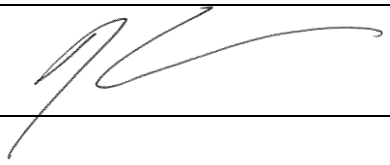
Genesis Health System
Administrative Policy

Policy Title:	**ANTICOAGULATION MANAGEMENT PROGRAM**	Effective Date:	06/15/11
Department:	Medication Management	Reviewed/Revised:	04/15/23, 04/15/22, 06/15/21
Owner Title:	Chief Clinical Officer/Chief Medical Officer	Review Cycle:	Annual

Owner Signature: 

I. POLICY:

This policy will establish procedures to procure, store, dispense and monitor anticoagulant medications in compliance with The Joint Commission National Patient Safety Goal (NPSG).03.05.01: Anticoagulation Therapy.

II. APPLICABLE HEALTH SYSTEM ENTITIES:

☐ All GHS Business Units:

☐ Crescent Laundry
☐ Crosstown Square
☐ Genesis Accountable Care Organization
☐ Genesis Convenient Care
☐ Genesis EAP
☐ Genesis FirstMed Pharmacy
☐ Genesis Family Medical Center
☐ Genesis Health Group
☐ Genesis Health Group, Aledo Rural Health
☐ Genesis Health Group, Erie Rural Health
☐ Genesis Health Services Foundation
☐ Genesis Home Medical Equipment
☐ Genesis Hospice
☒ Genesis Medical Center, Aledo
☒ Genesis Medical Center, Davenport
☒ Genesis Medical Center, DeWitt
☒ Genesis Medical Center, Silvis
☐ Genesis Occupational Health
☐ Genesis Philanthropy
☐ Genesis Psychology Associates
☐ Genesis VNA
☐ Genesis Workers Comp Plan & Trust

III. APPLICABLE ORGANIZATIONAL ROLES:

A. Physicians
B. Advanced Practice Professional (APP)/Allied Health Professional (AHP)Registered Nurses (RN)
C. Licensed Practical Nurses (LPN)
D. Pharmacists
E. Dietitians

IV. PURPOSE:

A. Anticoagulation is a high-risk treatment, which may lead to adverse drug events due to the complexity of therapy, dosing and monitoring. Standardized practices can reduce risks of adverse drug events associated with the use of anticoagulant medications which include, but are not limited to, unfractionated heparin, low molecular weight heparin (LMWH), warfarin, fondaparinux, argatroban, bivalirudin, and direct oral anticoagulants (DOACS) (ie. apixaban, betrixaban, dabigatran, edoxaban, and rivaroxaban).

B. The principles of the Genesis Medical Centers Anticoagulation Management Program are:

1. To use approved protocols and evidence--based practice guidelines for the initiation and maintenance of anticoagulant therapy that address medication selection; dosing, including adjustments for age and renal and liver function; drug interactions (drug-drug and drug-food); and other risk factors as applicable.
2. To use approved protocols and evidence-based practice guidelines for reversal of anticoagulation and management of bleeding events related to each anticoagulant medication.
3. To use approved protocols and evidence-based practice guidelines for perioperative management of all patients on oral anticoagulants.
4. To address the need for baseline and ongoing laboratory tests to monitor and adjust anticoagulant therapy.
5. To address anticoagulation safety practices through the following:
   a. Establishing a process to identify, respond to, and report adverse drug events, including adverse drug event outcomes
   b. Evaluating anticoagulation safety practices, taking actions to improve safety practices, and measuring the effectiveness of those actions in a time frame determined by the organization
6. To provide education to patients and families specific to the anticoagulant medication prescribed, including the following:
   a. adherence to the medication dose and schedule
   b. importance of follow-up appointments and laboratory testing, if applicable
   c. potential drug-drug and drug food interactions
   d. potential for adverse drug reactions
7. To use only oral unit-dose products, prefilled syringes, or premixed infusion bags when these types of products are available. (Exception: For pediatric patients, prefilled syringe products should only be used if specifically designed for children.)
8. To use programmable pumps in order to provide consistent and accurate dosing when heparin, argatroban, or bivalirudin is administered intravenously and continuously.

V. DEFINITIONS:

NA

VI. GENERAL CONSIDERATIONS:

A. Protocols, practices, and guidelines will be reviewed and evaluated on a regular basis.
B. Daily reports and/or clinical surveillance tool will be used to monitor INR results and other relevant lab values to ensure the safe and effective use of anticoagulants.
C. Recommendations and clinical interventions will be documented electronically in the patient's medical record.
D. Reversal of these medications should be managed per the anticoagulation reversal protocol.
E. Nursing Services will initiate and perform patient and/or caregiver education specific to the anticoagulant ordered/prescribed utilizing computerized educational materials, including, but not limited to, the self-administration of injectable anticoagulants that are ordered to be continued post-hospital discharge (ie. Lovenox, Arixtra).

VII. PRACTICE/PROCEDURE:

A. Warfarin:
    1. A baseline INR will be ordered by physician, APP/AHP, or Pharmacist prior to initiation of therapy, if not already ordered or available in the clinical record, unless justified by assessment of coagulation status.
    2. Current INR results will be used to monitor and adjust therapy (Appendix E).
    3. Patients on long-term warfarin therapy whose INR values are stable and within a desired therapeutic range will have an INR result available no less frequently than every seven days for the duration of an acute inpatient hospitalization (including inpatient rehabilitation).
    4. Pharmacists will perform a profile review on new warfarin orders to screen for contraindications (e.g., intramuscular injections) and drug interactions. Subsequent new, modified or discontinued medication orders will be reviewed for impact on INR results with the prescriber to be notified if potentially significant.
    5. Pharmacists will review doses and route of phytonadione orders for appropriateness prior to dispensing for reversal of warfarin-induced coagulopathies (Appendix B, Appendix F).
    6. Food and Nutrition Services is notified of all patients receiving warfarin and responds according to the hospital's established food/medication program (Food-Drug Interactions Policy).
B. Unfractionated Heparin (UFH):
    1. The appropriate Unfractionated Heparin (UFH) Protocol will be initiated by the prescribing physician/APP/AHP at the respective facility. Bolus dose and drip rates are calculated based on the patient's weight and indication. Appropriate laboratory monitoring will be done according to protocol.

2. Heparin IV rate changes and additional IV bolus doses based on PTT levels per protocol will be electronically entered as a patient order and verified by pharmacy before being completed by Nursing staff.

C. Low Molecular Weight Heparin (LMWH, i.e., Enoxaparin):

1. DVT prophylaxis and treatment dosing will be initiated by physician/APP/AHP order.
2. A baseline CBC and serum creatinine may be ordered by physician/APP/AHP prior to initiating therapy, with testing repeated as deemed appropriate while on therapy.
3. Therapeutic doses will be rounded to the nearest commercially available syringe size as noted in Appendix G.
4. Pharmacy will alert prescribers to dosing issues and/or contraindications related to weight, renal function, and inappropriate therapeutic duplication.

D. Indirect Factor Xa Inhibitor (Fondaparinux):

1. DVT prophylaxis and treatment dosing will be initiated by physician/APP/AHP order.
2. A baseline CBC and serum creatinine may be ordered by physician/APP/AHP prior to initiating therapy with testing repeated as deemed appropriate while on therapy
3. Pharmacy will alert prescribers to dosing issues and/or contraindications related to weight, renal function, and inappropriate therapeutic duplication.

E. Direct Thrombin Inhibitors:

1. Argatroban
    a. All argatroban infusions will be dispensed per the Genesis Drug Administration Guidelines.
    b. Dosing of argatroban for treatment of heparin-induced thrombocytopenia (HIT) will be initiated by the prescribing physician/APP/AHP. The initial infusion rate is calculated based on the patient's weight and clinical status.
    c. Baseline PTT should be drawn prior to starting
    d. Argatroban IV rate changes based on PTT levels will be done by Nursing staff according to the Argatroban Infusion Orders.
    e. When an order for argatroban is received, Pharmacy will review the patient profile to identify and discontinue all sources of heparin and LMWH.
    f. Documentation of heparin allergy will be recorded in the patient's permanent record, if confirmed by clinical course and laboratory testing.
2. Dabigatran (Pradaxa®)
    a. Pharmacy will alert prescribers to dosing issues and/or contraindications related to indication, renal function, drug administration, potential drug interactions and inappropriate therapeutic duplication.
    b. No baseline anticoagulation lab monitoring required prior to initiation of therapy; however, renal function should be assessed.

c. INR should be checked when switching from Warfarin to determine an appropriate start time.

d. Perioperative management will be based on the urgency of procedure, risk of bleeding, and renal function.

3. Bivalirudin (Angiomax®)
   a. Pharmacy will alert prescribers to dosing issues and/or contraindications related to indication, renal function, drug administration, potential drug interactions and inappropriate therapeutic duplication.
   b. Bolus dose and drip rates are calculated based on the patient's weight, indication, and renal function
   c. Baseline ACT or PTT (based on indication) should be drawn prior to starting
   d. Rates adjusted based on ACT or PTT depending on indication

F. Direct Factor Xa Inhibitors (apixaban (Eliquis®), betrixaban (Bevyxxa®), edoxaban (Savaysa®), rivaroxaban (Xarelto®))

1. Pharmacy will alert prescribers to dosing issues and/or contraindications related to indication, age, weight, renal function, hepatic function, potential drug interactions and inappropriate therapeutic duplication as appropriate.
2. No baseline anticoagulation lab monitoring required prior to initiation of therapy; however, renal function and liver function (when applicable) should be assessed.
3. INR should be checked when switching from Warfarin to determine an appropriate start time.
4. Perioperative management will be based on the urgency of procedure, risk of bleeding, and renal function.

VIII. REFERENCES:

The Joint Commission: NPSG.03.05.01, MM.05.01.01

IX. SUPERSEDES:

N/A

X. CROSS REFERENCE:

GHS Administrative Policy: Food-Drug Interactions
GHS Administrative Policy: High Risk/High Alert Medications

XI. ENDORSEMENTS:

Nursing Standards Committee, 01/23
Safe Medication Management Committee, 01/23
Pharmacy & Therapeutics Committee, 02/23

APPENDIX A

Adapted from:

Clinical Resource*, Comparison of Oral Anticoagulants. Pharmacist's Letter/Prescriber's Letter.* December 2018.

Clinical Resource, *Managing Bleeding with Direct Oral Anticoagulants. Pharmacist's Letter/Prescriber's Letter.* July 2018.

Clinical Resource, *Antithrombotic Management in Regional Anesthesia. Pharmacist's Letter/Prescriber's Letter.* June 2018.

Abbreviations: ACS = acute coronary syndrome; aPTT = activated partial thromboplastin time; A fib = atrial fibrillation; AV = arteriovenous; BID = twice daily; CABG = coronary artery bypass graft; CAD = coronary artery disease; CrCl = creatinine clearance; CV = cardiovascular; DVT = deep vein thrombosis; eGFR = estimated glomerular filtration rate; HF*r*EF = heart failure with reduced ejection fraction; INR = international normalized ratio; LMWH = low-molecular-weight heparin; MI = myocardial infarction; NNT = number needed to treat; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; PE = pulmonary embolism; P-gp = pglycoprotein; PT = prothrombin time; PTCA = percutaneous transluminal coronary angioplasty; TIA = transient ischemic attack; VTE = venous thromboembolism.

