa at goal 35.4% Anti-Xa above goal 50.5% Anti-Xa below goal 14.1% No bleeding complications	In the sub-group with a TBW more than 150 kg, 54.3% of patients had anti-factor Xa levels in the supratherapeutic range
Clin Drug Investig. 2020 Jan;40(1):33-40.	Retrospective observational cohort	241	Unable to pull article	Unable to pull article	BMI of 40-50 kg/m^2 Median therapeutic dose was 0.97 mg/kg q12h BMI of 50-60 kg/m^2 median therapeutic dose was 0.70 mg/kg q12 BMI over 60 kg/m^2 median therapeutic dose was 0.71 mg/kg q12 4.1% incidence of major bleeding	

References:

1. Hanni CM, Wilhelm SM, Korkis B, et al. *Hosp Pharm,* 2019; Dec; 54(6): 371–377. doi: 10.1177/0018578718802839
2. Lexi-Drugs. Lexicomp app. UpToDate Inc. Accessed September 6 2023.
3. Lemmens HJM, Bernstein DP, Brodsky JB. Estimating blood volume in obese and morbidly obese patients. *Obes Surg*, 2006;16:773-776

Appendix O

Currently Available EPIC Smartphrases

6.3.24

Name	Description
ACCENC	For full details regarding patient anticoagulation therapy management, look for the "anticoag visit" under the "Encounters" in the "Chart Review"
ACENCP	For full details regarding patient anticoagulation therapy management, look for the "anti coag visit" note under the "Encounters" tab in the "Chart Review". Providers may contact x at ###-###-#### ext. n"
ANTICOAGGASTROLETTER	Used in free form letter to inform patients of recommendation for a PPI when patient takes an anticoagulant and antiplatelet medications concomitantly
ANTICOAGGASTROPRODOC	Used in anticoag encounter progress note to document new order for PPI for gastroprotection
ANTICOAGGASTROPROTECTION	Provider message for patients who qualify for PPI therapy due to anticoagulation plus antiplatelet therapy
ASADCEMAILWITHREFENCES	Used by HFMG ACS practitioners to alert providers when a patient may be on aspirin inappropriately
ASADCTEF	Template for TEF messages to providers regarding patients who could potentially be on ASA therapy inappropriately
ASKDRABOUTDOACMANAGEMENTACC	Message to provider to inform that ACS manages DOAC patients and ask if provider would like patient to be enrolled
DOACHOLDTEF	Patient DOAC hold requiring ACS physician advice
DOACPROGRESSNOTE2	Trial template for standardized DOAC documentation
HFMGVTETOC	Template for HFMG ACS Pharmacist documentation of HFMG patient enrollment from ED
MYCHARTACCESSLETTERACC	Recommendation with numbers to call to sign up for MyChart
MYCHARTHOWTOACCESSLETTERSACC	Message for patient with summary for how to access letters in MyChart
NARPTID	Patient identified by name and birthdate
NONHFMGVTETOC	For documentation of non-HFMG patients with ED referral to HFMG ACS by ACS pharmacists
OUTSIDELABORDERINR	Standing lab order for PT/INR
PADOACDOSE	TEF use – describes recommended OAC dose for indication of PAD
WARFARINPROGRESSNOTE	Template for standardized warfarin progress note
WARFHOLDVTEORAF	TEF use – warfarin hold advice request to provider for VTE or AF

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Michael Ericksen, PharmD

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