County of Los Angeles **Department of Health Services**

Los Angeles County Department of Health Services
Practice Guideline

SUBJECT/TITLE: Management of Anticoagulation in Adults

PURPOSE: To provide evidence-based guidance for the initiation and management of patients receiving therapeutic anticoagulant therapy. These guidelines are intended to assist providers in managing anticoagulation in most clinical situations. They should not replace provider judgment or expert consultation.

ABBREVIATIONS:

VKA – vitamin K antagonist
IV – intravenous
LMWH – low molecular weight heparin
UFH – unfractionated heparin
DOAC – direct oral anticoagulant
VTE – venous thromboembolism
APLS – Antiphospholipid Syndrome
AF, AFib – atrial fibrillation
DTI – direct thrombin inhibitor
DVT – deep venous thrombosis
PE – pulmonary embolism
CrCl – creatinine clearance
ACS – acute coronary syndrome
PCI – percutaneous coronary intervention
HIT – heparin induced thrombocytopenia
NSTEMI – non-ST-elevation MI

BACKGROUND: Anticoagulant medications inhibit the formation of blood clots. Therapeutic anticoagulation in adults is used in many clinical situations, the most common of which include:

- treatment and prevention of venous thromboembolic (VTE) disease,
- treatment of acute myocardial infarction,
- prevention of valve thrombosis and arterial thromboembolism in patients with artificial heart valves, and
- prevention of stroke in patients with atrial fibrillation.

Historically, most patients requiring parenteral anticoagulation received subcutaneous low molecular weight heparin (LMWH) or intravenous unfractionated heparin (UFH). Those requiring oral anticoagulation received warfarin, a vitamin-K antagonist that has a narrow therapeutic index and requires frequent lab monitoring.

More recently, several non-vitamin K antagonist oral anticoagulants have been developed. These are alternately referred to as novel oral anticoagulant (NOAC) or direct oral anticoagulant (DOAC) medications. Rivaroxaban, apixaban, and edoxaban inhibit factor Xa; dabigatran is a direct thrombin inhibitor (DTI).

Multidisciplinary coordination is necessary to maximize the benefits of anticoagulation while minimizing the risk of adverse events. This practice guideline aims to provide evidence-based clinical guidance for the management of therapeutic anticoagulation.

GUIDELINES:

Medication Selection:

Factors influencing the choice of anticoagulant medication include the site of care (e.g. inpatient vs outpatient), clinical indication, potential drug-drug interactions, and patient-specific factors (e.g. comorbidities, renal function, liver function, and patient preference). The following table is a general guide to the indications, advantages, and disadvantages of anticoagulant medications. It is intended to aid the provider in selection of an appropriate medication. Dosing and monitoring are addressed in subsequent sections.

Table 1: How to Select an Anticoagulant Medication

	Clinical Indications											Route	Considerations
	Arterial emboli	ACS	APLS	Bridging	LV thrombus	Prosthetic valve	DVT/PE	HIT	Non-valvular AF	Valvular AF	PCI		
Heparin	X	X	X	X	X	X	X		X	X	X	IV	- Narrow therapeutic window - Frequent monitoring required - Can be used with renal impairment - Risk of heparin-induced thrombocytopenia
LMWH		X	X	X	X	X	X		X	X	X	Subcut	- Weight-based dosing - Caution with renal impairment - Can be used in pregnancy - Effective for malignancy-associated VTE
Argatroban								X				IV	- Can be used with renal impairment - Can be used for patients with history HIT and any other indication for anticoagulation
Fondaparinux		X		X			X					Subcut	- Weight-based dosing - Cannot be used with CrCl < 30
Warfarin	X		X		X	X	X		X	X		PO	- Many drug-drug and drug-food interactions - Narrow therapeutic window - Frequent lab monitoring required - Longer half-life - Can be used with renal impairment - Not for use in pregnancy
DOAC							X	X	X			PO	- Caution with morbid obesity (> 120kg) - Not for use in pregnancy - Caution with renal or hepatic impairment - Avoid use with dual P-gp/CYP3A inhibitors and dual P-gp/CYP3A inducers

Initiation, Dosing, and Monitoring of Individual Anticoagulants:

1. **Intravenous unfractionated heparin (UFH)** – refer to inpatient heparin policy

2. **Low molecular weight heparin (LMWH)**
   a. Enoxaparin dosing and administration
      i. Round dose to the nearest 10mg dose or calibrated syringe size (see Table 3)
      ii. Preferred injection sites are the anterolateral or posterolateral abdominal wall. If abdominal access is limited, the upper outer quadrants of the thighs or buttocks can be used. Do not inject into the arms