FORMULARY MEDICATIONS

- Direct Factor Xa Inhibitors
  - Apixaban
  - Rivaroxaban
- Indirect Factor Xa Inhibitors
  - Fondaparinux
- Vitamin K Antagonists
  - Warfarin
- Heparins
  - Unfractionated Heparin
  - Enoxaparin
- Direct thrombin Inhibitors
  - Dabigatran
  - Argatroban
  - Bivalirudin

Direct Factor Xa Inhibitors

Apixaban (*Eliquis*) (direct factor Xa inhibitor)	
Approved Indications and Usual Dose	● **Thromboembolism (e.g., stroke) prevention in nonvalvular A fib: 5 mg PO BID**; ● **VTE prevention post-hip or knee replacement:** 2.5 mg PO BID for 35 days [hip] or 12 days [knee] starting 12 to 24 hours post-op.[1] ● **DVT/PE treatment:** 10 mg BID for seven days, then 5 mg PO BID.[1] ● **DVT/PE prevention of recurrence:** 2.5 mg PO BID after at least six months of treatment.[1] ● **VTE prophylaxis in high risk ambulatory patients with cancer**: 2.5 mg PO BID for up to 6 months – guidance dosage from SSC and ISTH
Dosing Considerations	● **2 or more of the following (Age ≥80 years, weight ≤60 kg, serum creatinine ≥1.5):** reduce apixaban for A fib indication from 5 mg PO BID to 2.5 mg PO BID.[1] ● **Hemodialysis**: MAY consider reducing apixaban 5 mg PO BID to 2.5 mg PO BID based on limited data.[45,47]
Clinical Benefit In…	● **A fib**: for every 1,000 patients treated per year, apixaban prevents three more strokes, avoids ten major bleeds, and prevents four deaths compared to warfarin.[3] ● **Post-hip/knee replacement**: at least as effective as enoxaparin for preventing VTE; comparable bleeding.[4,5] ● **DVT/PE treatment/prevention of recurrence**: comparable to enoxaparin/warfarin for prevention of recurrent VTE or VTE death (combined endpoint); less bleeding.[40] ● **VTE prophylaxis in high risk ambulatory patients with cancer**: AVERT study demonstrated a significantly reduced VTE rate (7.2% on apixaban vs 10.2% on placebo) in patients with modified Khorana score ≥2 but also had a significantly increase drisk of major bleeding (3.5% on apixaban and 1.8% on placebo). NNT to prevent one VTE was 17, NNH was 59.[114]
Preprocedure Washout	● **Washout**: Duration to hold may vary depending on patient's renal function, contact a pharmacist for assistance. ● Last dose three days before surgery/procedure (i.e., 48-hour washout) with **moderate or high bleeding risk** (three to four days before if CrCl 15 to 29 mL/min).[8] ● Last dose two days before surgery/procedure (i.e., 24-hour washout) with **low bleeding risk** (three days before if CrCl 15 to 29 mL/min).[66]
Antidote/Reversal Agents	● Reversal Agents: Fixed dose Kcentra (do not give Kcentra if history of HIT) ● Activated charcoal may reduce apixaban absorption when given within six hours after apixaban administration.[59,60]

	● Dialysis is not expected to be an effective reversal method.[59,60] ● **See Appendix B for recommended reversal agent and recommended dose.**
Management in **surgical** patients before, during, and after **epidural or spinal anesthesia**	● Stop apixaban 72 hours before neuraxial block. Duration to hold may vary depending on patient's renal function, contact a pharmacist for assistance. ● Wait at least 6 hours after neuraxial catheter removal to start/restart apixaban. ● If apixaban is given to a patient with an indwelling epidural catheter (e.g., emergently or by accident), hold apixaban 26 to 30 hours before catheter removal.
Therapeutic Considerations	● Requires BID dosing.[1,2] ● Not recommended in patients with **prosthetic heart valves**.[1,2] ● **Severe liver impairment**: not recommended.[1] ● Prophylax for at least 10 to 14 days after hip or knee replacement, and up to 35 days, especially after hip replacement.[17] ● For VTE treatment, continue for at least three months.[18] Benefit of extended use may not outweigh risk in patients with high bleeding risk.[18] ● Not for event reduction post-MI with antiplatelets (increases bleeding risk without additional benefit).[6]
Laboratory Considerations	● May result in false positive lupus anticoagulant assay due to assay interference.[93] ● May prolong prothrombin time/INR or aPTT, but a normal result does not rule out a clinically important apixaban effect.[1] ● Regular monitoring not routinely recommended, but may use coagulation assays (calibrated chromogenic anti-FXa assay) in emergencies (i.e. trauma, urgent surgery/invasive procedures, major bleeding, overdose, acute thrombosis, renal/liver failure, adherence verification, drug-drug interactions).[93]
Switching To/From Other Anticoagulants	● See Appendix C
Select Drug Interactions	● Reduce dose by 50% with **strong inhibitors of BOTH CYP3A4 and P-gp** (e.g., itraconazole, ketoconazole, ritonavir). Avoid in patients already taking 2.5 mg BID.[1] ● Avoid **strong inducers of BOTH CYP3A4 and P-gp** (e.g., carbamazepine, phenobarbital,[2] phenytoin, St. John's wort, rifampin).[1,2] ● Dual antiplatelet therapy about doubles bleeding risk.[6] ● Administration with other anticoagulants, antiplatelets, or antifibrinolytics may increase the risk of bleed.

Formulary Status	• Formulary
Rivaroxaban (*Xarelto*) (direct factor Xa inhibitor)	
Approved Indications and Usual Dose	• **VTE prevention post-hip or knee replacement:** 10 mg once daily for 35 days [hip] or 12 days [knee] starting 6 to 10 hrs post-op, assuming hemostasis achieved[15] • **Thromboembolism (e.g., stroke) prevention in nonvalvular A fib:** 20 mg once daily with evening meal to improve absorption[15] • **DVT/PE treatment/prevention of recurrence:** 15 mg twice daily [**with food**] x 3 weeks, then 20 mg once daily [**with food** to improve absorption] for at least six months, then 10 mg once daily[15] • **CV risk reduction in patients with CAD or PAD:** 2.5 mg twice daily, **with aspirin** 75 to 100 mg once daily[15] • **VTE prevention in high risk ambulatory patients with cancer**: 10 mg PO QD for up to 6 months - guidance dosage from SSC and ISTH [114]
Dosing Considerations	• Check renal function at baseline, and when clinically indicated.[15,16] • A fib indication requires renal dosing (15 mg with evening meal for CrCl ≤50 mL/min).[15,16] Pharmacokinetic data suggest rivaroxaban 10 or 15 mg once daily in hemodialysis patients provides levels similar to patients in the pivotal A fib trial, but there are no clinical outcome data.[15,46] • For DVT/PE prevention and treatment and VTE prevention post-hip/knee replacement, avoid if CrCl <30 mL/min.[15,16] • For CV risk reduction in CAD/PAD, patients with eGFR <15 mL/min were excluded from clinical trial, and <1% of included patients had eGFR <30 mL/min.[52] • Moderate to severe hepatic impairment: avoid use.[15]
Clinical Benefit In…	• **Post-hip/knee replacement**: prevents 4 more VTEs compared to LMWH and causes 9 more serious bleeds per 1,000 patients treated for 14 days.[17] • **A fib**: comparable to warfarin for preventing stroke or systemic embolism in patients with relatively high stroke risk. Comparable major bleeding, but INR in therapeutic range only 55% of time. Lower rate of hemorrhagic stroke, higher rate of major GI bleed. Increase in events after stopping may reflect poor transition to warfarin, not hypercoagulability.[21] • **DVT treatment/prevention of recurrence**: comparable to enoxaparin/warfarin for prevention of recurrent VTE comparable major bleeding or clinically relevant nonmajor bleeding (combined endpoint).[22]

	● **PE treatment/prevention of recurrence**: comparable to enoxaparin/warfarin for prevention of recurrent VTE lower rate of major bleeding[23] ● **CV risk reduction in CAD or PAD (with aspirin)**: NNT = 71 for ~2 years to prevent one event (ischemic stroke, MI, CV death).[52] NNT = 147 for ~2 years to prevent one amputation in PAD.[58] About one in every 80 patients will have a major bleed.[52] ● **VTE prevention in high risk ambulatory patients with cancer**: CASSINI trial demonstrated primary efficacy outcome (symptomatic or screen-detected proximal lower extremity DVT or PE, symptomatic upper or lower extremity distal DVT, or VTE related death) in 6% of rivaroxaban patients and 8.8% of placebo patients – in the intention-to-treat population, was 2.6% (rivaroxaban) and 6.4% (placebo). Major bleeding occurred in 2% of rivaroxaban patients and 1% of placebo patients. NNT was 35, NNH was 101.[114]
Preprocedure Washout	● Duration to hold may vary depending on patient's renal function, contact a pharmacist for assistance. ● Last dose two days before surgery/procedure (i.e., 24-hour washout) with **low bleeding risk** (three days before if CrCl<30 mL/min).[66]Last dose three days before surgery/procedure (i.e., 48-hour washout) with **moderate or high bleeding risk** (three to four days before if CrCl <30 mL/min).[66]
Antidote/Reversal Agents	• **Reversal:** Consider activated charcoal within two to four hours after rivaroxaban administration.[62] Use could be considered within up to eight hours in an overdose situation.[64] Dialysis is not expected to be an effective reversal method.[63,64] • Reversal agent: Fixed dose Kcentra (do not give Kcentra if history of HIT) • See Appendix B for recommended reversal agents and doses.
Management in **surgical** patients before, during, and after **epidural or spinal anesthesia**	● Stop rivaroxaban 72 hours prior to neuraxial block. ● Wait at least 6 hours after catheter removal to start/restart rivaroxaban. ● If rivaroxaban is given to a patient with an indwelling epidural catheter (e.g., emergently or by accident), hold rivaroxaban for 22 to 26 hours before catheter removal.
Therapeutic Considerations	● For A Fib, some data suggest once-daily dosing insufficient, but BID dosing untested.[24] ● Not recommended in patients with prosthetic heart valves.[15,16] ● **Avoid in patients with moderate or severe liver impairment or liver disease with coagulopathy.[15]** ● **For VTE treatment, continue for at least three months.[18]** Benefit of extended use may not outweigh risk in patients with high bleeding risk.[18]

	• Caution in elderly.[16] Underweight patients have slightly increased levels/response.[15] • Prophylax for at least 10 to 14 days after hip or knee replacement, and up to 35 days, especially after hip replacement.[17] • **No benefit** over aspirin alone for prevention of recurrent ischemic stroke of **undetermined source**.[54] • **No benefit** for event reduction (death, MI, stroke) in HF*r*EF plus CAD, without A fib.[55] • FDA has declined to approve rivaroxaban for event reduction post-ACS; benefit may not outweigh bleeding risk.[56,57]
Switching To/From Other Anticoagulants	• **See Appendix C**
Laboratory Considerations	• Prothrombin time prolongation may be prolonged.[64] A normal PT/INR does not rule out a clinically important rivaroxaban effect.[62] • Regular monitoring not routinely recommended, but may use coagulation assays (calibrated chromogenic anti-FXa assay) in emergencies (i.e. trauma, urgent surgery/invasive procedures, major bleeding, overdose, acute thrombosis, renal/liver failure, adherence verification, drug-drug interactions).[93]
Select drug interactions	• Avoid use with **drugs that are BOTH** P-gp **and strong** CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, posaconazole, ritonavir [all contraindicated, per Canadian labeling]).[15,16] Caution with clarithromycin and fluconazole (Canadian labeling).[16] • In patients with CrCl 15 to <80 mL/min., the decision to use a combined P-gp/moderate CYP3A4 inhibitor (e.g., erythromycin) is a risk/benefit determination.[15] • Drugs that are P-gp **and strong** CYP3A4 inducers (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) may decrease efficacy.[15,16] Avoid.[15,16] • Avoid use with other anticoagulants.[15,16] Caution with antiplatelets, including clopidogrel.[15,16]
Formulary Status	• Formulary

Indirect Factor Xa Inhibitors

Fondaparinux (Arixtra) (indirect factor Xa inhibitor)	
Approved Indications and Usual Dose	● **Acute ST segment elevation myocardial infarction:** initial 2.5 mg IV, followed by 2.5 mg SUBQ once daily for the duration of hospitalization, up to 8 days, or until revascularization [77] ● **Deep venous thrombosis, acute, In conjunction with warfarin sodium:** 5 mg (body weight less than 50 kg), 7.5 mg (body weight of 50 to 100 kg), or 10 mg (body weight greater than 100 kg) SUBQ once daily for 5 to 9 days; initiate concurrent warfarin sodium therapy within 72 hours; continue fondaparinux until oral anticoagulant effect is therapeutic (INR, 2 to 3) [78] ● **Non-ST segment elevation myocardial infarction, acute:** 2.5 mg SUBQ daily for up to 8 days (guideline dosing) [80] ● **Postoperative deep vein thrombosis, Hip repair or replacement, knee replacement, or abdominal surgery; Prophylaxis:** 2.5 mg SUBQ once daily after hemostasis has been established (give initial dose 6 to 8 hours post-op); usual duration, 5 to 9 days; for hip fracture patients, an extended course of up to 24 days is recommended (manufacturer dosing) [78]; (hip or knee arthroplasty and hip fracture surgery) continue prophylaxis for at least 10 to 14 days, consider prophylaxis for up to 35 days (guideline dosing) [81] ● **Pulmonary embolism, acute, In conjunction with warfarin sodium when initial therapy is administered in a hospital:** 5 mg (body weight less than 50 kg), 7.5 mg (body weight of 50 to 100 kg), or 10 mg (body weight greater than 100 kg) SUBQ once daily for 5 to 9 days; initiate concurrent warfarin sodium therapy within 72 hours; continue treatment until oral anticoagulant effect therapeutic (INR, 2 to 3) [78] ● **Thrombosis of superficial vein of lower limb:** 2.5 mg SUBQ daily for 45 days (guideline dosing) [82]
Dosing Considerations	● **Renal impairment, CrCl less than 30 mL/min (VTE prophylaxis and treatment):** Contraindicated (manufacturer dosing) [79] ● **Renal impairment, CrCl 30 to 50 mL/min:** Use with caution (manufacturer dosing) [79] ● **Renal impairment, CrCl 20 to 50 mL/min (VTE prophylaxis):** 1.5 mg subQ once daily starting 6 hours or more (ideally 8 hours) postoperatively for 10 days for total hip or knee replacement or 28 to 35 days for hip fracture surgery (study dosing) [83] ● Geriatric: Use with caution[79] ● Body weight less than 50 kg (VTE prophylaxis): contraindiated[79]

