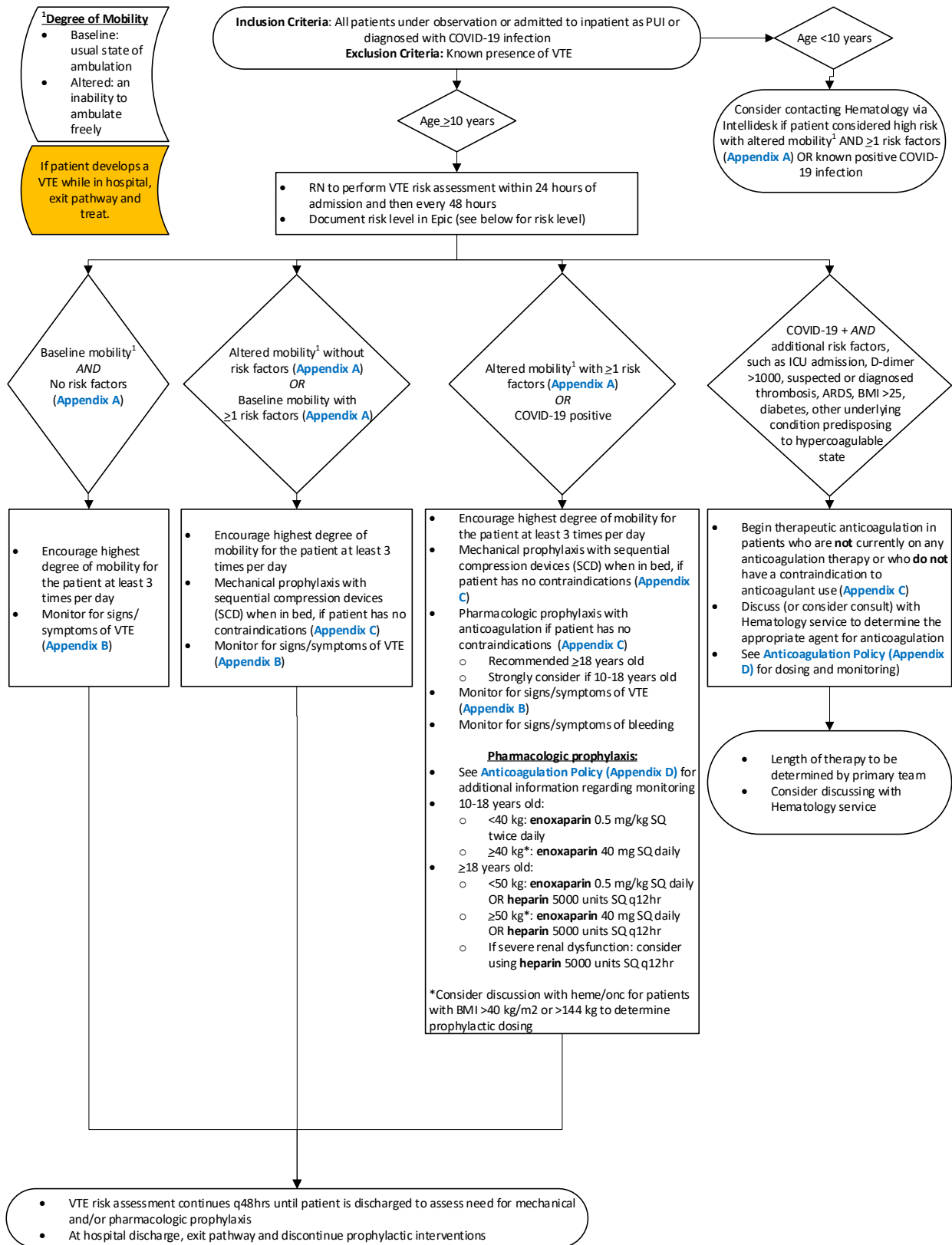


CLINICAL PATHWAY: COVID-19 Venous Thromboembolism (VTE) Prevention Clinical Pathway

THIS PATHWAY SERVES AS A GUIDE AND DOES NOT REPLACE CLINICAL JUDGMENT.



NEXT PAGE



CONTACTS: KENNETH BANASIAK, MD | DONNA BORUCHOV, MD | HEATHER SCHLOTT, MD | JOHN SCHREIBER, MD
 This pathway is subject to change, based on evolving recommendations from the CDC and CT DPH.

LAST UPDATED: 02.12.21



- Blood stream infection
- Central venous catheter (including non-tunneled, tunneled and PICCs)
- Cardiovascular low flow compromise
- History of VTE
- Severe dehydration
- Inflammatory disease (e.g. IBD, SLE)
- Severe systemic infection
- COVID-19 infection of any severity
- Medications: asparaginase, estrogen use, ie contraception (within past 2 months)
- Obesity (<18 yrs old: BMI > 95th percentile; ≥18 yrs old: BMI >30)
- Oncologic diagnosis
- Orthopedic procedures (e.g. hip or knee reconstruction)
- Pregnancy
- Nephrotic syndrome
- Thrombophilia (known history of, or family history of, clots)
- Sickle Cell disease
- Trauma (>1 lower extremity long bone fracture, complex pelvic fractures, spinal cord injury)
- Surgery within past 30 days



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Symptoms of VTE may include any or all of the following at the site of an extremity clot:

- Pain
- Tenderness
- Swelling
- Change in skin color (reddish or bluish skin color)
- Increased warmth to touch

Symptoms of a pulmonary embolism (PE) may include any or all of the following:

- Sudden shortness of breath (difficulty breathing)
- Patient reported anxiety (sense of “impending doom”)
- Rapid pulse (tachycardia)
- Sweating (diaphoresis)
- Sharp chest pain (may get worse with deep breaths)
- Unexplained cough (may cough up blood or be a dry cough)
- Fainting (syncope)

Adapted from: Children’s Hospital of Philadelphia Venous Thromboembolism (VTE) Prevention Clinical Pathway – Inpatient



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Contraindications to sequential compression devices (SCD):

- Suspected or existing DVT (can use GCS)
- Extremity to be used has an acute fracture
- Skin conditions affecting extremity (e.g. dermatitis, burn)
- Unable to achieve correct fit due to patient size
- Note: use SCD with caution if PIV access is in extremity to be used


Contraindications to pharmacologic anticoagulation:

- Absolute:
 - Known bleeding disorder or tendency to bleed
 - Evidence or risk of hemorrhage
 - Uncontrolled bleeding
 - Platelet count unable to be sustained >50,000mm³
 - Uncorrected coagulopathy
 - Acute stroke or brain ischemia
 - Allergy to heparin or enoxaparin [example: history of heparin-induced thrombocytopenia (HIT)]
- Relative:
 - Intracranial mass
 - Lumbar puncture or epidural catheter placement within last 4 hours
 - Epidural or lumbar catheter removal in prior 12 hours
 - Neurosurgical procedure or injury (e.g. complete spinal cord injury)
 - Pelvic fracture within past 48 hours
 - Uncontrolled hypertension
 - Anticipated procedure with risk of bleeding within 12 hours



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	Anticoagulation Protocol	Date of Origin:	October 01, 2008
	Approved By: Pharmacy & Therapeutics Committee, Clinical Council	Date Approved:	December 1, 2020

I. Purpose

The purpose of this document is to provide a standardized approach for the treatment and monitoring of patients requiring anticoagulant therapy (heparin, enoxaparin, warfarin, apixaban, rivaroxaban, and argatroban) and reversal agents (prothrombin complex (Kcentra), protamine and vitamin K). This protocol applies to any anticoagulation (including long-term prophylaxis) where the clinical expectation is that there will be a measurable systemic effect from the anticoagulant therapy, and/or the patient's laboratory values for coagulation will remain outside normal values.

II. Definitions

- | | |
|---|--|
| Anti-Xa - anti-factor Xa | IM-Intramuscular |
| aPTT- activated partial thromboplastin time | INR-International normalized ratio |
| CBC – Complete blood count | LMWH-low molecular weight heparin (e.g. Lovenox) |
| CrCl-Creatinine Clearance | PE-Pulmonary embolism |
| DVT-Deep vein thrombosis | PT-prothrombin time |
| HIT-Heparin induced thrombocytopenia | SQ-subcutaneous |
| | VTE-Venous thromboembolism |

III. Inclusion/Exclusion Criteria/Indications/Definitions

Inclusions: patients that are currently admitted who are new to anticoagulation therapy requiring initiation and/or maintenance of therapy, or those who have been on therapy in the past now need a new anticoagulation regimen.


Exclusions:

1. Patients on intravenous heparin for the purpose of maintaining catheter patency (e.g. heparin flushes or 1 unit/ml infusions)
2. Patients following cardiac surgery and cardiac catheterization procedures. These patients may be started on empiric heparin infusions, without establishing goal anti-Xa levels, until such time as the patient can be transitioned off all anticoagulation or onto oral anticoagulation/anti-platelet therapy.
3. Patients on routine short-term prophylactic anticoagulation for:
 - a) Venous thrombo-embolism prevention, **and**
 - b) The clinical expectation is that the systemic effect is minimal and/or brief, **and**
 - c) Laboratory values for coagulation will remain within, or close to normal values.
4. Patients on Extracorporeal Membrane Oxygenation (ECMO) – refer to Connecticut Children's: ECMO Anticoagulation Management Guideline
5. Patients who are managed chronically on an outpatient basis for chronic anticoagulation and have a patient-specific plan that has been previously identified and documented in the chart.



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6. Per attending discretion, patients who are deemed unqualified for protocol for various circumstances, which would be then identified further in the electronic health record.

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V. Rationale

Anticoagulation therapy poses risks to patients and potential for significant harm due to the complexity of dosing and monitoring, infrequent use in pediatric patients and interpatient variability in response. The use of standardized practices for anticoagulation therapy may reduce these risks.

VI. Key Points/Procedural Steps

- A. Specific recommendations for dosing, laboratory monitoring, and reversal are included for each specific anticoagulant in Appendices.
- B. Consider requesting a Hematology consult for any patient with unexpected thromboembolic disease, abnormal screening or pre-treatment laboratory values, multiple medical problems, obesity, or unusual or unexpected response to antithrombotic therapy. A Hematology consult is encouraged for patients who will be treated with long-term anticoagulant therapy for venous thromboembolic disease or ischemic stroke.
- C. Consider precautions and intervention strategies for anticoagulation:
 - 1. Epidural/spinal puncture increases risk of an epidural/spinal hematoma. Consider patient's anticoagulated state prior to insertion or removal of any needle or catheter within the epidural space.
 - 2. Increased risk of bleeding of active bleeding: Thrombocytopenia, Hypofibrinogenemia, Significant coagulopathy (e.g. liver failure, Disseminated Intravascular Coagulation (DIC)),
 - 3. Post-operative patients: Consider bleeding risk and clot stability at surgical site. Generally, warfarin, heparin, or enoxaparin may be initiated twenty-four (24) hours after surgery. Patients on direct oral anticoagulants (e.g. rivaroxaban and apixaban) can generally be initiated twenty four (24) to seventy two (72) hours depending on the bleeding risk of the surgery.



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4. HIT: In adults, the risk of HIT is greater after five (5) days of treatment on the first exposure and anytime if the patient has been treated with heparin in the past. The epidemiology of HIT in children has not as yet been established. Consult hematology, and discontinue all sources of heparin or enoxaparin for any of the following:
 - a) If a 50% decrease in platelet count occurs within 24 hours on or after day five (5) of initial heparin therapy, or
 - b) If a 50% decrease in platelet count occurs within 24 hours any day of heparin therapy in the patient who received heparin in the last three (3) months, or
 - c) If the total count is less than $100 \times 10^9/L$
 5. Avoid IM injections and arterial punctures during anticoagulation.
 6. Avoid aspirin or other antiplatelet drugs during anticoagulant therapy.
 7. Recent major surgery where the risk of bleeding is high (e.g. brain or spinal surgery)
 8. Recent stroke
- D. Use approved order set.
1. Include indication for use of anticoagulant and desired laboratory goal (e.g. INR, aPTT, anti-factor Xa) in the initial orders as appropriate.
For patients starting or continuing warfarin therapy, obtain a baseline INR and continue appropriate monitoring of INR during therapy.

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Appendix A – Heparin

1. Indications
 - a. Systemic thrombosis (e.g. DVT)
 - b. Abnormal cardiac physiology where the risk of thromboembolic disease is high
 - c. Arterial ischemic stroke
 - d. Thromboprophylaxis in medically ill patients ≥ 18 years of age
2. Laboratory monitoring for **thromboprophylaxis** dosing ≥ 18 years of age:
 - a) Baseline labs: CBC
 - b) Recommended maintenance labs: CBC at least weekly
3. Laboratory monitoring for **treatment** dosing:
 - a. Baseline labs (prior to initiation or in the previous 48 hours): CBC, aPTT, PT, and INR
 - b. Anti-Xa should be drawn four (4) hours after initiating heparin therapy and adjust dose according to the dosing adjustment table below. Repeat anti-Xa at least as often as noted in table below (minimum is daily).
 - c. Check CBC daily.
 - d. Send HIT screen (Heparin PF4 AB Screen RFLX Serotonin Release Assay) for:
 - (1) If the platelet count drops below 100 x 10⁹/L or by 50% in 24 hours on or after day five (5) of initial heparin therapy or any day of heparin therapy if the patient received heparin therapy in the last three (3) months.
 - (2) Please obtain a red and light blue top tubes and send to the coagulation lab for HIT screen. NOTE: Draw blood from fresh venipuncture. This sample cannot be contaminated with standard heparin; e.g., from arterial line.
4. Dosing
 - a. Thromboprophylaxis in patients ≥ 18 years of age, consider in patient with severe renal dysfunction: 5000 units subcutaneously every 12 hours
 - b. Treatment: Initiating Heparin:
 - (1) Bolus cautions: use in caution with patients that have a high risk for bleeding. This includes acute ischemic strokes, premature infants, and active bleeding or high risk for bleeding.