Table 2: Enoxaparin Dosing[i]

Clinical Indication	Usual dose (CrCl ≥ 30 mL/min)	Impaired renal function (CrCl below 30 mL/min)
Acute DVT and/or PE	1mg/kg subcut Q12h	1mg/kg subcut daily†
VTE prophylaxis in abdominal surgery	40mg subcut daily	30mg subcut daily
VTE prophylaxis in hip/knee replacement surgery	30mg subcut Q12h	30mg subcut daily
VTE prophylaxis in acute medical illness	40mg subcut daily	30mg subcut daily

†Heparin is preferred over LMWH in patients with impaired renal function (CrCl <30 ml/min). Enoxaparin may be used at renally-adjusted doses for short term transition to warfarin.

Table 3: Rounding enoxaparin dosage[ii]

Weight (kg)	How to round 1mg/kg dose	Syringe Size
Less than 100kg	Round to the nearest 10mg	60mg, 80mg, or 100mg
100-109	Administer 100mg	100mg
110-127	Administer 120mg	120mg
128-142	Administer 135mg	150mg
143-155	Administer 150mg	150mg
More than 155kg	Round as appropriate with 2 syringes	2 syringes

   b. Extreme weight:
      i. Weight > 150kg: recommended initial dose of enoxaparin is 150mg Q12h
      ii. Enoxaparin dose should be adjusted based on drug activity (Anti Xa) as explained in a later section
   c. Drug-drug interactions: Bleeding risk is increased with concomitant use of other anticoagulant medications (e.g. warfarin, DOACs) or medications with antiplatelet properties (e.g. aspirin, NSAIDs)

d. Laboratory monitoring:
   i. Routine monitoring of enoxaparin activity is not recommended
   ii. Monitoring may be indicated in the setting of obesity (weight > 144kg), pregnancy, and impaired renal function (CrCl < 30mL/min)
   iii. Lab titled "Anti Xa, LMWH" in ORCHID
   iv. Draw level **4 hours after** the 2nd or 3rd dose to monitor the **peak** level

Table 4: Baseline and maintenance lab tests for enoxaparin

Baseline	CBC, aPTT, PT/INR, renal and liver function	
Periodically	Platelets	
Drug activity	**When to monitor**[iii]	Monitoring recommended in pregnancy or weight > 144kg Consider monitoring when CrCl < 30mL/min
	Lab Test	Anti Xa, LMWH (draw 4 hours after dose for **peak** level)
	Target Anti Xa Range[iv]	**Enoxaparin Dosing:** / **Target Anti Xa Range:** Therapeutic Q12h dosing / 0.6 – 1.0 IU/mL Therapeutic Q24h dosing / > 1.0 IU/mL Prophylactic dosing / 0.1 – 0.3 IU/mL

Table 5: Enoxaparin dose adjustments based on peak Anti Xa levels[v]

Peak Anti Xa Level (units/mL)	Recommended Dosage Adjustment*
< 0.35	Increase dose by 25%
0.35 – 0.49	Increase dose by 10%
0.50 – 1.04	None
1.05 – 1.50	Decrease dose by 20%
1.51 – 2.00	• Delay next dose by 3 hours • Decrease dose by 30%
> 2.00	• Delay next dose until Anti Xa level < 0.5 • Decrease dose by 40%

*Suggested dose adjustments for therapeutic Q12 dosing

3. Warfarin

a. Choosing an initial dose of warfarin
b. Initial dosing should be tailored to patient bleed risk, potential sensitivity to warfarin, goal INR range, and potential drug interactions (Appendix A)
c. If patient was previously therapeutic on warfarin, resume previous therapeutic dose
d. For the warfarin-naïve patient, the **usual initial warfarin dose is 5mg**
e. Consider an initial dose less than 5mg in the following situations:

- Age over 60 years
- Weight less than 45kg
- Asian race (Filipino)
- Recent major surgery or high risk of bleeding
- Known or suspected congestive heart failure (CHF) or liver disease
- Malnourished or NPO for more than 3 days
- Significant drug interactions that are expected to enhance warfarin effect (Appendix A)