	● Body weight less than 50 kg (VTE treatment): use with caution[79]
Clinical Benefit In…	● VTE Prophylaxis and Treatment: Fondaparinux should be considered an alternative to low-molecular-weight heparins for prevention and treatment of deep vein thrombosis.
Preprocedure Washout	● Do not administer drug for at least 6 to 8 hours after surgery
Antidote/Reversal Agents	● No specific antidote – reversal uses nonspecific prohemostatic agents like aPCC (FEIBA) ● FEIBA (anti-inhibitor coagulant complex with factor VIII inhibitor bypassing activity, also known as activated prothrombin complex concentrate or aPCC) is recommended agent for reversal. FDA package insert states 50-100 units/kg (max 200 units/kg day) for control and prevention of bleeding,[112] however several studies have looked at lower doses (10-30 units/kg) and found them effective in limited studies.[109, 110] ● **See Appendix B for recommended reversal agent and recommended dose.**
Management in **surgical** patients before, during, and after **epidural or spinal anesthesia**	● Recent ASRA and ESRA consensus indicates a 3–4 days interval before performing regional anesthesia procedures and then resuming medications 12–24 h post procedure. [90]
Therapeutic Considerations	● Discontinue if platelet count <100,000/mm^3 [79] ● For SQ use ONLY, do not use IM ● **Geriatric:** Use with caution [79] ● **Body weight less than 50 kg (VTE prophylaxis):** Contraindicated [79] ● **Body weight less than 50 kg (VTE treatment):** Use with caution [79] ● In the OASIS-5 study, fondaparinux 2.5 mg QD for 8 days (or until hospital discharge) was not inferior to enoxaparin 1 mg/kg BID in reducing death, MI, or refractory ischemia compared to enoxaparin in patients with unstable angina or MI without ST-segment elevation. Compared to enoxaparin, fondaparinux significantly **reduced major bleeding** (which contributed to a significantly reduced mortality at 30 days).[104] ● In a study comparing LMWH + GPI, fondaparinux, bivalirudin, UFH, and UFH + GPI for efficacy in preventing major adverse cardiovascular events (MACE) after PCI, fondaparinux was least efficacious and the **least safe for major bleeding.**[103] ● PENTATHLON, PENTAMAKS, PENTHIFRA, and EPHESUS studies found fondaparinux reduced rate of VTE after knee and hip surgeries by ~50% compared to enoxaparin.

	Fondaparinux was associated with **an increased rate of major bleeding events**; however, these major bleeding events were not considered clinically relevant.[105, 106]
Switching To/From Other Anticoagulants	● See Appendix C

Laboratory Considerations	● Preferred method of measuring fondaparinux is anti-factor Xa levels
	● PT, aPTT are not useful for monitoring
	● Consider monitoring anti-factor Xa levels in:[107]
	  ● Pregnant patients
	  ● Children
	  ● Obese patients
	  ● Patients with renal impairment

Select drug interactions	● SSRIs (i.e. sertraline, paroxetine, fluoxetine, citalopram, escitalopram, vilazodone)[100] and SNRIs (i.e. desvenlafaxine, venlafaxine, levomilnacipran) may increase risk of bleeding[101] ● Administration with other antiplatelets, antithrombotics, and anticoagulants may increase risk of bleeding ● NSAIDs may increase the risk of bleeding[102]
Formulary Status	● Formulary

Vitamin K Antagonists

Warfarin (*Coumadin*) (inhibits formation of vitamin-K dependent clotting factors)	
Approved Indications	● Prevention/treatment of venous thrombosis/PE[25] ● Prevention/treatment of thromboembolism due to A fib or prosthetic heart valve[25] ● Secondary prevention post-MI[25] ● *Warfarin dosing variable and patient specific. Please see GHS Administrative policy "Anticoagulation Management Program" – Appendix E and F for additional information.*
Dosing Considerations	● Adjust per INR testing. Renal function minor determinant of warfarin response.[25] ● Preferred anticoagulant for A fib with CrCl <15 mL/min.[19]
Clinical Benefit In…	● **A fib**: prevents stroke (NNT = 32 vs placebo for one year to prevent one stroke).[27] ● **Post hip/knee replacement**: prevents 3 fewer major clots compared to LMWH and causes two more fatal bleeds per 1,000 patients treated for 14 days.[17]

	● **PE/DVT (with initial use of heparin)**: reduces risk of recurrence and mortality[28] ● **Post-MI**: reduces reinfarction, stroke, and mortality (INR 2.8 to 4.8);[29] warfarin (INR 2 to 2.5) plus aspirin (75 mg once daily) superior to aspirin alone or warfarin (INR 2.8 to 4.2) alone (combined endpoint).[30] ● **Rheumatic mitral valve disease (off-label)**: reduces embolic events and mortality in patients **with embolic history**; reduces embolic events in patients **with A fib**, promotes resolution of left atrial thrombus.[31-33] ● **Mechanical heart valve (off-label, Canada)**: reduces embolism and valve thrombosis.[34]
Preprocedure Washout	● Washout: five days[35]
Antidote/Reversal Agents	● If INR elevated but no bleeding: **See Appendix F** ● If INR elevated and significant bleeding: **See Appendix B**
Management in **surgical** patients before, during, and after **epidural or spinal anesthesia**	● Ideally, stop warfarin five days before neuraxial block, and confirm normalization of INR. ● In patients beginning warfarin pre-operatively (e.g., low-dose for thromboprophylaxis), check INR before neuraxial block if the first dose was given >24 hours earlier or if a second dose of warfarin has been given. ● Postoperatively, for patients on low-dose warfarin (for thromboprophylaxis) receiving epidural anesthesia, monitor for neurodeficits. Use drugs that minimize sensory and motor block to facilitate monitoring. ● Remove catheter when INR is <1.5 (e.g., within 12 to 24 hours after the first perioperative warfarin dose). ● Maintain catheter with caution if INR is 1.5 to 3. ● Check INR daily. If INR is >3, hold or reduce the warfarin dose. ● Monitor for neurodeficits for 24 hours after catheter removal.
Therapeutic Considerations	● INR monitoring required at least every four weeks.[25,26] Goal 2 to 3 for most indications.[18] ● Prophylax for at least 10 to 14 days after hip or knee replacement, and up to 35 days, especially after hip replacement.[17] ● Not more effective than aspirin for noncardioembolic stroke.[37] ● Preferred anticoagulant for A fib with CAD.[39] ● **For VTE treatment, continue for at least three months.[18]** Benefit of extended use may not outweigh risk in patients with high bleeding risk.[18,20]
Switching To/From Other Anticoagulants	● See Appendix C

Laboratory Considerations	● Laboratory Assessment of Bleeding Risk: INR ● May need to use Chromogenic Factor X in select patients whose INR is unreliable (i.e. patients with positive lupus anticoagulant)[94]
Select drug interactions	● Many drug and food interactions. ● Potential for significant interactions with inducers/inhibitors of CYP2C9, 2C19, 1A2, and 3A4. ● Use with antiplatelets increases bleeding risk. Benefit of combo (most data with aspirin or clopidogrel) may outweigh risk in certain patients, such as mechanical heart valve patients, or in A fib **plus** recent stent or recent CABG.[19,36,38,50]
Formulary Status	● Formulary

Heparins

Unfractionated Heparin	
Approved Indications and Usual Dose	● Dosing varies widely based on specific indication – seek most current drug reference for detailed information. ● Please refer to the electronic orders for specific treatment dosing: 1. Adult Unfractionated Heparin – Ischemic Stroke Protocol 2. Adult Unfractionated Heparin – Cardiac Indication (ACS, MI, Atrial Fib, Valvular Heart Disease) 3. Adult Unfractionated Heparin – DVT and/ or PE protocol
Dosing Considerations	● No renal adjustment necessary. ● Adjust based on aPTT based off heparin protocol.

Clinical Benefit In…	● Heparin is indicated for the prophylaxis and treatment of thromboembolic disorders (e.g., venous thromboembolism, pulmonary embolism) and thromboembolic complications associated with atrial fibrillation; prevention of clotting in arterial and cardiac surgery; as an anticoagulant for extracorporeal circulation and dialysis procedures. ● **Note:** Heparin lock flush solution is intended only to maintain patency of IV devices and is **not** to be used for systemic anticoagulant therapy.
Preprocedure Washout	● Heparin infusion washout – stop infusion 4 to 6 hours before procedure ● Heparin SQ – administer last dose the evening prior to the procedure
Antidote/Reversal Agents	● **Antidote: See Appendix B for recommended reversal agent and recommended dose.**
Management in **surgical** patients before, during, and after **epidural or spinal anesthesia**	<u>Subcutaneous</u> *Heparin, low-dose subcutaneous (5,000 units two or three times daily)* ● Wait 4 to 6 hours (or check coagulation labs) after heparin administration to perform neuraxial block, ● Check platelet count prior to catheter insertion/removal for patients receiving heparin for more than four days (due to possibility of heparin-induced thrombocytopenia). ● Postoperatively, a neuraxial catheter may be maintained despite low-dose subcutaneous heparin. Wait 4 to 6 hours after heparin administration to remove/manipulate catheter. May restart low-dose subcutaneous heparin 1 hour later. *Heparin, higher-dose subcutaneous (7,500 to 10,000 units twice daily, or a daily dose ≤20,000 units)* ● Wait 12 hours after heparin administration to perform neuraxial block, AND check coagulation labs. ● Check platelet count prior to catheter insertion/removal for patients receiving heparin for more than four days (due to possibility of heparin-induced thrombocytopenia). ● Postoperatively, the safety of maintaining a neuraxial catheter at these doses is unclear. Consider risk/benefit, and use drugs that minimize sensory and motor block to facilitate monitoring for neurodeficits. Monitor closely. ● May start/restart subcutaneous heparin 1 hour after catheter removal. *Heparin, therapeutic subcutaneous dose (>10,000 units per dose or >20,000 units total daily dose)*

	● Wait 24 hours after heparin administration to perform neuraxial block, AND check coagulation labs. ● Check platelet count prior to catheter insertion/removal for patients receiving heparin for more than four days (due to possibility of heparin-induced thrombocytopenia). ● May start/restart subcutaneous heparin 1 hour after catheter removal. <u>Intravenous</u> *Heparin infusion* ● Stop heparin drip 4 to 6 hours prior to neuraxial puncture AND check coagulation labs to ensure they are normal. ● Check platelet count prior to catheter insertion/removal for patients receiving heparin for more than four days (due to possibility of heparin-induced thrombocytopenia). ● Avoid use of other antithrombotics. Review med list daily. ● May start/restart heparin 1 hour after catheter removal.
Therapeutic Considerations	● Intravenous injection results in immediate anticoagulant activity, whereas subcutaneous injection results in 1 to 2 hour delay. ● The anticoagulant effect of heparin is not linear and increases disproportionately with increasing doses. [88]
Switching To/From Other Anticoagulants	● See Appendix C
Laboratory Considerations	● Heparin continuous infusions: monitor per GHS protocol using anti-Xa or PTT as appropriate ● If monitoring with anti-Xa levels, find out the last time patient took an anti-Xa inhibitor (i.e. apixaban, rivaroxaban). Anti-Xa inhibitors may cause unreliable anti-Xa levels for up to 72 hours.[95] ● Concurrent use of telavancin and oritavancin is contraindicated due to falsely elevated aPTT results[115, 116] ● Concurrent nitroglycerin may result in decreased PTT[117]
Select drug interactions	● Oral anticoagulants, platelet inhibitors, digitalis, tetracyclines, nicotine, or antihistamines [91] ● SSRIs (i.e. sertraline, paroxetine, fluoxetine, citalopram, escitalopram, vilazodone)[100] and SNRIs (i.e. desvenlafaxine, venlafaxine, levomilnacipran) may increase risk of bleeding[101] ● Other antiplatelets, antithrombotics, and anticoagulants may increase risk of bleeding ● NSAIDs may increase the risk of bleeding[102]