Table 1: Heparin Loading Dose (Maximum bolus dose: 5000 units)*:

All patients	75 Units/kg IV over 10 minutes
For patients that receive a bolus, obtain anti-Xa 4 hours after initiation of the heparin infusion.	
* See above bolus cautions. If bolus is omitted, obtain anti-Xa 6 hours after initiation of the heparin infusion then follow below table	



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Table 2: Initial Maintenance Infusion Dose (Maximum initial rate: 1300 units/hour):

Age < 12 months:	28 Units/kg/hour
Age 1-15 years and <70 kg:	20 Units/kg/hour
Age ≥ 16 years or ≥70 kg:	18 Units/kg/hour

Table 3: Dose Adjustments:

Anti-Xa	APTT	Heparin Bolus	Hold Infusion	Infusion Rate Change	Repeat anti-Xa
<0.1	< 50	50 Units/kg	0	+10%	4 hours
0.1-0.34	50-59	0	0	+10%	4 hours
0.35-0.7	60-85	0	0	0	12-24 hours
0.71-0.91	85-95	0	0	-10%	4 hours
0.92-1	96-120	0	30 min	-10%	4 hours
>1	>120	0	60 min	-15%	4 hours

Obtain anti-Xa 4 hours after initiation and any change in rate.

*When at least two consecutive anti-Xa values are in therapeutic range, a daily anti-Xa is recommended.

5. Usual Treatment Duration

- a. **DVT:** usually parenteral therapy (heparin infusion or LMWH) is continued for a minimum of seven (7) days.

Transition to appropriate long-term therapy:

- (1) Maintenance warfarin should be initiated on Day 1 or 2 of parenteral therapy (heparin infusion or LMWH). Parenteral anticoagulant (e.g. Heparin infusion or LMWH) should be continued for at least 5 days overlap **and** with two (2) consecutive daily INRs in therapeutic range prior to discontinuation. Documentation is needed in the chart if parenteral therapy is discontinued prior to above recommendation (e.g. supra-therapeutic INR).
- (2) Maintenance enoxaparin should be initiated immediately or within 1 hour of discontinuation of heparin therapy.
- (3) Other maintenance anticoagulant (e.g. Factor Xa inhibitor, Direct thrombin inhibitor) should be initiated as recommended per specific agent's manufacturer prescribing information.

- b. **Extensive thrombus or massive PE:** usually parenteral therapy (heparin infusion or LMWH) is continued for a minimum of seven (7) – fourteen (14) days


Transition to appropriate long-term therapy:

- (1) Maintenance warfarin should be initiated when patient is hemodynamically stable and able to transition to oral therapy. Heparin infusion or LMWH should be continued for at least 5 days overlap **and** with two (2) consecutive daily INRs in therapeutic range prior to discontinuation. Documentation is needed in the chart if parenteral therapy is discontinued prior to above recommendation (e.g. supra-therapeutic INR).



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- (2) Maintenance enoxaparin should be initiated immediately or within 1 hour of discontinuation of heparin therapy.
 - (3) Other maintenance anticoagulant (i.e. Factor Xa inhibitor, Direct thrombin inhibitor) should be initiated as recommended per specific agent's manufacturer prescribing information.
6. Procedure discontinuation recommendations:
 - a) Discontinue heparin infusions at least six (6) hours prior to surgery or biopsy. For cardiac surgery patients, discontinuation of heparin infusion is per discretion of Cardiology and/or Cardiothoracic (CT) Surgery.
 - b) Re-initiation following the procedure will be determined by the practitioner.
 7. For bleeding complications and reversal:
 - a) Discontinue heparin infusion if appropriate (due to rapid clearance of UFH, may only need to discontinue therapy for minor bleeding)
 - b) Check anti-Xa, aPTT, and CBC (e.g., heme positive stools, petechiae, purpura, epistaxis). If patient is also on warfarin, check PT/INR.
 - c) Please see Appendix C: Protamine for reversal



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Appendix B –Enoxaparin (Lovenox)

1. Indications:
 - a. Systemic thrombosis (e.g. DVT)
 - b. Thromboprophylaxis
2. Laboratory monitoring for **thromboprophylaxis**:
 - a. Baseline labs: CBC, PT, aPTT, and creatinine
 - b. Recommended maintenance labs: CBC and creatinine can be obtained once a month if stable.
 - c. Anti-Xa monitoring for thromboprophylaxis in patients that meet inclusion criteria. See above in Section IV- Inclusion/Exclusion
 - (1) Patients <18 yo anti-Xa goal is 0.2-0.4 units/ml
 - (2) Patients ≥18 yo are not routinely monitored
3. Laboratory monitoring for **treatment dosing**:
 - d) Baseline CBC, PT, aPTT, and creatinine
 - e) Maintenance labs:
 - (1) **CBC** a minimum of weekly for two weeks then monthly thereafter during therapy for all patients receiving enoxaparin.
 - (2) **Anti-Xa** monitoring: Level should be drawn four (4) to six (6) hours after the 1st or 2nd subcutaneous dose upon initiation, after any dose change, and when there is concern that the patient may be bleeding. Please see table 3 below for further monitoring.
 - (3) **HIT screen** if:
 - (i) If the platelet count drops below $100 \times 10^9/L$ or by 50% in 24 hours on or after day five (5) of initial enoxaparin therapy or any day of enoxaparin therapy if the patient received heparin/enoxaparin therapy in the last three (3) months.
 - (ii) Please obtain a red and light blue top tubes and send to the coagulation lab for heparin-induced thrombocytopenia (HIT) screen. NOTE: Draw blood from fresh venipuncture. THERE MUST BE NO CONTAMINATION FROM standard heparin; e.g., from arterial line.
 - f) Long term considerations:
 - (1) For patients on long term enoxaparin therapy (> three (3) months), consider bone densitometry studies at baseline and then every six (6) months to assess for possible osteoporosis.
 - (2) Accumulation of Enoxaparin: There is some evidence that enoxaparin may accumulate in the body over time; adjustments in dosing may be required. Consider measuring a PRE-dose anti-Xa level when indicated clinically. If anti-Xa is greater than 0.5 unit/ml, call hematology. Otherwise, continue as per the dosing table below.