Table 6: Warfarin initiation

Warfarin initiation nomogram for goal INR 2-3		
Day	**INR**	**Usual initiation**
1	NA	5mg
2	Less than 1.5	5mg
	1.5 – 1.9	2.5mg
	2.0 – 2.5	1-2.5mg
	Greater than 2.5	None
3	Less than 1.5	5-10mg
	1.5 – 1.9	2.5-5mg
	2.0 – 3.0	0-2.5mg
	Greater than 3.0	None
4	Less than 1.5	10mg
	1.5 – 1.9	5-7.5mg
	2.0 – 3.0	0-5mg
	Greater than 3.0	None
5	Less than 1.5	10mg
	1.5 – 1.9	7.5-10mg
	2.0 – 3.0	0-5mg
	Greater than 3.0	None

After Day 5:

After day 5, when INR is therapeutic, the daily maintenance dose can be estimated as:

$$\text{Estimated Maintenance Dose} = \frac{\text{(Sum of all doses given in past 7 days)}}{7}$$

f. Guide to warfarin overlap therapy
   i. When patients require urgent therapeutic anticoagulation, warfarin should be initiated in combination with a parenteral anticoagulant (such as LMWH or heparin). This is referred to as "overlap" therapy.
   ii. During overlap therapy, coverage with a parenteral anticoagulant should be continued at least 5 days and until the INR is at goal for 24 hours

Overlap therapy **recommended**
- Acute DVT or PE
- Acute cardiac thrombus
- Protein C or S deficiency

Overlap therapy **usually not indicated**
- Nonvalvular atrial fibrillation

   iii. Overlap therapy differs from perioperative bridging therapy (which refers to the use of parenteral anticoagulants during a temporary interruption of warfarin). Refer to perioperative bridging guidelines for additional guidance
   iv. Overlap therapy does not apply to initiation of other non-VKA oral anticoagulants
g. Drug-drug interactions with warfarin – refer to Appendix A
h. Drug-food interactions with warfarin – refer to Appendix B
i. Warfarin maintenance:

Table 7: Baseline and maintenance lab tests for warfarin

Baseline	CBC, PT/INR, aPTT, and liver function – to assess coagulation status		
Periodically	CBC (frequency of monitoring depends on patient's comorbidities)		
Drug activity	**Routine monitoring is mandatory†**		
	Lab test	INR	
	Suggested testing frequency‡	Labile INR	Every 1-2 weeks (minimum)
		Stable INR	Every 4-5 weeks (minimum)
		Extremely stable INR	Every 6-8 weeks (minimum)
	Target INR	Usual target INR	2.5 (range 2.0 – 3.0)
		Mechanical mitral valve	3.0 (range 2.5-3.5)

†Patients receiving extended warfarin therapy should be managed in an anticoagulation clinic.
‡Many factors can affect the necessary frequency of INR testing. See outpatient anticoagulation policies for specific recommendations

4. Direct Oral Anticoagulants (DOACs)

a. General:
   i. DOACs differ from vitamin K antagonists in their onset of action, half-life, drug-drug interactions, need for monitoring, and availability of antidotes.
   ii. DOACs are generally used without a requirement for monitoring of drug levels or coagulation times; this may be an advantage for patients in whom frequent monitoring is a greater burden
   iii. Patients with difficulty in controlling PT/INR may benefit from a DOAC because these agents have less variability in drug effect than vitamin K antagonists
   iv. Bleeding risk is increased when DOAC medications are combined with ADP antagonist medications, such as clopidogrel. Consultation with a cardiologist is recommended in this situation.

b. Laboratory Monitoring[vi]

Table 8: Baseline and maintenance lab tests for DOAC medications

Baseline	• CBC, PT/INR, and aPTT – to assess coagulation status • Renal, liver function – to determine appropriate agent and dose
Periodically	• CBC, renal function, and liver function • Frequency of monitoring depends on patient's comorbidities
Drug activity	Routine monitoring is not recommended

c. DOAC medications include:
   i. Factor Xa inhibitors – rivaroxaban, apixaban, edoxaban, betrixaban
   ii. Direct thrombin inhibitors – dabigatran

d. See the following tables for detailed suggestions regarding initiation, dosing, and drug-drug interactions
   i. For DOAC medications, creatinine clearance should be calculated with **actual** (rather than ideal) **body weight**