Formulary Status	• Formulary
Enoxaparin (*Lovenox)* (low-molecular-weight heparin)	
Approved Indications and Usual Dose	• Dosing varies widely based on specific indication, age, weight, and renal function – seek most current drug reference for detailed information.
Dosing Considerations	• Renal dosing < 30 ml/min varies widely based on specific indication, age, weight, and renal function – seek most current drug reference for detailed information. • No dose adjustment is recommended in patients with creatinine clearance 30 to 50 mL/min and creatinine clearance 50 to 80 mL/min. • If BMI ≥ 30, consider monitoring anti-Xa level and adjusting dose based on anti-Xa levels[95, 97, 98] • If BMI ≥ 40, consider increasing prophylactic dose to 40 mg SQ BID[97, 98] • If BMI ≥ 50, consider increasing prophylactic dose to 60 mg SQ BID[97, 98]
Clinical Benefit In…	• Enoxaparin is indicated for the prevention of ischemic complications of unstable angina and non-Q-wave myocardial infarction when concurrently administered with aspirin, and for the treatment of acute ST-segment elevation myocardial infarction managed medically or with subsequent percutaneous coronary intervention. It is also approved for the inpatient treatment of DVT with and without pulmonary embolism, and outpatient treatment of DVT in patients without pulmonary embolism, when given in conjunction with warfarin sodium [86]
Preprocedure Washout	• In patients receiving bridging anticoagulation with therapeutic dose enoxaparin, the American College of Chest Physicians suggests that the last preoperative dose of enoxaparin be administered ~24 hours prior to surgery
Antidote/Reversal Agents	• Protamine incompletely reverses factor Xa inhibition of LMWH though it completely neutralizes its antithrombin effect. Protamine reverses 60-75% of LMWH effects.[108] More than 50 mg of protamine may cause anticoagulation by Factor V inhibition and is NOT recommended.[108] • **See Appendix B for reversal dosing recommendations**
Management in **surgical** patients before, during, and	Prophylaxis Dose • Allow 12 hours after administration before neuraxial puncture. Consider a longer washout if CrCl <50 mL/min.[2]

after **epidural or spinal anesthesia**	• Post-op, **twice-daily prophylactic** dosing: give the first dose the next day (assuming surgical hemostasis has been achieved) AND no sooner than 12 hours after needle/catheter placement AND at least 4 hours after catheter removal. • Post-op, **once-daily (q 24 h) prophylactic** dosing: the first dose should be given at least 12 hours after needle/catheter placement. Catheter may be maintained, but do not use any additional drugs with antihemostatic effects. Wait 12 hours after the last dose of LMWH to remove catheter. Wait at least 4 hours after catheter removal to resume LMWH. • Check platelets if used for more than five days. <u>Treatment Dose</u> • Allow 24 hours after administration before neuraxial puncture. Consider a longer washout if CrCl <50 mL/min.[2] • Wait at least 4 hours after catheter removal to start/restart LMWH. • It is recommended that at least 24 hours elapse between needle/catheter placement and removal. • Check platelets if used for more than five days.
Therapeutic Considerations	• Elderly: Greater risk for hemorrhage; consider monitoring [84]Weight: Low-weight patients (men less than 57 kg and women less than 45 kg) are at greater risk for bleeding; monitoring recommended [84]Hematologic: Thrombocytopenia may occur; monitoring recommended and discontinue if platelet count falls below 100,000/mm(3) [84] • Hematologic: Use extreme caution in patients with history of heparin-induced thrombocytopenia (HIT) or heparin-induced thrombocytopenia with thrombosis (HITTS) and only if more than 100 days have elapsed since prior HIT episode and no circulating antibodies are present; monitoring required [85]
Switching To/From Other Anticoagulants	• See Appendix C
Laboratory Considerations	• Consider obtaining anti-Xa levels to monitor enoxaparin in/if: • BMI ≥30[95, 97, 98] • Body weight <57 kg (for men) or <45 kg (for women)[84] • Burn patients[96]

	● Elderly patients[84, 99] ● Borderline renal function (CrCl ~30 mL/min) or CrCl <30 mL/min[85] ● Pregnancy[99] ● Children or neonates[99] ● Bleeding or abnormal coagulation parameters occur[85] ● PT and aPTT are not adequate laboratory values to monitor enoxaparin[84]
Select drug interactions	● SSRIs (i.e. sertraline, paroxetine, fluoxetine, citalopram, escitalopram, vilazodone)[100] and SNRIs (i.e. desvenlafaxine, venlafaxine, levomilnacipran) may increase risk of bleeding[101] ● Other antiplatelets, antithrombotics, and anticoagulants may increase risk of bleeding ● NSAIDs may increase the risk of bleeding[102]
Formulary Status	● Formulary

Direct Thrombin Inhibitors

Dabigatran (*Pradaxa*) (direct thrombin inhibitor)	
Approved Indications and Usual Dose	● **Thromboembolism (e.g., stroke) prevention in nonvalvular A fib**: 150 mg BID[7] ● **DVT/PE treatment (following 5 to 10 days' treatment with a parenteral anticoagulant)/prevention of recurrence**: 150 mg BID. Start at the time of discontinuation of heparin drip.[7] ● **VTE prevention post-hip replacement**: 220 mg once daily x 28 to 35 days. If started on day of surgery [1 to 4 hrs post-op, assuming hemostasis achieved], initial dose is 110 mg.[7]
Dosing Considerations	● Check renal function at baseline and when clinically indicated.[7,8] ● Also see drug interactions section, below. ● **A fib:** use 75 mg BID if CrCl 15 to 30 mL/min.[7] No dosing information for CrCl <15 mL/min or dialysis.[7] ● **DVT/PE treatment/prevention and VTE prevention post-hip replacement**: no dosing information for CrCl ≤30 mL/min or dialysis.[7]

Clinical Benefit In…	● **A fib**: prevents about five more strokes per 1,000 patients per year than warfarin. Lower rate of hemorrhagic and ischemic stroke, higher rate of major GI bleed, comparable overall bleeding.[10] ● **Post-hip/knee replacement**: comparable to enoxaparin for prevention of VTE & mortality (combined endpoint); comparable major bleeding.[11-13] ● **DVT/PE treatment/prevention of recurrence**: comparable to warfarin for prevention of recurrent VTE or VTE death (combined endpoint); comparable major bleeding.[14]
Preprocedure Washout	● **Washout:** Duration to hold may vary depending on patient's renal function, contact a pharmacist for assistance. Last dose three days before surgery/procedure (i.e., 48-hour washout) with **moderate or high bleeding risk** (four to five days before if CrCl 15 to 50 mL/min).[66] Last dose two days before surgery/procedure (i.e., 24-hour washout) with **low bleeding risk** (three days before if CrCl 30 to 50 mL/min., four to five days before if CrCl 15 to 29 mL/min.).[66]
Antidote/Reversal Agents	● **Reversal:** Consider activated charcoal within two to four hours after dabigatran administration.[3] Diuresis promotes excretion.[69] ● **See Appendix B for recommended reversal agent and recommended dose.**
Management in **surgical** patients before, during, and after **epidural or spinal anesthesia**	● Stop dabigatran 120 hours before neuraxial puncture. However, if CrCl is <30 mL/min., guidelines suggest against neuraxial block in dabigatran patients. For patients with good renal function (see below), without additional bleeding risk factors such as age >65 years, hypertension, or antiplatelet use, earlier institution could be considered as follows: ● If CrCl is ≥80 mL/min., allow 72 hours between the last dabigatran dose and neuraxial puncture. ● If CrCl is 50 to 79 mL/min., allow 96 hours between the last dabigatran dose and neuraxial puncture. ● Wait at least 6 hours after catheter removal to start/restart dabigatran. ● If dabigatran is given to a patient with an indwelling epidural catheter (e.g., emergently or by accident), hold dabigatran for 34 to 36 hours before catheter removal.
Therapeutic Considerations	● Requires BID dosing for A fib and DVT/PE treatment/prevention indications.[7,8] ● Causes gastrointestinal symptoms in over 10% of patients.[7] ● Caution if 75 years or older, poor renal function, or underweight.[7-9] ● Contraindicated with mechanical heart valve, and not recommended with bioprosthetic valves.[7] ● Dispense/store in original package.[7,8] Once bottle opened, use within 4 months.[7,8]

	● For VTE treatment, continue for at least three months.[8,18] Benefit of extended use may not outweigh risk in patients with high bleeding risk.[18] ● Prophylax for at least 10 to 14 days after hip or knee replacement, and up to 35 days, especially after hip replacement.[17] ● Not for event reduction post-MI with antiplatelets (increases bleeding risk at all doses, with unproven benefit).[53]
Laboratory Considerations	● An elevated aPTT suggests the presence of dabigatran if other causes of an elevated aPTT are excluded, but it cannot be used to quantify the effect of dabigatran. A normal aPTT does not exclude a clinically important dabigatran effect, especially if an insensitive reagent is used.[61] ● A normal thrombin time probably excludes a clinically important dabigatran effect.[77] But a prolonged thrombin time does not distinguish clinically important from insignificant levels.[77] ● Dilute thrombin time calibrated to dabigatran is the preferred test.[61] ● Ecarin clotting time and the ecarin chromatographic assay correlate linearly with dabigatran levels.[61] ● Regular monitoring not routinely recommended, but may use coagulation assays (ecarin clotting time and dilute thrombin time) in emergencies (i.e. trauma, urgent surgery/invasive procedures, major bleeding, overdose, acute thrombosis, renal/liver failure, adherence verification, drug-drug interactions).[93]
Switching To/From Other Anticoagulants	● See Appendix C
Select Drug Interactions	**P-gp inhibitors** ● May increase dabigatran levels.[7,8] ● **A fib indication**: avoid P-gp inhibitors if CrCl <30 mL/min.[7] Reduce dose to 75 mg BID with ketoconazole or dronedarone if CrCl 30 to 50 mL/min.[7] ● **VTE/PE treatment/prevention (including post-hip replacement)**:[7] avoid use of P-gp inhibitors if CrCl <50 mL/min.[7] Consider separating by several hours if CrCl ≥50 mL/min (hip replacement indication).[7] **P-gp inducers** ● Avoid **P-gp inducers** could decrease dabigatran efficacy.[7,8]

	● Caution with antiplatelets.[7,8] Use with aspirin 100 mg or less can be considered.[8] Co-administration with aspirin or clopidogrel about doubles bleeding risk.[8] Caution with anticoagulants.[7,8] ● Drugs that increase gastric pH could reduce efficacy. Take dabigatran at least 2 hrs before antacids. Avoid antacids for 24 hrs after hip/knee replacement (Canada).[8]
Formulary Status	● Formulary
Argatroban (direct thrombin inhibitors)	
Approved Indications and Usual Dose	● VTE treatment and prophylaxis in setting of HIT ● Percutaneous coronary intervention (PCI) ● **Please refer to electronic Argatroban Infusion Order Set**
Dosing Considerations	● Moderate to severe hepatic impairment: see Argatroban Infusion Orders
Clinical Benefit In…	● Heparin-induced thrombocytopenia: In patients with strongly suspected or confirmed heparin-induced thrombocytopenia (HIT)
Preprocedure Washout	● Half-life of argatroban is approximately 1 hour and up to 3 hours in patients with severe hepatic impairment.[87]
Antidote/Reversal Agents	● No specific antidote - reversal uses nonspecific prohemostatic agents like FIEBA ● **See Appendix B** for recommended reversal agent and recommended dose
Management in **surgical** patients before, during, and after **epidural or spinal anesthesia**	● Neuraxial anesthesia is not recommended in these patientsNote: Literature review shows recommendation to hold 4 hrs ahead of planned procedure and 2 hrs after[88]
Therapeutic Considerations	● Hepatic impairment: Dose adjustments required. Reversal of anticoagulation effect may be prolonged. ● Argatroban may elevate PT/INR levels in the absence of warfarin. If warfarin is started, initial PT/INR goals while on argatroban may require modification[87]
Switching To/From Other Anticoagulants	● See Appendix C

Laboratory Considerations	● Heparin: Allow sufficient time for heparin's effect on aPTT to decrease before initiating Argatroban Injection therapy. ● Warfarin: Concomitant use results in increased prolongation of PT and INR
Select Drug Interactions	● Thrombolytic agents or glycoprotein IIb/IIIa antagonists: Safety and effectiveness of concomitant use with argatroban have not been established. [88] ● SSRIs (i.e. sertraline, paroxetine, fluoxetine, citalopram, escitalopram, vilazodone)[100] and SNRIs (i.e. desvenlafaxine, venlafaxine, levomilnacipran) may increase risk of bleeding[101] ● Other antiplatelets, antithrombotics, and anticoagulants may increase risk of bleeding ● NSAIDs may increase the risk of bleeding[102]
Formulary Status	● Formulary
Bivalirudin (Angiomax) (direct thrombin inhibitors)	