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Table 1: Enoxaparin Dosing: For CrCl ≥30 ml/min

	<1 month or <37 weeks	Age 1 to < 2 months (≥37 weeks)	Age > 2 months and < 18 yrs #	Age ≥ 18 yrs #
Treatment Dose*	1.7 mg/kg/dose SQ every 12 hours	1.5 mg/kg/dose SQ every 12 hours	1 mg/kg/dose SQ every 12 hours	1 mg/kg/dose SQ every 12 hours**
Prophylactic Dose	0.75 mg/kg/dose SQ every 12 hours		0.5 mg/kg/dose SQ every 12 hours. For adolescents greater than 40 kg, consider 40 mg SQ daily.	40 mg SQ daily† For adults less than 50 kg, consider 0.5 mg/kg/dose SQ daily.
*Maximum dose is 2 mg/kg/dose twice daily. If still not therapeutic after attaining this dose, consult hematology.				
# Based on total body weight up to 144 Kg and BMI <40kg/m ² . Consider discussion with hematology or a consult when dosing obese patients (>144 kg and ≥40 kg/m ²).				
** If Creatinine Clearance (CrCl) < 30 mL/min, dose at 1 mg/kg subcutaneously every 24 hours. Consider hematology consult when dosing renally impaired patients.				
†If CrCl < 30 mL/min, dose at 30 mg subcutaneously every 24 hours. Consider a hematology consult when dosing obese or renally impaired patients.				



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Table 2: Enoxaparin Dose Adjustments:

Anti-Xa level	Hold Next Dose	Dose Change	Repeat Anti-Factor Xa level
< 0.35 unit/ml	No	Increase by 25%	4 - 6 hours post next dose
0.35 to 0.49 unit/ml	No	Increase by 10%	4 – 6 hours post next dose
0.5 to 1 unit/ml	No	No change	See Table 3 for age based maintenance Anti-Xa monitoring
1.1 to 1.5 unit/ml	No	Decrease by 20%	4- 6 hours post next dose
1.6 to 2.0 unit/ml	Hold dose for 3 hours	Decrease by 30%	4 – 6 hours post next dose
> 2.0 unit/ml	For these patients, hold all doses, and repeat anti-Xa level every 12 hours until the anti- Xa level is < 0.5 unit/ml. Enoxaparin can then be restarted at a dose 40% less than was originally prescribed.		


Table 3: Enoxaparin Maintenance Anti-Xa Monitoring

Age	Treatment Dose Anti Xa Goal	Recommendations:
Neonates and infants (< 1 year of age)	0.5-1 units/ml*	Monitor once weekly, until two (2) anti-Xa levels are within the therapeutic range. May then monitor a minimum of every other week, or more frequent with concerns about deteriorating renal function.
Children (1 – 17 years of age)	0.5-1 units/ml*	Monitor a minimum of every other week while inpatient or more frequently with concerns about deteriorating renal function.
Adults (≥ 18 years of age)	0.5-1 units/ml* not routinely monitored	Do not require routine anti-Xa monitoring if patient has normal renal function, and is not obese (< 144 kg or BMI < 30 kg/m ²)
* In certain cases, where the risk of thrombosis is very high, the anti-Xa therapeutic range is 0.7 – 1.2 units/mL. For artificial heart valves, it is recommended that the range be 1 – 1.2 units/mL.		



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4. Usual Treatment Duration

- a. **DVT:** usually parenteral therapy is continued for a minimum of seven (7) days. Transition to appropriate long term therapy:
 - (1) If maintenance warfarin is planned, it should be instituted on day one (1) or two (2) of parenteral therapy (heparin infusion or LMWH). Parenteral anticoagulant (e.g. Heparin infusion or LMWH) should be continued for at least 5 days overlap **and** with two (2) consecutive daily INRs in therapeutic range prior to discontinuation. Documentation is needed in the chart if parenteral therapy is discontinued prior to above recommendation (e.g. supra-therapeutic INR).
 - (2) Other maintenance anticoagulant (e.g. Factor Xa inhibitor, Direct thrombin inhibitor) should be initiated as recommended per specific agent's manufacturer prescribing information.
- b. **Extensive thrombus or massive PE:** usually parenteral therapy (heparin infusion or LMWH) is continued for a minimum of seven (7) – fourteen (14) days. Transition to appropriate long-term therapy:
 - (1) Maintenance warfarin should be initiated when patient is hemodynamically stable and able to transition to oral therapy. Heparin infusion or LMWH should be continued for at least 5 days overlap **and** with two (2) consecutive daily INRs in therapeutic range prior to discontinuation. Documentation is needed in the chart if parenteral therapy is discontinued prior to above recommendation (e.g. supra-therapeutic INR).
 - (2) Maintenance enoxaparin should be initiated immediately or within 1 hour of discontinuation of heparin therapy.
 - (3) Other maintenance anticoagulant (i.e. Factor Xa inhibitor, Direct thrombin inhibitor) should be initiated as recommended per specific agent's manufacturer prescribing information.

5. Procedure discontinuation:

- a. Discontinue LMWH doses twelve to twenty four (12-24) hours prior to invasive procedure (e.g., surgery, biopsy, or lumbar puncture) for treatment dose. May consider discontinuing twelve (12) hours for low dose prophylaxis. For cardiac surgery patients, discontinuation of enoxaparin is per discretion of Cardiology and/or Cardiothoracic (CT) Surgery.
- b. Re-initiation following the procedure will be determined by the practitioner.


6. For bleeding complications and reversal:

- a. Discontinue enoxaparin if appropriate
- b. Check CBC, anti-Xa, and aPTT
- c. See Appendix C: Protamine for reversal



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Appendix C-Protamine

Consult with cardiology or CT surgery prior to initiating reversal in any patient who is post-cardiac surgery or who has complex congenital heart disease.