Table 9: Selection, Dosing, and Drug-Drug Interactions for Factor Xa Inhibitors

	Rivaroxaban	Apixaban (nonformulary)	Edoxaban (nonformulary)
Nonvalvular Atrial Fibrillation (NVAF)	**CrCl > 50** 20mg PO daily, or 15mg (if combined w/ clopidogrel)° **CrCl 15-50** 15mg PO daily	**Standard dose:** 5mg PO bid **Reduced dose:** 2.5mg PO bid (with any two of: age ≥80, wt ≤60kg, SCr ≥1.5)	**CrCl > 95** Not recommended **CrCl 51-95** 60mg PO daily **CrCl 15-50** 30mg PO daily **CrCl < 15** Not recommended
Acute VTE Treatment	**CrCl ≥ 30** 15mg PO BID for 21 days, then 20mg PO daily **CrCl < 30** Not recommended	**Standard dose:** 10mg PO BID for 7 days, then 5mg PO BID **CrCl < 25** Not recommended	**AFTER 5-10 days of a parenteral anticoagulant** **Standard dose:** 60mg PO daily **Reduced dose:** 30mg PO daily (if CrCl 15-50 or wt ≤60kg) **CrCl < 15** Not recommended
Secondary prophylaxis of VTE	**CrCl ≥ 30** 20mg PO daily, or 10mg PO daily† **CrCl < 30** Not recommended	**CrCl ≥ 25** 5mg PO BID, or 2.5mg PO BID‡ **CrCl < 25** No clinical studies	Not FDA approved
Post-op VTE prophylaxis	**Start 6-10 hours post-op** **THA** 10mg PO daily for 35 days **TKA** 10mg PO daily for 12 days **CrCl < 30** Not recommended	**Start 12-24 hours post-op** **THA** 2.5mg PO BID for 25 days **TKA** 2.5mg PO BID for 12 days **CrCl < 30** No clinical studies	Not FDA approved
Drug-Drug Interactions	**Do not use in combination with:** -Dual P-gp and strong CYP3A4 inhibitors* -Dual P-gp and strong CYP3A4 inducers* **Avoid use with** dual P-gp and moderate CYP3A4 inducers if CrCl < 80 **Bleeding risk is increased** when combined with anticoagulant, antiplatelet, NSAID, SSRI, and SNRI medications	**Dual P-gp and strong CYP3A4 Inhibitors** -Doses >2.5mg BID: reduce dose by 50% -2.5mg BID: avoid use **Dual P-gp and strong CYP3A4 Inducers** -Avoid use **Bleeding risk is increased** when combined with anticoagulant, antiplatelet, NSAID, SSRI, and SNRI medications	**P-gp Inhibitors** -NVAF: no dose reduction recommended -VTE treatment: 30mg PO once daily **P-gp Inducers** -Avoid use **Bleeding risk is increased** when combined with anticoagulant, antiplatelet, and NSAID medications

†EINSTEIN CHOICE trial °PIONEER AF-PCI trial
‡AMPLIFY-EXTEND trial

Abbreviations: CrCl – creatinine clearance (mL/min); SCr – serum creatinine; THA – total hip arthroplasty; TKA – total knee arthroplasty

*Examples of P-glycoprotein and CYP3A4 inhibitors and inducers. **Consult references such as Micromedex or Lexi-Comp for complete drug interaction information.**

P-gp inhibitors: amiodarone, itraconazole, ketoconazole, macrolides, quinidine, ritonavir, verapamil
CYP3A4 inhibitors: amiodarone, azoles, diltiazem, isoniazid, macrolides, quinolones, ritonavir, valproic acid
P-gp inducers: carbamazepine, rifampin, St John's wort
CYP3A4 inducers: carbamazepine, phenobarbital, phenytoin, pioglitazone, rifampin, rifabutin, St John's wort

Table 10: Initiation, Dosing, and Drug-Drug Interactions for Dabigatran

Indications	Dosing
Nonvalvular Atrial Fibrillation (NVAF)	**CrCl > 30** 150mg PO BID **CrCl 15-30** 75mg PO BID **CrCl < 15** Not recommended
Acute VTE Treatment	**AFTER 5-10 days of a parenteral anticoagulant** **CrCl > 30** 150mg PO BID **CrCl < 30** Not recommended
Secondary prophylaxis of VTE	**CrCl ≥ 30** 150mg PO BID **CrCl < 30** Not recommended
Post-op VTE prophylaxis[7]	**Start 1-4 hours post-op** **THA** 110mg PO once, then 220mg po daily for 28-35 days **TKA** 110mg PO once, then 220mg po daily for 10-14 days **CrCl < 30** Not recommended
Drug-Drug Interactions	**Do not use in combination with P-gp inhibitors if CrCl < 50** **P-gp Inhibitors*** -NVAF with CrCl 30-50: 75mg PO BID -NVAF with CrCl < 30: not recommended -Acute VTE with CrCl < 50: not recommended **P-gp Inducers*** -Avoid use **Bleeding risk is increased** when combined with anticoagulant, antiplatelet, NSAID, SSRI, and SNRI medications
*Examples of P-glycoprotein and CYP3A4 inhibitors and inducers. **Consult references such as Micromedex or Lexi-Comp for complete drug interaction information.**	
P-gp inhibitors: amiodarone, itraconazole, ketoconazole, macrolides, quinidine, ritonavir, verapamil P-gp inducers: carbamazepine, rifampin, St John's wort	