Approved Indications and Usual Dose	● **Ischemic heart disease, percutaneous coronary intervention**
	  ● If initiating bivalirudin during PCI: Initial: 0.75 mg/kg bolus immediately prior to procedure, followed immediately by 1.75 mg/kg/hour for the duration of procedure. During the procedure, may determine ACT 5 minutes after bolus dose and administer an additional bolus of 0.3 mg/kg if necessary. After the procedure, may continue the infusion at 1.75 mg/kg/hour for up to 4 hours if needed
	  ● If initiating bivalirudin prior to PCI or diagnostic angiography for non-STE ACS (off-label): IV: Initial: Administer an initial 0.1 mg/kg bolus, followed by 0.25 mg/kg/hour; continue until diagnostic angiography or PCI. If PCI is determined to be necessary, give an additional bolus of 0.5 mg/kg and increase infusion rate to 1.75 mg/kg/hour during PCI
	● **Heparin-induced thrombocytopenia (HIT) (off-label use):** IV: Initial dose: 0.15 to 0.2 mg/kg/hour; adjust to aPTT 1.5 to 2.5 times baseline value
	
	****** Bivalirudin has only been studied with concomitant asprin******

Dosing Considerations	● For use in PCI:
	  ● CrCl ≥30 mL/minute: No dosage adjustment necessaryCrCl <30 mL/minute: Decrease infusion rate to 1 mg/kg/hourDialysis: Decrease infusion rate to 0.25 mg/kg/hour
	
	● For use in HIT (off-label use):
	  ● CrCl >60 mL/minute: 0.13 mg/kg/hour
	  ● CrCl 30 to 60 mL/minute: 0.08 to 0.1 mg/kg/hour

	● CrCl <30 mL/minute: 0.04 to 0.05 mg/kg/hour ● Intermittent hemodialysis (IHD): 0.07 mg/kg/hour ● CRRT (eg, CVVH or CVVHDF): 0.03 to 0.07 mg/kg/hour
Clinical Benefit In…	● Patients unable to tolerate heparin as an alternative to argatroban
Preprocedure Washout	● See **Appendix B** for recommended reversal agent and recommended dose.
Antidote/Reversal Agents	● No specific antidote - reversal uses nonspecific prohemostatic agents like FIEBA ● See **Appendix B** for recommended reversal agent and recommended dose.
Management in **surgical** patients before, during, and after **epidural or spinal anesthesia**	● Consider discontinuation with account of half-life elimination and confirm with aPTT: ● Normal renal function and mild renal impairment: 25 minutes ● Moderate renal impairment: 34 minutes ● Severe renal impairment: 57 minutes ● Dialysis: 3.5 hours
Therapeutic Considerations	● Half-life will be prolonged in renal dysfunction
Switching To/From Other Anticoagulants	● See Appendix C
Laboratory Considerations	● aPTT. PT/INR levels may become elevated in the absence of warfarin. If warfarin is initiated, initial PT/INR goals while on bivalirudin may require modification.
Select Drug Interactions	● SSRIs (i.e. sertraline, paroxetine, fluoxetine, citalopram, escitalopram, vilazodone)[100] and SNRIs (i.e. desvenlafaxine, venlafaxine, levomilnacipran) may increase risk of bleeding[101] ● Other antiplatelets, antithrombotics, and anticoagulants may increase risk of bleeding ● NSAIDs may increase the risk of bleeding[102]
Formulary Status	● Formulary

NONFORMULARY

- Direct factor Xa inhibitor
  - Betrixaban
  - Edoxaban

Direct Factor Xa Inhibitors

Betrixaban (*Bevyxxa*) (direct factor Xa inhibitor)	
Approved Indications and Usual Dose	● **VTE prevention in acutely ill medical, non-surgical patients with moderate or severely limited mobility plus other VTE risk factors**: 160 mg x 1, then 80 mg once daily **with food**, for 35 to 42 days.[48]
Dose Adjustments and Considerations	● **CrCl 15 to <30 mL/min (calculated using actual body weight):** 80 mg x 1, then 40 mg once daily **with food** for 35 to 42 days.[48] ● **CrCl <15 mL/min:** avoid use.[91] ● **Concommitant use of P-gp inducers (i.e. phenytoin, rifampin, carbamazepine, St. John's wort, etc.):** avoid use.[91] ● **Concomitant use of P-gp inhibitors (i.e. amiodarone, carvedilol, macrolides, verapamil, etc.)**: reduce initial dose to 80 mg rally as a single dose, followed by 40 mg orally once daily for 35-42 days; monitor patients closely for signs/symptoms of blood loss.[91] ● CrCl <15 mL/min, dialysis patients, and patients likely to need dialysis within three months were excluded from the clinical trial used for FDA approval.[49] ● It is unknown if betrixaban is removed by hemodialysis.[48] ● **Moderate to severe hepatic impairment:** avoid betrixaban use.[91]
Clinical Benefit In…	● **VTE prevention in acutely ill medical patients**: vs about 10 days' treatment with enoxaparin, NNT to prevent one **symptomatic event** (symptomatic DVT, non-fatal PE, or VTE death) = 167.[48] NNT = 63 to prevent one **asymptomatic or symptomatic** VTE.[49] Comparable major bleeding, but NNH = 90 for clinically important (but nonmajor) bleeding that may require prescriber contact, intervention (e.g., drug discontinuation), or patient discomfort.[48] NNT = 170 to prevent one VTE-related readmission.[51]
Preprocedure Washout	● **Washout:** Duration to hold may vary depending on patient's renal function, contact a pharmacist for assistance. Expect anticoagulant activity to persist for at least 72 hours post-dose.[75]

Antidote/Reversal Agents	● **Agents:** Fixed dose Kcentra (do not give Kcentra if history of HIT) ● **Reversal: See Appendix B for recommended reversal agent and recommended dose.**
Management in **surgical** patients before, during, and after **epidural or spinal anesthesia**	● Stop betrixaban at least three days before neuraxial block. In patients taking a P-glycoprotein inhibitor, or taking a dose >80 mg/day, allow a washout of 76 to 135 hours.If CrCl is <30 mL/min., guidelines suggest against neuraxial block in betrixaban patients. However, if used in patients with CrCl 15 to 29 mL/min., allow a washout of 76 to 135 hours. Duration to hold may vary depending on patient's renal function, contact a pharmacist for assistance. ● Wait at least 5 hours after neuraxial catheter removal to start/restart betrixaban. ● If betrixaban is given to a patient with an indwelling epidural catheter (e.g., emergently or by accident), hold betrixaban for at least 72 hours before catheter removal.
Therapeutic Considerations	● Approval was based on the APEX clinical trial.[48] Enrolled patients were at high risk of VTE. Patients were required to have an elevated D-dimer or be 75 years or older, in addition to having restricted mobility plus decompensated heart failure, acute respiratory failure, infection, ischemic stroke, or acute rheumatic disease.[49] ● Notable APEX **exclusion criteria** included body weight <45 kg; dual antiplatelet therapy; recent significant bleeding, trauma, peptic ulcer disease, or major surgery; potential need for major surgery; active lung cancer; or low platelets.[49] ● Not indicated for patients with prosthetic heart valves due to lack of data.[48] ● Avoid use in hepatic impairment.[48] ● Less than 6% of betrixaban patients in the trial used for FDA approval had a CrCl of 15 to <30 mL/min.[49] ● Few APEX enrollees had a history of cancer or VTE. Only 18% received a reduced dose due to P-gp interaction.[49]
Laboratory Considerations	● **Laboratory Assessment of Bleeding Risk:** Prolongs PT/INR and aPTT, but these cannot be relied upon to asses bleeding risk.[76]
Switching To/From Other Anticoagulants	● See Appendix C
Select Drug Interactions	● Reduce dose to 40 mg once daily (after 80 mg loading dose) with **strong P-gp inhibitors** (e.g., amiodarone, azithromycin, clarithromycin, ketoconazole, verapamil).[48] ● Patients with CrCl 15 to <30 mL/min requiring a strong P-gp inhibitor were excluded from the clinical trial used for FDA approval.[49] Avoid in such patients.[48] ● Caution with antiplatelets.[48] Not studied in patients requiring dual antiplatelet therapy.[49]

Formulary Status	● Non-formulary
Edoxaban (*Savaysa)* (direct factor Xa inhibitor)	
Approved Indications and Usual Dose	● **Thromboembolism (e.g., stroke) prevention in nonvalvular A fib in patients with CrCl >50 to ≤95 mL/min:**60 mg once daily. [41] ● **DVT/PE treatment (following 5 to 10 days' treatment with a parenteral anticoagulant):** 60 mg once daily; 30 mg once daily if body weight ≤60 kg.[41]
Dosing Considerations	● **A fib:** 60 mg once daily for CrCl >50 to ≤95 mL/min, or 30 mg once daily for CrCl 15 to 50 mL/min. **Not for use in patients with CrCl >95 mL/min** due to increased risk of ischemic stroke[41] ● **DVT/PE treatment:** 30 mg once daily for CrCl 15 to 50 mL/min.[41] ● CrCl <15 mL/min: not recommended.[41] ● Moderate to severe hepatic impairment: not recommended.[41]
Clinical Benefit In…	● **A fib**: about as effective as warfarin, with lower risk of major bleeding (six fewer bleeds per 1,000 patients per year).[42] (Also see "Therapeutic Considerations," below.) ● **DVT/PE treatment**: About as effective as warfarin, with less bleeding (18 fewer bleeds [composite of major plus clinically relevant nonmajor bleeding] per 1,000 patients per year).[43]
Preprocedure Washout	**Washout:** Duration to hold may vary depending on patient's renal function, contact a pharmacist for assistance. Last dose three days before surgery/procedure (i.e., 48-hour washout) with **moderate or high bleeding risk** (three to four days before if CrCl 15 to 29 mL/min).[66] Last dose two days before surgery/procedure (i.e., 24-hour washout) with **low bleeding risk** (three days before if CrCl 15 to 29 mL/min).[66]
Antidote/Reversal Agents	● Consider activated charcoal within two to four hours after edoxaban ingestion.[62] ● Dialysis is not expected to be an effective reversal method.[67,68] ● **Reversal agent:** fixed dose Kcentra (do not give Kcentra if history of HIT) – **see Appendix B**
Management in **surgical** patients before, during, and after **epidural or spinal anesthesia**	● Stop edoxaban 72 hours before neuraxial block. ● Wait at least 6 hours after catheter removal to restart edoxaban. ● If edoxaban is given to a patient with an indwelling epidural catheter (e.g., emergently or by accident), hold edoxaban for 20 to 28 hours before catheter removal.

Therapeutic Considerations	● For A fib, concerns that efficacy may be less than warfarin at higher CrCl is reflected in the U.S. prescribing information. Numerical differences are small and not statistically significant.[41,44] ● In the ARISOTLE and ENGAGE-AF trials, apixaban was associated with significantly reduced risk for stroke/systemic embolism, stroke, and ischemic stroke compared with LOW DOSE edoxaban (30 mg adjusted to 15 mg) but efficacy did not vary significantly when apixaban was compared to HIGH DOSE edoxaban (60 mg adjusted to 30 mg). NOTE: this was based upon indirect comparison analysis from the two trials.[113] ● Both edoxaban 60 mg/day and 30 mg/day were non-inferior to warfarin for risk of first ischemic or hemorrhagic stroke or systemic embolic rate in ENGAGE AF-TIMI 48 study. In same study, edoxaban was associated with significantly lower rates of major bleeding (2.75% high-dose group, 1.61% low-dose group, 3.43% warfarin), though rate of major GI bleeding was increased in high-dose edoxaban compared to warfarin (1.51% vs 1.23%).[42] ● Not recommended in patients with mechanical heart valves or moderate to severe mitral stenosis.[41] ● For VTE treatment, continue for at least three months.[18] Benefit of extended use may not outweigh risk in patients with high bleeding risk.[18] ● **Not recommended in moderate or severe hepatic impairment.[41]**
Switching To/From Other Anticoagulants	● **See Appendix C**
Laboratory Considerations	● Prothrombin time/INR and aPTT may be prolonged by edoxaban, but a normal result does not rule out a clinically important edoxaban effect.[62] The preferred test is anti-factor Xa activity calibrated to edoxaban, if available.[62] ● Regular monitoring not routinely recommended, but may use coagulation assays (calibrated chromogenic anti-FXa assay) in emergencies (i.e. trauma, urgent surgery/invasive procedures, major bleeding, overdose, acute thrombosis, renal/liver failure, adherence verification, drug-drug interactions).[93]
Select Drug Interactions	● Use with anticoagulants not recommended.[41,44] Caution with antiplatelets.[41,44] ● Avoid rifampin (P-gp inducer).[41] ● Reduce dose to 30 mg once daily for DVT/PE indication in patients taking certain P-gp inhibitors (e.g., azithromycin, clarithromycin, erythromycin, itraconazole [oral], ketoconazole [oral], quinidine, or verapamil).[41]
Formulary Status	● Non-formulary