1. Indications:
 - a. Protamine for reversal of heparin and LMWH therapy for significant bleeding
2. Dosing for Heparin Reversal
 - a. Discontinue heparin infusion (due to rapid clearance, may only need to discontinue therapy for minor bleeding)
 - b. Check anti-Xa, aPTT, and CBC
 - c. Dose protamine as instructed in below table based on the heparin received in the last two (2) hours to max of 50 mg of protamine

Table 1: Protamine dosing for heparin


Time since last heparin	Dose of Protamine per 100 Units of Heparin
<30 min	1 mg
30-59 min	0.5 - 0.7 mg
60-120 min	0.4 - 0.5 mg
>120 min	0.3– 0.4 mg

2. Dosing for Enoxaparin Reversal
 - a. Discontinue enoxaparin
 - b. Check CBC, anti-Xa, and aPTT
 - c. Dose protamine as instructed in table below to max of 50 mg of protamine

Table 2: Protamine dosing for enoxaparin

Time since last enoxaparin	Dose of protamine
≤8 hours*	1 mg of protamine per 1 mg of enoxaparin
>8 hours or 2 nd dose of protamine is needed	0.5 mg of protamine per 1 mg of enoxaparin

*There is the potential that the effect of the protamine may wane before the effect of enoxaparin is no longer significant.

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Appendix D – Warfarin (Coumadin)

1. Indications

Therapeutic Indication		Goal INR*
Mechanical prosthetic heart valve adult guidelines break this down by specific valves implanted*	Mitral valve replacement	2.5 – 3.5
	Aortic valve replacement	2 - 3
	On-X Aortic valve (Initial 3 months after insertion)	2 - 3
	On-X Aortic valve (> 3 months after insertion)	1.5 - 2
Atrial fibrillation, mitral valve regurgitation, dilated cardiomyopathy		2 - 3
Systemic venous thrombosis, cerebral sinovenous thrombosis		2 –3
Status Post (S/P) Fontan procedure		2 - 3
Kawasaki disease with giant aneurysm		2 - 3
Long term prophylaxis Central Venous Line (CVL)-related thrombosis		1.5 – 1.8
*Goal INR for standard valves. Goal INR may vary at the discretion of Hematology-Oncology, Cardiology and/or CT Surgery.		

2. Laboratory Monitoring


- a. Initiation of warfarin in patient with **no known history** of warfarin use:
 - (1) Obtain baseline PT/INR, CBC (if not done in the last 48 hours)
 - (2) Obtain daily PT/INRs for at least 3-5 days then follow below schedule, at least twice weekly CBC for one week.
 - (3) INR minimum monitoring schedule:
 - i. PT/INR should be checked every 2-3 days for the first two weeks.
 - ii. Then check weekly for 3-4 weeks
 - iii. Then if stable, every 2 weeks for 4 weeks
 - iv. Then if stable every 3 weeks for 6 weeks
 - v. Then if stable every 4 weeks, thereafter.
 - vi. If any warfarin dose adjustment is made or if interacting medications are started or discontinued, check PT/INR 3-5 days after the change then follow above sequence starting with weekly INRs.

- b. Continuing warfarin in patient with an **established maintenance** dose:
 - (1) Obtain baseline PT/INR, CBC (if not done in the last 48 hours)
 - (2) A daily INR should be obtained for 2-4 days, then INRs can be obtained less often if INR is stable or as listed above.



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3. Dosing

- a. Warfarin should be given daily at the same time each day, preferably in the evening. Round warfarin doses to the nearest whole tablet whenever possible. The smallest increment of change possible is 0.5 mg (one-half of a 1 mg tablet).
- b. Warfarin has multiple drug-drug and drug-food interactions which should be taken account when initiated or continuing therapy. Use current drug information resource (e.g. Lexicomp) or contact dietary or pharmacy as appropriate. Increased lab monitoring or decreased dosing may be required for therapeutic INR.
- c. **Initiation (Day 1) Warfarin Dose:**
 - (1) 0.2 mg/kg/day (maximum 10 mg po daily)
 - (2) For patients who have one or more of the following: *not receiving heparin*, liver dysfunction, history of Fontan procedure, or a baseline INR > 1.2. Initial dose of 0.1 mg/kg/day (maximum 5 mg po daily)

d. Dose Adjustments (Days 2 to 4):

Adjustments to the dose are made based on the results of the INR as follows:

INR	Warfarin Adjustment
1.1-1.39	Repeat initial dose.
1.4-3.09	50% of initial dose.
3.1-3.5	25% of initial dose.
>3.5	Hold until INR < 3.5 then restart at 50% less than previous dose.
When the INR is therapeutic two (2) days in a row, discontinue the heparin or low molecular weight heparin. If treatment for VTE or PE, also need to be on heparin or low molecular weight heparin for at least 5 days overlap with warfarin.	


e. Maintenance Dose for day ≥ 5 of therapy

INR Goal 2 - 3	Warfarin Adjustment	INR Goal 2.5 – 3.5
1.1-1.49	Increase dose by 20%.	< 2
1.5-1.99	Increase dose by 10%	2 – 2.4
2.0-3.09	No change	2.5 – 3.5
3.1-3.5	Decrease dose by 10%	3.6 – 4
>3.5	Hold until INR therapeutic then restart at 20% less than previous dose (check INR every other day)	> 4



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3. Procedure discontinuation recommendations:
 - a) Provider will determine if interruption of warfarin is necessary for procedure. Of note, it may take ~5 days to normalize a patient's INR. Provider and surgeon will need to determine goal INR prior to procedure. If warfarin is interrupted, bridging with appropriate anticoagulant (e.g. heparin infusion or enoxaparin) should be considered. For cardiac surgery patients, discontinuation of warfarin is per discretion of Cardiology and/or Cardiothoracic (CT) Surgery.
 - b) Re-initiation following the procedure will be determined by the practitioner.

5. For bleeding complications and reversal:
 - a) Discontinue warfarin if appropriate
 - b) Check CBC, PT/INR
 - c) See Appendix E: Vitamin K for reversal and Appendix I: Prothrombin Complex (KCentra) for reversal for life threatening bleed or emergent surgery



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Appendix E - Phytonadione (Vitamin K)

Consult with cardiology or CT surgery prior to initiating reversal in any patient who is post-cardiac surgery or who has complex congenital heart disease.

- Preferred route of administration for reversal is subcutaneous, intravenous, or oral. Intramuscular route is not preferred due to increase of intramuscular hemorrhage.