5. Argatroban – requires consultation with hematology/oncology

a. Indication: heparin-induced thrombocytopenia

Table 11: Initiation and Dosing of Argatroban

<table>
<tr><th>Indication</th><th colspan="2">Heparin-Induced Thrombocytopenia (HIT)</th></tr>
<tr><td>Dosing</td><td colspan="2">Usual starting dose: 2 mcg/kg/minute (maximum: 20 mg/hour)
Hepatic impairment (Child-Pugh B/C): 0.5 mcg/kg/minute
Critically ill patients (multi-organ failure): 0.2 mcg/kg/minute</td></tr>
<tr><td>Baseline labs</td><td colspan="2">CBC, aPTT, PT/INR , renal and liver function</td></tr>
<tr><td>Monitoring parameters</td><td colspan="2">• Check aPTT and INR every morning and 2-6 hours after starting or after any rate change
• Hold argatroban for 2 hours if INR > 4 and/or aPTT > 130</td></tr>
<tr><td>Infusion Management</td><td colspan="2">Adjust argatroban according to aPTT level (goal 75-100 seconds)
<table>
<tr><th>aPTT (sec)</th><th>Action</th></tr>
<tr><td>Less than 50</td><td>Increase infusion rate by 25%</td></tr>
<tr><td>50-74</td><td>Increase infusion rate by 10%</td></tr>
<tr><td>75-100</td><td>No change</td></tr>
<tr><td>101-130</td><td>Decrease infusion rate by 50%</td></tr>
<tr><td>Greater than 130</td><td>Stop infusion for 2 hours, then decrease infusion rate by 50%</td></tr>
</table></td></tr>
<tr><td>Overlap with warfarin</td><td colspan="2">• Argatroban increases INR
• If argatroban is overlapped with warfarin, interpret INR carefully. Consider hematology consult.</td></tr>
</table>

6. Fondaparinux

a. Indication: patients requiring anticoagulation that have suspected acute heparin-induced-thrombocytopenia (HIT) or a confirmed history of HIT

b. Dose and schedule are dependent on body weight and renal function.

Table 12: Initiation and Dosing of Fondaparinux

<table>
<tr><td>Indication</td><td>Anticoagulation in patients with acute (suspected) or remote HIT</td></tr>
<tr><td>Therapeutic Dosing</td><td>Therapeutic dose is based on body weight and renal function
<table>
<tr><th>CrCl (mL/min)</th><th colspan="3">Patient weight (kg)</th></tr>
<tr><th></th><th>Less than 50 kg</th><th>50-100 kg</th><th>Above 100 kg</th></tr>
<tr><td>Above 50</td><td>5mg Q24h</td><td>7.5mg Q24h</td><td>10mg Q24h</td></tr>
<tr><td>30 – 50</td><td>2.5mg Q24h</td><td>5mg Q24h</td><td>7.5mg Q24h</td></tr>
<tr><td>Below 30</td><td colspan="3">Contraindicated</td></tr>
</table></td></tr>
<tr><td>Prophylactic Dosing</td><td>Prophylactic use is contraindicated in patients if CrCl < 30 mL/min and patients weighing less than 50kg
<table>
<tr><th>CrCl (mL/min)</th><th>Prophylactic Dose</th></tr>
<tr><td>Above 50</td><td>2.5mg Q24h</td></tr>
<tr><td>Below 50</td><td>2.5mg Q48h</td></tr>
</table></td></tr>
<tr><td>Baseline Labs</td><td>CBC, aPTT, PT/INR , renal and liver function</td></tr>
<tr><td>Procedural considerations</td><td>• The clearance half-life in normal renal function is 17 to 21 hours. It is advisable to hold the drug for 24 to 48 hours prior to invasive procedures with a high bleeding risk.
• Wait at least 12 hours before starting or resuming fondaparinux after surgery.</td></tr>
</table>

Transition between anticoagulant agents:

Table 13: Transition from DOAC agents to warfarin

<table>
<tr><th></th><th>Transition to warfarin</th></tr>
<tr><td>Rivaroxaban to warfarin</td><td>
• No clinical trial data available
• Rivaroxaban affects INR, so INR measurements during coadministration with warfarin may not reflect the appropriate dose of warfarin
Transition Options
• Discontinue rivaroxaban and begin both a parenteral anticoagulant and warfarin at the time the next dose of rivaroxaban would have been taken (XARELTO package insert information)[8]
• Overlap rivaroxaban and VKA therapy until the INR is within the therapeutic range (ASH 2018 guidelines)[9]
</td></tr>
<tr><td>Apixaban to warfarin</td><td>
• Apixaban affects INR, so INR measurements during coadministration with warfarin may not reflect the appropriate dose of warfarin
Transition Options
• Discontinue apixaban and begin both a parenteral anticoagulant and warfarin at the time the next dose of apixaban would have been taken (ELIQUIS package insert information)[10]
• Overlap apixaban and VKA therapy until the INR is within the therapeutic range (ASH 2018 guidelines)
</td></tr>
<tr><td>Edoxaban to warfarin</td><td>
Transition Options[11]
• Oral option:
- For patients taking 60 mg edoxaban, reduce dose to 30 mg and begin warfarin concomitantly
- For patients taking 30 mg edoxaban, reduce dose to 15 mg and begin warfarin concomitantly
- Once a stable INR ≥ 2.0 is achieved, discontinue edoxaban and continue warfarin (INR should be measured just prior to daily dose of edoxaban to minimize influence of edoxaban on INR)
• Parenteral option:
- Discontinue edoxaban and administer a parenteral anticoagulant and warfarin at the time of the next scheduled edoxaban dose
</td></tr>
<tr><td>Dabigatran[12] to warfarin</td><td>
• Dabigatran may affect INR. INR reflects warfarin's effect best after dabigatran has been stopped for at least 2 days
<table>
<tr><th>CrCl (mL/min)</th><th>Instructions:</th></tr>
<tr><td>CrCl ≥ 50</td><td>Start warfarin 3 days before discontinuing dabigatran</td></tr>
<tr><td>CrCl 30-50</td><td>Start warfarin 2 days before discontinuing dabigatran</td></tr>
<tr><td>CrCl 15-30</td><td>Start warfarin 1 day before discontinuing dabigatran</td></tr>
<tr><td>CrCl < 15</td><td>No recommendations available</td></tr>
</table>
</td></tr>
</table>

Table 14: Transition from DOAC agents to other rapid-onset anticoagulants

From	To	Instructions:
Rivaroxaban	**Any rapid-onset anticoagulant** (IV UFH, LMWH, fondaparinux, or DOACs)	Stop rivaroxaban. Start other anticoagulant when the next dose of rivaroxaban was scheduled to be given.
Apixaban		Stop apixaban. Start other anticoagulant when the next dose of apixaban was scheduled to be given.
Edoxaban		Stop edoxaban. Start other anticoagulant when the next dose of edoxaban was scheduled to be given.
From	**To**	**Instructions:**
Dabigatran	IV UFH, LMWH, fondaparinux	Stop dabigatran. Start parenteral anticoagulant: - 12 hr after last dose of dabigatran (if CrCl ≥ 30 ml/min) - 24 hr after last dose of dabigatran (if CrCl < 30 ml/min)
	Other DOAC	Stop dabigatran. Start new DOAC when next dose of dabigatran was scheduled to be given[13]

Table 15: Transition from parenteral anticoagulants to other anticoagulants

From	To	Instructions:
LMWH (therapeutic dose)	**Rivaroxaban**	Discontinue LMWH. Start rivaroxaban 0-2 hours before the time of the next scheduled evening dose of LMWH.
	Apixaban	Discontinue LMWH. Start apixaban at time of next scheduled dose of LMWH.
	Edoxaban	Discontinue LMWH. Start edoxaban at time of next scheduled dose of LMWH.
	Dabigatran	Discontinue LMWH. Start dabigatran 0-2 hours before the time of next scheduled dose of LMWH.
	Warfarin	Begin warfarin when clinically indicated. Continue LMWH until INR is therapeutic (note that in the setting of acute VTE, LMWH should be given with warfarin for a minimum of 5 days **and** until the INR is therapeutic)
	UFH	Discontinue LMWH. Start UFH 0-4 hours before the time of the next scheduled dose of LMWH. If bleeding risk is high, consider omitting initial heparin bolus.[14],[15]
UFH	**Rivaroxaban**	Discontinue IV heparin. Start rivaroxaban immediately.
	Apixaban	Discontinue IV heparin. Start apixaban immediately.
	Edoxaban	Discontinue IV heparin. Start edoxaban 4 hours later.
	Dabigatran	Discontinue IV heparin. Start dabigatran immediately.
	LMWH	Discontinue IV heparin. Start enoxaparin within 1 hour
	Warfarin	Begin warfarin when clinically indicated. Continue IV heparin INR is therapeutic (note that in the setting of acute VTE, heparin should be given with warfarin for a minimum of 5 days **and** until the INR is therapeutic)