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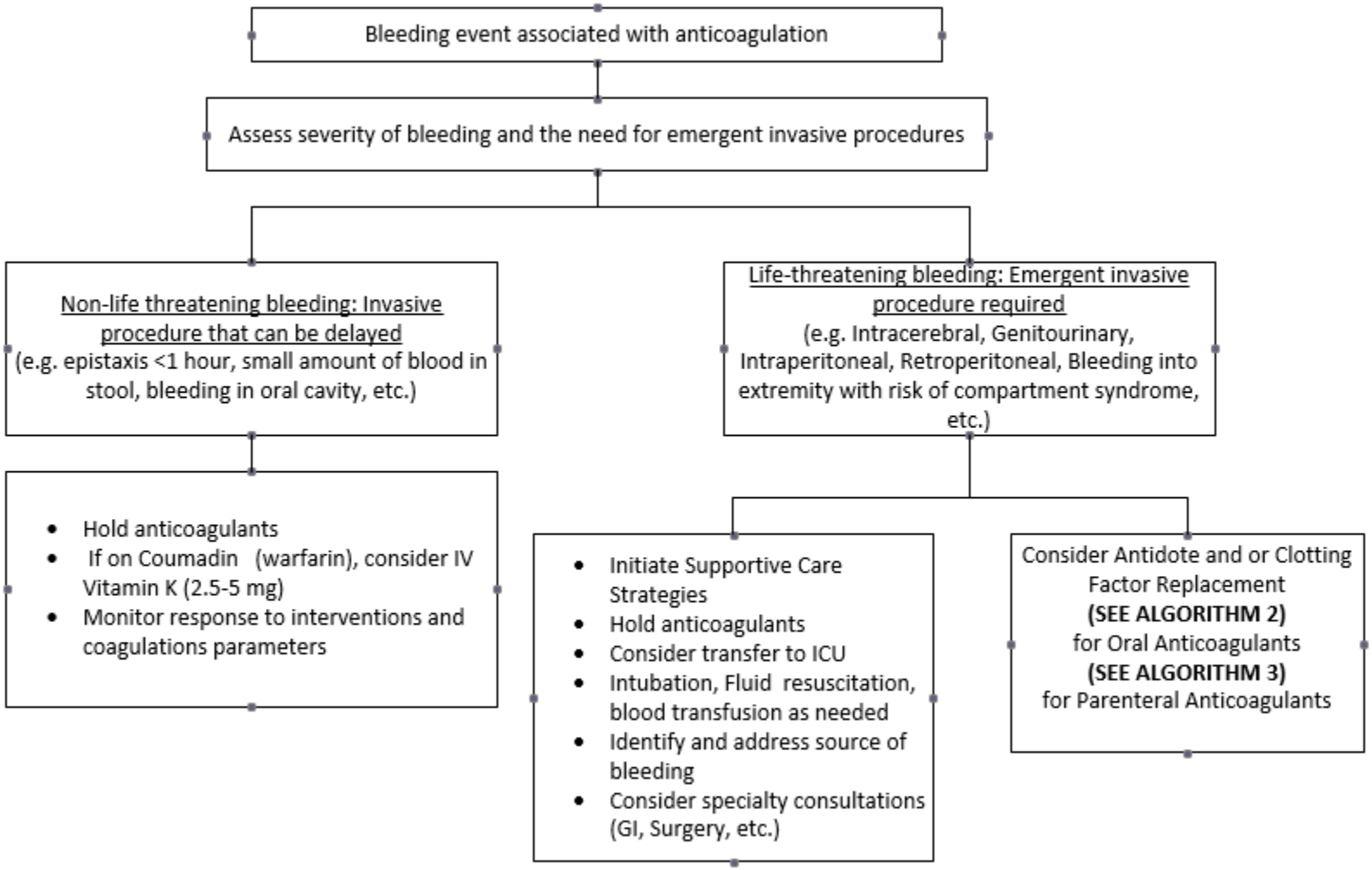
APPENDIX B

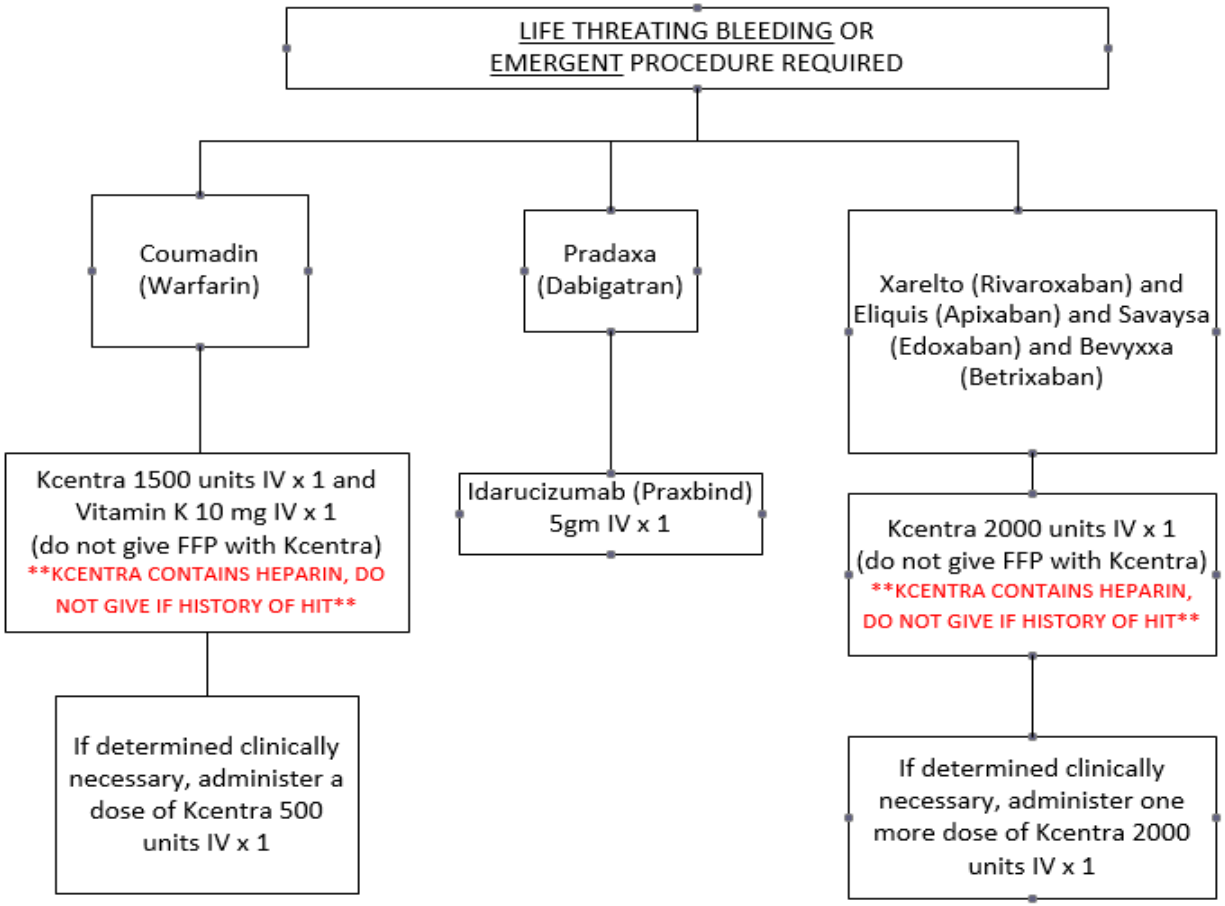
Algorithm 1 – Management of Bleeding in Patients on Anticoagulants*



*This chart does not replace careful clinical judgement. Consider recommendations in context with individual patient characteristics, time since last dose of anticoagulant, renal function, half life of anticoagulant, etc.

APPENDIX B

Algorithm 2 - Oral Anticoagulant Reversal*



*This chart does not replace careful clinical judgement. Consider recommendations in context with individual patient characteristics, time since last dose of anticoagulant, renal function, half life of anticoagulant, etc.

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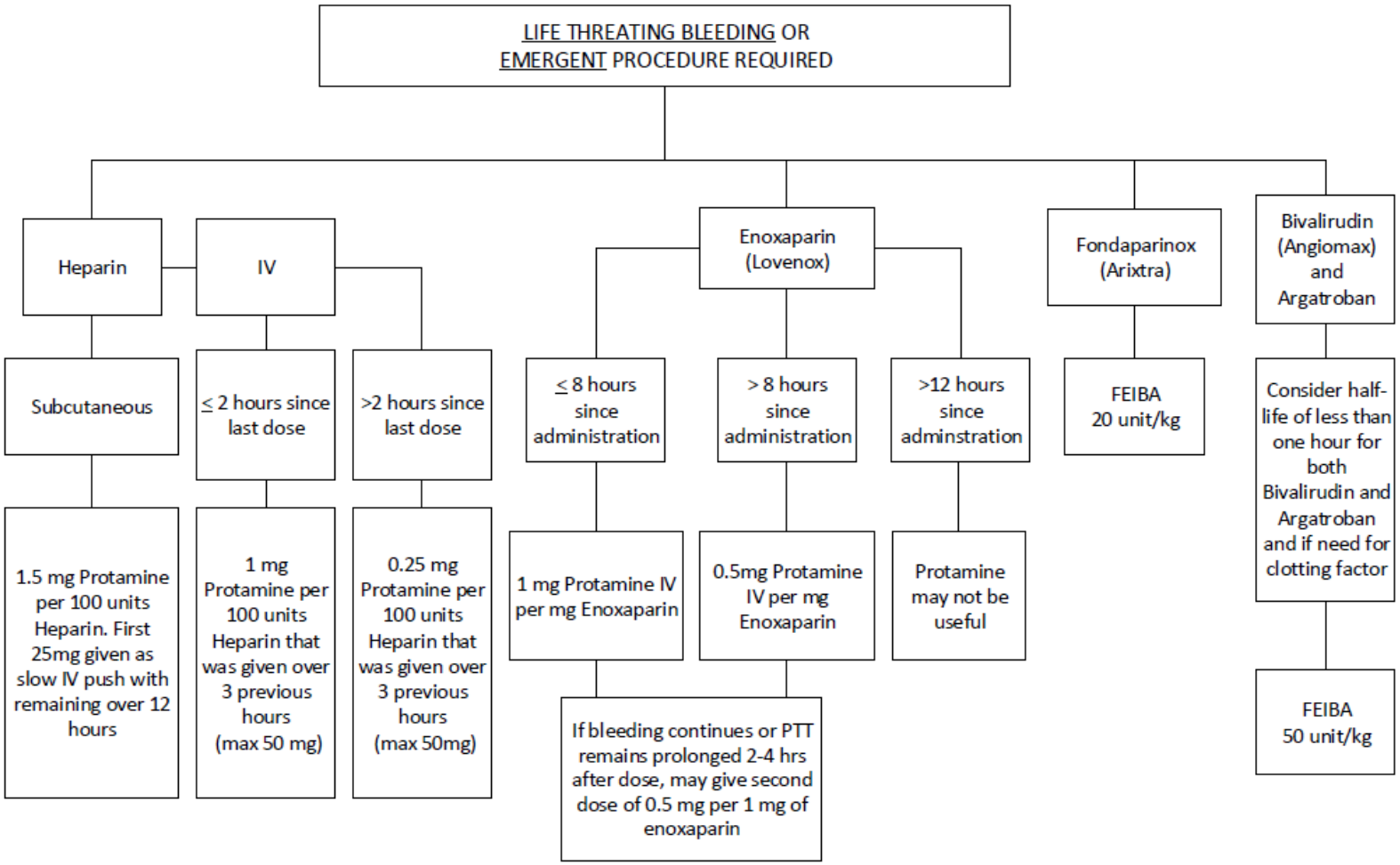
APPENDIX B

Algorithm 3 - Parenteral Anticoagulant Reversal*



*This chart does not replace careful clinical judgement. Consider recommendations in context with individual patient characteristics, time since last dose of anticoagulant, renal function, half life of anticoagulant, etc.