INR	Bleeding	Intervention
4.1 to <10	No clinically significant bleeding OR mild to moderate controlled bleeding	Hold warfarin until INR is in target range Recheck INR in am Adjust warfarin dosing regimen as necessary per protocol
≥10	No clinically significant bleeding OR mild to moderate controlled bleeding	Hold warfarin Administer IV or SQ vitamin K 0.03 mg/kg (max: 2 mg) or 0.5-2 mg. Can give an additional dose if needed. Recheck INR in am. Adjust warfarin dosing as necessary per protocol
Any INR Value	Serious bleeding (not life threatening)	Hold warfarin Administer IV or SQ vitamin K 0.03 mg/kg (max: 2 mg) or 0.5-2 mg. Can give an additional dose if needed. Recheck INR in 12 hours. Adjust warfarin dosing as necessary per protocol
Any INR Value	Life threatening (e.g. intracranial hemorrhage)	Hold warfarin Administer IV or SQ vitamin K 0.03 mg/kg (max: 5 mg). Can give an additional dose if needed. Consider adding Kcentra. ¹ Recheck INR in 12 hours. Adjust warfarin dosing as necessary per protocol
Any INR Value	Rapid Reversal will not require further oral anticoagulant	Hold warfarin Administer IV or SQ vitamin K 0.03 mg/kg (max: 5 mg) or 2-5 mg. Can give an additional dose if needed. Recheck INR in 12 hours. Adjust warfarin dosing as necessary per protocol
Any INR Value	Rapid reversal will require further oral anticoagulant	Hold warfarin Administer IV or SQ vitamin K 0.03 mg/kg (max: 2 mg) or 0.5 to 2 mg. Can give an additional dose if needed. Recheck INR in 12 hours. Adjust warfarin dosing as necessary per protocol

¹See Appendix I for further guidance



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Appendix F - Argatroban

1. Indications
 - a. Heparin Induced Thrombocytopenia (HIT)
 - b. If patient is on ECMO, follow heparin induced thrombocytopenia ECMO protocol.

Consider a hematology consultation prior to starting argatroban for interpretation of HIT antibody results and assistance in management of argatroban. Dosing recommendations in pediatrics is significantly lower than in adults.

2. Laboratory monitoring:
 - a. Baseline labs (prior to initiation or in the previous 48 hours): CBC, aPTT, PT, INR, liver profile – recommend consulting hematology prior to holding anticoagulation to obtain baseline labs
 - c. APTT should be drawn two (2) hours after initiating argatroban therapy and adjust dose according to the dosing adjustment table below. Repeat APTT at least as often as noted in table below (minimum is daily).
 - d. Check CBC daily
3. Dosing
 - a. Treatment: Initiating Argatroban ≤ 16 years of age:
 - (1) Discontinue heparin infusion at initiation of argatroban
 - (2) Dosing will be based on actual body weight and do not adjust dosing weight even with fluctuations in body weight.
 - (3) For patients with normal liver function
 1. ≤ 16 years of age: 0.75 mcg/kg/min
 - (4) For hepatic impairment (serum bilirubin ≥2 mg/dL) or critically ill
 1. ≤ 16 years of age: 0.2mcg/kg/min

Table 1: Argatroban Dose Adjustments ≤ 16 years of age:


APTT	Hold Infusion	Normal Liver Function Infusion Rate Change	Hepatic Impairment Infusion Rate Change	Repeat aPTT
< 50	0	0.25 mcg/kg/min	0.05 mcg/kg/min	2 hours
50-59	0	0.1 mcg/kg/min	0.025 mcg/kg/min	2 hours
60-85	0	No change	No change	12-24 hours
86 -95.9	0	-0.1 mcg/kg/min	-0.025 mcg/kg/min	2 hours
96-120	60 min	-0.25mcg/kg/min	-0.05 mcg/kg/min	2 hours
>120	120 min*	-0.25 mcg/kg/min*	-0.05 mcg/kg/min*	2 hours

*Restart when aPTT is <86



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4. Dosing for patients >16 years of age

a. Initiation >16 years of age

- (1) Discontinue heparin infusion at initiation of argatroban
- (2) Dosing will be based on actual body weight and do not adjust dosing weight even with fluctuations in body weight.
- (3) For patients with normal liver function
 - 1. >16 years of age: 2 mcg/kg/min
- (4) For hepatic impairment (serum bilirubin \geq 2 mg/dL) or critically ill which includes heart failure, multiple organ system failure, severe anasarca, post-cardiac surgery.
 - 1. >16 years of age: 0.5 mcg/kg/min

Table 2: Argatroban Dose Adjustments > 16 years of age:

APTT	Hold Infusion	Normal Liver Function Infusion Rate Change	Hepatic Impairment Infusion Rate Change	Repeat aPTT
< 50	0	1 mcg/kg/min	0.25 mcg/kg/min	2 hours
50-59	0	0.5 mcg/kg/min	0.1 mcg/kg/min	2 hours
60-85	0	No change	No change	12-24 hours
86 -95.9	0	-0.5 mcg/kg/min	-0.1 mcg/kg/min	2 hours
96-120	60 min	-1 mcg/kg/min	-0.25 mcg/kg/min	2 hours
>120	120 min*	-1 mcg/kg/min*	-0.25 mcg/kg/min*	2 hours

*Restart when aPTT is <86

5. Transition to long-term therapy for adults and pediatrics:

- a. Prior to starting oral anticoagulant, ensure platelets have substantially recovered.
- b. There is a significant drug-lab interaction between argatroban and INR. INRs will be falsely elevated. Use the table below (page 18) to ensure that INRs are therapeutic prior to discontinuing argatroban.
- c. Ensure overlap of oral warfarin and intravenous anticoagulation of 5 (five) days AND INR off argatroban is in therapeutic range for 2 (two) consecutive days.

6. Procedure discontinuation:

- a. Discontinuation of argatroban is per discretion of practitioner. For cardiac surgery patients, discontinuation of argatroban is per discretion of Cardiology and/or Cardiothoracic (CT) Surgery.
- b. Re-initiation following the procedure will be determined by the practitioner.


7. For bleeding complications and reversal:

- a. Discontinue argatroban infusion *if appropriate* (due to rapid clearance, may only need to discontinue therapy for minor bleeding)
- b. Check aPTT and CBC if bleeding (e.g., heme positive stools, petechiae, purpura, epistaxis).