Table 16: Transition from warfarin to other anticoagulants

From	To	Instructions:
Warfarin	**Rivaroxaban**	Discontinue warfarin. Start rivaroxaban when INR is below 3.0
	Apixaban	Discontinue warfarin. Start apixaban when INR is below 2.0
	Edoxaban	Discontinue warfarin. Start edoxaban when the INR is ≤ 2.5
	Dabigatran	Discontinue warfarin. Start dabigatran when INR is below 2.0
	IV UFH	Discontinue warfarin. Start IV UFH when INR is below 2.0

Anticoagulant education:

1. Inpatient setting
    a. Patients are provided medication-specific education regarding any anticoagulant medication that is initiated or changed at the time of hospital discharge
    b. Education may be provided by transition-of-care pharmacy team, the discharge nurse, or the primary nurse
2. Outpatient setting – refer also to outpatient anticoagulation policies
    a. Warfarin
        i. Patient will be managed in a dedicated anticoagulation clinic and will receive warfarin-specific education
    b. Non-warfarin anticoagulants
        i. Patient may be managed in an anticoagulation clinic, by primary care, or by a specialty care clinic (such as hematology/oncology or cardiology). Patient will receive medication-specific education any time an anticoagulant medication is initiated or changed

Reversal of anticoagulation: Refer to "Reversal of Anticoagulation" practice guideline

Perioperative management of anticoagulation: Refer to "Perioperative management of anticoagulation" practice guideline

Appendix A – Clinically Significant Drug Interactions with Warfarin

- Most drug interactions with warfarin will start to take effect within 3-5 days of concurrent therapy
- Some notable exceptions (e.g. amiodarone, carbamazepine, rifampin) will start to affect warfarin within 7-14 days of concurrent therapy
  - Warfarin dose may need to be reduced by 25-50% if a patient is on amiodarone concurrently
  - Warfarin dose may need to be increased by 50% or more if a patient is on rifampin concurrently
- This list is not all-inclusive. Reliable references such as Micromedex or Lexi-Comp must be consulted for complete drug interaction information.

Drug-drug interactions with warfarin[16]		
Enhance effect of warfarin (increase INR)		**Decrease effect of warfarin (decrease INR)**
Alcohol (acute)	**Fenofibrate**	Aluminum hydroxide
Allopurinol	**Fluorouracil**	Barbiturates
Amiodarone	**Fluoxetine**	Bonsetan
Anabolic steroids	**Fluvoxamine**	Carbamazepine
Antimicrobials, especially:	Gemfibrozil	Cholestyramine
- **Fluoroquinolones**	Isoniazid	Dicloxacillin
- **Metronidazole**	Levothyroxine	Estrogens
- **TMP/SMX**	**Methotrexate**	Griseofulvin
Azole Antifungals	**Paroxetine**	Mesalamine
Capecitabine	**Procarbazine**	Nafcillin
Carboplatin	Propafenone	Oral contraceptives
Celecoxib	Proton pump inhibitors	Phenobarbital
Chloral hydrate	Protease inhibitors	**Phenytoin**
Citalopram	**Ropinirole**	Ribavirin
Clofibrate	**Sertraline**	Rifabutin
Cyclophosphamide	**Statins**	**Rifampin**
Diazoxide	**Sulfisoxazole**	Ritonavir
Diltiazem	Sulfonamide	Sucralfate
Disulfiram	Sulfonylurea	Vitamin K
Doxorubicin	**Tamoxifen**	
Escitalopram	**Venlafaxine**	
Ethacrynic acid	**Vincristine**	
Etoposide		

- Bold text implies major drug interaction
- TMP/SMX = trimethoprim/sulfamethoxazole