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APPENDIX C

GENESIS
IN THIS TOGETHER

Transition of Anticoagulants

From	To	Action
Apixaban	Argatroban/ Bivalirudin/ Enoxaparin/ Dalteparin/ Fondaparinux/ Heparin SQ	Discontinue other anticoagulant and begin new anticoagulant at time of next scheduled dose.
Apixaban	Warfarin	When going from apixaban to warfarin, consider the use of parenteral anticoagulation as a bridge (e.g., start heparin infusion or therapeutic enoxaparin AND warfarin 12 hours after last dose of apixaban and discontinue parenteral anticoagulant when INR is therapeutic). Apixaban affects INR so that initial INR measurements during the transition may not be useful for determining the appropriate dose of warfarin.
Argatroban	Apixaban, Betrixaban, Dabigatran, Edoxaban, or Rivaroxaban	Start apixaban, betrixaban, dabigatran, edoxaban, or rivaroxaban within 2 hours of discontinuation of argatroban infusion.
Argatroban	Enoxaparin/ Dalteparin/ Fondaparinux/ Heparin	If no hepatic insufficiency, start parenteral anticoagulant within 2 hours of discontinuing argatroban infusion. If there is hepatic insufficiency, start parenteral anticoagulant 2-4 hours after discontinuing argatroban infusion. **The use of enoxaparin/dalteparin/heparin assumes the patient does not have heparin allergy or heparin-induced thrombocytopenia.*
Argatroban	Warfarin	Argatroban must be continued when warfarin is initiated at expected daily dose (no loading dose) and co-administration should continue for at least 5 days. Argatroban falsely elevates the INR. Measure INR daily while argatroban and warfarin are co-administered. ● After 3-5 days of co-therapy with warfarin, and if the INR is >4.0, temporarily suspend the argatroban for 4 hours, then check the INR. ● If the INR is <2.0, restart argatroban and consider warfarin dose adjustment. Repeat process every 24-48 hours until the INR is ≥2.0. ● If the INR is ≥2.0, and at least a 5-day warfarin-argatroban overlap has been achieved, discontinue argatroban and continue warfarin. ● If the INR is >3.0, consider warfarin dose adjustment. Argatroban may need to be restarted if warfarin-argatroban overlap has not been prescribed for 5 days.

Betrixaban	All other anticoagulants	Since betrixaban is currently only available as a prophylaxis dose, initiate the next anticoagulant as clinically needed irrespective of time of last betrixaban dose. ** If patient has been on betrixaban (or other direct anti-Xa inhibitors) within 72 hours of starting a heparin infusion, monitor with PTT instead of anti-Xa until the patient has been off of direct anti-Xa inhibitors for >72 hours

Bivalirudin	Argatroban/ Dalteparin/ Enoxaparin/ Fondaparinux/ Heparin	Initiate parenteral anticoagulant within 2 hours after discontinuation of bivalirudin. **The use of heparin/dalteparin/enoxaparin assumes the patient does not have heparin allergy or heparin-induced thrombocytopenia. In cases of high bleeding risk, consider omitting initial bolus when transitioning to heparin infusion.*
Bivalirudin	Apixaban/ Betrixaban Dabigatran/ Edoxaban/ Ravaroxaban	Initiate apixaban, betrixaban, dabigatran, edoxaban, or rivaroxaban within 2 hours after discontinuation of bivalirudin infusion.
Bivalirudin	Warfarin	Bivalirudin must be continued when warfarin is initiated and co-administration should continue for at least 5 days. Bivalirudin elevates the INR. ● After 3-5 days of co-therapy with warfarin, temporarily suspend the bivalirudin for 4 hours, then check the INR. ● If the INR is <2.0, restart the bivalirudin and consider warfarin dose adjustment. Repeat process every 24-28 hours until the INR is 2.0. ● If the INR is 2.0, and at least a 5-day warfarin-bivalirudin overlap has been achieved, discontinue bivalirudin and continue warfarin. ● If the INR is >3.0, consider warfarin dose adjustment. Bivalirudin may need to be restarted if warfarin-bivalirudin overlap has not been prescribed for 5 days.
Dabigatran	Argatroban/ Bivalirudin/ Enoxaparin/ Dalteparin/ Fondaparinux/ Heparin	Initiate parenteral anticoagulant when next dose of dabigatran would have been taken. If patient's creatinine clearance has reduced to <15 mL/min while on dabigatran, longer wash out period may be needed before starting new anticoagulant. However, no recommendations can be made. In cases of increased bleeding risk, consider a risk benefit analysis before omitting initial bolus when transitioning to heparin infusion.
Dabigatran	Apixaban, Betrixaban Edoxaban, or Rivaroxaban	Initiate apixaban, betrixaban, edoxaban, or rivaroxaban when the next dose of dabigatran would have been taken. If patient's creatinine clearance has been reduced to <15 mL/min, while on dabigatran, a longer wash out period may be needed before starting the new anticoagulant. However, no recommendation can be made.
Dabigatran	Warfarin	Dabigatran can increase INR, so INR will better reflect warfarin's effect only after dabigatran has been stopped for ≥2 days. ● For CrCl >50 mL/min, start warfarin 3 days before discontinuing dabigatran ● For CrCl 30-50 mL/min, start warfarin 2 days before discontinuing dabigatran ● For CrCl 13-30 mL/min, start warfarin 1 day before discontinuing dabigatran ● For CrCl <15 mL/min, no recommendations can be made

Dalteparin	Argatroban/ Bivalirudin/ Enoxaparin/ Fondaparinux/ Heparin	From therapeutic dalteparin doses: Initiate parenteral anticoagulant when next dalteparin dose is expected to be given. From prophylaxis dalteparin doses: Initiate parenteral anticoagulant as clinically needed irrespective of time of dalteparin dose. In cases of increased bleeding risk, consider risk benefit analysis before omitting initial bolus when transitioning to heparin infusion.
Dalteparin	Apixaban, Betrixaban Dabigatran, Edoxaban, or Rivaroxaban	From therapeutic dalteparin doses: Initiate apixaban, betrixaban, dabigatran, edoxaban, or rivaroxaban when next dalteparin dose is expected to be given. From prophylaxis dalteparin doses: Initiate apixaban, betrixaban, dabigatran, edoxaban, or rivaroxaban as clinically needed irrespective of time of dalteparin dose.

Dalteparin	Warfarin	From therapeutic anticoagulation doses: Overlap therapeutic dalteparin dose with warfarin for at least 5 days AND until INR is in therapeutic range for 24 hours. From prophylaxis dalteparin doses: Initiate warfarin as clinically needed irrespective of time of last dalteparin dose.
Edoxaban	Argatroban/ Bivalirudin/ Dalteparin/ Enoxaparin/ Fondaparinux/ Heparin	Discontinue edoxaban and start the parenteral anticoagulant at the time the next dose of edoxaban scheduled to be taken. In cases of increased bleeding risk, consider a risk benefit analysis before omitting initial bolus when transitioning to heparin infusion. ** If patient has been on edoxaban (or other direct anti-Xa inhibitors) within 72 hours of starting the heparin infusion, monitor with PTT instead of anti-Xa until the patient has been off of direct anti-Xa inhibitors for >72 hours
Edoxaban	Apixaban, Betrixaban, Dabigatran, or Rivaroxaban	Wait 24 hours after last dose of edoxaban to initiate apixaban, betrixaban, dabigatran, or rivaroxaban
Edoxaban	Warfarin	Oral option: For patients taking 60 mg of edoxaban, reduce the dose to 30 mg and begin warfarin concomitantly. For patients receiving 30 mg of edoxaban, reduce the edoxaban dose to 15 mg and begin warfarin concomitantly. INR must be measured at least weekly and just prior to the daily dose of edoxaban to minimize the influence of edoxaban on INR measurements. Once a stable INR 2.0 is achieved, edoxaban should be discontinued and the warfarin continued. Parenteral option: Discontinue edoxaban and administer a parenteral anticoagulant and warfarin at the time of the next scheduled edoxaban dose. Once a stable INR 2.0 is achieved, the parenteral anticoagulant should be discontinued and the warfarin continued.
Enoxaparin	Argatroban/ Bivalirudin/ Dalteparin/ Fondaparinux/ Heparin	From therapeutic enoxaparin doses: Initiate parenteral anticoagulant when next enoxaparin dose is expected to be given. In cases of increased bleeding risk, consider a risk benefit analysis before omitting initial bolus when transitioning to heparin infusion. From prophylaxis enoxaparin doses: Initiate parenteral anticoagulant as clinically needed irrespective of time of last enoxaparin dose. In cases of increased bleeding risk, consider a risk benefit analysis before omitting initial bolus when transitioning to heparin infusion.

Enoxaparin	Apixaban, Betrixaban Dabigatran, Edoxaban, or Rivaroxaban	From therapeutic enoxaparin doses: Initiate apixaban, betrixaban, dabigatran, edoxaban, or rivaroxaban when next enoxaparin dose is expected to be given. From prophylaxis enoxaparin doses: Initiate apixaban, betrixaban, dabigatran, edoxaban, or rivaroxaban as clinically indicated irrespective of time of last enoxaparin dose.
Enoxaparin	Warfarin	From therapeutic enoxaparin doses: Overlap therapeutic dose enoxaparin with warfarin for at least 5 days AND until INR is in therapeutic range for 24 hours. From prophylaxis enoxaparin doses AND assuming patient does not have a new thrombosis: If immediate therapeutic anticoagulation is not desired: Initiate warfarin as clinically needed irrespective of time of last enoxaparin dose.
Fondaparinux	Argatroban/ Bivalirudin/ Dalteparin/ Enoxaparin/ Heparin	From therapeutic fondaparinux doses: Initiate parenteral anticoagulant when next fondaparinux dose is expected to be given. In cases of high bleeding risk, consider omitting initial bolus when transitioning to heparin infusion. From prophylaxis fondaparinux doses: Initiate parenteral anticoagulant as clinically needed irrespective of time of last fondaparinux dose.
Fondaparinux	Apixaban, Betrixaban, Dabigatran, Edoxaban, or Rivaroxaban	From therapeutic fondaparinux doses: Initiate apixaban, betrixaban, dabigatran, edoxaban, or rivaroxaban when next fondaparinux dose is expected to be given. From prophylaxis fondaparinux doses: Initiate apixaban, betrixaban, dabigatran, edoxaban, or rivaroxaban as clinically indicated irrespective of time of fondaparinux dose.
Fondaparinux	Warfarin	From therapeutic fondaparinux doses: Overlap therapeutic dose fondaparinux with warfarin for at least 5 days AND until INR is in therapeutic range for 24 hours. From prophylaxis fondaparinux doses AND assuming patient does not have a new thrombosis: Initiate warfarin as clinically indicated irrespective of time of fondaparinux dose
Heparin infusion	Argatroban/ Bivalirudin/ Enoxaparin/ Dalteparin/ Fondaparinux	Initiate parenteral anticoagulant within 2 hours after discontinuation of heparin infusion.
Heparin infusion	Apixaban, Betrixaban, Dabigatran, Edoxaban, or Rivaroxaban	Initiate apixaban, betrixaban, dabigatran, edoxaban, or rivaroxaban within 2 hours after discontinuation of heparin infusion.
Heparin infusion	Warfarin	If immediate therapeutic anticoagulation is desired: Overlap therapeutic heparin dose with warfarin for at least 5 days AND until INR is in therapeutic range for 24 hours. If immediate therapeutic anticoagulation is not desired: Initiate warfarin as clinically needed irrespective of time of last heparin dose.

Rivaroxaban (doses 15 mg/ day)	Argatroban/ Bivalirudin/ Enoxaparin/ Fondaparinux/ Heparin	Discontinue rivaroxaban and give the first dose of the other anticoagulant at the time that the next rivaroxaban dose is expected to be given. In cases of high bleeding risk, consider omitting initial bolus when transitioning to heparin infusion. ** If patient has been on rivaroxaban (or other direct anti-Xa inhibitors) within 72 hours of starting the heparin infusion, monitor with PTT instead of anti-Xa until the patient has been off of direct anti-Xa inhibitors for >72 hours
Rivaroxaban (doses 15 mg/ day)	Warfarin	When going from rivaroxaban to warfarin, consider the use of parenteral anticoagulant as a bridge (eg, start heparin infusion or therapeutic enoxaparin and warfarin when next dose of rivaroxaban would have been taken). Discontinue the parenteral anticoagulant when INR is therapeutic 2). The INR may be affected by rivaroxaban for 24 hours.
Rivaroxaban (doses 15 mg/ day)	Apixaban, Betrixaban, Dabigatran, or Edoxapan	Discontinue rivaroxaban and give the first dose of the other anticoagulant at the time that the next rivaroxaban dose would have been taken.
Rivaroxaban (doses O mg/day)	All other anticoagulants	Initiate other anticoagulants as clinically needed irrespective of time of last rivaroxaban dose
Warfarin	Apixaban	Wait until INR is <2, then initiate apixaban.
Warfarin	Betrixaban	Wait until INR is <2, then initiate betrixaban
Warfarin	Dabigatran	Wait until INR is <2, then initiate dabigatran.