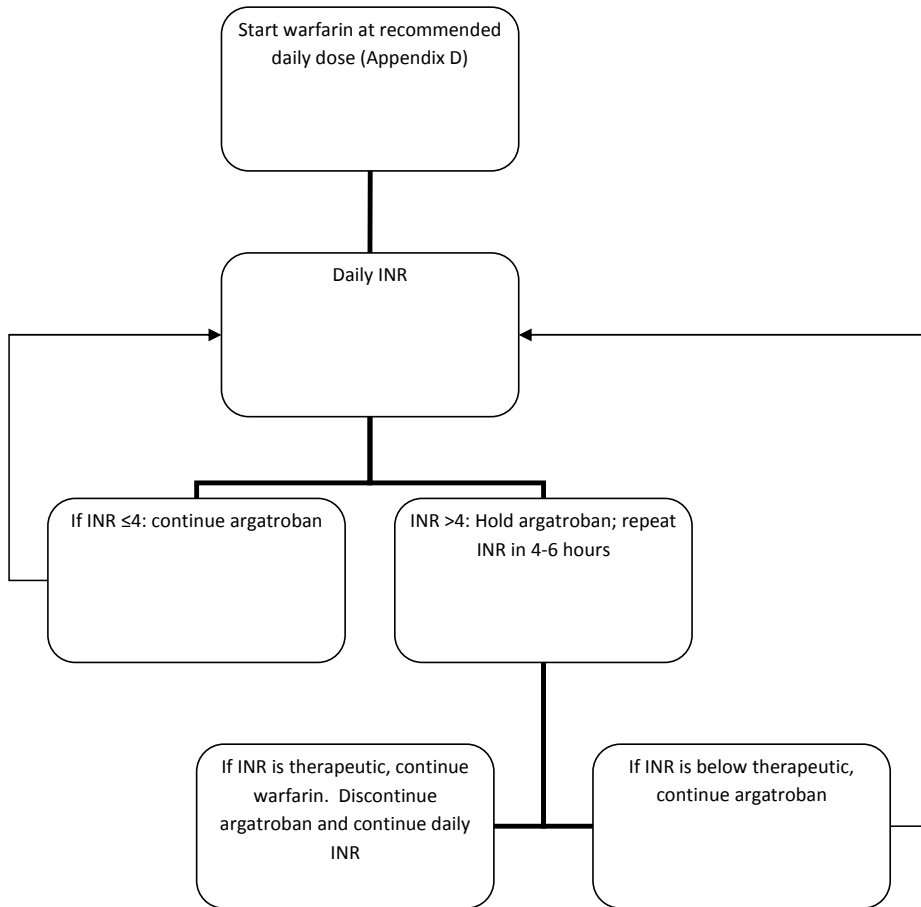



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c. See Appendix I: Prothrombin complex (Kcentra) in patients that have life threatening bleeding (e.g. intracranial hemorrhage) or require emergent surgery *in patients where the benefit may outweigh the risk.*



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Appendix G-Rivaroxaban

1. Indications
 - a. Heparin Induced Thrombocytopenia (HIT)
 - b. Non-valvular atrial fibrillation
 - c. Systemic thrombosis


Restricted to hematology/oncology and cardiology in patients ≥18 years of age. Dosing has not been established and currently not approved for patients <18 years of age

2. Laboratory monitoring:
 - a. Baseline labs (prior to initiation or in the previous 48 hours): CBC and SCr. Liver function, aPTT, PT/INR can be obtained if clinically indication.
 - b. Maintenance labs:
 - ii. CBC: a minimum of weekly for two weeks then if stable monthly while inpatient
3. Adult dosing – assess current medication list for interacting medications that may require a change in recommended dose or therapy. CYP3A4 and P-glycoprotein inhibitors have significant interactions with rivaroxaban.
 - a. For non-valvular atrial fibrillation,
 - (1) Rivaroxaban 20 mg oral once daily with food
 - (2) CrCl 15-50 ml/min: 15 mg once daily
 - (3) CrCl <15 ml/min: not recommended
 Note: CrCl <30 ml/min were excluded from clinical trials
 - b. HIT with or without thrombosis
 - (1) Rivaroxaban 15 mg twice daily with food for 21 days OR until platelet recovery whichever is longer followed by 20 mg once daily with food.
 - c. Systemic thrombosis
 - (1) Rivaroxaban 15 mg twice daily with food for 21 days followed by 20 mg once daily with food.
 Note: CrCl <30 ml/min avoid use.
 - d. For concurrent drug interactions:
 - (1) Strong dual CYP3A4 and P-glycoprotein inhibitors listed below (e.g. ketoconazole, ritonavir): Avoid concomitant use
 - (2) Strong dual CYP3A4 and P-glycoprotein inducers listed below (e.g. rifampin, phenytoin): Avoid concomitant use
 - (3) Please use up to date drug reference to determine interactions
4. Transitioning between anticoagulants:
 - a. From another anticoagulant to rivaroxaban:
 - (1) LMWH to rivaroxaban:
 1. For VTE indication, consider initiating rivaroxaban 6-12 hours after last dose of LMWH (if twice daily)



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2. For other indications, consider initiating rivaroxaban 10 hours after the last dose of LMWH (if twice daily)
 - (2) Heparin continuous infusion or argatroban to rivaroxaban: start rivaroxaban when parenteral anticoagulant is discontinued if aPTT or anti-Xa were within therapeutic range
 - (3) Warfarin to rivaroxaban: Discontinue warfarin and initiate rivaroxaban when INR <3; if risk of bleeding, could consider when INR is near 2.
- b. From rivaroxaban to another anticoagulant:
 - (1) Rivaroxaban to LMWH or heparin continuous infusion: start parenteral anticoagulant when next dose of rivaroxaban was scheduled to be given
 - (2) Rivaroxaban to warfarin: Rivaroxaban may cause elevation in INR. Can consider overlapping therapy for two (2) or more days to achieve a therapeutic INR. May also discontinue rivaroxaban and initiate warfarin with bridge of parenteral anticoagulant to achieve a therapeutic INR.
7. Procedure discontinuation:
 - a. Depending on the bleed risk of the procedure and patient's renal function, rivaroxaban should be discontinued twenty four (24) to forty eight (48) hours prior to procedure or at discretion of the practitioner. For cardiac surgery patients, discontinuation of rivaroxaban is per discretion of Cardiology and/or Cardiothoracic (CT) Surgery.
 - b. Re-initiation following the procedure will be determined by the practitioner.
8. For bleeding complications and reversal:
 - a. Discontinue rivaroxaban if appropriate
 - b. Check CBC, aPTT, PT/INR if bleeding (e.g., heme positive stools, petechiae, purpura, epistaxis).
 - c. See Appendix I: Prothrombin complex (Kcentra) for reversal in patients that have life threatening bleeding (e.g. intracranial hemorrhage) or require emergent surgery.