Appendix B – Clinically Significant Food Interactions with Warfarin

<table>
<tr><th colspan="2">Food and Nutrition interactions with warfarin[17]</th></tr>
<tr><td colspan="2">
• Patients on long term warfarin therapy can be sensitive to the fluctuating levels of vitamin K from both external dietary sources and internal gastrointestinal sources.
• Increased dietary intake of vitamin K can reduce the effectiveness of warfarin and decrease the INR.
• Promote consistent intake of dietary vitamin K and not avoidance.
• Since warfarin is a highly protein-bound drug, malnourished patients with low albumin levels will have higher concentrations of unbound drug and may experience faster INR response. Conversely, patients receiving enteral nutrition will have more bound drug due to the high protein concentration in these products.
• For patients receiving tube feeds:
- Hold the tube feeds 1 hour before and after warfarin administration
- If on cycled tube feeding, administer warfarin at a time when tube feeds are off
</td></tr>
<tr><th>Enhances effect of warfarin
(increases INR)</th><th>Decreases effect of warfarin
(decreases INR)</th></tr>
<tr><td>Alcohol (acute ingestion)
Cranberry juice
Dong Quai
Danshen
Evening primrose oil
Fenugreek
Ginko
Glucosamine
Grapefruit
Licorice
Omega-3 fatty Acids
Willow bark</td><td><u>Foods with high vitamin K</u>:
Leafy green vegetables
- Spinach
- Kale
- Chard
- Cabbage
- Romaine lettuce
- Mustard greens
Oils
- Canola oil
- Mayonnaise
- Soybean oil
Asparagus
Avocado
Bok Choy
Broccoli
Brussels sprouts
Green beans
Green onions
Green peppers

<u>Other</u>:
Co-Enzyme Q10
Ginseng
Goldenseal
Green tea
St. John’s Wort
Yarrow</td></tr>
</table>

References:

[i] Lovenox: Highlights of Prescribing Information. http://products.sanofi.us/lovenox/lovenox.pdf. Accessed 5/17/2019

[ii] Adapted from Wyoming Medical Center protocol. https://wyomingmedicalcenter.org/documents/WMC_Anticoagulation_Protocol.pdf

[iii] ACCP Antithrombotic Therapy and Prevention of Thrombosis Panel. Executive summary: antithrombotic therapy and prevention of thrombosis, 9th ed. Chest. 2012;141(2 suppl):

[iv] Quest Diagnostics. https://www.questdiagnostics.com/testcenter/TestDetail.action?ntc=30292. Accessed 5/28/2019

[v] Adapted from Mongale P, et al. Chest 2001; 119 (suppl 1):344-370 and University of Washington https://depts.washington.edu/anticoag/home/tags/enoxaparin

[vi] Conway SE, Hwang AY, Ponte CH, et al. Laboratory and clinical monitoring of direct acting oral anticoagulants: what clinicians need to know. Pharmacotherapy 2017;37(2):236-248

[7] Falck-Ytter Y, Francis CW, Johanson NA. et al. Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 suppl):e278S-e325S. doi: 10.1378/chest.11-2404.

[8] Xarelto: Highlights of Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/202439s017lbl.pdf Accessed May 30, 2019

[9] Witt DM, Nieuwlaat R, Clark NP, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy. Blood Adv. 2018;2(22):3257.

[10] Eliquis: Highlights of Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/202155s012lbl.pdf Accessed May 30, 2019

[11] Savaysa: Highlights of Prescribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206316lbl.pdf. Accessed May 30, 2019

[12] Pradaxa: Highlights of Prescribing Information. http://bidocs.boehringer-ingelheim.com/BIWebAccess/ViewServlet.ser?docBase=renetnt&folderPath=/Prescribing%20Information/PIs/Pradaxa/Pradaxa.pdf. Accessed 5/30/2019

[13] UW Anticoagulation guidelines

[14] UW Anticoagulation Guidelines http://depts.washington.edu/anticoag/home/sites/default/files/Conversion%20among%20parenteral%20anticoagulants.pdf

[15] Hellerslia V, Mehta P. Transition of Anticoagulants 2016. http://www.thomasland.com/AnticoagTransitions_2016.pdf Accessed June 2019.

[16] Hull RD, Garcia DA, Vazquez SR. Biology of warfarin and modulators of INR control. In J Tirnauer, L Leung (Eds.) *UpToDate*. Available from https://www.uptodate.com/contents/biology-of-warfarin-and-modulators-of-inr-control?search=biology%20of%20warfarin&source=search_result&selectedTitle=2~149&usage_type=default&display_rank=1 Accessed on May 30, 2019.

[17] Hull RD, Garcia DA, Vazquez SR. Warfarin and other VKAs: dosing and adverse effects. J Tirnauer, L Leung (Eds.) *UpToDate*. Available from https://www.uptodate.com/contents/warfarin-and-other-vkas-dosing-and-adverse-effects?search=warfarin%20food%20interactions&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2 Accessed on May 30, 2019.