Warfarin	Rivaroxaban	Wait until INR is <3, then initiate rivaroxaban.
Warfarin	Edoxaban	Wait until INR is ≤ 2.5, then initiate edoxaban

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APPENDIX D

INCOMING ORDER / ON PROFILE	apixaban (Eliquis)	argatroban	aspirin	betrixaban (Bevyxxa)	cangrelor (Kengreal)	clopidogrel (Plavix)	dabigatran (Pradaxa)	edoxaban (Savaysa)	enoxaparin (Lovenox)	fondaparinux (Arixtra)	heparin	prasugrel (Effient)	rivaroxaban (Xarelto)	ticagrelor (Brilinta)	warfarin (Coumadin)
apixaban (Eliquis)	TD	TD	Y	TD	Y	Y	TD	TD	TD	TD	TD	Y	TD	Y	TD
argatroban	TD	TD	Y	TD	Y	Y	TD	TD	TD	TD	TD	Y	TD	Y	TD
aspirin	Y	Y	TD	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	See note	Y
betrixaban (Bevyxxa)	TD	TD	Y	TD	Y	Y	TD	TD	TD	TD	TD	Y	TD	Y	TD
cangrelor (Kengreal)	Y	Y	Y	Y	TD	TD	Y	Y	Y	Y	Y	TD	Y	See note	Y
clopidogrel (Plavix)	Y	Y	Y	Y	TD	TD	Y	Y	Y	Y	Y	TD	Y	TD	Y
dabigatran (Pradaxa)	TD	TD	Y	TD	Y	Y	TD	TD	TD	TD	TD	Y	TD	Y	TD
edoxaban (Savaysa)	TD	TD	Y	TD	Y	Y	TD	TD	TD	TD	TD	Y	TD	Y	TD
enoxaparin (Lovenox)	TD	TD	Y	TD	Y	Y	TD	TD	TD	TD	TD	Y	TD	Y	INR
fondaparinux (Arixtra)	TD	TD	Y	TD	Y	Y	TD	TD	TD	TD	TD	Y	TD	Y	INR
heparin (no flushes)	TD	TD	Y	TD	Y	Y	TD	TD	TD	TD	Y	Y	TD	Y	INR
prasugrel (Effient)	Y	Y	Y	Y	TD	TD	Y	Y	Y	Y	Y	TD	Y	TD	Y
rivaroxaban (Xarelto)	TD	TD	Y	TD	Y	Y	TD	TD	TD	TD	TD	Y	TD	Y	TD
ticagrelor (Brilinta)	Y	Y	See note	Y	See note	TD	Y	Y	Y	Y	Y	TD	Y	TD	Y
warfarin (Coumadin)	TD	TD	Y	TD	Y	Y	TD	TD	INR	INR	INR	Y	TD	Y	Y

Y	OK to give these two medication together
INR	Therapeutic Duplication - Generally should not be given together when INR is greater than 1.9 - Verify with pharmacy
TD	Therapeutic Duplication - Do not give together unless verified with Pharmacy
***	If platelet count falls below 100,000, thrombocytopenia may be developing. Review with Pharmacy
See note	Maximim maintainence dose of aspirin 81 mg daily. Aspirin 325mg may be given upon initiation (ie during acute ACS)
See note	Ticagrelor may be administered any time during or immediately following discontinuing cangrelor infusion

APPENDIX E

WARFARIN INITIATION GUIDELINES

For hospitalized warfarin-naïve patients in whom an INR can be checked on a daily basis

DAY	INR	DOSE
1	Baseline INR	5 mg
2	less than 1.5	5 mg
	1.5 - 1.9	2.5 mg
	2 - 2.5	1 - 2.5 mg
	greater than 2.5	0
3	less than 1.5	5 - 10 mg
	1.5 - 1.9	2.5 - 5 mg
	2 - 3	0 - 2.5 mg
	greater than 3	0
4	less than 1.5	10 mg
	1.5 - 1.9	5 - 7.5 mg
	2 - 3	0 - 5 mg
	greater than 3	0
5	less than 1.5	10 mg
	1.5 - 1.9	7.5 - 10 mg
	2 - 3	0 - 5 mg
	greater than 3	0
6	less than 1.5	7.5 - 12.5 mg
	1.5 - 1.9	5 - 10 mg
	2 - 3	0 - 7.5 mg
	greater than 3	0

Crowther MA, et. al. *Arch Intern Med* 1999:159(1):46-8

- Several studies have confirmed that 5 mg initiation achieves therapeutic anticoagulation as rapidly as 10 mg but with a lower frequency of supratherapeutic INRs.
- The **anticoagulant** effect may be seen within 24 hours due to inhibition of Factor VII, but the **antithrombotic** effect (Factor II inhibition) is delayed for 72-96 hours. Bridge a minimum of 4 to 5 days and until the INR is therapeutic to ensure the patient is antithrombotic.
- Monitor INR daily until within therapeutic range for at least 2 consecutive days. Time to steady state = approximately 10 days.

Warfarin Dosing Considerations

Day 1 Initiate therapy at expected maintenance dose
USUAL INITIATION DOSE = 5 MG
Assess for risk factors for increased sensitivity to warfarin and consider a lower starting dose (e.g., **2.5 mg**):

- Elderly (age over 75 yrs)
- Malnutrition/NPO greater than 3 days
- Concomitant drugs affecting warfarin metabolism
- Elevated baseline INR
- Concurrent disease states (liver failure, uncompensated CHF, malignancy, fever/infection, diarrhea, clinical hyperthyroidism)

Day 2 Check INR (partially reflects 1st dose only)

- If INR < 1.5, give same dose
- If INR 1.5 or >, give lower dose

Day 3 Check INR (partially reflects first 2 doses)

- INR < 1.5 suggests a higher than average maintenance dose will be needed
- 1.5-2 suggests an average maintenance dose will be needed
- INR > 2 suggests a lower than average maintenance dose will be needed

- An increase of 0.2-0.3 per day represents an optimal response
- Any increase of 0.4 per day or greater should prompt a warfarin dose reduction or hold in further warfarin administration
- **Dose adjustments need to take into consideration the 36-48 hour delay in peak response of the INR to the previous dose. An INR result is a reflection of the prior 2 to 3 doses**
- Consider effect of compliance, diet, herbals, vitamin K on INR

SIGNIFICANT WARFARIN DRUG INTERACTIONS

Increased Warfarin Effect	Suggested Management
Amiodarone	Decrease warfarin dose by 1/3-1/2
Azole Antifungals	Decrease warfarin dose 25-75%; Monitor INR frequently
Cimetidine	Use non-interacting H2 antagonist (e.g., famotidine)
Fluoroquinolones	AVOID concomitant use with ciprofloxacin; Monitor INR frequently with all fluoroquinolones
Macrolide Antibiotics	Erythromycin (AVOID if possible) > clarithromycin > azithromycin
Metronidazole	AVOID if possible; Warfarin dose may need to be decreased by up to 1/2
Sulfamethoxazole/Trimethoprim	AVOID if possible; Effect can be seen in 1 to 2 days
Decreased Warfarin Effect	**Suggested Management**
Barbiturates	May require 30-60% increase in warfarin dose; seen within 1-3 weeks
Nafcillin	Monitor INR; May require an increase in warfarin dose
Rifampin	AVOID if possible; Warfarin dose may need to be increased by 2- to 3-fold

This list is not all-inclusive; INR should be monitored after initiating, modifying or discontinuing any drug or herbal therapy
06/2009/ejl

APPENDIX F

RECOMMENDATIONS FOR MANAGING ELEVATED INRs OR BLEEDING IN PATIENTS ON WARFARIN

CLINICAL SITUATION	INR	MANAGEMENT
No significant bleeding	Greater than therapeutic goal but less than 4.5	• **Lower dose or omit dose and resume when INR therapeutic** • If INR only minimally above therapeutic range, **dose reduction may not be necessary**
	4.5 - 10	• **Omit next one or two doses**, monitor more frequently and **resume at adjusted dose when INR in therapeutic range** • **Vitamin K is not routinely recommended** • **If at increased risk of bleeding, may omit dose and give vitamin K (1 to 2.5 mg PO)** • **If more rapid reversal required (i.e. urgent surgery), give vitamin K (5 mg or less PO)** with the expectation that a **reduction of INR will occur in 24 hours**; if INR is still high, additional **vitamin K (1 to 2 mg PO)** can be given
	Greater than 10	• **HOLD WARFARIN** • Give **vitamin K (2.5 to 5 mg PO)** with the expectation that the **INR will be reduced substantially in 24 to 48 hours** • Monitor more frequently and use additional vitamin K if necessary • Resume therapy at adjusted dose when INR is therapeutic
Serious or life-threatening bleeding♥	Any elevation of INR due to warfarin administration	• **HOLD WARFARIN** • Give **vitamin K (5 to 10 mg slow IV infusion)** • Give FFP or Kcentra (do not give Kcentra if history of HIT), depending on urgency of situation • Vitamin K can be repeated every 12 hours if necessary, depending on INR

♥ **i.e.. intracranial, retroperitoneal, hemodynamic compromise, requiring transfusion**

FFP= fresh frozen plasma, **rVIIa**= recombinant factor VIIa

Adapted from CHEST 2012;141(2):173S-176S.

- When using vitamin K, the lowest dose possible to reverse the effects should be given. Excessively large doses of vitamin K do not reverse anticoagulation faster. **ANY DOSE OF VITAMIN K GREATER THAN 10 MG SHOULD BE CONSIDERED EXCESSIVE.**

- With **IV** vitamin K, coagulation factors increase in 1 to 2 hours and **INR VALUES RETURN TO NORMAL AFTER 12 TO 14 HOURS**. With **ORAL** vitamin K, coagulation factors increase in 6 to 12 hours and **INR VALUES RETURN TO NORMAL WITHIN 24 TO 48 HOURS.**

- After correction with vitamin K, particularly with high doses (i.e. greater than 5 mg), **FUTURE INRs MAY BE AFFECTED FOR 7 DAYS OR MORE**. Heparin or LMWH should be considered during this period of **WARFARIN RESISTANCE** for those patients who require continuous anticoagulation (e.g. mechanical heart valves).

- PO vitamin K is only available as a 5 mg tablet. A 2.5 mg dose may be obtained by splitting the tab. For doses which cannot be obtained with the tablet (e.g. 1 mg), the injectable solution can be given PO (either undiluted or mixed with orange juice, milk or chocolate milk just prior to administration to improve palatability).

- It is recommended that IV vitamin K be administered as a slow infusion, not to exceed 1 mg per minute. When IV vitamin K is ordered, it is dispensed in a 50 ml NS piggyback and all doses are infused over 30 minutes.

SUMMARY OF THE ROUTE OF VITAMIN K

ROUTE	ADVANTAGES	DISADVANTAGES
ORAL	• Safest route • **Preferred route** if no major bleeding • Low risk of anaphylaxis • No IV site needed • **More predictable response and quicker onset of action compared to subQ**	• Slower onset of action than IV • Warfarin resistance
IV	• Fastest onset of action • Preferred route for severe bleeding situations	• Risk of anaphylaxis • Must be given by slow IV infusion • Warfarin resistance
SUBQ	• No IV site needed • Consider as option only if NPO, urgent reversal not required, and/or no IV access	• **Relatively contraindicated** • Delayed onset • Erratic absorption • Unpredictable response
IM		• **Contraindicated due to significant risk for hematoma formation**

APPENDIX G

ENOXAPARIN DOSE ROUNDING GUIDELINES

Genesis Medical Center

Enoxaparin is a low-molecular-weight heparin (LMWH) used in the prevention and treatment of thromboembolic events. While the recommended dosing for prophylaxis is a fixed once daily or twice daily regimen, treatment doses are based on weight and typically ordered as either 1 mg per kg every 12 hours or 1.5 mg per kg every 24 hours. Lovenox® is commercially available in a concentration of 100 mg per ml enoxaparin, prepackaged in syringes containing 30 mg, 40 mg, 60 mg, 80 mg or 100 mg, and in a concentration of 150 mg per ml enoxaparin, prepackaged in syringes containing 120 mg or 150 mg.

One of the risks identified with the use of LMWHs is that of administering the wrong dose because the barrel of Lovenox® (enoxaparin) prefilled syringes lack sufficient milliliter gradations. To help minimize the potential for an administration error, it is recommended that the dose be rounded to the nearest available syringe size.

In order to standardize the dose and syringe size of Lovenox® (enoxaparin) injection to be dispensed and administered for weight-based treatment regimens, all doses ordered on a mg/kg basis will be rounded to the nearest available syringe size as follows:

Dose ordered (mg)	**Dose Administered (= Syringe Size Used)**
30-35	30 mg
36-49	40 mg
50-69	60 mg
70-89	80 mg
90-109	100mg
110-135	120mg
136-150	150mg
Over 150	Closest combination of syringes