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Appendix H-Apixaban

1. Indications
 - a. Heparin Induced Thrombocytopenia (HIT)
 - b. Non-valvular atrial fibrillation
 - c. Systemic thrombosis

Restricted to hematology/oncology and cardiology in patients ≥18 years of age. Dosing has not been established and currently not approved for patients <18 years of age

2. Laboratory monitoring:
 - a. Baseline labs (prior to initiation or in the previous 48 hours): CBC and SCr. Liver function, aPTT, and PT/INR can be obtained if clinically indication.
 - b. Maintenance labs:
 - iii. CBC: a minimum of weekly for two weeks then monthly while inpatient
3. Adult dosing – assess current medication list for interacting medications that may require a change in recommended dose or therapy. CYP3A4 and P-glycoprotein inhibitors have significant interactions with apixaban.
 - e. For non-valvular atrial fibrillation,
 - (1) Apixaban 5 mg oral twice daily
 - (2) Apixaban 2.5 mg oral twice daily in patients that have at least 2 of the following: Serum Creatinine ≥1.5 mg/dL, age ≥80 years, and weight ≤60 kg
 - f. HIT with or without thrombosis
 - (1) Apixaban 10 mg twice daily for 7 days OR until platelet recovery whichever is longer followed by 5 mg twice daily.
 - g. Systemic thrombosis
 - (1) Apixaban 10 mg twice daily for 7 days followed by 5 mg twice daily.
Note: patients with SCr >2.5 mg/dL or CrCl <25 ml/min were excluded from the clinical trials.
 - h. For concurrent drug interactions:
 - (1) Strong dual CYP3A4 and P-glycoprotein inhibitors (e.g. ketoconazole, ritonavir):
 1. Doses >2.5 mg twice daily: reduce dose by 50%
 2. Doses 2.5 mg twice daily: not recommended
 - (2) Strong dual CYP3A4 and P-glycoprotein inducers (e.g. rifampin, phenytoin): not recommended
 - (3) Please use up to date drug reference to determine interactions


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4. Transitioning between anticoagulants:
 - a. From another anticoagulant to apixaban:
 - (1) LMWH to apixaban: initiate apixaban when the next dose was scheduled for parenteral anticoagulant
 - (2) Heparin continuous infusion to apixaban: start apixaban when parenteral anticoagulant is discontinued if aPTT was within therapeutic range
 - (3) Warfarin to apixaban: Discontinue warfarin and initiate apixaban when INR <2
 - b. From apixaban to another anticoagulant:
 - (1) Apixaban to LMWH or heparin continuous infusion: start parenteral anticoagulant when next dose of apixaban was scheduled to be given
 - (2) Apixaban to warfarin: Apixaban may cause elevation in INR. Can consider overlapping therapy for two (2) or more days to achieve a therapeutic INR. May also discontinue apixaban and initiate warfarin with bridge of parenteral anticoagulant to achieve a therapeutic INR.
9. Procedure discontinuation:
 - a. Depending on the bleed risk of the procedure and patient's renal function, apixaban should be discontinued twenty four (24) to forty eight (48) hours prior to procedure or at discretion of the practitioner. For cardiac surgery patients, discontinuation of apixaban is per discretion of Cardiology and/or Cardiothoracic (CT) Surgery.
 - b. Re-initiation following the procedure will be determined by the practitioner.
10. For bleeding complications and reversal:
 - a. Discontinue apixaban if appropriate
 - b. Check CBC, aPTT, PT/INR (e.g., heme positive stools, petechiae, purpura, epistaxis).
 - c. See Appendix I: Prothrombin complex (Kcentra) for reversal in patients that have life threatening bleeding (e.g. intracranial hemorrhage) or require emergent surgery.



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Appendix I – Prothrombin complex (Kcentra)

Consult with cardiology or CT surgery prior to initiating reversal in any patient who is post-cardiac surgery or who has complex congenital heart disease.

1. Indications: Kcentra requires a hematology/oncology or cardiology to approve prior to ordering reversal
 - a. Reversal for **life threatening bleeding** (e.g. intracranial bleeding) **or emergent surgery** of warfarin, apixaban (Eliquis), rivaroxaban (Xarelto), and non-formulary direct oral anticoagulants (dabigatran (Pradaxa), edoxaban (Savaysa), and betrixaban (Bevyxxa))
 - b. Depending on indication of anticoagulant: there is an increased risk for arterial and venous thromboembolic complications both fatal and nonfatal following reversal.
2. Dosing for warfarin reversal
 - a. Discontinue warfarin
 - b. Check INR and CBC
 - c. Dose Kcentra as instructed in below table, Vitamin K also should be given concurrently

Table 1: Kcentra dosing for warfarin

INR	Units of Factor IX of Kcentra (Recommended Maximum)
2 to <4	25 units/kg (2,500 units)
4-5	35 units/kg (3,500 units)
>6	50 units/kg (5,000 units)

3. Dosing for other anticoagulants direct oral anticoagulant and direct thrombin inhibitor for life threatening bleeding: Argatroban, apixaban (Eliquis), rivaroxaban (Xarelto), dabigatran (Pradaxa), edoxaban (Savaysa), and betrixaban (Bevyxxa)
 - a. Discontinue anticoagulant if appropriate
 - b. Check CBC, PT/INR, and aPTT


Table 2: Kcentra dosing for other anticoagulants

Other anticoagulants	Units of Factor IX of Kcentra (Recommended Maximum)
Argatroban, apixaban (Eliquis), rivaroxaban (Xarelto), dabigatran (Pradaxa), edoxaban (Savaysa), and betrixaban (Bevyxxa)	50 units/kg (5,000 units)



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Appendix J - Non-formulary anticoagulants

1. The following anticoagulants (not fully inclusive list) are not on the formulary but may need to be continued from outpatient: dabigatran (Pradaxa), edoxaban (Savaysa), and betrixaban (Bevyxxa). Currently these have not been FDA approved in pediatrics and being investigated.
2. If non-formulary anticoagulants are continued inpatient, follow standard non-formulary procedure.
3. Use current drug information resource (e.g. lexicomp) and guidelines for dosing adjustment and recommended laboratory monitoring.
4. Laboratory monitoring (Not limited to the below):
 - a. Baseline labs and upon admission if continuing home medication (prior to initiation or in the previous 48 hours): CBC and SCr. Liver function, aPTT, PT/INR can be obtained if clinically indication.
 - b. Maintenance labs:
 - i. CBC: a minimum of weekly for two weeks then monthly while inpatient
5. Procedure discontinuation:
 - a. Depending on the bleed risk of the procedure, anticoagulant half-life, and patient's renal function, the anticoagulant should be discontinued at least twenty four (24) to forty eight (48) hours prior to procedure or at discretion of the practitioner. Please review up to date drug information resource to determine anticoagulant's half-life and recommendations on appropriate holding prior to procedure. For cardiac surgery patients, discontinuation of anticoagulant is per discretion of Cardiology and/or Cardiothoracic (CT) Surgery.
 - b. Re-initiation following the procedure will be determined by the practitioner.
5. For bleeding complications and reversal:
 - a. Discontinue therapy if appropriate
 - b. Check CBC, aPTT, PT/INR
 - c. See Appendix I: Prothrombin complex (Kcentra) for reversal in patients that have life threatening bleeding (e.g. intracranial hemorrhage) or require emergent surgery.



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